Aprotinin and the risk of death and renal dysfunction in patients undergoing cardiac surgery: a meta-analysis of epidemiologic studies

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CRD summary
This review concluded that the observational evidence indicated an increased risk of adverse renal outcomes and long-term mortality with aprotinin use during cardiac surgery. This was generally a well-conducted review. However, a number of issues with the review, as well as issues with confounding from observational evidence, mean that the conclusion needs to be interrupted with some caution.

Authors' objectives
To determine the effect of aprotinin on renal dysfunction and death after cardiac surgery; and to explore potential sources of heterogeneity.

Searching
MEDLINE and EMBASE were searched from inception to May 2008. Search terms were not reported, but are available on request from the authors. Reference lists of identified articles were checked to identify additional studies. No language restrictions were imposed.

Study selection
Observational studies that evaluated aprotinin use during cardiac surgery were eligible for inclusion. Studies were required to include a comparison group, adjust for potential confounders, and report effect estimates with 95% confidence intervals (CIs) or sufficient information to enable their calculation. Outcomes of interest were death (short-term or long-term), renal dysfunction and renal failure.

In the included studies, full-dose aprotinin was used in most studies; the actual dose was not reported. Comparisons included epsilonaminocaproic acid, tranexamic acid, no antifibrinolytic therapy and no aprotinin (a combination of the other treatment options). No information was provided about the patients included in the studies, other than they underwent cardiac surgery. Renal dysfunction was defined by the included studies in a number of different ways; short-term mortality included inpatient death and was within 30 days of surgery; long-term mortality was defined as up to five years and up to ten years.

Two reviewers independently selected the studies, with any disagreements resolved by discussion.

Assessment of study quality
Two reviewers independently assessed studies using the Newcastle-Ottawa scale for observational studies. Disagreements were resolved by discussion.

Data extraction
Data were extracted to calculate risk ratios (RRs) and corresponding 95% confidence intervals (CIs) of patients experiencing renal outcomes and short-term mortality; hazard ratios (HRs) and corresponding 95% confidence intervals were calculated for long-term mortality. Odds ratios (ORs) were assumed to be unbiased estimates of the risk ratio or hazard ratio as the incident rates were low for the outcomes of interest.

Two reviewers independently undertook data extraction, with any disagreements resolved by discussion.

Methods of synthesis
For studies that only reported stratified results, data were pooled using the Mantel-Haenszel fixed-effect model to obtain an overall effect estimate. Pooled risk ratios and hazard ratios with corresponding 95% confidence intervals were calculated using the DerSimonian and Laird random-effects model.
Heterogeneity was assessed using the Cochran's Q and the I² statistic. Stratified analyses were conducted to explore the effect of: comparison drugs, renal outcome definition, adjustment for transfused red blood cells, and adjustment for any intraoperative variables. Meta-regression analyses assessed the impact of: comparison drugs; patients with diabetes, congestive heart failure or hypertension at baseline; time on cardiopulmonary bypass; adjustment for red blood cell transfusion; adjustment for other intraoperative variables; and study quality. Sensitivity analyses assessed the impact of omitting each individual study, combining all death outcomes (short and long-term) and including secondary analyses. Publication bias was assessed by visual inspection of funnel plots and using the Egger and Begg tests.

**Results of the review**

Eleven studies (n=119,330 patients) were included in the review. The quality of the studies was not reported.

The use of aprotinin was associated with a significant increased risk of renal dysfunction (RR 1.42, 95% CI 1.13 to 1.79; 10 studies) and long-term death (HR 1.22, 95% CI 1.08 to 1.39; three studies). The use of aprotinin was associated with a non-significant increased risk of needing dialysis (RR 1.17, 95% CI 0.99 to 1.38; five studies) and short-term death (RR 1.16, 95% CI 0.84 to 1.58; six studies).

There was evidence of significant heterogeneity for renal dysfunction (I²=73%) and for short-term death (I²=72%). No significant heterogeneity was found for the need for dialysis or long-term death.

Results of the stratified analyses produced similar effect estimates. Meta-regression analyses found duration of cardiopulmonary bypass time to be a significant source of heterogeneity for renal dysfunction - for every ten minutes increase in cardiopulmonary bypass time, there was an associated 29% increased risk of renal dysfunction.

Sensitivity analyses produced altered results only for the need for dialysis outcome; this became statistically significant when one large study was excluded and when transfusion-adjusted effect estimate of another study was replaced with the non-adjusted results. It was reported that publication bias was possibly present for renal dysfunction, as determined by the funnel plot and the Egger test (p=0.04); and need for dialysis as determined by the Begg test (p=0.05).

**Authors' conclusions**

Despite some studies that reported no association between aprotinin and renal outcomes during cardiac surgery, observational evidence indicated an increased risk that could not be fully explained by need for transfused red blood cells. Observational studies also suggested an increased risk of long-term mortality associated with aprotinin as compared to various comparators used in these studies, although residual confounding could not be ruled out.

**CRD commentary**

The review question was clear and was supported by specific inclusion criteria. The authors searched two relevant databases and reference lists without language restriction. The authors did not search systematically for unpublished studies; publication bias was assessed and found possibly to be present for the renal outcomes. The authors attempted to minimise bias and errors during the review process by carrying out study selection, data extraction and the quality assessment in duplicate. The quality of the studies was not reported, so the reliability of the included studies and the synthesis derived from them was uncertain.

Limited information was provided regarding the characteristics of the individual studies and the participants included in them. Information provided about the studies indicated that they varied in comparison group and outcome definition. Combining the results in meta-analyses may not have been appropriate, given the variability of the studies and the statistical heterogeneity in the some of the meta-analyses. The assumption that odds ratios were an unbiased estimate of the hazard ratio was incorrect; it was not clear the extent to which this substitution occurred and the impact of this. This was generally a well-conducted review. However, a number of issues with the review, as well as issues with confounding from observational evidence, mean that the conclusion should be interrupted with some caution.

**Implications of the review for practice and research**

The authors did not state any implications for practice or further research.
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