

The risk of aprotinin: a conflict of evidence

Bleeding is one of the largest contributors to risk of death after heart surgery. This fact comes as no surprise because patients are given heparin, the oxygenator depletes clotting factors and platelets, and the surgeon cuts and sews heart chambers and blood vessels. In current practice, some individuals receive anticoagulants or are treated with platelet-inhibiting drugs before surgery, adding further to their mortality risk. Since the blood-sparing effect of aprotinin was first reported,¹ research has repeatedly shown that the drug reduces blood loss and the need for transfusion.^{2,3} From the outset, concern was raised that there might be enhanced complications attributable to a procoagulant effect,⁴ so welcome reassurance was received when a meta-analysis of 35 randomised trials—3879 patients undergoing coronary-artery bypass grafting—showed no increased risk of myocardial infarction, renal failure, or stroke,⁵ in line with results of previous meta-analyses (table).^{6,7}

In a recent observational study by Dennis Mangano and colleagues,⁸ cardiac, renal, and cerebral complications were reported that were as much as doubled in frequency in patients treated with aprotinin as compared to patients not receiving antifibrinolytics, thus contradicting the conclusions of the meta-analyses. This finding is an interesting twist: such conflicts usually arise when observational studies suggest an effect not seen in later confirmatory trials.⁹ The difference between evidence from the randomised trials and this multivariable-adjusted cohort study demands more careful discussion than the blithe explanation that industry-sponsored studies carry unavoidable bias.⁸ Two probable explanations exist: either the observational study was subject to sources of bias that did not affect the randomised trials, or the randomised trial findings are not generalisable to the patients who receive these drugs in real practice.

In the observational study, use of aprotinin was a clinical decision taken in high-risk patients. As a result, large differences were present between patient groups: antifibrinolytic recipients were more likely to have liver, renal, and pulmonary disease, diabetes, hypertension, and angina, and to be deprived (as judged by ethnic origin and education). They also had substantially higher rates of previous surgery and vascular interventions than did patients not receiving antifibrinolytics.⁸ Mangano and colleagues used propensity scoring to adjust for such differences. This method can only adjust for observed confounders, whereas randomisation protects against unknown confounders.⁹ An example of a serious unmeasured factor is the use of aprotinin in response to difficulties arising during surgery (such as large blood-loss or long cardiopulmonary-bypass time) rather than as part of a planned intervention. Another limitation of propensity scoring is inclusion of irrelevant predictors, which reduces the efficiency of the control on relevant predictors.¹⁰ Finally, Mangano's group had earlier reported substantial intercountry differences in antifibrinolytic use and morbidity and mortality.¹¹ With their design of the propensity score (all antifibrinolytics in one group), this variation cannot be properly adjusted for.

Differential exclusion is another concern in any study. On the basis of a previous publication,¹² 691 patients were seemingly excluded from the study, including 448 for an inadequate dose and 226 for receiving multiple antifibrinolytics. Of these 691 excluded individuals 50 died (7.2%), compared to a mortality of only 2.6% among included patients. If participants receiving an inadequate dose were more likely to die than those who received the full dose, Mangano's conclusion is even more confusing and contradictory. Exclusion of patients who receive multiple antifibrinolytics violates the intention-to-treat principle.

Limitations of the available trials must also be acknowledged. By comparison with Mangano's cohort, participants in the randomised trials were generally younger, male, and healthier.⁵ Most of the studies were done in the 1990s, and comparatively older and sicker people are referred for surgery now. In particular,

	Sedrakyan, ⁵ 2004	Levi, ⁶ 1999	Henry, ⁷ 2001
Mortality	0.96 (0.65–1.40)	0.55 (0.34–0.90)	0.87 (0.63–1.19)
Myocardial infarction	0.85 (0.63–1.14)	1.13 (0.76–1.67)	0.97 (0.69–1.36)
Renal failure	1.01 (0.55–1.83)	..	1.19 (0.79–1.79)
Stroke	0.53 (0.31–0.90)	..	0.43 (0.16–1.19)
Any thrombosis	..	..	0.64 (0.31–1.31)
Atrial fibrillation	0.90 (0.78–1.03)	..	..

Table: Relative risk estimates for aprotinin (95% CI) from three systematic reviews

real-world patients might be at higher risk for renal disease than individuals selected for the trials. These possibilities could be investigated further by looking at the risk profile of people who met inclusion criteria for the trials.

The costs of postoperative complications are high and conflicting evidence now exists about whether use of aprotinin increases⁸ or tends to reduce⁵ them. A large randomised trial comparing different antifibrinolytics seems fully justified, and we await the findings of the BART trial in Canada.¹³ Perhaps further trials of aprotinin are needed, but they should be designed to answer specific unresolved questions,² such as: what is the risk of adverse outcomes in high-risk groups?

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The rise and fall of sleeping sickness

Human African trypanosomiasis (HAT) (sleeping sickness), is much feared. Trypanosome parasites, transmitted by tsetse flies, proliferate in patients' blood, lymphatics, and later CNS, in which they induce progressive neurological dysfunction then death.¹ *Trypanosoma brucei gambiense* and *T brucei rhodesiense*² cause a chronic disease in central and western Africa and an acute form in eastern and southern Africa, respectively. More than 90% of cases are the gambiense form.

HAT was largely under control in the mid-20th century but by the 1990s was back with a vengeance.³ Wars in many African countries were rampant and national HAT programmes, chronically under-funded, were in disarray. The fragmented efforts of a few charities and non-governmental organisations were insufficient to contain the disease. Production of HAT drugs was in jeopardy.

By 1997, an estimated 450 000 people were afflicted. The most recent WHO figures now put numbers at no

higher than 70 000.⁴ A coordinated but sometimes precarious campaign has precipitated the decline. For example, in 1999, WHO received the licence for eflornithine, a compound registered for late-stage gambiense disease. But no one would make it until another condition materialised. Eflornithine suppresses the growth of facial hair, a disorder perceived as lucrative to Gillette. Médecins Sans Frontières, lobbying hard on access to essential medicines,^{4,5} fuelled public outrage. What clearer example of the failings of profit-driven drug-design could there be?

At this point, France's drug giant Aventis stepped in. They agreed to produce eflornithine for HAT. By May, 2001, Aventis made an unprecedented US \$25 million agreement promising all of their HAT drugs to WHO gratis for 5 years plus cash to underpin control activities. Their goal according to Jean Jannin: "to create the conditions enabling a process of disease elimination." Bayer also donated suramin. Another boost came in December, 2000, when the Bill & Melinda Gates