

Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints

Marcel Levi, Manon E Cromheecke, Evert de Jonge, Martin H Prins, Bas J M de Mol, Ernest Briët, Harry R Büller

Summary

Background Excessive bleeding may complicate cardiac surgery, and is associated with increased morbidity and mortality. Pharmacological strategies to decrease perioperative bleeding have been investigated in a large number of controlled trials, most of which have shown a decrease in blood loss. However, most studies lacked sufficient power to detect a beneficial effect on clinically more relevant outcomes. We did a meta-analysis of all randomised, controlled trials of the three most frequently used pharmacological strategies to decrease perioperative blood loss (aprotinin, lysine analogues [aminocaproic acid and tranexamic acid], and desmopressin).

Methods Studies were included if they reported at least one clinically relevant outcome (mortality, rethoracotomy, proportion of patients receiving a transfusion, or perioperative myocardial infarction) in addition to perioperative blood loss. In addition, a separate meta-analysis was done for studies concerning complicated cardiac surgery.

Findings We identified 72 trials (8409 patients) that met the inclusion criteria. Treatment with aprotinin decreased mortality almost two-fold (odds ratio 0.55 [95% CI 0.34–0.90]) compared with placebo. Treatment with aprotinin and with lysine analogues decreased the frequency of surgical re-exploration (0.37 [0.25–0.55], and 0.44 [0.22–0.90], respectively). These two treatments also significantly decreased the proportion of patients receiving any allogeneic blood transfusion. By contrast, the use of desmopressin resulted in a small decrease in perioperative blood loss, but was not associated with a beneficial effect on other clinical outcomes. Aprotinin and lysine analogues did not increase the risk of perioperative myocardial infarction; however, desmopressin was associated with a 2.4-fold increase in the risk of this complication. Studies in patients undergoing complicated cardiac surgery showed similar results.

Interpretation Pharmacological strategies that decrease perioperative blood loss in cardiac surgery, in particular aprotinin and lysine analogues, also decrease mortality, the need for rethoracotomy, and the proportion of patients receiving a blood transfusion.

Lancet 1999; **354**: 1940–47

Departments of Vascular Medicine (M Levi MD, Prof H R Büller MD), **Internal Medicine** (M Levi, Prof E Briët MD), **Cardiopulmonary Surgery** (M E Cromheecke MD, Prof B J M de Mol MD), **Intensive Care** (Ede Jonge MD) and **Clinical Epidemiology and Biostatistics** (M H Prins MD), **Academic Medical Centre, University of Amsterdam, Amsterdam, Netherlands**

Correspondence to: Dr Marcel Levi, Department of Vascular Medicine/Internal Medicine, Academic Medical Centre F-4, Meibergdreef 9, 1105 AZ Amsterdam, Netherlands (e-mail: m.m.levi@amc.uva.nl)

Introduction

Although the complication rate of coronary-artery bypass grafting or heart-valve replacement has decreased, excessive perioperative bleeding is still common.¹ Management of perioperative blood loss requires transfusion of packed cells and other blood products; these procedures increase the risk of immunological complications, and of transmission of infectious agents. In some medical centres, at least a quarter of all blood-product use is for patients undergoing cardiac surgery, which imposes a substantial burden on the limited supply of these products. Moreover, excessive postoperative bleeding may result in the need for re-exploration, which is associated with additional morbidity and mortality.^{1,2}

Factors that contribute to blood loss in cardiac surgery are related to surgical damage to large blood vessels and acquired defects in haemostasis. The impaired function of the haemostatic system is due to several factors, such as loss of platelets and impairment of platelet function, haemodilution, administration of heparin during cardiopulmonary bypass, and inadequate functioning of the fibrinolytic system.³

Several approaches which aim to keep blood loss to a minimum and to decrease transfusion requirements in patients undergoing cardiac surgery have been developed. Among these strategies, administration of pharmacological agents, of which there are three main types,⁴ is the most widely used. One such agent is aprotinin—a 58-aminoacid polypeptide, mainly derived from bovine lung, parotid gland, or pancreas—which directly inhibits the activity of various serine proteases, including plasmin, coagulation factors (such as kallikrein and thrombin), or coagulation inhibitors. Aprotinin can preserve platelet function and inhibit accelerated fibrinolysis during cardiopulmonary bypass. Lysine analogues, such as aminocaproic acid and tranexamic acid, are potent inhibitors of fibrinolysis. Treatment with these agents can decrease blood loss in various bleeding disorders. Desmopressin (deamino D-arginine vasopressin [DDAVP]) is a vasopressin analogue that induces release of the contents of endothelial-cell-associated Weibel-Palade bodies, including von Willebrand factor. The administration of desmopressin results in a pronounced increase in the plasma concentration of von Willebrand factor (and associated coagulation factor VIII), leading to potentiation of primary haemostasis.

All three pharmacological interventions have been studied in a large number of clinical trials, many of which used a randomised, controlled study design. Owing to their size, most of the trials, however, lacked sufficient power to detect significant differences in important clinical outcomes, such as mortality and the need for re-exploration. Two previous meta-analyses of such trials (including 33 and 60 studies, respectively) focused mainly on perioperative blood loss and the need for transfusion.^{5,6} Both analyses found that these interventions significantly decreased the perioperative exposure of cardiac surgery

patients to blood products. We now report our findings of a meta-analysis of 72 randomised, controlled trials of the effect of pharmacological strategies that decrease perioperative blood loss on mortality, rethoracotomy, the number of patients receiving any transfusion, and the occurrence of adverse effects, in particular perioperative myocardial infarction.

Methods

Literature search

We did a literature search of MEDLINE and EMBASE databases for the period 1966 to December, 1998. Terms used for the search were both MESH terms and (part of) the textwords "heart surgery", "heart valve prosthesis", "myocardial revascularization", "coronary artery bypass", or "heart bypass", in combination with "hemostatics", "antifibrinolytic agents", "aprotinin", "trasyol", "tranexamic acid", "cyklokapron", "aminocaproic acid", "caprolest", "desmopressin", or "DDAVP". The search results were then limited to "humans" and "clinical trials". All titles and abstracts of the remaining studies were screened for controlled clinical trials investigating the efficacy of one of the three pharmacological strategies used to decrease perioperative blood loss, and associated clinical outcomes. The references in all reports were cross-checked for other potentially relevant studies, and the manufacturers of the pharmacological agents were asked to indicate missing trials or unpublished data. Studies were included irrespective of the type of publication or the language used. Investigators involved in studies that reported incomplete data were asked to provide additional information, if available.

For the analysis, we included only studies that examined at least one clinically relevant outcome (ie, mortality, frequency of rethoracotomy, proportion of patients receiving a transfusion and the number of transfusions, and incidence of perioperative myocardial infarction) in addition to perioperative blood loss. Studies that were not truly randomised trials were excluded from the analysis. Other reasons for exclusion were trials done in children and double publications.

Methodological grading

An assessment of the methodological quality of the selected randomised, controlled trials was made by two independent investigators on the basis of the following criteria: correct randomisation procedure, inclusion of consecutive patients, double-blind study design, similar baseline characteristics among study groups, similar treatment of groups (aside from the intervention), adequate assessment of endpoints, and statement of the fate of all patients who entered the trial. For fulfilment of each of these criteria, a score of 1 point was given (maximum score 7) to each article.

Data extraction and outcome definition

Data from the study reports were independently recorded by two investigators and entered into separate databases. The results were compared, and disagreements were resolved by consensus. Investigators were contacted for clarification, if necessary.

Perioperative mortality was defined as mortality during hospital stay for cardiac surgery, irrespective of the cause of death. Rethoracotomy was defined as the need for re-exploration within 72 h after the initial operation, whatever the reason. The proportion of patients receiving at least 1 unit of allogeneic red blood cells was calculated. In almost all studies, a packed-cell volume between 0.20 and 0.30, or active bleeding in combination with cardiovascular instability, was used as an indicator for transfusion. Also, the use of plasma and platelet concentrates was recorded. The mean number of units of red cells transfused per patient was calculated, and, if reported in mL, transfusion requirements were converted to units (1 unit being 275 mL). Blood loss was defined as mL lost from a chest drain within 24 h after the operation. The occurrence of myocardial infarction was defined on the basis of increased cardiac enzyme concentration and results of electrocardiography.

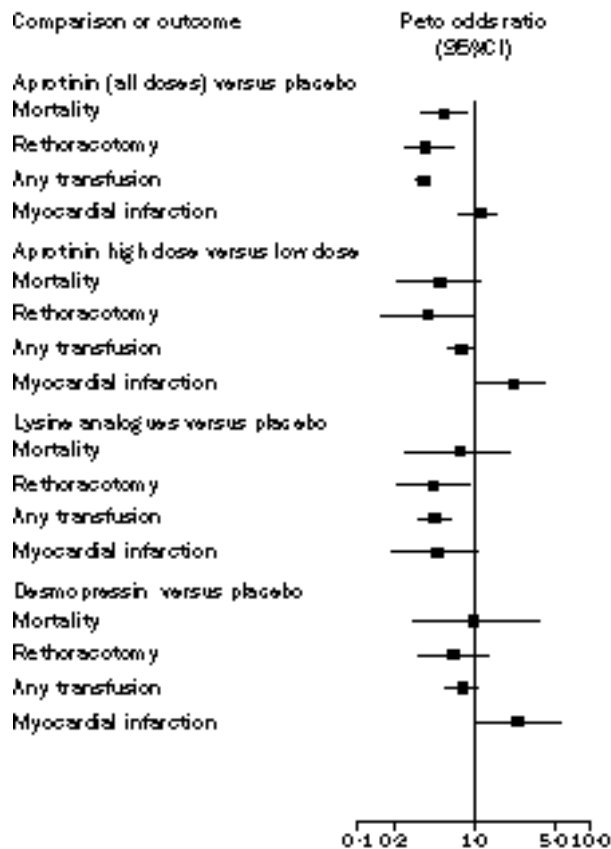


Figure 1: Summary of the results of the main meta-analysis

Analysis

We analysed the effect of each of the three pharmacological interventions (ie, aprotinin, lysine analogues, and desmopressin) versus placebo on the various outcome variables. Since some studies addressed the issue of whether a lower aprotinin dose than the conventional regimen (ie, 3×280 mg [3×2 million kallikrein inhibitor units]) was equally effective, we did a separate analysis of studies directly comparing this conventional dose with a lower dose (ranging from 1×70 mg to 3×140 mg). Treatment with lysine analogues consisted of tranexamic acid (dose 3–10 g) or aminocaproic acid (10–30 g). The dose of desmopressin was 0.3–0.6 µg/kg in all studies. A direct comparison between the various treatment strategies was done only if sufficient trials were available, which was only the case for treatment with aprotinin versus lysine analogues.

A separate analysis was done for those studies concerning complicated cardiac surgery, which we defined as repeat cardiac surgery in patients who were using aspirin preoperatively; both conditions are associated with greater blood loss and associated complications.^{1,3} Finally, all outcome events were separately analysed for only those studies with the highest methodological score (7 points).

Data were analysed with RevMan version 3.1, and odds ratios with 95% CI for dichotomous data were calculated according to the fixed-effects model of Peto and Mantel-Haenszel, and the random-effects model of DerSimonian and Laird. Data presented are derived from the fixed-effects model. Continuous data (units of red cells per patient and blood loss) were analysed by the weighted-mean-difference method. Tests for heterogeneity were done with each meta-analysis (and were not significant).

Results

Literature search and methodological grading

The search yielded 128 clinical trials, and reference cross-checking resulted in 14 additional studies. Of these 142 trials, 95 were apparently randomised, controlled

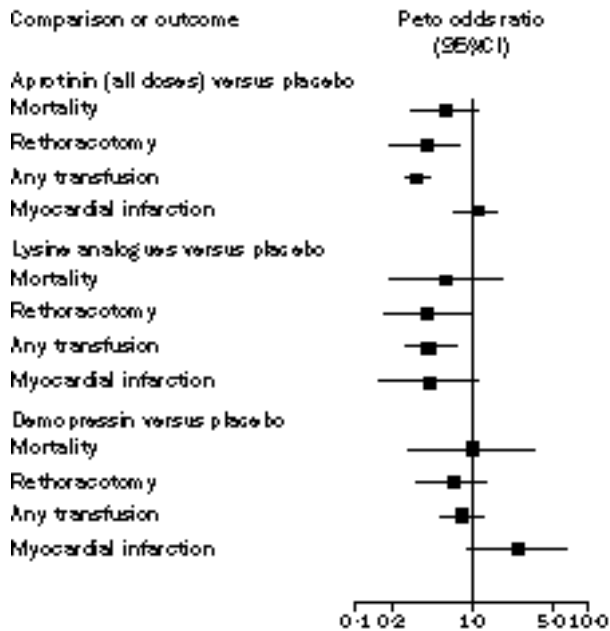


Figure 2: Summary of the results of the meta-analysis in patients undergoing complicated cardiac surgery

studies.⁷⁻¹⁰¹ Nine studies were excluded because no clinical outcome other than blood loss was available,⁷⁻¹⁵ eight studies were found not to be randomised after more thorough analysis,¹⁶⁻²³ five studies concerned cardiac surgery in children,²⁴⁻²⁸ and there was one double report.^{29,36} After exclusion of these 23 reports,⁷⁻²⁹ the remaining 72 trials were further analysed. 45 trials compared aprotinin with placebo;³⁰⁻⁷⁴ 16 trials compared lysine analogues and placebo;^{31,58,61-63,65,75-85} and 16 trials compared desmopressin and placebo.^{66,75,86-99} In addition, 12 studies compared treatment with the conventional dose of aprotinin with lower doses of aprotinin.^{30,38,40,41,44,46,48,50,56,59,69,70} Lastly, in eight trials, a direct comparison was made between treatment with aprotinin and lysine analogues.^{31,58,61-63,65,100,101} There was only one trial directly comparing desmopressin with aprotinin,⁶⁶ and one trial directly comparing desmopressin with lysine analogues.⁷⁵

Of the 45 trials in which aprotinin was studied, 31 yielded the highest methodological score of 7, whereas 11 and three studies had scores of 6 and 5, respectively. Reasons for a score lower than 7 were that the study was not completely double-blind throughout its execution (nine studies), or that subsets of patients were not accounted for (five studies). Other reasons were differences in treatment (other than with the study agent) between the study groups (one study), and an incorrect randomisation procedure (two studies). Of 17 studies with lysine analogues, 11 had a methodological score of 7, five had a score of 6 (all not completely double-blind), and one a score of 5 (not completely double-blind and incorrect randomisation procedure). Of the 16 desmopressin studies, 12 studies had the maximum methodological score, three had 6 points (all not completely double-blind), and one study a score of 5 points (not completely double-blind and differences in treatment between the study groups). The results of the meta-analysis on all studied clinical outcomes of the three interventions are summarised in figure 1. In figure 2 the outcome of the subset of studies in complicated heart surgery is shown.

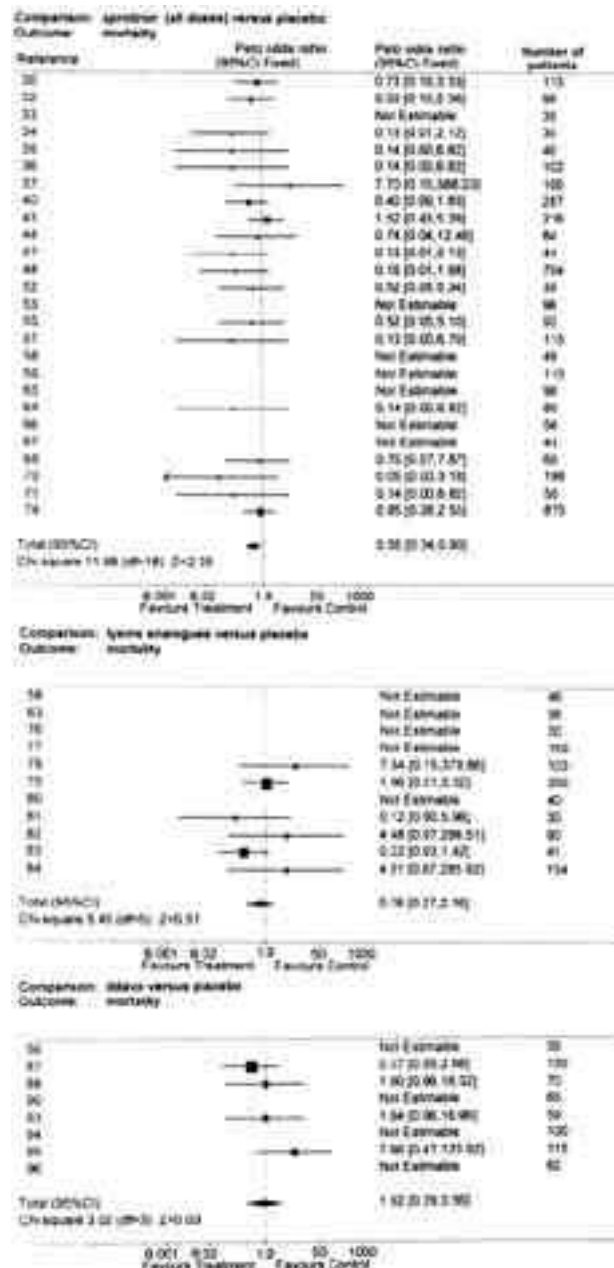


Figure 3: Overview and meta-analysis of randomised controlled trials comparing effect of treatment with aprotinin, lysine analogues, or desmopressin with placebo on mortality

A not estimable result indicated no deaths in both treatment groups. There were 25 deaths in 1687 aprotinin-treated patients, compared with 43 deaths in 1525 control patients. In 604 patients treated with lysine analogues, there were seven deaths compared with eight deaths in 466 controls. Mortality in desmopressin-treated patients and controls was five of 372 and five of 330, respectively.

Mortality

Data on perioperative mortality were available from 26 studies (3212 patients) in which aprotinin was compared with placebo. A meta-analysis of these data showed an almost two-fold decrease in mortality (from 2.8% to 1.5%, odds ratio 0.55 [95% CI 0.34-0.90]; figure 3). Analysis of only those studies with the highest methodological score (7 points) did not significantly change this result (0.53 [0.28-0.98]). In six studies (693 patients) the conventional dose of aprotinin was compared with a lower dose (figure 1). These studies showed a non-significant decrease in mortality in patients

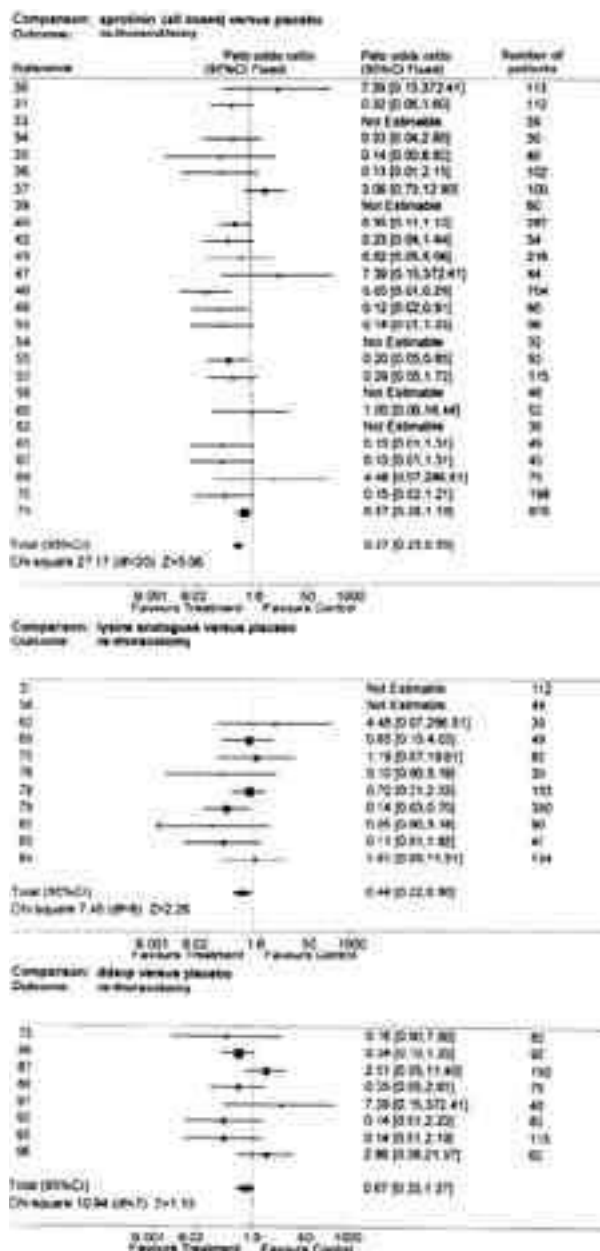


Figure 4: Overview and meta-analysis of randomised controlled trials comparing effect of treatment with aprotinin, lysine analogues, or desmopressin with placebo on rethoracotomy
 There were 40 rethoracotomies in 2130 aprotinin-treated patients and 77 rethoracotomies in 1514 control patients. Of 564 patients treated with lysine analogues, 11 patients underwent a rethoracotomy compared with 22 of 462 controls. In desmopressin-treated patients and controls, there were 13 of 343 and 19 of 351 rethoracotomies, respectively.

assigned the conventional regimen compared with patients assigned lower doses (0.50 [0.21–1.18]).

Data on mortality were retrieved from 11 placebo-controlled studies with lysine analogues (1070 patients), showing an odds ratio for mortality in the lysine-analogue

groups of 0.78 [0.27–2.16]; figure 3). Mortality in patients assigned desmopressin was recorded in eight trials (702 patients) and did not differ from that in patients assigned placebo (1.02 [0.29–3.56]). The low rate of mortality in the limited number of studies directly comparing the various treatment regimens did not allow a proper analysis.

In complicated surgery (figure 2), the odds ratios for mortality in patients assigned aprotinin and patients assigned lysine analogues were 0.59 (0.30–1.16) and 0.59 (0.19–1.80), respectively. Mortality in patients undergoing complicated surgery was identical in placebo and desmopressin groups.

Rethoracotomy

Data on the need for rethoracotomy were available from 26 studies (3644 patients) comparing aprotinin with placebo. All reported rethoracotomies, irrespective of the reason (which was usually excessive bleeding) were included in the study. Meta-analysis of these data showed that the frequency of re-exploration was 5.0% in patients assigned aprotinin and 1.8% in patients assigned placebo (0.37 [0.25–0.55]; figure 4). The meta-analysis of studies with the highest methodological score yielded an identical result. Patients assigned the conventional dose of aprotinin had a lower risk of rethoracotomy than those assigned lower doses (0.41 [0.16–1.04]; figure 1). Treatment with lysine analogues (11 studies, 1026 patients; figure 4) also significantly decreased the rate of rethoracotomy from 4.7% to 1.9% (0.44 [0.22–0.90]) and this result was also not changed by including studies with the highest rating only. Data on rethoracotomy were retrieved from eight placebo-controlled trials with desmopressin (including 694 patients), showing a non-significant odds ratio of 0.67 (0.33–1.37) in favour of desmopressin treatment.

The rate of thoracotomy could be analysed in six trials directly comparing aprotinin with lysine analogues (comparing 565 patients). Neither therapy was superior in its reduction of the rate of rethoracotomy (0.92 [0.28–3.07]).

The effects of the pharmacological interventions on the incidence of re-exploration in complicated cardiac surgery are shown in figure 2. Studies concerning complicated surgery in which either aprotinin or lysine analogues were compared with placebo showed a decrease in the need for rethoracotomy (aprotinin versus placebo 0.40 [0.20–0.79] and lysine analogues versus placebo 0.40 [0.18–0.92], respectively). The odds ratio for rethoracotomy in desmopressin-treated patients undergoing complicated surgery was 0.67 (0.33–1.37).

Proportion of patients receiving blood transfusions

Treatment with aprotinin and with lysine analogues resulted in a substantial decrease in the proportion of patients receiving any blood transfusion. Meta-analysis of 40 placebo-controlled trials of aprotinin (4821 patients)

	Aprotinin versus placebo	Aprotinin conventional dose versus lower doses	Lysine analogues versus placebo	Aprotinin versus lysine analogues	Desmopressin versus placebo
Number of studies (number of patients)	43 (4937)	12 (1186)	16 (1374)	8 (782)	16 (1215)
Decrease in blood loss (mL)*	446.5 (456.5–436.4)	130.7 (120.8–140.5)	264.6 (271.9–257.5)	49.5 (63.7–35.3)	114.1 (84.2–144.0)
Decrease in transfusion (unit/patient)*	0.98 (0.95–1.01)	0.15 (0.13–0.17)	0.94 (0.83–1.04)	0.18 (0.16–0.19)	0.12 (–0.04–0.28)

*Weighted mean difference (95% CI).

Effect of pharmacological interventions on blood loss and number of transfused units

showed an odds ratio of 0.37 (0.32–0.42). The mean percentage of patients receiving any transfusion was 62.7% in the placebo group compared with 42.5% in the aprotinin group. The conventional dose of aprotinin was more effective than lower doses (0.75 [0.58–0.98]). The odds ratio for receiving any transfusion in patients treated with lysine analogues was 0.46 (0.34–0.64, 14 studies with 801 patients). In a small number of trials directly comparing aprotinin with lysine analogues (seven trials, 635 patients), there was a significant decrease in the risk of receiving a blood transfusion in the aprotinin groups (0.69 [0.48–0.98]). The odds ratio for the risk of receiving a blood transfusion after desmopressin treatment compared with placebo was 0.79 (0.56–1.11, data from seven studies comprising 578 patients). In studies of complicated cardiac surgery, the overall proportion of patients receiving a blood transfusion was higher, but the pharmacological agents still induced a significant decrease (figure 2). The odds ratios for the decrease in the proportion of patients receiving any blood transfusion after treatment with aprotinin (15 studies), lysine analogues (seven studies), and desmopressin (five studies) were 0.33 (0.26–0.42), 0.43 (0.26–0.72), and 0.82 (0.55–1.23), respectively.

Blood loss and number of transfused units

The effect on blood loss and the number of units of red cells transfused for all three interventions is presented in the table. All three pharmacological strategies resulted in a significant decrease in blood loss. Treatment with the conventional dose of aprotinin resulted in less perioperative blood loss and fewer units of red cells transfused per patient than with treatment with lower doses of aprotinin, although the differences were small. In trials in which aprotinin and lysine analogue treatment were directly compared, the decrease in blood loss and red-cell transfusion was slightly greater in patients assigned aprotinin.

Perioperative myocardial infarction

The occurrence of perioperative myocardial infarction was studied in 18 trials (1995 patients) of aprotinin treatment versus placebo (mean rate 6.1%). As shown in figure 1, the odds ratio for the frequency of perioperative myocardial infarction in these trials was 1.13 (0.76–1.67). The rate of perioperative myocardial infarction was two times higher (8.1% *vs* 3.9%) in patients in whom treatment with the conventional dose of aprotinin was compared with lower doses (2.15 [1.12–4.11], seven trials, 666 patients). In six trials (725 patients), in which treatment with lysine analogues was compared with placebo, no significant difference in the frequency of perioperative myocardial infarction was observed (0.48, 0.20–1.13). In five of seven trials in which desmopressin was administered and the incidence of myocardial infarction was recorded, there was a trend towards a higher incidence of perioperative myocardial infarction in desmopressin-treated patients. In the meta-analysis, desmopressin treatment was associated with an almost 2.4-fold increased risk of perioperative myocardial infarction compared with placebo (2.39 [1.02–5.60]). Analysis of studies in complicated cardiac surgery (figure 2) or limitation of the analysis to only those studies with the highest methodological score did not change these outcomes.

Discussion

Our meta-analysis shows that pharmacological interventions that significantly decrease perioperative blood loss in cardiac surgery may also have a beneficial effect on clinically more relevant outcomes, such as perioperative mortality, the need for rethoracotomy, and the need for a blood transfusion. In particular, treatment with aprotinin and lysine analogues appears to be effective in this regard. When the analysis was limited to studies in complicated cardiac surgery, defined as repeat surgery or surgery in patients who were taking aspirin preoperatively, a similar effect was seen.

We compared the effect of the pharmacological strategies on all outcome events: aprotinin and lysine analogues were the most effective agents, with aprotinin being somewhat more effective than lysine analogues. The latter observation is supported by the direct comparison between aprotinin and lysine analogues in a small number of studies, which showed a two-fold reduction in the number of patients receiving any transfusion, and a trend towards a lower frequency of rethoracotomy, in those receiving aprotinin. The beneficial effect of aprotinin and lysine analogues could be explained by a parallel mechanism—ie, the inhibition of accelerated fibrinolysis and the potential improvement of platelet function. Both mechanisms may play an important part in perioperative bleeding in cardiac surgery. By decreasing excessive bleeding, the need for re-exploration to achieve haemostasis can be prevented; this result will positively affect perioperative mortality.^{1,2} As an additional mechanism, we postulate that the rather specific antiprotease effect of aprotinin may inhibit proinflammatory mediators that may be detrimental in postoperative patients.

Desmopressin had a modest effect on the decrease in perioperative blood loss, but this effect was not translated into a significant decrease in transfusion requirements, rethoracotomy rates, or mortality. The analysis of studies in complicated cardiac surgery did not show a beneficial effect of desmopressin in this respect. An earlier meta-analysis of studies in which desmopressin was used to decrease perioperative blood loss confirmed this weak efficacy of desmopressin, but suggested that a beneficial effect of desmopressin was particularly apparent in patients with a large amount of perioperative blood loss or those taking aspirin preoperatively.¹⁰² This latter finding was not confirmed by our analysis, although our definition of complicated surgery might not completely overlap with the earlier situations in which desmopressin seemed to be effective. The effect of desmopressin on the decrease in perioperative blood loss and related adverse events seemed to be smaller than the effect of the other two interventions. Direct comparisons between desmopressin and aprotinin, and desmopressin and lysine analogues (one randomised trial each), confirm this difference in efficacy.

In earlier meta-analyses, a similar decrease in blood loss and transfusion requirements by the three pharmacological interventions was observed; one of these reports also indicated a decrease in the risk of rethoracotomy in patients treated with aprotinin.^{5,6} Our meta-analysis includes new trials not previously analysed. Moreover, we actively pursued data on relevant outcome measures, such as mortality and the frequency of rethoracotomy or perioperative myocardial infarction, by trying to contact the authors of articles that did not report

these events. Lastly, we did a separate analysis for studies with the highest methodological score, thereby introducing a method of control for effects as a result of bias due to inadequate study design. However, analysis of these methodologically most robust studies did not change the outcome of the analysis.

Pharmacological strategies to improve haemostasis during and after surgery may have a procoagulant potential, which can result in an increased risk of thrombotic adverse events. One of these thrombotic adverse events in cardiac surgery is the occurrence of perioperative myocardial infarction—eg, that due to thrombotic occlusion of the bypass grafts. There is a lot of controversy about whether this theoretical complication represents a genuine concern in clinical practice.¹⁰³ Some anecdotal observations, uncontrolled studies, and retrospective subgroup analyses of clinical trials indicate that this may indeed be the case,¹⁰⁴ whereas randomised controlled studies have not shown a significant difference in the occurrence of myocardial infarction, but may have been underpowered to observe such an effect. There have been several methodologically sound studies in which the occurrence of graft occlusion in aprotinin-treated patients was systematically investigated. Most of these trials show no significant differences between patients assigned aprotinin and controls.^{41,43,53,59,73,74} In only one study was a small increase in the proportion of patients with an occluded graft after aprotinin treatment observed.⁵⁴ Our meta-analysis of the occurrence of perioperative myocardial infarction did not show an increased frequency of this complication in the aprotinin-treated patients compared with placebo-treated patients. There was, however, an increased incidence of perioperative myocardial infarction in the comparison between the conventional dose of aprotinin and the lower dose of aprotinin. This observation is hard to explain. We postulate that the higher dose of aprotinin is indeed prothrombotic, causing a higher frequency of perioperative myocardial infarction, and that this effect is attenuated in the analysis of trials with differing doses of aprotinin. However, when only the placebo-controlled studies of the higher dose of aprotinin were analysed, there was no difference in frequency of myocardial infarction between aprotinin and placebo groups (data not shown). Hence, our meta-analysis cannot draw definitive conclusions on a possibly increased rate of perioperative myocardial infarction due to aprotinin dose. Also, this possible disadvantage of the higher dose of aprotinin needs to be offset against the apparent benefit of this treatment in comparison with the lower dose in terms of mortality and the risk of rethoracotomy. In addition, some studies indicate that the rate of stroke may be lower in aprotinin-treated patients,^{40,105} although there is no convincing evidence to support this suggestion so far.

Treatment with lysine analogues was not associated with an increased risk of perioperative myocardial infarction, but was associated with a trend towards a decrease in the frequency of this complication. However, we emphasise that a meta-analysis may easily miss a specific subset of patients for whom an intervention such as administration of aprotinin or lysine analogues may be harmful. The analysis of studies with desmopressin showed a significantly higher frequency of perioperative myocardial infarction in desmopressin-treated patients. This effect was consistent in almost all studies from which data on myocardial infarction were available. At first sight,

the fact that the agent that had the least effect on the decrease in blood loss and associated clinical events, was the one most prominently associated with this complication might seem surprising. However, the mechanism of action of desmopressin, in particular directed at the improvement of primary haemostasis, is definitively different from the effect of the antifibrinolytic agents, such as aprotinin and lysine analogues, and this difference is apparently important for the development of myocardial infarction. Moreover, not only does desmopressin have a prohaemostatic effect, it may also induce haemodynamic changes, which may play a part in the occurrence of perioperative myocardial infarction.

This meta-analysis further supports the use of aprotinin or lysine analogues in clinical practice. However, only a large prospective controlled trial with mortality as the primary outcome will provide definitive evidence. At present, there are insufficient data to allow a definite conclusion that aprotinin treatment results in a better clinical outcome than lysine analogues, although some preliminary analyses suggest a slight benefit of aprotinin. However, the question of which agent to use in patients undergoing cardiac surgery will also be based on costs.

Contributors

Marcel Levi, Manon Cromheecke, and Evert de Jonge did the literature search and the analysis of the included studies; Martin Prins provided statistical support; and Bas de Mol, Ernest Briët, and Harry Büller were involved in overall coordination, data-extraction, and analysis and interpretation of the data.

Acknowledgments

ML is an Investigator of the Royal Dutch Academy of Arts and Sciences. HB is an Established Investigator of the Netherlands Heart Foundation.

References

- 1 Dacey LJ, Munoz JJ, Baribeau YR, et al. Rexploration for hemorrhage following coronary artery bypass grafting: incidence and risk factors. Northern New England Cardiovascular Disease Study Group. *Arch Surg* 1998; **133**: 442–47.
- 2 Unsworth-White MJ, Herriot A, Valencia O. Resternotomy for bleeding after cardiac operation: a marker for increase morbidity and mortality. *Ann Thorac Surg* 1995; **59**: 664–67.
- 3 Harker LA. Bleeding after cardiopulmonary surgery. *N Engl J Med* 1986; **314**: 1446–48.
- 4 Mannucci PM. Hemostatic drugs. *N Engl J Med* 1998; **339**: 245–53.
- 5 Fremes SE, Wong BI, Lee E, et al. Metaanalysis of prophylactic drug treatment in the prevention of postoperative bleeding. *Ann Thorac Surg* 1994; **58**: 1580–88.
- 6 Laupacis A, Ferguson D. The International Study of Peri-operative Transfusion (ISPOT) Investigators. Drugs to minimise perioperative blood loss in cardiac surgery: meta-analyses using perioperative blood transfusion as the outcome. *Anesth Analg* 1997; **85**: 1258–67.
- 7 Gschossman J, Pracki P, Struck E. Efficacy of aprotinin in different doses and autologous blood transfusions in cardiac surgery. *Cardiovasc Surg* 1994; **2**: 716–19.
- 8 Carrel T, Bauer E, Laske A, von Segesser L, Turina M. Low-dose aprotinin for reduction of blood loss after cardiopulmonary bypass. *Lancet* 1991; **337**: 673.
- 9 Mastroroberto P, Chello M, Zofrea S, Marchese AR. Suppressed fibrinolysis after administration of low-dose aprotinin: reduced level of plasmin- α_2 -plasmin inhibitor complexes and postoperative blood loss. *Eur J Cardiothor Surg* 1995; **9**: 143–45.
- 10 Kawasuji M, Ueyama K, Sakakibara N, et al. Effect of low-dose aprotinin on coagulation and fibrinolysis in cardiopulmonary bypass. *Ann Thorac Surg* 1993; **55**: 1205–29.
- 11 VanderSalm TJ, Ansell JE, Okike ON, et al. The role of epsilon-aminocaproic acid in reducing bleeding after cardiac operation: a double-blind randomized study. *J Thorac Cardiovasc Surg* 1996; **112**: 1125–27.
- 12 Andersson TLG, Solem JO, Tengborn L, Vinge E. Effects of desmopressin acetate on platelet aggregation, von Willebrand factor, and blood loss after cardiac surgery with extracorporeal circulation. *Circulation* 1990; **81**: 872–78.
- 13 Frankville DD, Harper GB, Lake CL, Johns RA. Hemodynamic consequences of desmopressin administration after cardiopulmonary bypass. *Anesthesiol* 1991; **74**: 988–96.

- 14 Brown MR, Swygert TH, Whitten CW, Hebel R. Desmopressin acetate following cardiopulmonary bypass: evaluation of coagulation parameters. *J Cardiothorac Anesth* 1989; **3**: 726–29.
- 15 Eberle B, Mayer E, Hafner G, et al. High-dose epsilon-aminocaproic acid versus aprotinin: antifibrinolytic efficacy in first time coronary operations. *Ann Thorac Surg* 1998; **65**: 667–73.
- 16 Gherli T, Porcu A, Padua G, et al. Riduzione del sanguinamento negli interventi in circolazione extracorporea mediante l'uso di alte dosi di aprotinina. *Minerva Cardiol* 1992; **40**: 121–26.
- 17 Dietrich W, Barankay A, Diltthey G, et al. Reduction of homologous blood requirement in cardiac surgery by intraoperative aprotinin application: clinical experience in 152 cardiac surgical patients. *Thorac Cardiovasc Surgeon* 1989; **37**: 92–98.
- 18 Blauhut B, Cross C, Neeck S, Doran JE, Späth P, Lunsgaard-Hansen P. Effects of high-dose aprotinin on blood loss, platelet function, fibrinolysis, complement, and renal function after cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1991; **101**: 958–67.
- 19 Nakashima A, Matsuzaki F, Fukumura F, et al. Tranexamic acid reduces blood loss after cardiopulmonary bypass. *ASAIO J* 1993; **39**: M185–19.
- 20 Lazenby WD, Russo I, Zadeh BJ, et al. Treatment with desmopressin acetate in routine coronary artery bypass surgery to improve postoperative hemostasis. *Circulation* 1990; **82** (suppl): IV413–19.
- 21 Chuang H-I, Hornig Y-J, Li Y, et al. Clinical assessment of desmopressin to reduce loss in patients after cardiopulmonary bypass. *Acta Anaesthesiol Sin* 1993; **31**: 35–42.
- 22 Lambert W, Brisebois FJ, Wharton TJ, Carrier RC, Boyle D, Rowe BH. The effectiveness of low dose tranexamic acid in primary cardiac surgery. *Can J Anaesth* 1998; **45**: 571–74.
- 23 Osaka M, Fujuda I, Ohuchi H. Aprotinin and recombinant human erythropoietin reduce the need for homologous blood transfusion in cardiac surgery. *Nippon Kyobu Geka Gakkai Zasshi* 1998; **46**: 846–53.
- 24 Boldt J, Knothe C, Zickmann B, Wege N, Dapper F, Hempelmann G. Comparison of two aprotinin dosage regimens in pediatric patients having cardiac operations. *J Thorac Cardiovasc Surg* 1993; **105**: 705–11.
- 25 Zonis Z, Seear M, Reichert C, Sett S, Allen C. The effect of preoperative tranexamic acid on blood loss after cardiac operations in children. *J Thorac Cardiovasc Surg* 1996; **111**: 982–87.
- 26 Seear MD, Wadsworth LD, Rogers PC, Sheps S, Ashmore PG. The effect of desmopressin acetate (DDAVP) on postoperative blood loss after cardiac operations in children. *J Thorac Cardiovasc Surg* 1989; **98**: 217–29.
- 27 Reynolds LM, Nicolson SC, Jobs DR, et al. Desmopressin does not decrease bleeding after cardiac operation in young children. *J Thorac Cardiovasc Surg* 1993; **106**: 954–58.
- 28 Miller BE, Tosone SR, Tam VK, et al. Hematologic and economic impact of aprotinin in reoperative pediatric cardiac operations. *Ann Thor Surg* 1998; **66**: 535–40.
- 29 Royston D, Bidstrup BP, Taylor KM, Sapsford RN. Effect of aprotinin on need for blood transfusion after repeat open-heart surgery. *Lancet* 1987; **ii**: 1289–91.
- 30 Cosgrove DM, Heric B, Lytle BW, et al. Aprotinin therapy for reoperative myocardial revascularization: a placebo-controlled study. *Ann Thorac Surg* 1992; **54**: 1031–38.
- 31 Speekenbrink RGH, Vonk ABA, Wildevuur CRH, Eijssman L. Hemostatic efficiency of dipyridamole, tranexamic acid, and aprotinin in coronary bypass grafting. *Ann Thorac Surg* 1995; **59**: 438–42.
- 32 Swart MJ, Gordon PC, Hayse-Gregson PB, et al. High-dose aprotinin in cardiac surgery: a prospective, randomised study. *Anaesth Intensive Care* 1994; **22**: 529–33.
- 33 Dietrich W, Spannagl M, Jochum M, et al. Influence of high-dose aprotinin treatment on blood loss and coagulation patterns in patients undergoing myocardial revascularization. *Anesthesiology* 1990; **73**: 1119–26.
- 34 Dietrich W, Diltthey G, Spannagl M, Jochum M, Braun SL, Richter JA. Influence of high-dose aprotinin on anticoagulation, heparin requirement, and celite- and kaolin-activated clotting time in heparin pretreated patients undergoing open-heart surgery. *Anesthesiology* 1995; **83**: 679–89.
- 35 Liu B, Belboul A, Radberg G, et al. Effect of reduced aprotinin dosage on blood loss and use of blood products in patients undergoing cardiopulmonary bypass. *Scand J Thorac Cardiovasc Surg* 1993; **27**: 149–55.
- 36 Bidstrup BP, Royston D, Sapsford RN, Taylor KM. Reduction in blood loss and blood use after cardiopulmonary bypass with high dose aprotinin (Trasylol). *J Thorac Cardiovasc Surg* 1989; **97**: 364–72.
- 37 Alvarez JM, Quiney NF, McMillan D, et al. The use of ultra-low-dose aprotinin to reduce blood loss in cardiac surgery. *J Cardiothorac Vasc Anesth* 1995; **9**: 29–33.
- 38 Speekenbrink RGH, Wildevuur CRH, Sturk A, Eijssman L. Low-dose and high-dose aprotinin improve hemostasis in coronary operations. *J Thorac Cardiovasc Surg* 1996; **112**: 523–30.
- 39 Vedrinne C, Girard C, Jegqden O, et al. Reduction in blood loss and blood use after cardiopulmonary bypass with high-dose aprotinin versus autologous fresh whole blood transfusion. *J Cardiothorac Vasc Anesth* 1992; **6**: 319–23.
- 40 Levy JH, Pifarre R, Schaff HV, et al. A multicentre, double-blind, placebo-controlled trial of aprotinin for reducing blood loss and the requirement for donor-blood transfusion inpatients undergoing repeat coronary artery bypass grafting. *Circulation* 1995; **92**: 2236–44.
- 41 Havel M, Grabenwöger F, Schneider J, et al. Aprotinin does not decrease early graft patency after coronary artery bypass grafting despite reducing postoperative bleeding and use of donated blood. *J Thorac Cardiovasc Surg* 1994; **107**: 807–10.
- 42 Murkin JM, Lux J, Shannon NA, et al. Aprotinin significantly decreases bleeding and transfusion requirements in patients receiving aspirin and undergoing cardiac operations. *J Thorac Cardiovasc Surg* 1994; **107**: 554–61.
- 43 Lemmer JH, Stanford W, Bonney SL, et al. Aprotinin for coronary bypass operations: efficacy, safety, and influence on early saphenous vein graft patency. *J Thorac Cardiovasc Surg* 1994; **107**: 543–53.
- 44 Green D, Sanders J, Eiken M, et al. Recombinant aprotinin in coronary artery bypass graft operations. *J Thorac Cardiovasc Surg* 1995; **110**: 963–70.
- 45 Havel M, Teufelsbauer H, Knöbl P, et al. Effect of intraoperative aprotinin administration on postoperative bleeding in patients undergoing cardiopulmonary bypass operation. *J Thorac Cardiovasc Surg* 1991; **101**: 968–72.
- 46 Bailey CR, Kelleher AA, Wielogorski AK. Randomised placebo-controlled double-blind study of three aprotinin regimens in primary cardiac surgery. *Br J Surg* 1994; **81**: 969–73.
- 47 Hardy JF, Desroches J, Belisle S, Perrault J, Carrier M, Robitaille D. Low-dose aprotinin infusion is not clinically useful to reduce bleeding and transfusion of homologous blood products in high-risk cardiac surgical patients. *Can J Anaesth* 1993; **40**: 625–31.
- 48 Lemmer JH Jr, Dilling EW, Morton JR, et al. Aprotinin for primary coronary artery bypass grafting: a multicenter trial of three dose regimens. *Ann Thorac Surg* 1996; **62**: 1659–68.
- 49 Deleuze O, Losance DY, Feliz A, et al. Réduction des pertes sanguines per et postopératoires par l'aprotinine (Trasylol) au cours de la circulation extracorporelle. *Arch Mal Coeur* 1991; **84**: 1797–802.
- 50 Bailey CR, Wielogorski AK. Randomised placebo-controlled double blind study of two low dose aprotinin regimens in cardiac surgery. *Br Heart J* 1994; **71**: 349–53.
- 51 Ray MJ, Marsh NA, Just SJE, Perrin EJ, O'Brien MF, Hawson GAT. Preoperative platelet dysfunction increases the benefit of aprotinin in cardiopulmonary bypass. *Ann Thorac Surg* 1997; **63**: 57–63.
- 52 Orchard MA, Goodchild CS, Prentice CRM, et al. Aprotinin reduces cardiopulmonary bypass-induced blood loss and inhibits fibrinolysis without influencing platelets. *Br J Haematol* 1993; **85**: 533–41.
- 53 Bidstrup BP, Underwood SR, Sapsford RN, Streets E. Effect of aprotinin (Trasylol) on aorta-coronary bypass graft patency. *J Thorac Cardiovasc Surg* 1993; **105**: 147–53.
- 54 Laub GW, Riebman JB, Chen C, et al. The impact of aprotinin on coronary artery bypass graft patency. *Chest* 1994; **106**: 1370–75.
- 55 Rodrigus IE, Vermeyen KM, de Hert SG, Amsel BJ, Walter PJ. Efficacy and safety of aprotinin in aortocoronary bypass and valve replacement operations: a placebo-controlled randomized double-blind study. *Perfusion* 1996; **11**: 313–38.
- 56 Mohr R, Goor DA, Lusky A, Lavee J. Aprotinin prevents cardiopulmonary bypass-induced platelet dysfunction: a scanning electron microscope study. *Circulation* 1992; **86** (suppl): 405–09.
- 57 Baele PL, Ruiz-Gomez J, Londot C, Sauvage M, van Dyck MJ, Robert A. Systematic use of aprotinin in cardiac surgery: influence of total homologous exposure and hospital cost. *Acta Anaesth Belg* 1992; **43**: 103–12.
- 58 Menichetti A, Tritapepe L, Ruvolo G, et al. Changes in coagulation patterns, blood loss and blood use after cardiopulmonary bypass: aprotinin vs tranexamic acid vs epsilon aminocaproic acid. *J Cardiovasc Surg* 1996; **37**: 401–07.
- 59 Kalanhgos A, Tayyareci G, Prêtre R, Di Dio P, Sezerman O. Influence of aprotinin on early graft thrombosis in patients undergoing myocardial revascularization. *Eur J Cardiothorac Surg* 1994; **8**: 651–56.
- 60 Hardy JF, Bélisle S, Couturier A, Robitaille D. Randomized, placebo-controlled, double-blind study of an ultra-low-dose aprotinin regimen in reoperative and/or complex cardiac operations. *J Card Surg* 1997; **12**: 15–22.
- 61 Corbeau JJ, Monrigal JP, Jacob JP, et al. Comparaison des effets de l'aprotinine et de l'acide tranexamique sur le saignement en chirurgie cardiaque. *Ann Fr Anesth Réanim* 1995; **14**: 154–61.
- 62 Penta de Peppo A, Pierri MD, Scafuru A, et al. Intraoperative antifibrinolysis and blood-saving techniques in cardiac surgery: prospective trial of 3 antifibrinolytic drugs. *Tex Heart Inst J* 1995; **22**: 231–36.

- 63 Landymore RW, Murphy JT, Lummis H, Carter C. The use of low-dose aprotinin, ϵ -aminocaproic acid or tranexamic acid for prevention of mediastinal bleeding in patients receiving aspirin before coronary artery bypass operations. *Eur J Cardiothorac Surg* 1997; **11**: 798–800.
- 64 Harder MP, Eijnsman L, Roozendaal KJ, van Oeveren W, Wildevuur CRH. Aprotinin reduces intraoperative and postoperative blood loss in membrane oxygenator cardiopulmonary bypass. *Ann Thorac Surg* 1991; **51**: 936–41.
- 65 Pugh SC, Wielogorski AK. A comparison of the effects of tranexamic acid and low-dose aprotinin on blood loss and homologous blood usage in patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth* 1995; **9**: 240–44.
- 66 Rocha E, Hidalgo F, Llorens R, Melero JM, Arroyo JL, Paramo JA. Randomized study of aprotinin and DDAVP to reduce postoperative bleeding after cardiopulmonary bypass surgery. *Circulation* 1994; **90**: 921–27.
- 67 Rossi M, Storti S, Martinelli L, et al. A pump-prime aprotinin dose in cardiac surgery: appraisal of its effect on the hemostatic system. *J Cardiothorac Vasc Anesth* 1997; **11**: 835–39.
- 68 Jamieson WRE, Dryden PJ, O'Connor JP, Sadeghi H, Ansley DM, Merrick PM. Beneficial effect of both tranexamic acid and aprotinin on blood loss reduction in reoperative valve replacement surgery. *Circulation* 1997; **96** (suppl): 96–101.
- 69 Çiçek S, Demirkiliç U, Kuralay E, Özal E, Tatar H. Postoperative aprotinin: effect on blood loss and transfusion requirements in cardiac operations. *Ann Thorac Surg* 1996; **61**: 1372–76.
- 70 Minohara S, Asada K, Kondo K, et al. Effect of aprotinin on bleeding and graft patency after coronary artery bypass grafting. *Nippon Kyobu Geka Gakkai Zasshi* 1997; **45**: 821–24.
- 71 Carrera A, Martinez MV, Garcia-Guiral M, Herrero E, Peral A, Planas A. Use of high doses of aprotinin in cardiac surgery. *Rev Espan Anestesiol Reanim* 1994; **41**: 13–19.
- 72 Klein M, Keith PR, Dauben HP, et al. Aprotinin counterbalances an increased risk of perioperative hemorrhage in CABG patients pretreated with aspirin. *Eur J Cardiothorac Surg* 1998; **14**: 360–66.
- 73 Lass M, Simic O, Ostermeyer J. Re-graft patency and clinical efficacy of a protinin in elective bypass surgery. *Cardiovasc Surg* 1997; **5**: 604–07.
- 74 Alderman EL, Levy JH, Rich JB, et al. The IMAGE investigators. Analyses of coronary graft patency after aprotinin use: results from the International Multicentre Aprotinin Graft Patency Experience (IMAGE) trial. *J Thorac Cardiovasc Surg* 1998; **116**: 716–30.
- 75 Horrow JC, van Riper DF, Strong MD, Brodsky I, Parmet JL. Hemostatic effects of tranexamic acid and desmopressin during cardiac surgery. *Circulation* 1991; **84**: 2063–70.
- 76 Shorre-Lesserson L, Reich DL, Vela-Cantos F, Ammar T, Ergin MA. Tranexamic acid reduces transfusions and mediastinal drainage in repeat cardiac surgery. *Anaesth Analg* 1996; **83**: 18–26.
- 77 Horrow JC, Hlavacek J, Strong MD, et al. Prophylactic tranexamic acid decreases bleeding after cardiac operations. *J Thorac Cardiovasc Surg* 1990; **99**: 70–74.
- 78 Vandersalm TJ, Kaur S, Lancey RA. Reduction of bleeding after heart operations through the prophylactic use of epsilon-aminocaproic acid. *J Thorac Cardiovasc Surg* 1996; **112**: 1098–107.
- 79 Delrossi AJ, Ceraianu AC, Botros S, Lemole GM, Moore R. Prophylactic treatment of postperfusion bleeding using EACA. *Chest* 1989; **96**: 27–30.
- 80 Daily PO, Lamphere JA, Demitsky WP, Adamson RM, Dans NF. Effect of prophylactic epsilon-aminocaproic acid on blood loss and transfusion requirements in patients undergoing first-time coronary artery bypass grafting: a randomized, prospective, double-blind study. *J Thorac Cardiovasc Surg* 1994; **108**: 99–108.
- 81 Coffey A, Pittmam J, Halbrook H, Fehrenbacher J, Beckman D, Hormuth D. The use of tranexamic acid to reduce postoperative bleeding following cardiac surgery: a double-blind randomized trial. *Am Surgeon* 1995; **61**: 566–68.
- 82 Brown RS, Thwaites BK, Mongan PD. Tranexamic acid is effective in decreasing postoperative bleeding and transfusions in primary coronary artery bypass operations: a double-blind, placebo-controlled trial. *Anesth Analg* 1997; **85**: 963–70.
- 83 Dryden PJ, O'Connor P, Jamieson WRE, et al. Tranexamic acid reduces blood loss and transfusion in reoperative cardiac surgery. *Can J Anaesth* 1997; **44**: 934–41.
- 84 Hardy JF, Bélisle S, Dupont C, et al. Prophylactic tranexamic acid and ϵ -aminocaproic acid for primary myocardial revascularization. *Ann Thorac Surg* 1998; **65**: 371–76.
- 85 Pinosky ML, Kennedy DJ, Fishman RL, et al. Tranexamic acid reduces bleeding after cardiopulmonary bypass when compared to epsilon aminocaproic acid and placebo. *J Card Surg* 1997; **12**: 330–38.
- 86 de Prost D, Barbier-Boehm G, Hazebrucq J, et al. Desmopressin has no beneficial effect on excessive postoperative bleeding or blood product requirements associated with cardiopulmonary bypass. *Thromb Haemost* 1992; **68**: 106–10.
- 87 Hackmann T, Gascoyne RD, Naiman SC, et al. A trial of desmopressin (1-deamino-8-D-arginine vasopressin) to reduce blood loss in uncomplicated cardiac surgery. *N Engl J Med* 1989; **321**: 1437–43.
- 88 Salzman EW, Weinstein MK, Weintraub RM. Treatment with desmopressin acetate to reduce blood loss after cardiac surgery. *N Engl J Med* 1986; **314**: 1402–06.
- 89 Reich DL, Hammerschlag BC, Rand JH, et al. Desmopressin acetate is a mild vasodilator that does not reduce blood loss in uncomplicated cardiac surgical procedures. *J Cardiothorac Vasc Anesth* 1991; **5**: 142–45.
- 90 Marquez J, Koehler S, Strelec SR, et al. Repeated dose administration of desmopressin acetate in uncomplicated cardiac surgery: a prospective, blinded, randomized study. *J Cardiothorac Vasc Anesth* 1992; **6**: 674–76.
- 91 Dilthey G, Dietrich W, Spannagl M, Richter JA. Influence of desmopressin acetate on homologous blood requirements in cardiac surgery patients pretreated with aspirin. *J Cardiothorac Vasc Anesth* 1993; **7**: 425–30.
- 92 Ansell J, Klassen V, Lew R, et al. Does desmopressin acetate prophylaxis reduce blood loss after valvular heart operations? A randomized, double-blind study. *J Thorac Cardiovasc Surg* 1992; **104**: 117–23.
- 93 Gratz I, Koehler J, Olsen D, et al. The effect of desmopressin acetate on postoperative hemorrhage in patients receiving aspirin therapy before coronary artery bypass operations. *J Thorac Cardiovasc Surg* 1992; **104**: 1417–22.
- 94 Rocha E, Llorens R, Paramo JA, Arcas R, Cuesta B, Trenor AM. Does desmopressin acetate reduce blood loss after surgery in patients on cardiopulmonary bypass? *Circulation* 1988; **77**: 1319–23.
- 95 Mongan PD, Hosking MP. The role of desmopressin acetate in patients undergoing coronary artery bypass surgery: a controlled clinical trial with thrombelastographic risk stratification. *Anesthesiology* 1992; **77**: 38–46.
- 96 Hedderich GS, Petsikass DJ, Cooper BA, et al. Desmopressin acetate in uncomplicated coronary artery bypass surgery: a prospective randomized clinical trial. *Can J Surg* 1990; **33**: 33–37.
- 97 Temeck BK, Bachenheimer LC, Katz NM, Coughlin SS, Wallace RB. Desmopressin acetate in cardiac surgery: a double-blind randomized study. *South Med J* 1994; **87**: 611–15.
- 98 Sheridan DP, Card RT, Pinilla JC, et al. Use of desmopressin acetate to reduce blood transfusion requirements during cardiac surgery in patients with acetylsalicylic-acid-induced platelet dysfunction. *Can J Surg* 1994; **37**: 33–37.
- 99 Spyt TJ, Weerasena NA, Brain WH. The effects of desmopressin acetate (DDAVP) on haemostasis and blood loss in routine coronary artery bypass surgery: a randomized, double-blind trial. *Perfusion* 1990; **5** (suppl): 57–61.
- 100 Bennett-Guerrero E, Sorohan J, Gurevich ML, et al. Cost-benefit and efficacy of aprotinin compared with ϵ -aminocaproic acid in patients having repeated cardiac operations: a randomized, blinded trial. *Anesthesiology* 1997; **87**: 1373–80.
- 101 Mongan PD, Brown RS, Thwaites BK. Tranexamic acid and aprotinin reduce postoperative bleeding and transfusions during primary coronary revascularisation. *Anesth Analg* 1998; **87**: 258–65.
- 102 Cattaneo M, Harris AS, Strömberg U, Mannucci PM. The effect of desmopressin on reducing blood loss in cardiac surgery: a meta-analysis of double-blind placebo-controlled trials. *Thromb Haemost* 1995; **74**: 1064–70.
- 103 Royston D. High-dose aprotinin therapy: a review of the first five years' experience. *J Cardiothorac Vasc Anesth* 1992; **6**: 76–100.
- 104 van der Meer J, Hillege HL, Ascoop CA, et al. Aprotinin in aortocoronary bypass surgery: increased risk of vein graft occlusion and myocardial infarction? Supportive evidence from a retrospective study. *Thromb Haemost* 1996; **75**: 1–3.
- 105 Smith PK, Muhlbaier LH. Aprotinin: safe and effective only with the full-dose regimen. *Ann Thorac Surg* 1996; **62**: 1575–77.