Statement by the Committee of the Association of Cardiothoracic Anaesthetists

on the use of aprotinin in cardiac surgery

Excessive postoperative bleeding is a serious hazard for patients who have heart surgery that frequently results in transfusions - with their attendant risks - of red blood cells and other blood products. In addition, re-opening of the chest to control the bleeding is sometimes required, often in the intensive care unit. This is associated with an increased risk of sternal and mediastinal infection, which may result in the death of the patient.

Aprotinin is often used to minimise blood loss in cardiac surgery, particularly in patients undergoing repeat or complex surgery, and is very effective in reducing the number of patients needing transfusion. (1-3) In this context, the publication of a study on behalf of the Multicenter Study of Perioperative Ischemia (McSPI) Research Group in the January 26, 2006 issue of *The New England Journal of Medicine* has suggested that the continued use of aprotinin is not prudent. (4) The published conclusions, that use of aprotinin is associated with serious complications, such as renal failure, myocardial infarction or heart failure, and stroke, are the subject of intense discussion in cardiac surgical units worldwide.

Some members of the Association of Cardiothoracic Anaesthetists (ACTA) collected data for this observational study, but we note that none of the clinical investigators in the McSPI group is listed as an author of the paper. The McSPI study enrolled 4,374 patients undergoing coronary artery bypass surgery with cardiopulmonary bypass at 69 cardiac surgical centres in 17 countries and evaluated four sub-groups of patients. The four groups were patients that received aprotinin, tranexamic acid, epsilon-aminocaproic acid (not available in the UK), or no agent.

The main strength of this observational study is in the large number of patients enrolled. Because the study was neither randomized nor blinded, the data are subject to selection bias and so, confounding. Propensity-adjusted, multivariable logistic regression analyses

were used to control for between-group differences at baseline. It is unclear whether this statistical manipulation is able to overcome the likely bias that aprotinin may have been used in the sickest patients. It is also probable that there were variations in practice between centres that may require additional complex statistical adjustments. Current practice in many centres in the UK reserves the use of aprotinin for complex surgery, those patients taking antiplatelet drugs, and those with bleeding disorders.

Unfortunately, the *NEJM* paper did not discuss the clinically important benefits of aprotinin in the prevention of bleeding, reducing the risks of re-operation for bleeding and exposure to blood and blood products, so presented an unbalanced view of the issues involved. The more robust data from the large number of randomized trials of aprotinin, that have been subjected to meta-analyses and systematic review, indicates that aprotinin is not associated with an increased mortality, incidence of MI or renal dysfunction. In addition, aprotinin may be associated with a reduction in the incidence of stroke (3), and have protective effects on the kidney (5).

The concerns raised in the *NEJM* paper are not new and have been addressed previously by more robust research indicating that appropriate use of aprotinin, within the terms of the product licence, is both effective and safe. Whilst there are other pharmacological agents and mechanical methods that are also effective in reducing blood loss and transfusion, we believe that it is inappropriate and inadvisable to stop using aprotinin, as this might disadvantage a significant number of patients. Until further data are made available to support the *NEJM* paper, or until formal recommendations are issued by regulatory authorities, the committee of ACTA suggests that its members continue to consider carefully the potential risks of aprotinin against the risks of bleeding in individual patients.

16 March 2006

References

1. Henry DA, Moxey AJ, Carless PA, *et al.* Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2001; 1: CD001886.
2. Sedrakyan A, Treasure T, Elefteriades JA. Effect of aprotinin on clinical outcomes in coronary artery bypass graft surgery: a systematic review and meta-analysis of randomized clinical trials. *J Thorac Cardiovasc Surg* 2004; **128**: 442-8.
3. Fergusson D, Glass KC, Hutton B, Shapiro S. Randomized controlled trials of aprotinin in cardiac surgery: Could clinical equipoise have stopped the bleeding? *Clin Trials* 2005; **2**: 218-29.
4. Fauli A, Gomar C, Campistol JM *et al*. Kidney-specific proteins in patients receiving aprotinin at high- and low- dose regimens during coronary artery bypass graft with cardiopulmonary bypass. *Eur J Anaesth* 2005; 22: 666-71.
5. Mangano DT, Tudor IC, Dietzel C. The risk associated with aprotinin in cardiac surgery. *N Engl J Med* 2006; 354: 353-65.