Antifibrinolytics in cardiac surgical patients receiving aspirin: a systematic review and meta-analysis
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CRD summary
This review concluded that antifibrinolytic agents were effective for reducing chest-tube drainage and transfusion requirements for low risk patients undergoing cardiac surgery who were receiving aspirin, but there was no benefit for adverse events. The authors’ conclusions are reasonable and likely to be reliable, provided they are applied to a low risk population.

Authors’ objectives
To assess the efficacy and adverse events associated with antifibrinolytic agents in patients undergoing cardiac surgery who are maintained on aspirin.

Searching
MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were searched, with no language restrictions, up to July 2008. Search terms were provided. The reference lists of identified papers were also searched.

Study selection
Randomised controlled trials (RCTs) of prophylactic antifibrinolytics in adults undergoing coronary artery bypass graft and/or valve surgery, who were maintained or started on aspirin therapy during the preoperative period, were eligible for inclusion. Aspirin exposure had to be within seven days prior to surgery.

The included trials evaluated aprotinin and lysine analogues (tranexamic acid and aminocaproic acid). In the majority of trials the comparator was placebo or no intervention; in a small number of trials, the two antifibrinolytics were compared directly to each other. Where reported, the participants were predominantly male and the mean age ranged from 54 to 63.8 years. The majority of trials were of patients undergoing on-pump coronary artery bypass graft surgery that was predominantly elective. There were also single trials of re-operative coronary artery bypass graft surgery, coronary artery bypass graft with or without valve surgery and off-pump coronary artery bypass graft surgery. In approximately half of the trials patients received aspirin in the 24 hours before surgery. Seven different efficacy outcomes were of interest, as well as adverse events.

Three researchers independently performed the searches and study selection and disagreement was resolved by consensus.

Assessment of study quality
Studies were assessed for allocation concealment, risk of selection bias, performance bias, attrition bias, detection bias and reporting bias. This was undertaken independently by two researchers and disagreements were resolved by consensus.

Data extraction
For continuous outcomes, the mean and standard deviation for the intervention and control group were extracted and the mean difference and 95% confidence intervals calculated. For dichotomous data, the number of events in each group was extracted and the odds ratio and 95% confidence intervals calculated. To be classified as a zero adverse event, there had to be an explicit description of the absence of the specific adverse event. Authors were contacted for additional data where necessary. Where possible, patients excluded because of re-exploration for surgical bleeding were included for this outcome.

Two researchers independently extracted the data and disagreements were resolved by consensus.
Methods of synthesis
Data were pooled in a meta-analysis using random-effects models. Trials were stratified for the meta-analyses based on intervention and comparator (aprotinin versus placebo, lysine analogue versus placebo and aprotinin versus lysine analogues), as well as pooled overall where the comparator was placebo. The $I^2$ statistic was used to assess heterogeneity. Funnel plots were used to assess risk of publication bias. There were also pre-planned sensitivity analyses.

Results of the review
Seventeen randomised controlled trials (RCTs) were included (n=1620 patients). Twelve RCTs were double blind and the remaining were open-label or no details of blinding were provided. Five trials reported an adequate method of allocation concealment, but for most of the remaining trials it was unclear.

Chest-tube drainage: Both aprotinin (12 RCTs, n=992 patients) and lysine analogues (three RCTs, n=259 patients) were more effective than placebo at reducing chest-tube drainage; this was statistically significant for both interventions. For the overall pooling, the mean difference between antifibrinolytic and placebo was 374 millilitres (mL) (95% confidence interval (CI): 275 to 473). Statistical heterogeneity was high for the overall pooling and the two subgroups. There was no statistically significant difference in chest-tube drainage between aprotinin and lysine analogues based on three trials (mean difference 24 mL, 95% CI: -12 to 60; n=502 patients), and there was no statistical heterogeneity.

Transfusion: Patients receiving an antifibrinolytic were significantly less likely to receive any blood products than those receiving placebo (odds ratio 0.37, 95% CI: 0.27 to 0.49; n=935 patients) based on 10 trials of aprotinin and one of a lysine analogue. There was also a statistically significant benefit for patients receiving an antifibrinolytic agent compared to placebo for mean number of packed red blood cells transfused per patient, the mean number of units transfused for all blood products and proportion of patients receiving at least one unit of packed red blood cells. There was evidence of statistical heterogeneity for the analysis of mean number of units of packed red blood cells transfused.

Other outcomes: There was no statistically significant difference between patients receiving an antifibrinolytic agent compared to placebo for the following outcomes: need for surgical re-exploration (nine trials reporting 17 events for 461 patients); mortality (seven trials reporting five deaths in 646 patients); myocardial infarction (seven trials reporting 14 events in 361 patients); stroke (five trials reporting six events in 241 patients); and thrombotic complications (11 trials reporting 28 events in 786 patients). None of the trials reported on renal failure.

Sensitivity analyses: Sensitivity analyses investigated the impact of excluding individual trials on the pooled estimates of effect; excluding the three trials with greatest impact on chest-tube drainage, or excluding some trials that were not of on-pump coronary artery bypass graft, did not alter the results. Analysis investigating effect of aprotinin dose, whether last exposure to aspirin was more than 48 hours prior to surgery, use of a transfusion algorithm at time of recording test-tube drainage, and trial quality, also did not alter the results. Based on the funnel plots, the authors reported no evidence of publication bias.

Authors' conclusions
Antifibrinolytic agents were effective for reducing chest-tube drainage and transfusion requirements in patients undergoing cardiac surgery who were receiving aspirin. There was no significant difference in adverse events, including mortality and surgical re-exploration, with antifibrinolytic agents compared to placebo, but the population was predominantly low risk.

CRD commentary
There was a clearly stated review question and a number of appropriate databases were searched for studies with no language restrictions, reducing the risk of missing relevant studies. Methods were used to reduce error and bias in study selection, data extraction and quality assessment. It was appropriate to pool the trials in a meta-analysis. Subgroup and sensitivity analyses were undertaken to explore clinical heterogeneity and the robustness of the results. Statistical heterogeneity was also assessed. For the chest-tube drainage outcome the heterogeneity remained unexplained, although a possible source was suggested. The authors' conclusions are reasonable and are likely to be reliable, provided they are applied to a low risk population.
Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that further large trials are required to determine the optimal balance of antiplatelet and antifibrinolytic effects in cardiac surgery for higher risk patients. Clinically relevant endpoints should include renal failure.

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