
References

Aprotinin and cardiac surgery: a sorry tale of evidence misused

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Although evidence from clinical trials is crucial to the advancement of modern medicine, its quality varies considerably. Counterintuitively, high-quality evidence can be ignored and low-quality evidence may lead to the
restriction in the use of a drug that has been proved to be effective and, most probably, safe. This editorial will review the history of aprotinin in cardiac surgery; examine why evidence of efficacy was ignored; why drug regulatory agencies around the world suspended the licence for aprotinin; and why some have now reversed that decision and lifted the suspension.

In a landmark randomized controlled trial (RCT) by Royston and colleagues that was published in 1987, aprotinin was coincidentally found to dramatically reduce blood loss and the need for transfusion in re-do open heart surgery.1 In a systematic review published in 2005, Ferguson and colleagues found that, by 2002, a further 63 papers had been published since 1987.2 Cumulative meta-analysis of these RCTs found it was clear that aprotinin greatly decreased the need for peri-operative transfusion with an odds ratio (OR) stabilizing at 0.25 by the time of the twelfth study published in June 1992. Yet, over the next decade, a further 52 RCTs were undertaken. Ferguson and colleagues’ explanations as to why these RCTs were undertaken were that they had both failed to cite prior publications and to perform adequate literature searches. However, by 1993, published research on aprotinin was recognized by drug regulatory agencies such as the Food and Drug Administration (FDA) in the USA which approved its use for reducing blood loss during coronary artery bypass graft (CABG) surgery.3

Safety concerns

During the early 2000s, aprotinin was approved in several EU countries for use in patients undergoing CABG surgery. However, in December of 2007, its UK licence was suspended on the basis of advice from the Commission on Human Medicines (CHM). In February 2008, aprotinin’s licence was also suspended by the European Commission. The background to the suspensions is four observational studies and one RCT identifying that aprotinin was associated with an increased mortality.

The first observation study to cast doubt on the safety of aprotinin was by Mangano and colleagues and was published in 2006.4 This was an observational, prospective, cohort study involving 4374 adults undergoing CABG surgery, which assessed aprotinin, aminocaproic acid, and tranexamic acid vs no agent. The study found that aprotinin was associated with an increased risk of renal failure, myocardial infarction, heart failure, stroke, encephalopathy, and an increased mortality (2.8 vs 1.3%, P=0.02).

Neither aminocaproic acid nor tranexamic acid was found to be associated with an increased risk of renal, cardiac, or cerebral events and the reduction of blood loss was similar for all three drugs. A second observational study by Karkouti and colleagues, published in the same year, found that aprotinin may be associated with renal dysfunction.5 As a consequence, in 2006, the FDA listed renal dysfunction along with anaphylaxis, graft occlusion, and stroke amongst the drug’s safety concerns.6 However, the association of aprotinin and renal failure was disputed by Furnary and colleagues in 2007 who reported that this was a confounding variable and that renal impairment was related to an increased packed red cell transfusion in the setting of cardiac surgery.6

In 2007, Mangano and colleagues published a further analysis of the same data set that was used in the 2006 paper,7 and the authors reported that aprotinin was independently predictive of 5-yr mortality.

Another source of concern about aprotinin’s safety came from in-house research that Bayer contracted using a research organization called i3 Drug Safety. A preliminary report in 2006 on CABG patients from Bayer’s database showed a higher risk of death and acute renal failure in aprotinin recipients compared with patients who had received other antifibrinolytics, but that this risk was not a definitive association.8

In 2008, the next important study, Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART), was published.9 The BART study was very influential because, unlike previous observational studies, it was a blinded RCT comparing aprotinin, tranexamic acid, and aminocaproic acid in patients undergoing high-risk cardiac surgery. The primary nominated outcome was massive postoperative bleeding and 30-day mortality was a secondary outcome. The trial was terminated early by the safety committee because of a non-significant increased mortality associated with aprotinin. Indeed, the published BART study reported a significantly higher 30-day mortality in patients receiving aprotinin compared with both lysine analogues [relative risk (RR) 1.53; 95% CI, 1.06–2.22] although there was less massive bleeding in the aprotinin group (RR 0.79; 95% CI, 0.59–1.05) for both comparisons. On the background of the previous evidence from observational studies, this RCT was the final nail in the coffin for aprotinin and precipitated the suspension of its licence.

Limitations of the studies

Limitations in Mangano and colleagues 2006 study suggest that its conclusions may not have been reliable. First, the study was observational, non-blinded, without randomization, and used unmatched groups. The National Institute for Clinical Excellence (NICE) classifies the quality of such evidence as Level 2+; associated with a high risk of confounding or bias and a significant risk that the relationship is not causal.10 Propensity-adjusted, multivariable logistic regression analyses were used to control for between-group differences at baseline. However, it is not clear whether such analysis could overcome the likely bias that aprotinin may have been used in the sickest patients.11 Cited risk factors for adverse outcomes were sometimes inappropriate, for example, duration of education. Moreover, values for propensity scores were missing for over 400 patients and the reasons why patients received any specific agent or no agent were unclear. There were likely to be variations in practices between countries and centres, and outcomes were not clearly defined. In addition, the authors failed to report details of the surgery itself, such as whether the surgery was on- or off-pump, time on-pump, and number of coronary
vessels bypassed. These variables are likely to influence not only choice of antifibrinolytic agent but also outcome, and are, therefore, a source of indication bias. These multiple sources of confounding raised concerns regarding the validity of both of Mangano and colleagues’ papers.

The Cardiovascular and Renal Drugs Advisory Committee of the FDA reviewed the evidence from the studies, but could not endorse it because of questions about the methodologies used, and because the data had not been independently reviewed by the FDA. As far as the i3 Drug Safety study is concerned, a fundamental flaw was that the data set used was unsuitable to assess risk of haemostatic agents in cardiac surgery. There was also a failure of study administrators to take into account the proportion of patients on chronic dialysis when assessing the need for postoperative dialysis.

Whilst the BART study had the benefit of being a blinded RCT, a number of serious limitations were identified in the BART study:

- The unexplained exclusion of 137 patients from the analysis after randomization. A re-analysis which included these originally excluded patients reduced the statistical significance of the mortality signal for aprotinin.
- There was an unusually large number of reclassifications of outcomes from the originally reported data, with a large (~75%) change rate in primary outcome (massive postoperative bleeding). Reclassifications were in opposite directions for aprotinin vs tranexamic acid and aminocaproic acid, favouring the latter, and these changes increased with the duration of the study.
- The trend in mortality for the excluded patients in the study was opposite that for the included patients.
- The way in which heparin was used for anticoagulation during cardiopulmonary bypass was inconsistent and sometimes even inappropriate.
- There was a lack of appropriate monitoring of patients’ anticoagulation with the activated clotting time—the reagent could have been influenced by aprotinin.
- The findings of the BART study were not replicated because when data from other RCTs were analysed together with exclusion of data from the BART study, aprotinin was not associated with a higher risk of death compared with other antifibrinolytics. This was also the case for a recently published large meta-analysis which included the BART study in its data set. Large-scale observational studies such as that by Pagano and colleagues have not reported the safety concerns highlighted in the BART study.

**Influence of BART trial on systematic review and meta-analysis**

The latest Cochrane review of anti-fibrinolytic use to minimize perioperative allogeneic blood transfusion includes data from the published BART trial. This meta-analysis found that aprotinin use in patients undergoing cardiac surgery was associated with an increased mortality compared with the lysine analogues (RR 1.30; 95% CI 1.02–1.89). Given that 70% of the weight of the meta-analysis came from the published BART study, these findings are unsurprising. If one then repeats the meta-analysis using data and RevMan software available from the Cochrane review website but excluding the BART study data, the mortality associated with aprotinin is not significantly different from the lysine analogues (RR 1.10; 95% CI 0.62–1.94). The conclusion that aprotinin results in an increased risk of death therefore seems to be unwarranted.

Another meta-analysis of nine RCTs by Takagi and colleagues, which included data from the BART study, found a 45% increase in mortality associated with aprotinin relative to tranexamic acid (RR 1.45; 95% CI 1.00–2.11, P = 0.05). Again, the outcome of this analysis is likely to have been swayed by the BART study results leading to an erroneous conclusion.

**Influence of BART trial on guidelines**

The 2011 Update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines reversed a Class 1(A) recommendation from an earlier guideline published in 2007 that ‘low-dose aprotinin is indicated to reduce the number of patients requiring blood transfusion and to reduce the total blood loss in patients having cardiac procedure.’ The new recommendations, which have been downgraded to a Class III(A), acknowledge that aprotinin reduces the number of adult patients requiring blood transfusion and reducing total blood loss and the need for re-exploration in patients undergoing heart surgery but do not recommend its use for routine conservation because the risks outweighed the benefits.

The first cited piece of evidence for this change was specifically the higher 30-day mortality reported in the published BART study. The second piece of evidence was based on a 2009 published Cochrane review of anti-fibrinolytics that included data from the BART study. Interestingly, although the published review did not find aprotinin to have a statistically significant higher mortality compared with either tranexamic acid or aminocaproic acid, the guidelines group pooled the lysine analogues data and compared aprotinin with both the lysine analogues, finding a significantly higher mortality associated with aprotinin (RR 1.49; 95% CI 1.12–1.98). If the guideline development group used evidence from the published BART study which is flawed and a meta-analysis including the same flawed data, then its decision-making may have been perversely influenced leading to unsound recommendations.

**Lifting of the licence suspension**

Health Canada took the initiative to review the BART study and re-analyse the data publishing its findings in September 2011. As a result of the study weaknesses, an expert advisory panel on aprotinin concluded that the BART study could not be reliably used to assess the benefit–risk balance of this drug. The review also determined that the benefits of
Aprotinin outweigh the risks when used for patients undergoing CABG surgery and that the evidence does not suggest an increased risk of death in this context.\textsuperscript{13}

Subsequently, the CHM also performed a comprehensive review of the evidence on the use of antifibrinolytics. This review prompted the European Medicines Agency (EMA) to release a statement in February 2012, indicating that the benefits of aprotinin outweigh its risks in appropriately managed patients undergoing isolated CABG surgery and recommended to the EU that the suspension of the licence for aprotinin in this context be lifted.\textsuperscript{14}

**Conclusion**

Clearly, aprotinin effectively reduces blood loss and the need for transfusion associated with heart surgery and currently in Canada and the EU, Health Canada, and the EMA believe the accumulated evidence of the benefits of aprotinin outweigh its risks in isolated CABG surgery.\textsuperscript{21,22} In other countries such as the USA, aprotinin may never be used again even if its licence is fully reinstated because manufacturers may decide that the product liability is too high. So, a drug that has great patient benefits will remain unavailable to many patients around the world because of evidence from weak observationals studies and the flawed evidence of one published RCT that undermined confidence in the drug’s safety. Evidence is essential to drive medicine forward into the future, but we need to remain careful as to how it is created and vigilant to how it is evaluated, published, and interpreted.

**Declaration of interest**

R.P.A. was a member of the ad hoc Scientific Advisory Group for the Committee for Human Medicinal Products on aprotinin that was held on 11th October 2011.

**References**


