Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion (Review)

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[Intervention Review]

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ABSTRACT

Background

Concerns regarding the safety of transfused blood have led to the development of a range of interventions to minimise blood loss during major surgery. Anti-fibrinolytic drugs are widely used, particularly in cardiac surgery, and previous reviews have found them to be effective in reducing blood loss, the need for transfusion, and the need for re-operation due to continued or recurrent bleeding. In the last few years questions have been raised regarding the comparative performance of the drugs. The safety of the most popular agent, aprotinin, has been challenged, and it was withdrawn from world markets in May 2008 because of concerns that it increased the risk of cardiovascular complications and death.

Objectives

To assess the comparative effects of the anti-fibrinolytic drugs aprotinin, tranexamic acid (TXA), and epsilon aminocaproic acid (EACA) on blood loss during surgery, the need for red blood cell (RBC) transfusion, and adverse events, particularly vascular occlusion, renal dysfunction, and death.

Search methods

We searched: the Cochrane Injuries Group's Specialised Register (July 2010), Cochrane Central Register of Controlled Trials (*The Cochrane Library 2010*, Issue 3), MEDLINE (Ovid SP) 1950 to July 2010, EMBASE (Ovid SP) 1980 to July 2010. References in identified trials and review articles were checked and trial authors were contacted to identify any additional studies. The searches were last updated in July 2010.

Selection criteria

Randomised controlled trials (RCTs) of anti-fibrinolytic drugs in adults scheduled for non-urgent surgery. Eligible trials compared anti-fibrinolytic drugs with placebo (or no treatment), or with each other.

Data collection and analysis

Two authors independently assessed trial quality and extracted data. This version of the review includes a sensitivity analysis excluding trials authored by Prof. Joachim Boldt.

Main results

This review summarises data from 252 RCTs that recruited over 25,000 participants. Data from the head-to-head trials suggest an advantage of aprotinin over the lysine analogues TXA and EACA in terms of reducing perioperative blood loss, but the differences were small. Compared to control, aprotinin reduced the probability of requiring RBC transfusion by a relative 34% (relative risk [RR] 0.66, 95% confidence interval [CI] 0.60 to 0.72). The RR for RBC transfusion with TXA was 0.61 (95% CI 0.53 to 0.70) and was 0.81 (95% CI 0.67 to 0.99) with EACA. When the pooled estimates from the head-to-head trials of the two lysine analogues were combined and compared to aprotinin alone, aprotinin appeared more effective in reducing the need for RBC transfusion (RR 0.90; 95% CI 0.81 to 0.99).

Aprotinin reduced the need for re-operation due to bleeding by a relative 54% (RR 0.46, 95% CI 0.34 to 0.62). This translates into an absolute risk reduction of 2% and a number needed-to-treat (NNT) of 50 (95% CI 33 to 100). A similar trend was seen with EACA (RR 0.32, 95% CI 0.11 to 0.99) but not TXA (RR 0.80, 95% CI 0.55 to 1.17). The blood transfusion data were heterogeneous and funnel plots indicate that trials of aprotinin and the lysine analogues may be subject to publication bias.

When compared with no treatment aprotinin did not increase the risk of myocardial infarction (RR 0.87, 95% CI 0.69 to 1.11), stroke (RR 0.82, 95% CI 0.44 to 1.52), renal dysfunction (RR 1.10, 95% CI 0.79 to 1.54) or overall mortality (RR 0.81, 95% CI 0.63 to 1.06). Similar trends were seen with the lysine analogues, but data were sparse. These data conflict with the results of recently published non-randomised studies, which found increased risk of cardiovascular complications and death with aprotinin. There are concerns about the adequacy of reporting of uncommon events in the small clinical trials included in this review.

When aprotinin was compared directly with either, or both, of the two lysine analogues it resulted in a significant increase in the risk of death (RR 1.39, 95% CI 1.02, 1.89), and a non-significant increase in the risk of myocardial infarction (RR 1.11 95% CI 0.82, 1.50). Most of the data contributing to this added risk came from a single study - the BART trial (2008).

Authors' conclusions

Anti-fibrinolytic drugs provide worthwhile reductions in blood loss and the receipt of allogeneic red cell transfusion. Aprotinin appears to be slightly more effective than the lysine analogues in reducing blood loss and the receipt of blood transfusion. However, head to head comparisons show a lower risk of death with lysine analogues when compared with aprotinin. The lysine analogues are effective in reducing blood loss during and after surgery, and appear to be free of serious adverse effects.

PLAIN LANGUAGE SUMMARY

Anti-fibrinolytic drugs for reducing blood loss and the need for red blood cell transfusions during and after surgery.

Aprotinin, although effective in reducing bleeding, had a higher rate of death than tranexamic acid and aminocaproic acid, which appeared free of serious side-effects. Aprotinin has been withdrawn from world markets because of safety concerns. This review of over 250 clinical trials found that anti-fibrinolytic drugs used at the time of major surgery reduce bleeding, the need for transfusions of red blood cells and the need for repeat surgery because of bleeding. With the exception of aprotinin the drugs appear safe.

BACKGROUND

Public concern regarding the safety of transfused blood has prompted a reconsideration of the role of allogeneic blood transfusion (whole blood or packed red cells from an unrelated donor). The risks associated with receiving transfusion of allogeneic blood that has been screened by a competent blood transfusion program are considered minimal, with very low risks of transmission of HIV, and hepatitis C (Whyte 1997). However, this only applies where there is a safe, plentiful, well-regulated supply. The majority of the world's population does not have access to such a system, and the risks of transfusion in developing countries may be much higher (McFarland 1997). Concerns of patients and clinicians regarding blood safety have generated enthusiasm for the use of technologies intended to reduce the use of allogeneic blood (Bryson 1998; Forgie 1998; Huet 1999; Laupacis 1997). Although allogeneic blood transfusion has had a unique place in medical practice, we are obliged to examine the evidence on the benefits, harms and costs of a range of techniques designed to minimise the use of this resource. Some of the alternatives to allogeneic blood have their own risks, and are expensive (Coyle 1999; Fergusson 1999).

Perioperative bleeding is one of the major indications for allogeneic blood transfusions worldwide (Levy 2006). However, massive surgical blood loss is a serious problem that affects many cardiac surgery patients in particular and has been shown to have a strong, independent association with in-hospital mortality (Karkouti 2004). There is also considerable evidence that blood loss that leads to the transfusion of blood products is harmful, and that the degree of harm is directly related to the amount of blood loss (Karkouti 2006). To reduce perioperative blood loss a number of pharmacological agents have been used, these include the anti-fibrinolytic drugs aprotinin, tranexamic acid (TXA), and epsilon aminocaproic acid (EACA).

Aprotinin is a non-specific, serine protease inhibitor, derived from bovine lung, with anti-fibrinolytic properties. It acts as an inhibitor of several serine proteases, including trypsin, plasmin, plasma-kallikrein and tissue kallikrein. Aprotinin also inhibits the contact phase activation of coagulation that both initiates coagulation and promotes fibrinolysis (Fritz 1983; Royston 1998). During cardiopulmonary bypass (CPB) the negatively charged surface of the CPB circuit activates factor XII, converting prekallikrein to kallikrein which further activates factor XII. This positive feedback loop acts to intensify the intrinsic coagulation cascade. By inhibiting plasma kallikrein, aprotinin minimises derangements in coagulation and fibrinolysis (Smith 1998). There is also evidence that aprotinin exerts an indirect preservative effect on platelet function during extracorporeal circulation (ECC) (Mohr 1992). In many countries aprotinin is specifically indicated for the reduction of blood loss during cardiopulmonary bypass.

TXA and EACA are synthetic lysine analogues (synthetic derivatives of the amino acid lysine) that act as effective inhibitors of fibrinolysis. TXA and EACA act principally by blocking the lysine binding sites on plasminogen molecules, inhibiting the formation of plasmin and therefore inhibiting fibrinolysis (Faught 1998). Tranexamic acid is about ten times more potent than aminocaproic acid and binds much more strongly to both the strong and weak sites of the plasminogen molecule than EACA (Faught 1998; Mannucci 1998).

Why it is important to do this review

The efficacy of these three anti-fibrinolytic drugs to reduce perioperative blood loss and allogeneic blood transfusion has been studied extensively. Systematic reviews of these drugs (Henry 1999; Laupacis 1997; Levi 1999; Munoz 1999; Sedrakyan 2004) have shown that the use of aprotinin is associated with statistically significant reductions in allogeneic blood transfusion requirements and re-operation due to bleeding. Systematic reviews have also shown TXA to be effective in reducing exposure to allogeneic blood transfusion without significant increases in adverse effects (Henry 1999; Laupacis 1997). In the case of EACA, the evidence of effect is equivocal with most systematic reviews severely hampered by the small number of trials of this agent.

Based on the evidence of efficacy anti-fibrinolytic drugs have become widely used, particularly in cardiac surgery. Because of their mode of actions there have been longstanding concerns about the possibility of adverse effects, with most attention directed at the risk of thrombosis and renal failure. However meta-analyses of randomised trials, including previous versions of this Cochrane review (Henry 1999;Henry 2007), have been reassuring in providing no convincing evidence of an increased risk of these events in treated subjects. However, in the case of aprotinin, this view of an attractive benefit to harm ratio was thrown into doubt by the publication of several large non-randomised studies (Mangano 2006; Mangano 2007;Schneeweiss 2008). The serious safety concerns raised by these and other studies prompted the United States Food and Drug Administration (FDA) to re-evaluate its position regarding the use of aprotinin in cardiac surgery, some thirteen years after it was initially approved for prophylactic treatment to reduce perioperative blood loss and blood transfusion (Ferguson 2007). Aprotinin was finally removed from world markets in May 2008. The other drugs reviewed here are still in use.

In the light of these developments and in order to inform decisions about the use of the two lysine analogues as an alternative to aprotinin in cardiac surgery we have updated the Cochrane systematic review of the three anti-fibrinolytic drugs used as blood-sparing agents in surgery. This review updates previous estimates of the efficacy of aprotinin, tranexamic acid, and epsilon aminocaproic acid in reducing perioperative allogeneic blood transfusion in elective surgery. In light of the adverse findings from pharmaco-epidemiological studies we also provide updated estimates of the effects of these drugs on clinical outcomes such as all-cause mortality, thrombosis and renal failure.

OBJECTIVES

To examine the evidence for the efficacy of aprotinin, tranexamic acid, and epsilon aminocaproic acid in reducing allogeneic blood transfusion, and the evidence for any effect on clinical outcomes such as mortality and re-operation rates and complications such as thrombosis and renal failure.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) with a concurrent control group, or randomised head-to-head comparative trials.

Types of participants

The study participants were adults (over 18 years). Trials were included if participants aged less than 18 years were enrolled, but the type of surgery was predominantly carried out in adult patients. The surgery performed was primarily elective but trials were included if urgent cases were proportionately similar across trial arms.

Types of interventions

The interventions considered are the anti-fibrinolytic agents: aprotinin, tranexamic acid (TXA), and epsilon-aminocaproic acid (EACA).

Types of outcome measures

Primary outcomes

- the proportion of patients who were transfused with allogeneic blood, autologous blood, or with both;
- the amounts of allogeneic and autologous blood transfused.

Secondary outcomes

- perioperative blood loss,
- re-operation due to bleeding,
- mortality,
- post-operative complications (myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism, any thrombosis, renal failure),
- length of hospital stay.

Search methods for identification of studies

We did not limit the searches by date language or publication status

Electronic searches

The original review drew on the literature search that was constructed as part of the International Study on Perioperative Transfusion (ISPOT) (Laupacis 1997). The original search is listed in full in Appendix 1.

July 2006 update

To maximise the sensitivity for the retrieval of all potentially relevant studies, the electronic searches of MEDLINE were initially unrestricted and updated to July 2006. In MEDLINE, two search filters were then used to restrict the electronic searches and improve the specificity of the updated searches. Firstly, the ISPOT filter, which identifies blood transfusion trials, and secondly, a modified version of the Cochrane Collaboration filter, which primarily identifies randomised controlled trials. These search filters were coupled with the specified MeSH headings and the relevant text-word terms. These restricted searches were updated in MEDLINE to July 2006. Electronic database searches of Excerpta Medica (EMBASE) were updated to July 2006 using similar search strategies to those used in MEDLINE.

July 2010 update

Searches were carried out in July 2010 as part of a larger project to identify trials in the use of antifibrinolytics.
We searched the following databases;

- the Cochrane Injuries Group's Specialised Register (searched July 2010),
- Cochrane Central Register of Controlled Trials (*The Cochrane Library 2010*, Issue 3),
- MEDLINE (Ovid SP) 1950 to July 2010,
- EMBASE (Ovid SP) 1980 to July 2010.

Full details of the search strategies are presented in Appendix 2.

Searching other resources

The web sites of International Health Technology Assessment Agencies were also searched through the International Network of Agencies of Health Technology Assessment (INAHTA), and the International Society of Technology Assessment in Health Care (ISTAHC). The Internet was widely searched using Google™ and Google™ Scholar. Contact was also made with experts in the field to identify reports or projects in progress relevant to the review.
The reference lists of related reviews and identified articles were checked for relevant trials. In addition references in the identified trials were checked and authors contacted, where possible, to identify any additional published or unpublished data.

Data collection and analysis

Electronic database searches were carried out by the Cochrane Injuries Group Trials Search Co-ordinator, who then collated the results and passed them on to the author (KK).

Selection of studies

The titles and abstracts identified in the electronic searches were independently screened by two authors to identify trials in which adult patients, scheduled for elective or urgent surgery, were randomised to either/or aprotinin, TXA, EACA or to a control group, who did not receive the intervention. From the results of the screened electronic searches, bibliographic searches, and contacts with experts, two of the authors independently selected trials that met previously defined inclusion criteria.

Data extraction and management

At least two authors independently extracted study characteristics and outcomes using an article extraction form. The extraction form was used to record information regarding randomisation criteria, methodology descriptions, the presence of a transfusion protocol, the type of surgery involved, treatment outcomes, and general comments.

Data on the following outcomes were recorded on the data extraction form: the number of patients exposed to allogeneic blood, the amount of allogeneic blood transfused, the number of patients receiving any transfusion (allogeneic blood, autologous blood, or both), the number of patients experiencing post-operative complications (thrombosis, myocardial infarction, renal failure), and mortality. Data were also recorded on blood loss, and the proportion of patients requiring re-operation for bleeding. Information regarding demographics (age, sex), type of surgery, and the presence or absence of a transfusion protocol was also recorded. Data were extracted for allogeneic blood transfusion if they were expressed as whole blood or packed red cells. Data were extracted regarding dose size for each drug regimen.

Assessment of risk of bias in included studies

Articles that met the inclusion criteria were independently assessed for methodological quality by two authors using criteria proposed by Schulz 1995. Disagreements were resolved by consensus. Methodological quality scores obtained for each trial using the criteria proposed by Schulz 1995 were then entered into Review Manager using the Cochrane Collaboration's tool for assessing risk of bias presented in Higgins 2009.

The following domains were assessed for each study:

- sequence generation,
- allocation concealment,
- blinding.

We completed a risk of bias table for each study, incorporating a description of the study's performance against each of the above domains and our overall judgement of the risk of bias for each entry is as follows; 'Yes' indicates low risk of bias, 'Unclear' indicates unknown risk of bias (not enough information was reported to assess methodological quality); and 'No' indicates a high risk of bias.

Assessment of reporting biases

Funnel plots were inspected for evidence of publication bias.

Data synthesis

Extraction of trial data was performed by one author and checked by the review team's statistician if necessary. Data were checked and entered into Review Manager by one author. Articles identified as duplicate publications were combined to obtain one set of data. The study report with the greatest number of patients was then represented in the analysis. Studies that did not report data for the number or proportion of patients transfused with allogeneic blood, or the amounts of allogeneic blood transfused, were not included for review. However, trials not reporting blood transfusion data that could be used in the meta-analysis were still included if they reported adverse event data. For dichotomous outcome data to be included in the analysis, trial reports had to provide either numeric data, that is the numbers of events that occurred in the treatment and control groups, or where there were no events recorded numerically, the trial report had to provide a clear statement qualifying and/or quantifying specific events had or had not occurred.

All analyses were performed using Review Manager software. Data on the numbers of patients exposed to allogeneic blood, and the numbers of patients in each treatment arm, were entered into Review Manager. The relative risks (RR) for allogeneic blood transfusion in the intervention group as compared with the control group, and the corresponding 95% confidence intervals (CI), were calculated for each trial using the random effects model. The presence of heterogeneity of treatment effect was assessed using the Q statistic, which has an approximate chi-square distribution with degrees of freedom equal to the number of studies minus one (Der Simonian 1986). A P-value less than or equal to 0.1 was used to define statistically significant heterogeneity. Statistical heterogeneity was also assessed using the I^2 test. The I^2 test describes the percentage of total variation across studies due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity and larger values show increasing heterogeneity. Substantial heterogeneity is considered to exist when $I^2 > 50\%$ (Higgins 2002).

The mean number of units of allogeneic blood transfused to each group, and the corresponding standard deviations, were also entered. As the majority of trials reported the means and standard deviations for the amount of blood transfused in all patients in each comparison group, the data included a number of zero values for those patients not receiving transfusion. The data are therefore likely to be highly skewed. Wherever possible, the mean and standard deviation for the numbers of units of blood transfused in those receiving transfusion were recalculated. The new mean was calculated by dividing the total number of units transfused in the group by the number of patients transfused. The reported standard deviation and mean were used to calculate the sum of squares of the numbers of units transfused for the group. As this is equal to the sum of squares of the numbers of units transfused in those receiving transfusion, the new standard deviation was calculated using this, the new mean and the number of patients transfused. Thus the new values estimate the average amount of blood received by those transfused in each group. The new values were then entered into Review Manager to obtain the mean difference (MD) and 95% CIs to express the average reduction in the number of units of allogeneic blood given to those patients transfused. Data in millilitres (mls) were converted to units by dividing by 300.

Subgroup analysis and investigation of heterogeneity

Analysis of *a-priori* subgroups was performed to determine whether effect sizes varied according to factors such as;

- the type of surgery,
- the use of transfusion protocols,
- dose regimen, and
- trial methodological quality.

The editorial group is aware that a clinical trial by Prof. Joachim Boldt has been found to have been fabricated (Boldt 2009). As the editors who revealed this fabrication point out (Reinhart 2011; Shafer 2011), this casts some doubt on the veracity of other studies by the same author. All Cochrane Injuries Group reviews which include studies by this author have therefore been edited to show the results with this author's trials included and excluded. Readers can now judge the potential impact of trials by this author on the conclusions of the review.

R E S U L T S

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Two hundred and fifty-two trials met the inclusion criteria. Four trials were excluded (refer to 'Characteristics of excluded studies' section of this review). Of the 252 included trials, 131 evaluated aprotinin, 60 evaluated tranexamic acid (TXA), and 12 evaluated epsilon aminocaproic acid (EACA) versus control. Forty-nine trials studied head-to-head comparisons of aprotinin, TXA, and EACA with or without an untreated control. Of these 49 trials, 25 compared aprotinin with TXA, 12 compared aprotinin with EACA, seven compared TXA with EACA, and five compared aprotinin with TXA and EACA. Trials were conducted in many countries including:

United States (n = 45), Germany (n = 24), UK (n = 17), Canada (n = 17), Italy (n = 16), Spain (n = 14), Belgium (n = 12), France (n = 10), Turkey (n = 9), Australia (n = 8), Sweden (n = 8),The Netherlands (n = 8), Japan (n = 7), China (n = 6), Austria (n = 5), Israel (n = 5), Switzerland (n = 5), Finland (n = 5), Czech Republic (n = 3), Denmark (n = 3), Taiwan (n = 2), Ireland (n = 2), Greece (n = 2), Poland (n = 2), Brazil (n = 1), Chile (n = 1), Dubai (n=1), Egypt (n = 1), India (n = 1), Norway (n = 1), Oman (n=1), Saudi Arabia (n=1) and South Africa (n = 1). Three studies were multicentre trials, one conducted across sites in the UK and the United States, one in sites in Australia, New Zealand, Asia and Europe and one in sites in the United States and Canada. The majority of included trials were published in English. Thirteen trials required translation (Carrera 1994; Corbeau 1995; Cvachovec 2001; Deleuze 1991; Gherli 1992; Hei 2005; Kahveci 1996; Katzel 1998; Kratzer 1997; Locatelli 1990; Maccario 1994; Trinh-Duc 1992; Utada 1997). The data from these trials were included in the analysis.

Of the 252 included trials, 173 were conducted in cardiac surgery, 53 trials were in orthopaedic surgery, 14 involved liver surgery, five were conducted in vascular surgery, four involved thoracic surgery, one involved gynaecological surgery, one involved neurosurgery, and one trial was in orthognathic surgery.

The trial conducted by Lemmer 1994 stratified patients according to the type of procedure being performed, that is, either primary CABG or redo CABG surgery. Patients from each group were then randomised to either aprotinin or placebo. The data obtained from each of these two groups (primary CABG and redo CABG) have been analysed separately by the authors. Therefore from this single trial (Lemmer 1994), two comparisons of aprotinin versus control have been obtained. This review presents the data from this trial as follows:

(1) Lemmer_1 1994: represents those patients who underwent primary CABG and were randomised to either aprotinin or placebo.

(2) Lemmer_2 1994: represents those patients who underwent redo CABG and were randomised to either aprotinin or placebo.

Description of Dose Regimens

Aprotinin dose range

Three dose stratifications were used: (1) high-dose aprotinin, (2) low-dose aprotinin, and, (3) cardiopulmonary bypass (CPB) pump prime aprotinin. For the purposes of this review, any aprotinin regimen that did not follow the 'full Hammersmith' regimen, including those studies that described their regimens as 'half Hammersmith', were classified as low-dose aprotinin. For those trials that did not involve cardiac surgery, classification of the dose-regimen was based on the total quantity of aprotinin administered. Trials were classified as 'high-dose' where participants received a total dose equal to or exceeding five million kallikrein inactivator units (KIU) or 700mg of aprotinin.

High-dose aprotinin, described as the 'full Hammersmith' regimen, entails an initial loading dose of two million kallikrein inactivator units (KIU) of aprotinin given intravenously (IV) (280mg) over a 20 to 30 minute period commencing at the induction of anaesthesia, followed by a continuous infusion of 500,000 KIU per hour (70mg/hr) until the end of the operation. In addition, two million KIU of aprotinin (280mg) is added to the oxygenator prime or pump prime of the CPB. A 'half Hammersmith' regimen is described as follows: a loading dose of one million KIU (140mg) of aprotinin infused over a 20 to 30 minute period followed by a continuous IV infusion of 250,000 KIU of aprotinin per hour, until the end of the operation. An additional dose of one million KIU is added to the pump prime.

'Prime' dose aprotinin, for the purposes of this review, included those regimens that added aprotinin to the pump prime solution of the CPB exclusively. The dose of aprotinin used in the 'prime' regimen varied between trials. Sixteen trials studied the efficacy of 'prime' dose aprotinin and reported data on the proportion of participants exposed to allogeneic blood transfusion. Of these trials 12 studied a 'prime' dose of two million KIU of aprotinin, two studied a 'prime' dose of one million KIU of aprotinin, one studied a 'prime' dose of 500,000 KIU of aprotinin, and one trial studied a 'prime' dose of 25,000 KIU/kg (range 1.375 to 2.3 million KIU in total) of aprotinin.

Tranexamic acid (TXA) dose range

Of the 65 trials that studied the efficacy of TXA versus placebo or control (current standard practice) and were included in the meta-analysis of allogeneic blood transfusion exposure; 34 involved cardiac surgery, 27 involved orthopaedic surgery, two involved liver surgery, one trial involved gynaecological surgery and one trial involved vascular surgery. Dose regimens for TXA varied significantly between trials with varying dose sizes and time frames for drug delivery. Of the 34 trials involving cardiac surgery, the TXA loading or bolus dose ranged from 2.5mg/kg to 100mg/kg. The maintenance dose of TXA for the cardiac trials, ranged from 0.25mg/kg/hr to 4.0mg/kg/hr delivered over 1 to 12 hours. Similar variation was observed in trials not involving cardiac surgery. More detailed information regarding dose regimens is provided in the 'Characteristics of included studies' section of this review.

Epsilon aminocaproic acid (EACA) dose range

Of the 16 trials that studied the efficacy of EACA versus placebo or control (current standard practice) and were included in the meta-analysis of allogeneic blood transfusion exposure; 11 involved cardiac surgery, four involved orthopaedic surgery, and one involved liver surgery. Dose regimens for EACA also varied significantly between trials. Generally trials used different dose sizes and time frames for drug delivery. The EACA loading or bolus dose ranged from 80mg to 15g or 75 to 150mg/kg. The maintenance dose of EACA ranged from 1g/hr to 2g/hr or 12.5mg/kg/hr to 30mg/kg/hr infused over varying time periods. More detailed information regarding dose regimens is provided in the 'Characteristics of included studies' section of this review.

Transfusion 'triggers' / thresholds

Of the 189 trials of aprotinin, TXA, and EACA versus control included in the analysis of allogeneic blood transfusion exposure, 158 trials (84%) reported the use of a transfusion protocol, the remainder did not report the use of a transfusion protocol. Of those trials that reported the use of a transfusion protocol, all included a transfusion "trigger" value, that being the haemoglobin or haematocrit value, at which point a transfusion of allogeneic and/or autologous blood, was considered necessary. There was significant variation between trials in the type and value of transfusion threshold used. The lowest transfusion threshold level for haemoglobin was 5.0g/dL with blood being transfused if the haemoglobin level during CPB fell below 5.0g/dL (Green 1995). The transfusion protocol used by Brown 1997 advocated a haemoglobin threshold level of 6.0g/dL during CPB, whereas other trials involving CPB advocated a haemoglobin threshold level of 7.0g/dL, or haematocrit levels (Hct) between 18% to 20% during CPB. In general, post-operative transfusion threshold levels ranged from Hb 7.0g/dL to 10.0g/dL, or Hct 20% to 30%.

Risk of bias in included studies

For further details regarding the performance of the studies against each domain, please see the 'Risk of bias' tables (Figure 1; Figure 2). A summary of the information in the tables is given below. Additionally, a visual summary of judgements about each methodological quality item for each included trial is shown in Figure 1.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

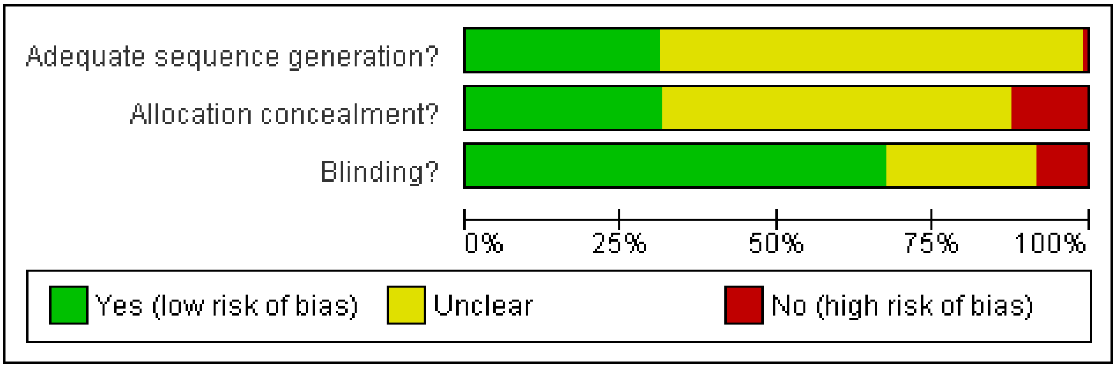


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Generation of allocation sequences

The method used to generate allocation sequences was judged to be adequate in only 78 trials. For all but two of the remaining trials the method used to generate allocation sequences was judged to be unclear. For two trials the method of randomisation that was judged to be inadequate. Refer to results presented in the 'Risk of bias' tables.

Allocation concealment

Only 79 trials were judged to have adequately concealed treatment allocation. For 31 trials the method used to conceal treatment allocation was judged to be inadequate. For the remaining trials allocation concealment was judged to be unclear. Refer to results presented in the 'Risk of bias' tables.

Blinding

For 170 trials blinding was judged to be adequate (double blinded), and unclear for 61 trials. Refer to results presented in the 'Risk of bias' tables.

Inclusion of all randomised participants

Of those trials able to be assessed for methodological quality, 124 trials either reported there were no exclusions, or used intention-to-treat analysis. In 80 trials, where exclusions were reported, these exclusions were judged unlikely to cause bias. For 37 trials exclusions were either judged to be excessive and likely to cause bias, or were not reported.

Effects of interventions

Aprotinin

There were 108 trials of aprotinin versus control that reported data on the proportion of patients exposed to allogeneic blood transfusion. These trials included a total of 11,172 patients, of whom 6259 were randomised to receive aprotinin and 4913 patients were randomised to a control group who did not receive aprotinin. The apparent imbalance between the aprotinin and control groups resulted from pooling data across different aprotinin dose groups within trials. Overall, the use of aprotinin significantly reduced the rate of allogeneic blood transfusion by a relative 34% (RR 0.66, 95% CI 0.60 to 0.72) compared to control. Heterogeneity between these trials was statistically significant ($Chi^2 = 961.52$, df = 107, P <0.00001; $I^2 = 89\%$). The absolute risk reduction (ARR) was 20% (RD -0.20, 95% CI -0.24 to -0.17).

Type of surgery

There were 84 trials of aprotinin versus control that involved cardiac surgery and provided data on the number of patients exposed to allogeneic blood transfusion. These trials included a total of 9497 patients, of whom 5329 were randomised to receive aprotinin and 4168 patients were randomised to a control group who did not receive aprotinin. Overall, the use of aprotinin in cardiac surgery significantly reduced the need for allogeneic blood transfusion by a relative 32% (RR 0.68, 95% CI 0.63 to 0.73) compared to control. (The effect with the Boldt 1991 trial excluded was unchanged (RR 0.68 (95% CI 0.63 to 0.73).) Heterogeneity between these trials was statistically significant ($Chi^2 = 329.48$, df = 83, P <0.00001; $I^2 = 75\%$). The ARR was 21% (RD -0.21, 95% CI -0.24 to -0.18).

There were 15 trials of aprotinin versus control that involved orthopaedic surgery and provided data on the number of patients exposed to allogeneic blood transfusion. These trials included a total of 1146 patients, of whom 655 were randomised to receive aprotinin and 491 patients were randomised to a control group who did not receive aprotinin. Overall, the use of aprotinin in orthopaedic surgery significantly reduced the need for allogeneic blood transfusion by a relative 32% (RR 0.68, 95% CI 0.52 to 0.89) compared to control. Heterogeneity between these trials was statistically significant ($Chi^2 = 45.47$, df = 14, P <0.0001; $I^2 = 69\%$). The ARR was 13% (RD -0.13, 95% CI -0.20 to -0.05).

There were three trials of aprotinin versus control that involved thoracic surgery and provided data on the number of patients exposed to allogeneic blood transfusion. These trials included a total of 78 patients, of whom 38 were randomised to receive aprotinin and 40 patients were randomised to a control group who did not receive aprotinin. The use of aprotinin in thoracic surgery significantly reduced the need for allogeneic blood transfusion by a relative 71% (RR 0.29, 95% CI 0.14 to 0.59). Heterogeneity between these trials was not statistically significant ($Chi^2 = 0.37$, df = 2, P = 0.83; $I^2 = 0\%$).

There were two trials of aprotinin versus control that involved vascular surgery and provided data on the number of patients exposed to allogeneic blood transfusion. These trials included a total of 188 patients, of whom 105 were randomised to aprotinin and 83 patients were randomised to a control group who did not receive aprotinin. The use of aprotinin in vascular surgery had no effect on the need for allogeneic blood transfusion (RR 1.00, 95% CI 0.97 to 1.03). Heterogeneity between these trials was not statistically significant ($Chi^2 = 0.01$, df = 1, P = 0.84; $I^2 = 0\%$).

There were two trials of aprotinin versus control that involved liver surgery and provided data on the number of patients exposed to allogeneic blood transfusion. These trials included a total of 177 patients, of whom 87 were randomised to aprotinin and 90 patients were randomised to a control group who did not receive

aprotinin. The use of aprotinin in liver surgery reduced the need for allogeneic blood transfusion by a relative 42% (RR 0.58, 95% CI 0.37 to 0.90). Heterogeneity between these trials was not statistically significant ($Chi^2 = 1.03$, df = 1, P = 0.31; $I^2 = 3\%$).
Data from the trials involving neurosurgery, and orthognathic surgery could not be analysed due to the small number of trials in each of these surgical subgroups.

Effect of transfusion protocols

There were 87 trials that compared aprotinin with control and reported the use of transfusion protocols. These trials included a total of 9974 patients, of whom 5599 were randomised to aprotinin and 4375 were randomised to a control group who did not receive aprotinin. In those trials where a transfusion protocol was used, aprotinin significantly reduced the need for allogeneic blood transfusion by a relative 35% (RR 0.65, 95% CI 0.59 to 0.71). Heterogeneity between these trials was statistical significant ($Chi^2 = 924.12$, df = 86, P < 0.00001; $I^2 = 91\%$). (The effect was unchanged with the Boldt 1991 trial excluded (RR 0.65 (95% CI 0.59 to 0.71).)
There were 21 trials of aprotinin versus control that reported data on the number of patients exposed to allogeneic blood transfusion but did not report the use of a transfusion protocol. These trials included a total of 1198 patients, of whom 660 were randomised to aprotinin and 538 were randomised to a control group who did not receive aprotinin. The use of aprotinin statistically significantly reduced the need for allogeneic blood transfusion by a relative 29% (RR 0.71, 95% CI 0.61 to 0.84) compared to control. Heterogeneity between these trials was statistically significant ($Chi^2 = 49.74$, df = 20, P = 0.0002; $I^2 = 60\%$).

Effect of dose

In those trials that used a low-dose aprotinin regimen the RR of requiring an allogeneic blood transfusion was 0.65 (95% CI 0.55 to 0.77) compared to control. Whereas in those trials that used a high-dose aprotinin regimen the RR of receiving an allogeneic blood transfusion was 0.66 (95% CI 0.61 to 0.71) compared to control. Therefore there was little difference in effect between high-dose and low-dose aprotinin. In cardiac surgery when aprotinin was given as a prime-dose only, the RR of requiring allogeneic blood transfusion was 0.83 (95% CI 0.71 to 0.96). There was statistically significant heterogeneity present in all three subgroups (P >0.0001; I^2 >74%).
The study conducted by Green 1995 was not included in this analysis as it only provided aggregate data for the number of patients exposed to allogeneic blood transfusion, without stratifying allogeneic blood transfusion exposure by dose.
When the high-dose analysis excludes the Boldt 1991 trial, the effect remains 0.66 (95% CI 0.61 to 0.71).

Volume of blood transfused

Seventy-four trials of aprotinin versus control provided data on the volume of allogeneic blood transfused in all patients. These trials included a total of 7820 patients, of whom 4198 were randomised to aprotinin and 3622 were randomised to a control group who did not receive aprotinin. The use of aprotinin resulted in a significant saving of 1.02 units of allogeneic blood (MD -1.02 units, 95% CI -1.26 to -0.79 units). Heterogeneity between these trials was statistically significant ($Chi^2 = 1627.35$, df = 69, P <0.00001; $I^2 = 96\%$).
Forty trials of aprotinin versus control provided data on the volume of allogeneic blood transfused in those patients transfused. These trials provided data for a total of 3563 patients, of whom 1680 were treated with aprotinin and 1883 did not receive aprotinin treatment. In those patients transfused the use of aprotinin resulted in a significant saving of 0.98 units of allogeneic blood per patient (MD -0.98 units, 95% CI -1.29 to -0.66 units). Heterogeneity between these trials was statistically significant ($Chi^2 = 197.82$, df = 36, P < 0.00001; $I^2 = 82\%$).

Blood loss - all surgery combined

A total of 16 trials of aprotinin versus control reported intra-operative blood loss data. These trials included a total of 883 patients, of whom 449 were randomised to aprotinin and 434 were randomised to a control group. These trials involved cardiac surgery (n = 7), orthopaedic surgery (n = 5), thoracic surgery (n = 2), liver surgery (n = 2) and vascular surgery (n = 1). In aggregate, aprotinin treatment reduced intra-operative blood loss on average by around 192 mls per patient (MD -191.87 mls, 95% CI -280.45 to -103.28 mls). Heterogeneity between these trials was statistically significant ($Chi^2 = 40.04$, df = 16, P = 0.0008; $I^2 = 60\%$).
A total of 87 trials of aprotinin versus control reported post-operative blood loss data. These trials included a total of 7896 patients, of whom 4394 were randomised to aprotinin and 3502 were randomised to a control group. These trials involved cardiac surgery (n = 75), orthopaedic surgery (n = 7), thoracic surgery (n = 2), orthognathic surgery (n = 1), liver surgery (n = 1), and vascular surgery (n = 1). In aggregate, aprotinin treatment significantly reduced post-operative blood loss on average by around 346 mls per patient (MD -345.88 mls, 95% CI -383.47 to -308.29 mls). Heterogeneity between these trials was statistically significant ($Chi^2 = 620.49$, df = 86, P <0.00001; $I^2 = 86\%$).
A total of 17 trials of aprotinin versus control reported total blood loss data (intra-operative and post-operative blood loss combined). These trials included a total of 1789 patients, of whom 932 patients were randomised to aprotinin and 857 were randomised to a control group. These trials involved cardiac surgery (n = 7) and orthopaedic surgery (n = 10). In aggregate, the use of aprotinin significantly reduced perioperative blood loss by around 416 mls per patient (MD -415.95 mls, 95% CI -520.38 to -311.51 mls). Het-

erogeneity between these trials was statistically significant (Chi^2 = 66.96, df = 16, P <0.0001; I^2 = 76%).

Blood loss - cardiac surgery

Seven trials of aprotinin versus control involving cardiac surgery reported intra-operative blood loss data. These trials included a total of 470 patients, of whom 242 were randomised to aprotinin and 228 were randomised to a control group. Aprotinin treatment in cardiac surgery appeared to be only marginally effective in reducing intra-operative blood loss (MD -148.18 mls, 95% CI -240.21 to -56.14 mls). Heterogeneity between these trials was statistically significant (Chi^2 = 13.63, df = 6, P = 0.03; I^2 = 56%).

Seventy-five trials of aprotinin versus control involving cardiac surgery reported post-operative blood loss data. These trials included a total of 7371 patients, of whom 4132 were randomised to aprotinin and 3239 were randomised to a control group. The use aprotinin in cardiac surgery reduced post-operative blood loss on average by 370 mls per patient (MD -369.62 mls, 95% CI -408.95 to -330.29 mls). Heterogeneity between these trials was statistically significant (Chi^2 = 513.91, df = 74, P <0.00001; I^2 = 86%). The effect excluding the trials Boldt 1991 and Boldt 1994 is MD -378.45 (95% CI -417.99 to -338.92).

Seven trials of aprotinin versus control involving cardiac surgery reported total blood loss data (intra-operative and post-operative blood loss combined). These trials included a total of 1359 patients, of whom 716 were randomised to aprotinin and 643 were randomised to a control group. The use of aprotinin in cardiac surgery significantly reduced the total volume of blood lost during the perioperative period (MD -448.86 mls, 95% CI -612.82 to -284.91 mls). Heterogeneity between these trials was statistically significant (Chi^2 = 42.60, df = 6, P<0.00001; I^2 = 86%).

Blood loss - orthopaedic surgery

Five trials of aprotinin versus control involving orthopaedic surgery reported intra-operative blood loss data. These trials included a total of 201 patients, of whom 103 were randomised to aprotinin and 98 were randomised to a control group. The use of aprotinin in orthopaedic surgery did not reduce the volume of blood lost during the intra-operative period (MD -151.05 mls, 95% CI -317.63 to 15.52 mls). Heterogeneity between these trials was not statistically significant (Chi^2 = 6.62, df = 4, P = 0.16; I^2 = 40%).

Seven trials of aprotinin versus control involving orthopaedic surgery reported post-operative blood loss data. These trials included a total of 318 patients, of whom 160 were randomised to aprotinin and 158 were randomised to a control group. The use of aprotinin in orthopaedic surgery was only marginally effective in reducing post-operative blood loss (MD -113.58 mls, 95% CI -223.69 to -3.46 mls). Heterogeneity between these trials was statistically significant (Chi^2 = 18.56, df = 6, P = 0.005; I^2 = 68%).

Ten trials of aprotinin versus control involving orthopaedic surgery reported total blood loss data (intra-operative and post-operative blood loss combined). These trials included a total of 430 patients, of whom 216 were randomised to aprotinin and 214 were randomised to a control group. Aprotinin reduced the total volume of blood lost during the perioperative period on average by around 399 mls per patient (MD -399.09 mls, 95% CI -562.81 to -235.37 mls). Heterogeneity between these trials was statistically significant (Chi^2 = 22.67, df = 9, P = 0.007; I^2 = 60%).

Re-operation for bleeding

Sixty-one trials of aprotinin versus control reported data on re-operation for bleeding. These trials included a total of 6117 patients, of whom 3392 were randomised to aprotinin and 2725 were randomised to a control group who did not receive aprotinin. The use of aprotinin significantly reduced the need for re-operation for bleeding by a relative 54% (RR 0.46, 95% CI 0.34 to 0.62). Heterogeneity between these trials was not significant (Chi^2 = 35.44, df = 42, P = 0.75; I^2 = 0%). The Boldt 1994 trial had no events, and therefore provided no data to this analysis. When aprotinin was used in cardiac surgery, the RR of requiring re-operation due to bleeding was 0.46 (95% CI 0.34 to 0.63). Again heterogeneity between these trials was not significant (Chi^2 = 34.56, df = 39, P = 0.67; I^2 = 0%).

Mortality

Sixty-three trials of aprotinin versus control reported data on mortality. These trials included a total of 8876 patients, of whom 4889 were randomised to aprotinin and 3987 were randomised to a control group who did not receive aprotinin. The use of aprotinin was not associated with an increased risk of death (RR 0.81, 95% CI 0.63 to 1.06). Heterogeneity between these trials was not significant (Chi^2 = 29.54, df = 43, P = 0.94; I^2 = 0%). In the case of cardiac surgery, the use of aprotinin was not associated with an increased risk of death (RR 0.84, 95% CI 0.64 to 1.10).

Myocardial infarction

Forty-nine trials of aprotinin versus control reported data for myocardial infarction. These trials included a total of 7137 patients, of whom 4032 were randomised to aprotinin and 3105 were randomised to a control group who did not receive aprotinin. The use aprotinin did not increase the risk of myocardial infarction (RR 0.87, 95% CI 0.69 to 1.11). Heterogeneity between these trials was not statistically significant (Chi^2 = 27.71, df = 38, P = 0.89; I^2 = 0%). When aprotinin was used in cardiac surgery, the relative risk of myocardial infarction was not statistically significant (RR 0.90, 95% CI 0.71 to 1.14).

Stroke

Twenty-three trials of aprotinin versus control reported data for stroke. These trials included a total of 3122 patients, of whom 1862 were randomised to aprotinin and 1260 were randomised to a control group who did not receive aprotinin. The use aprotinin did not increase the risk of stroke (RR 0.82, 95% CI 0.44 to 1.52). Heterogeneity between these trials was not statistically significant (Chi^2 = 11.97, df = 19, P = 0.89; I^2 = 0%). The use of aprotinin in cardiac surgery was not associated with an increased risk of stroke (RR 0.81, 95% CI 0.40 to 1.67).

Deep vein thrombosis

Sixteen trials of aprotinin versus control reported data for deep vein thrombosis (DVT). These trials included a total of 1456 patients, of whom 854 were randomised to aprotinin and 602 were randomised to a control group who did not receive aprotinin. The use aprotinin did not increase the risk of deep vein thrombosis (RR 0.78, 95% CI 0.47 to 1.29). Heterogeneity between these trials was not statistically significant (Chi^2 = 6.22, df = 11, P = 0.86; I^2 = 0%). Three cardiac trials reported data for DVT. The use of aprotinin was not associated with a statistically significant increased risk of DVT (RR 1.29, 95% CI 0.36 to 4.58).

Pulmonary embolus

Four trials of aprotinin versus control reported data for pulmonary embolus (PE). These trials included a total of 585 patients, of whom 304 were randomised to aprotinin and 281 were randomised to a control group who did not receive aprotinin. The use of aprotinin did not statistically significantly increase the risk of PE (RR 1.49, 95% CI 0.42 to 5.29).

Renal failure / dysfunction

Twenty-seven trials of aprotinin versus control reported data for renal failure / dysfunction. These trials included a total of 5185 patients, of whom 2904 were randomised to aprotinin and 2281 were randomised to a control group who did not receive aprotinin. The use aprotinin did not statistically significantly increase the risk of renal failure / dysfunction (RR 1.10, 95% CI 0.79 to 1.54). Heterogeneity between these trials was not statistically significant (Chi^2 = 7.64, df = 16, P = 0.96; I^2 = 0%). Although there appeared to be a trend toward an increased risk of renal failure/dysfunction when aprotinin was used in cardiac surgery, the result was not statistically significant (RR 1.07, 95% CI 0.76 to 1.51).

Length of hospital stay

Twenty-three trials of aprotinin versus control reported data for hospital length of stay. These trials included a total of 2017 patients, of whom 1011 were randomised to aprotinin and 1006 were randomised to a control group who did not receive aprotinin. Aprotinin treatment did not reduce the length of hospital stay (MD -0.25 days, 95% CI -0.71 to 0.20 days). Heterogeneity between these trials was statistically significant (Chi^2 = 50.13, df = 22, P = 0.0006; I^2 = 56%).

Tranexamic acid

Sixty-five trials compared TXA with control, and reported data on the number of patients exposed to allogeneic blood transfusion. These trials included a total of 4842 patients, of whom 2528 were randomised to TXA and 2314 were randomised to a control group who did not receive TXA. The use of TXA significantly reduced the need for allogeneic blood transfusion by a relative 39% (RR 0.61, 95% CI 0.53 to 0.70). Heterogeneity between these trials was statistically significant (Chi^2 = 249.33, df = 63, P <0.0001; I^2 = 75%). This represents an absolute risk reduction of 18% (RD -0.18, 95% CI -0.22 to -0.14).

Type of surgery

Thirty-four trials of TXA versus control involved cardiac surgery. These trials included a total of 3006 patients, of whom 1578 were randomised to TXA, and 1428 were randomised to a control group who did not receive TXA. There was a significant 32% relative reduction in the rate of exposure to allogeneic blood transfusion in those patients treated with TXA (RR 0.68, 95% CI 0.57 to 0.81). Heterogeneity between these trials was statistically significant (Chi^2 = 137.35, df = 33, P <0.00001; I^2 = 76%).

Twenty-seven trials of TXA versus control involved orthopaedic surgery. These trials included a total of 1381 patients of whom of whom 722 were randomised to TXA and 659 were randomised to a control group who did not receive TXA. Again there was a significant RR reduction of 51% in those participants treated with TXA (RR 0.49, 95% CI 0.39 to 0.62). Heterogeneity between these trials was statistically significant (Chi^2 = 53.86, df = 25, P = 0.0007; I^2 = 54%).

Two trials of TXA versus control involved liver surgery. These trials included a total of 296 patients of whom 148 were randomised to TXA and 148 were randomised to a control group who did not receive TXA. In liver surgery treatment with TXA did not reduce the risk of receiving an allogeneic blood transfusion (RR 0.16, 95% CI 0.00 to 32.47). Heterogeneity between these trials was statistically significant (Chi^2 = 14.23, df = 1, P = 0.0002; I^2 = 93%).

One trial of TXA versus control involved vascular surgery. This trial included 59 patients of whom 30 were randomised to TXA and 29 were randomised to a control group who did not receive TXA. In vascular surgery treatment with TXA reduced the risk of receiving an allogeneic blood transfusion (RR 0.56, 95% CI 0.33 to 0.96).

One trial of TXA versus control involved gynaecological surgery. This trial included 100 patients of whom 50 were randomised to

TXA and 50 were randomised to a control group who did not receive TXA. In gynaecological surgery treatment with TXA did not reduce the risk of receiving an allogeneic blood transfusion (RR 1.50, 95% CI 0.75 to 3.01).

Effect of transfusion protocols

Fifty-six trials of TXA versus control reported the use of transfusion protocols and provided data on the number of patients exposed to allogeneic blood transfusion. These trials included a total of 4125 patients, of whom 2156 were randomised to TXA and 1969 were randomised to a control group who did not receive TXA. The use of TXA reduced the need for allogeneic blood transfusion by a relative 43% (RR 0.57, 95% CI 0.48 to 0.67). Heterogeneity between these trials was statistically significant (Chi² = 248.97, df = 55, P <0.00001; I² = 78%). There were nine trials that did not report the use of transfusion protocols. These trials included a total of 717 patients of whom 372 were randomised to TXA and 345 were randomised to a control group. The use of TXA reduced the need for allogeneic blood transfusion compared to control (RR 0.76, 95% CI 0.61 to 0.96). Heterogeneity between these trials was statistically significant (Chi² = 15.48, df = 7, P = 0.03; I² = 55%).

Although the baseline rate of transfusion remained relatively constant across both subgroups (transfusion protocol 44% versus no transfusion protocol 45%) transfusion rates in the intervention arms was collectively greater in those trials that did not report the use of a transfusion protocol compared to those trials that did use a transfusion protocol to guide transfusion practice (37% versus 26%, respectively).

Volume of blood transfused

Twenty-three trials of TXA versus control reported data on the volume of blood transfused in all patients. These trials included a total of 1814 patients, of whom 943 were randomised to TXA and 871 were randomised to a control group. The use of TXA resulted in a saving of 0.87 units of allogeneic blood per patient (MD -0.87 units, 95% CI -1.20 to -0.53 units). Heterogeneity between these trials was statistically significant (Chi² = 154.24, df = 20, P <0.00001; I² = 87%).

Thirteen trials of TXA versus control provided data on the volume of blood transfused in those patients transfused. All 481 patients received allogeneic blood transfusion. The use of TXA did not statistically significantly reduce the volume of blood transfused compared to control (MD -0.34 units, 95% CI -0.80 to 0.11 units). Heterogeneity between these trials was statistically significant (Chi² = 45.89, df = 12, P < 0.0001; I² = 74%).

Blood loss - all surgery combined

A total of 17 trials of TXA versus control reported intra-operative blood loss data. These trials included a total of 1173 patients, of whom 599 were randomised to TXA and 574 were randomised to a control group. These trials involved cardiac surgery (n = 4), orthopaedic surgery (n = 12) and gynaecological surgery (n = 1). In aggregate, TXA treatment reduced intra-operative blood loss (MD -121.41 mls, 95% CI -180.19 to -62.63 mls). Heterogeneity between these trials was statistically significant (Chi² = 49.05, df = 16, P <0.0001; I² = 67%).

A total of 35 trials of TXA versus control reported post-operative blood loss data. These trials included a total of 2501 patients, of whom 1285 were randomised to TXA and 1216 were randomised to a control group. These trials involved cardiac surgery (n = 22) orthopaedic surgery (n = 12) and gynaecological surgery (n = 1). In aggregate, TXA treatment significantly reduced post-operative blood loss on average by around 247 mls per patient (MD -247.17 mls, 95% CI -294.76 to -199.58 mls). Heterogeneity between these trials was statistically significant (Chi² = 248.36, df = 34, P <0.00001; I² = 86%).

A total of 28 trials of TXA versus control reported total blood loss data (intra-operative and post-operative blood loss combined). These trials included a total of 1712 patients, of whom 875 patients were randomised to TXA and 837 were randomised to a control group. These trials involved cardiac surgery (n = 6), orthopaedic surgery (n = 20), gynaecological surgery (n = 1) and liver surgery (n = 1). In aggregate, the use of TXA significantly reduced perioperative blood loss by around 414 mls per patient (MD -414.06 mls, 95% CI -525.19 to -302.92 mls). Heterogeneity between these trials was statistically significant (Chi² = 249.58, df = 27, P <0.00001; I² = 89%).

Blood loss - cardiac surgery

Four trials of TXA versus control involving cardiac surgery reported intra-operative blood loss data. These trials included a total of 244 patients, of whom 138 were randomised to TXA and 106 randomised to a control group. The use of TXA in cardiac surgery reduced intra-operative blood loss on average by around 167 mls per patient (MD -166.76 mls, 95% CI -331.24 to -2.27 mls). There is some evidence of statistical heterogeneity between these trials (Chi² = 5.36, df = 3, P = 0.15; I² = 44%).

Twenty-two trials of TXA versus control involving cardiac surgery reported post-operative blood loss data. These trials included a total of 1597 patients, of whom 827 were randomised to TXA and 770 were randomised to a control group. On average, TXA treatment reduced post-operative blood loss by around 273 mls per patient compared to control (MD -272.87 mls, 95% CI -328.85 to -216.89 mls). Heterogeneity between these trials was statistically significant (Chi² = 83.41, df = 21, P <0.00001; I² = 75%).

Six trials of TXA versus control involving cardiac surgery reported total blood loss data (intra-operative and post-operative blood loss combined). These trials included a total of 391 patients, of whom 210 were randomised to TXA and 181 were randomised to a control group. TXA treatment reduced the total amount of blood lost during the perioperative period by around 300 mls per patient (MD -300.47 mls, 95% CI -470.74 to -130.21 mls). Heterogeneity between these trials was statistically significant (Chi^2 = 12.19, df = 5, P = 0.03; I^2 = 59%).

Blood loss - orthopaedic surgery

Twelve trials of TXA versus control involving orthopaedic surgery reported intra-operative blood loss data. These trials included a total of 829 patients, of whom 411 were randomised to TXA and 418 were randomised to a control group. The use of TXA in orthopaedic surgery reduced intra-operative blood loss by around 116 mls per patient (MD -115.52 mls, 95% CI -187.88 to -43.16 mls). Heterogeneity between these trials was statistically significant (Chi^2 = 42.52, df = 11, P <0.0001; I^2 = 74%).

Twelve trials of TXA versus control involving orthopaedic surgery reported post-operative blood loss data. These trials included a total of 804 patients, of whom 408 were randomised to TXA and 396 were randomised to a control group. On average, TXA treatment in orthopaedic surgery reduced post-operative blood loss by around 229 mls per patient (MD -228.52 mls, 95% CI -321.76 to -135.27 mls). Heterogeneity between these trials was statistically significant (Chi^2 = 125.01, df = 11, P <0.00001; I^2 = 91%).

Twenty trials of TXA versus control involving orthopaedic surgery reported total blood loss data (intra-operative and post-operative blood loss combined). These trials included a total of 1201 patients, of whom 605 were randomised to TXA and 596 were randomised to a control group. The use of TXA in orthopaedic surgery significantly reduced the total amount of blood lost during the perioperative period (MD -446.19 mls, 95% CI -554.61 to -337.78 mls). Heterogeneity between these trials was statistically significant (Chi^2 = 85.30, df = 19, P <0.00001; I^2 = 78%).

Re-operation for bleeding

Twenty-seven trials of TXA versus control reported data on re-operation for bleeding. These trials included a total of 2386 patients, of whom 1224 were randomised to TXA and 1162 were randomised to a control group. The use of TXA did not statistically significantly decrease the risk of re-operation for bleeding (RR 0.80, 95% CI 0.55 to 1.17). Heterogeneity between these trials was not statistically significant (Chi^2 = 12.66, df = 23, P = 0.96; I^2 = 0%). Of the 27 trials of TXA that reported data for this outcome 26 involved cardiac surgery. Therefore in the context of cardiac surgery the use of TXA did not statistically significantly reduce the risk of re-operation for bleeding (RR 0.79, 95% CI 0.54 to 1.17).

Mortality

Thirty trials of TXA versus control reported mortality data. These trials included a total of 2917 patients, of whom 1478 were randomised to TXA and 1439 were randomised to a control group. The use of TXA was not associated with an increased risk of death (RR 0.60, 95% CI 0.33 to 1.10). Heterogeneity between these trials was not statistically significant (Chi^2 = 10.00, df = 17, P = 0.90; I^2 = 0%). Of the 30 trials of TXA that reported data for mortality 23 involved cardiac surgery. The use of TXA in cardiac surgery was not associated with an increased risk of death (RR 0.58, 95% CI 0.26 to 1.28).

Myocardial infarction

Twenty-one trials of TXA versus control reported data for myocardial infarction. These trials included a total of 2186 patients, of whom 1117 were randomised to TXA and 1069 were randomised to a control group who did not receive TXA. The use of TXA was not associated with an increased risk of myocardial infarction (RR 0.79, 95% CI 0.41 to 1.52). Heterogeneity between these trials was not statistically significant (Chi^2 = 7.84, df = 12, P = 0.80; I^2 = 0%). Of the 21 trials of TXA that reported data for myocardial infarction 19 involved cardiac surgery. The use of TXA in cardiac surgery did not increase the risk of myocardial infarction (RR 0.74, 95% CI 0.37 to 1.47).

Stroke

Eighteen trials of TXA versus control reported data for stroke. These trials included a total of 2027 patients, of whom 1050 were randomised to TXA and 977 were randomised to a control group. The use of TXA was not associated with a statistically significant increase in the risk of stroke (RR 1.23, 95% CI 0.49 to 3.07). Heterogeneity between these trials was not statistically significant (Chi^2 = 3.18, df = 7, P = 0.87; I^2 = 0%). Of the 18 trials of TXA that reported data for this outcome 17 involved cardiac surgery. In this surgical setting the risk of stroke was not statistically significantly increased with the use of TXA (RR 1.44, 95% CI 0.53 to 3.91).

Deep vein thrombosis

Twenty-three trials of TXA versus control reported data for deep vein thrombosis. These trials included a total of 1472, of whom 746 were randomised to TXA and 726 were randomised to a control group. TXA treatment did not appear to be associated with an increase in the risk of developing a DVT (RR 0.71, 95% CI 0.35 to 1.43). Heterogeneity between these trials was not statistically significant (Chi^2 = 5.71, df = 11, P = 0.89; I^2 = 0%). Of the 23 trials of TXA that reported data for DVT four involved cardiac surgery. Of the 422 patients that underwent cardiac surgical procedures two patients developed a DVT. These were single events occurring in the control arms of two separate trials.

Pulmonary embolism

Fourteen trials of TXA versus control reported data for pulmonary embolism. These trials included a total of 1006 patients, of whom 527 were randomised to TXA and 479 were randomised to a control group who did not receive TXA. The use of TXA did not increase the risk of developing a pulmonary embolus (RR 0.67, 95% CI 0.23 to 1.99). Heterogeneity between these trials was not statistically significant ($Chi^2 = 2.81$, df = 7, P = 0.90; $I^2 = 0\%$). Of the 16 trials that reported data for pulmonary embolism six involved cardiac surgery. Of the 569 patients that underwent cardiac surgical procedures only two patients developed a pulmonary embolus. As was the case with deep vein thrombosis these were single events occurring in the control arms of two separate trials.

Renal failure / dysfunction

Nine trials of TXA versus control provided data for renal failure / dysfunction. These nine cardiac surgery trials included a total of 912 patients, of whom 454 were randomised to TXA and 458 were randomised to a control group. Treatment with TXA did not appear to increase the risk of developing renal failure or renal dysfunction (RR 0.89, 95% CI 0.33 to 2.37). Heterogeneity between these trials was not statistically significant ($Chi^2 = 2.52$, df = 6, P = 0.87; $I^2 = 0\%$).

Hospital length of stay

Ten trials of TXA versus control provided data for hospital length of stay. These trials included a total of 772 patients, of whom 379 were randomised to TXA and 393 were randomised to a control group. The use of TXA did not significantly impact on the length of hospital stay (MD -0.34 days, 95% CI -0.82 to 0.13 days). Heterogeneity between these trials was statistically significant ($Chi^2 = 18.42$, df = 9, P = 0.03; $I^2 = 51\%$). For the five trials that involved cardiac surgery the use of TXA did not significantly reduce the length of hospital stay (MD -0.08 days, 95% CI -0.34 to 0.18 days).

Epsilon aminocaproic acid

Sixteen trials of EACA versus control provided data on the number of patients exposed to allogeneic blood transfusion. These trials included a total of 1035 patients, of whom 530 were randomised to EACA and 505 were randomised to a control who did not receive EACA. The use of EACA significantly reduced the need for allogeneic blood transfusion by a relative 19% (RR 0.81, 95% CI 0.67 to 0.99). Heterogeneity between these trials was statistically significant ($Chi^2 = 41.12$, df = 15, P = 0.0003; $I^2 = 64\%$). This represents an absolute risk reduction of 10% (RD -0.10, 95% CI -0.18 to -0.03).

Type of surgery

Eleven trials of EACA versus control involved cardiac surgery. These trials included a total of 649 patients, of whom 338 were randomised to EACA and 311 were randomised to a control group. When used in cardiac surgery EACA reduced the need for allogeneic blood transfusion by a relative 30% (RR 0.70, 95% CI 0.52 to 0.93). There is some evidence of statistical heterogeneity between these trials ($Chi^2 = 16.38$, df = 10, P = 0.09; $I^2 = 39\%$). Four trials of EACA versus control involved orthopaedic surgery. These trials included a total of 304 patients, of whom 150 were randomised to EACA and 154 patients were randomised to a control group. The use of EACA in orthopaedic surgery did not reduce the need for allogeneic blood transfusion compared to control (RR 1.00, 95% CI 0.93 to 1.08). Heterogeneity between these trials was not statistically significant ($Chi^2 = 1.01$, df = 3, P = 0.80; $I^2 = 0\%$). One trial of EACA involved liver surgery. For this single trial the relative risk of requiring an allogeneic blood transfusion was 0.93 (95% CI 0.80 to 1.08).

Effect of transfusion protocols

Of the 16 trials of EACA versus control that provided data for the number of patients exposed to allogeneic blood transfusion, 15 reported the use of a transfusion protocol to guide transfusion practice. Therefore stratification of the data by the presence or absence of a transfusion protocol was uninformative.

Volume of blood transfused

Six trials of EACA versus control provided data for the volume of blood transfused in all patients. These trials included a total of 432 patients, of whom 215 were randomised to EACA and 217 were randomised to a control group who did not receive EACA. On average, the use of EACA reduced the volume of allogeneic blood transfused by 1.3 units per patient (MD -1.30 units, 95% CI -2.14 to -0.45 units). Heterogeneity between these trials was statistically significant ($Chi^2 = 23.45$, df = 5, P = 0.0003; $I^2 = 79\%$). Three trials of EACA versus control provided data for the volume of blood transfused in those patients transfused. When the volume of allogeneic blood transfused was assessed in only those patients that actually received a blood transfusion the use of EACA did not reduce the amount of blood transfused (MD 0.22 units, 95% CI -0.34 to 0.79 units). Heterogeneity between these trials was not statistically significant ($Chi^2 = 0.56$, df = 2, P = 0.76; $I^2 = 0\%$).

Blood loss - all surgery combined

Five trials of EACA versus control reported intra-operative blood loss data. These trials included a total of 353 patients, of whom 175 were randomised to EACA and 178 were randomised to a control group. These trials involved cardiac surgery (n = 2) and orthopaedic surgery (n = 3). In aggregate, EACA treatment reduced the amount of blood lost during the intra-operative period by around 157 mls per patient (MD -156.63 mls, 95% CI -276.92 to -36.33 mls). Heterogeneity between these trials was not statistically significant ($Chi^2 = 5.01$, df = 4, P = 0.29; $I^2 = 20\%$).

Fourteen trials of EACA versus control reported post-operative blood loss data. These trials included a total of 1174 patients, of whom 580 were randomised to EACA and 594 were randomised to a control group. These trials involved cardiac surgery (n = 12) and orthopaedic surgery (n = 2). In aggregate, EACA treatment reduced post-operative blood loss on average by 207 mls per patient (MD -207.49 mls, 95% CI -276.43 to -138.54 mls). Heterogeneity between these trials was statistically significant ($Chi^2 = 97.46$, df = 13, P < 0.00001; $I^2 = 87\%$).

Two trials of EACA versus control reported total blood loss data (intra-operative and post-operative blood loss combined). These orthopaedic trials included a total of 92 patients, of whom 44 were randomised to EACA and 48 were randomised to a control group. The use of EACA in orthopaedic surgery was only marginally effective in reducing blood loss during the perioperative period (MD -299.69 mls, 95% CI -522.54 to -76.84 mls). Heterogeneity between these trials was not statistically significant ($Chi^2 = 0.73$, df = 1, P = 0.39; $I^2 = 0\%$).

Blood loss - cardiac surgery

Two trials of EACA versus control involving cardiac surgery reported intra-operative blood loss data. These trials included a total of 79 patients, of whom 40 patients were randomised to EACA and 39 were randomised to a control group. On average, the use of EACA in cardiac surgery reduced the amount of blood lost during the intra-operative period by around 214 mls per patient (MD -213.58, 95% CI -310.03 to -117.13 mls). Heterogeneity between these trials was not statistically significant ($Chi^2 = 0.12$, df = 1, P = 0.73; $I^2 = 0\%$).

Twelve trials of EACA versus control involving cardiac surgery reported post-operative blood loss data. These trials included a total of 946 patients, of whom 467 were randomised to EACA and 479 were randomised to control group who did not receive EACA treatment. The use of EACA in cardiac surgery reduced the amount of blood lost during the post-operative period on average by around 200 mls per patient (MD -200.27 mls, 95% CI -273.44 to -127.09 mls). Heterogeneity between these trials was statistically significant ($Chi^2 = 97.18$, df = 11, P <0.00001, $I^2 = 89\%$).

Blood loss - orthopaedic surgery

Three trials of EACA versus control involving orthopaedic surgery provided intra-operative blood loss data. These trials included a total of 274 patients, of whom 135 were randomised to EACA and 139 were randomised to a control group. EACA treatment in orthopaedic surgery did not reduce the amount of blood lost during the intra-operative period (MD -40.66 mls, 95% CI -236.71 to 155.38 mls). Heterogeneity between these trials was not statistically significant ($Chi^2 = 2.10$, df = 2, P = 0.35; $I^2 = 5\%$).

Two trials of EACA versus control involving orthopaedic surgery reported post-operative blood loss. These trials included a total of 228 patients, of whom 113 were randomised to EACA and 115 were randomised to a control group. The use of EACA in orthopaedic surgery reduced blood loss during the post-operative period by around 285 mls per patient (MD -285.06 mls, 95% CI -452.73 to -117.39 mls). Heterogeneity between these trials was not statistically significant ($Chi^2 = 0.18$, df = 1, P = 0.67; $I^2 = 0\%$).

Two trials of EACA versus control involving orthopaedic surgery reported total blood loss data (intra-operative and post-operative blood loss combined). These trials included a total of 92 patients, of whom 44 were randomised to EACA and 48 were randomised to a control group. The use of EACA in orthopaedic surgery reduced blood loss during the perioperative period by around 300 mls per patient (MD -299.69 mls, 95% CI -522.54 to -76.84 mls). Heterogeneity between these trials was not statistically significant ($Chi^2 = 0.73$, df = 1, P = 0.39; $I^2 = 0\%$).

Re-operation for bleeding

Eight trials of EACA versus control reported data on the number of patients requiring re-operation for bleeding. These trials included a total of 922 patients, of whom 470 were randomised to EACA and 452 were randomised to a control group. The use of EACA was not associated with an increased risk of re-operation compared to control (RR 0.32, 95% CI 0.11 to 0.99). Heterogeneity between these trials was not statistically significant ($Chi^2 = 1.84$, df = 5, P = 0.87, $I^2 = 0\%$). Of the eight trials of EACA that reported data on re-operations, seven involved cardiac surgery. In this surgical setting the use of EACA did not increase the risk of re-operation (RR 0.35, 95% CI 0.11 to 1.17).

Mortality

Eight trials of EACA versus control reported data on mortality. These trials included a total of 988 patients, of whom 504 were randomised to EACA and 484 were randomised to a control group. The use of EACA was not associated with a statistically significant increased risk of death compared to control (RR 1.07, 95% CI 0.44 to 2.57). Heterogeneity between these trials was not statistically significant ($Chi^2 = 2.30$, df = 5, P = 0.81; $I^2 = 0\%$). Of the eight trials of EACA that reported data on mortality six involved cardiac surgery. In this surgical setting the use of EACA did not statistically significantly increase the risk of death (RR 1.65, 95% CI 0.50 to 5.43).

Myocardial infarction

Seven trials of EACA versus control reported data for myocardial infarction. These trials included a total of 896 patients, of whom 456 were randomised to EACA and 440 were randomised to a control group. The use of EACA was not associated with an increased risk of myocardial infarction compared to control (RR 0.88, 95% CI 0.48 to 1.63). Heterogeneity between these trials was not statistically significant (Chi² = 3.44, df = 4, P = 0.49; I² = 0%). Of the seven trials of EACA that reported data on myocardial infarction six involved cardiac surgery. In this surgical setting the use of EACA did not increase the risk of myocardial infarction (RR 0.88, 95% CI 0.48 to 1.63).

Stroke

Eight trials of EACA versus control reported data for stroke. These trials included a total of 936 patients, of whom 477 were randomised to EACA and 459 were randomised to a control group. The use of EACA was not associated with an increased risk of stroke compared to control (RR 0.62 95% CI 0.16 to 2.36). Heterogeneity between these trials was not statistically significant (Chi² = 1.84, df = 4, P = 0.77; I² = 0%). Of the eight trials of EACA that reported data on stroke, seven involved cardiac surgery. In this surgical setting the use of EACA did not increase the risk of stroke (RR 0.70, 95% CI 0.16 to 3.10).

Deep vein thrombosis

Four trials of EACA versus control reported data for DVT. These trials included a total of 304 patients, of whom 150 were randomised to EACA and 154 were randomised to a control group. The use of EACA was not associated with an increased risk of DVT compared to control (RR 0.78, 95% CI 0.20 to 3.03). Heterogeneity between these trials was not statistically significant (Chi² = 1.02, df = 1, P = 0.31; I² = 2%).

Pulmonary embolism

Three trials of EACA versus control provided data for pulmonary embolism. These trials included a total of 274 patients, of whom 135 were randomised to EACA and 139 were randomised to a control group. The use of EACA was not associated with an increased risk of pulmonary embolism compared to control (RR 0.34, 95% CI 0.06 to 2.13). Heterogeneity between these trials was not statistically significant (Chi² = 0.00, df = 1, P = 0.97; I² = 0%).

Renal failure / dysfunction

Two trials of EACA versus control reported data for renal failure / dysfunction. These trials included a total of 235 patients, of whom 117 were randomised to EACA and 118 were randomised to a control group. The use of EACA was not associated with an increased risk of renal failure / dysfunction (RR 0.41, 95% CI 0.14 to 1.22). Heterogeneity between these trials was not statistically significant (Chi² = 0.48, df = 1, P = 0.49; I² = 0%).

Hospital length of stay

Two trials of EACA versus control reported data for hospital length of stay. These trial included a total of 228 patients, of whom 113 were randomised to EACA and 115 were randomised to a control group. The use of EACA did not impact of the length of hospital stay (MD 0.58 days, 95% CI -3.17 to 4.33 days). Heterogeneity between these trials was statistically significant (Chi² = 3.13, df = 1, P = 0.08; I² = 68%).

Aprotinin versus tranexamic acid

Twenty-one trials of aprotinin versus TXA reported data on the number of patients exposed to allogeneic blood transfusion. These trials included a total of 4185 patients, of whom 2124 were randomised to aprotinin and 2061 were randomised to TXA. There was no statistically significant difference in the rates of allogeneic blood transfusion between those patients treated with aprotinin compared to those treated with TXA (RR 0.90, 95% CI 0.81 to 1.01). Heterogeneity between these trials was statistically significant (Chi² = 60.78, df = 20, P <0.0001; I² = 67%). The effect with Mengistu 2008 excluded was RR 0.92 (95% CI 0.82 to 1.02).

Type of surgery

Eighteen of the 21 trials of aprotinin versus TXA that reported data on the number patients exposed to allogeneic blood transfusion involved cardiac surgery. These trials included a total of 3983 patients, of whom 2025 were randomised to aprotinin and 1958 were randomised to TXA. Compared to TXA, aprotinin reduced the rate of allogeneic blood transfusion (RR 0.87, 95% CI 0.76 to 0.99). Heterogeneity between these trials was statistically significant (Chi² = 45.01, df = 17, P = 0.0002; I² = 62%). When data from Mengistu 2008 were excluded, RR was 0.88 (95% CI 0.78 to 1.01).

Effect of transfusion protocols

Of the 21 trials of aprotinin versus TXA that reported data on the number patients exposed to allogeneic blood transfusion, all but one reported the use of a transfusion protocol to guide transfusion practice. Therefore stratification of the data by the presence or absence of a transfusion protocol proved uninformative.

Volume of blood transfused

Ten trials of aprotinin versus TXA provided data on the volume of allogeneic blood transfused in all patients. These trials included a total of 992 patients, of whom 496 were randomised to aprotinin and 496 were randomised to TXA. There was a small but statistically significant difference between aprotinin and TXA in the volume of allogeneic blood transfused (MD -0.24 units, 95% CI -0.45 to -0.04 units). Heterogeneity between these trials was not statistically significant (Chi^2 = 10.87, df = 9; P = 0.28; I^2 = 17%). (When data from Mengistu 2008 were removed, MD was -0.21 units, 95% CI -0.39 to -0.02 units). Six trials of aprotinin versus TXA provided data on the volume of allogeneic blood transfused in those patients transfused. These trials provided data for 207 transfused patients, of whom 97 were treated with aprotinin and 110 were treated with TXA. There was no statistically significant difference between aprotinin and TXA in the volume of allogeneic blood transfused in those patients transfused (MD -0.07 units, 95% CI -0.44 to 0.30 units). Heterogeneity between these trials was not statistically significant (Chi^2 = 0.97, df = 5, P = 0.97; I^2 = 0%).

Blood loss

Thirteen trials of aprotinin versus TXA involving cardiac surgery provided data for post-operative blood loss. These trials included a total of 831 patients, of whom 412 were randomised to aprotinin and 419 were randomised to TXA. On average, aprotinin appeared to be more effective in reducing post-operative blood loss than TXA (MD -145.81 mls, 95% CI -209.99 to -81.62 mls). Heterogeneity between these trials was statistically significant (Chi^2 = 33.86, df = 12, P = 0.0007; I^2 = 65%). (When data from Mengistu 2008 were removed, MD was -131.54 mls, 95% CI -192.15 to -70.94 mls.)

Re-operation for bleeding

Seventeen trials of aprotinin versus TXA provided data on the number of patients requiring re-operation for bleeding. These trials included a total of 4010 patients, of whom 2005 were randomised to aprotinin and 2005 were randomised to TXA. Aprotinin appeared to reduce the need for re-operation compared to TXA (RR 0.69, 95% CI 0.51 to 0.93). Heterogeneity between these trials was not statistically significant (Chi^2 = 8.90, df = 13, P = 0.78; I^2 = 0%). The BART study (Fergusson 2008) provided 61.4% (weight) of the information for this outcome.

Mortality

Seventeen trials of aprotinin versus TXA reported mortality data. These trials included a total of 4130 patients, of whom 2060 were randomised to aprotinin and 2070 were randomised to TXA. There was no statistically significant difference between aprotinin and TXA (RR 1.35, 95% CI 0.94 to 1.93). Heterogeneity between these trials was not statistically significant (Chi^2 = 6.78, df = 9, P = 0.66, I^2 = 0%). BART study data (Fergusson 2008) dominated the analysis of this outcome (65.5% weight).

Myocardial infarction

Thirteen trials of aprotinin versus TXA reported data for myocardial infarction. These trials included a total of 3574 patients, of whom 1778 were randomised to aprotinin and 1796 were randomised to TXA. There was statistically significant difference between aprotinin and TXA (RR 1.00, 95% CI 0.71 to 1.42). Heterogeneity between these trials was not statistically significant (Chi^2 = 6.18, df = 10, P = 0.80; I^2 = 0%). The BART study (Fergusson 2008) provided 49.6% (weight) of the information for this outcome.

Stroke

Six trials of aprotinin versus TXA reported data for stroke. These trials include a total of 2030 patients of whom 1017 were randomised to aprotinin and 1013 were randomised to TXA. There was no statistically significant difference between aprotinin and TXA (RR 0.88, 95% CI 0.52 to 1.47). Heterogeneity between these trials was not statistically significant (Chi^2 = 1.91, df = 4, P = 0.75; I^2 = 0%). BART study data (Fergusson 2008) dominated the analysis of this outcome (88.5% weight).

Renal failure / dysfunction

Six trials of aprotinin versus TXA reported data for renal failure / dysfunction. These trials included a total of 2238 patients, of whom 1119 were randomised to aprotinin and 1119 were randomised to TXA. There was no statistically significant difference between aprotinin and TXA (RR 1.02, 95% CI 0.79 to 1.31). Heterogeneity between these trials was not statistically significant (Chi^2 = 1.20, df = 3, P = 0.75; I^2 = 0%). BART study data (Fergusson 2008) dominated the analysis of this outcome (94.5% weight).

Hospital length of stay

Six trials of aprotinin versus TXA reported data for hospital length of stay. These trials include a total of 2174 patients, of whom 1090 were randomised to aprotinin and 1084 were randomised to TXA. There was no statistically significant difference between aprotinin and TXA (MD -0.05, 95% CI -0.92 to 0.83 days). There was some evidence of statistical heterogeneity between these trials (Chi^2 = 9.14, df = 5, P = 0.10; I^2 = 45%).

Aprotinin versus epsilon aminocaproic acid

Twelve trials of aprotinin versus EACA reported data on the number of patients exposed to allogeneic blood transfusion. These trials included a total of 2200 patients, of whom 1102 were randomised to aprotinin and 1098 were randomised to EACA. The use of aprotinin significantly reduced the rate of allogeneic blood transfusion compared to EACA (RR 0.82, 95% CI 0.76 to 0.89).

Heterogeneity between these trials was not statistically significant ($Chi^2 = 9.33$, df = 11, P = 0.59; $I^2 = 0\%$).

Type of surgery

Of the 12 trials of aprotinin versus EACA that reported data on the number of patients exposed to allogeneic blood transfusion, 10 involved cardiac surgery and two involved orthopaedic surgery. Compared to EACA, aprotinin reduced the rate of allogenic blood transfusion in cardiac surgery (RR 0.82, 95% CI 0.76 to 0.89) but not in orthopaedic surgery (RR 0.82, 95% CI 0.48 to 1.40).

Effect of transfusion protocols

Of the 12 trials of aprotinin versus EACA that reported data on the number of patients exposed to allogeneic blood transfusion, nine reported the use of a transfusion protocol to guide transfusion practice and three did not. For the nine trials that reported the use of a transfusion protocol, aprotinin reduced the rate of allogeneic blood transfusions compared to EACA by a relative 18% (RR 0.82, 95% CI 0.76 to 0.89). Heterogeneity between these trials was not statistically significant ($Chi^2 = 6.45$, df = 8, P = 0.60; $I^2 = 0\%$). For those trials that did not report the use of a transfusion protocol there was no statistically significant difference aprotinin and EACA (RR 0.78, 95% CI 0.47 to 1.31). Heterogeneity between these trials was not statistically significant ($Chi^2 = 2.86$, df = 2, P = 0.24; $I^2 = 30\%$).

Volume of blood transfused

Five trials of aprotinin versus EACA reported data for the volume of allogeneic blood transfused in all patients. These trials included a total of 329 patients, of whom 166 were randomised to aprotinin and 163 were randomised to EACA. There was no statistically significant difference between aprotinin and EACA (MD -0.21 units, 95% CI -0.55 to 0.14 units). Heterogeneity between these trials was not statistically significant ($Chi^2 = 5.14$, df = 4, P = 0.27; $I^2 = 22\%$). Two trials of aprotinin versus EACA provided data for the volume of allogeneic blood transfused in those patients transfused. These trials included a total of 63 transfused patients, of whom 28 were treated with aprotinin and 35 were treated with EACA. There was no statistically significant difference between aprotinin and EACA treatment (MD -0.18 units, 95% CI -0.63 to 0.28 units). Heterogeneity between these trials was not statistically significant ($Chi^2 = 0.66$, df = 1, P = 0.41; $I^2 = 0\%$).

Blood loss

There were seven trials of aprotinin versus EACA involving cardiac surgery that reported post-operative blood loss data. These trials included a total of 454 patients, of whom 230 were randomised to aprotinin and 224 were randomised to EACA. Aprotinin appeared to be marginally more effective in reducing post-operative blood loss than EACA (MD -111.43 mls, 95% CI -220.64 to -2.21 mls). Heterogeneity between these trials was statistically significant ($Chi^2 = 25.74$, df = 6, P = 0.0002; $I^2 = 77\%$).

Re-operation for bleeding

Six trials of aprotinin versus EACA reported data on the number of patients requiring re-operation for bleeding. These trials included a total of 2075 patients, of whom 1034 were randomised to aprotinin and 1041 were randomised to EACA. Although aprotinin appeared to be more effective than EACA in reducing the number patients requiring re-operation due to bleeding the difference did not reach statistical significance (RR 0.70, 95% CI 0.49 to 1.00). Heterogeneity between these trials was not statistically significant ($Chi^2 = 0.93$, df = 2, P = 0.63; $I^2 = 0\%$). However, the data from the BART study (Fergusson 2008) provided 90.1% of the information (weight) for this outcome. The results of this one trial showed that aprotinin was statistically significantly more effective than EACA in reducing the risk of re-operation for bleeding (RR 0.67, 95% CI 0.46 to 0.98).

Mortality

There were five trials of aprotinin versus EACA that reported mortality data. These trials included a total of 1891 patients, of whom 949 were randomised to aprotinin and 942 were randomised to EACA. Although the result failed to reach statistical significance, there appeared to be a trend toward an increased risk of death in the aprotinin group compared to EACA (RR 1.51, 95% CI 0.99 to 2.30). Again, the results of the BART study (Fergusson 2008) provided most of the information for this outcome (89.9% weight). Heterogeneity between these trials was not statistically significant ($Chi^2 = 0.26$, df = 3, P = 0.97; $I^2 = 0\%$).

Myocardial infarction

Four trials of aprotinin versus EACA reported data for myocardial infarction. These trials included a total of 1676 patients, of whom 830 were randomised to aprotinin and 846 were randomised to EACA. There was no statistically significant difference in the risk of myocardial infarction between aprotinin and EACA (RR 1.42, 95% CI 0.90 to 2.22). Heterogeneity between these trials was not statistically significant ($Chi^2 = 1.27$, df = 3, P = 0.74; $I^2 = 0\%$). Data from the BART study (Fergusson 2008) dominated this outcome (68.2% weight).

Stroke

Two trials of aprotinin versus EACA reported data for stroke (cerebrovascular accident). These trials included a total of 1578 patients, of whom 785 were randomised to aprotinin and 793 were randomised to EACA. There was no difference in the risk of stroke between aprotinin and EACA (RR 1.05, 95% CI 0.60 to 1.85).

Heterogeneity between these trials was not statistically significant (Chi^2 = 0.27, df = 1, P = 0.60; I^2 = 0%). The BART study (Fergusson 2008) results provided 94.2% of the information for this outcome.

Deep vein thrombosis

Four trials of aprotinin versus EACA reported data for deep vein thrombosis. These trials included a total of 300 patients, of whom 153 were randomised to aprotinin and 147 were randomised to EACA. One trial reported three cases of DVT all of which occurred in EACA treated patients (RR 0.14, 95% CI 0.01 to 2.51). There were no reported cases of DVT in the three remaining trials.

Pulmonary embolism

Three trials of aprotinin versus EACA reported data for pulmonary embolism. These trials included a total of 270 patients, of whom 138 were randomised to aprotinin and 132 were randomised to EACA. Three events of pulmonary embolism were reported; two in aprotinin treated patients and one in EACA treated patients. There was no statistically significant difference between aprotinin and EACA treatment (RR 1.33, 95% CI 0.10 to 18.42). Heterogeneity between these trials was not statistically significant (Chi^2 = 1.45, df = 1, P = 0.23; I^2 = 31%).

Renal failure / dysfunction

Two trials of aprotinin versus EACA reported data for renal failure / dysfunction. These trials included a total of 1595 patients, of whom796 were randomised to aprotinin and 799 were randomised to EACA. Although the analysis was dominated by the data from the BART study (71.6% weight) there was no statistically significant difference between aprotinin and EACA in the number patients experiencing renal failure / dysfunction (RR 1.33, 95% CI 0.59 to 2.99). Heterogeneity between these trials was moderate (Chi^2 = 2.12, df = 1, P = 0.15; I^2 = 53%).

Hospital length of stay

Two trials of aprotinin versus EACA reported data for hospital length of stay. These trials included a total of 1605 patients, of whom 803 were randomised to aprotinin and 802 patients were randomised to EACA. There was no statistically significant difference between aprotinin and EACA (MD -0.49 days, 95% CI -1.74 to 0.77 days).

Tranexamic acid versus epsilon aminocaproic acid

Eight trials provided direct 'head-to-head' comparisons of TXA and EACA and reported data on the number of patients exposed to allogeneic blood transfusion. These trials included a total of 2003 patients, of whom 1000 were randomised to TXA and 1003 were randomised to EACA. There was no statistically significant difference between TXA and EACA in the rates of allogeneic blood transfusion (RR 0.97, 95% CI 0.77 to 1.21). Heterogeneity between these trials was statistically significant (Chi^2 = 14.01, df = 7, P = 0.05; I^2 = 50%). All eight trials included in this analysis reported the use of a transfusion protocol to guide transfusion practice. Six of the eight trials included in this analysis involved cardiac surgery. A subgroup analysis of the data from these cardiac trials showed that the relative risk of receiving an allogeneic blood transfusion in patients treated with TXA compared to patients treated with EACA was 1.07 (95% CI 0.79 to 1.46).

Volume of blood transfused

Three trials of TXA versus EACA provided data for the volume of allogeneic blood transfused in all patients. These trials included a total of 268 patients, of whom 136 were randomised to TXA and 132 were randomised to EACA. There was no statistically significant difference between TXA and EACA (MD -0.28 units, 95% CI -0.59 to 0.03 units). Heterogeneity between these trials was not statistically significant (Chi^2 = 0.96, df = 2, P = 0.62; I^2 = 0%). Four trials of TXA versus EACA provided data for the volume of allogeneic blood transfused to those patients transfused. These trials included a total of 133 patients, of whom 59 were randomised to TXA and 74 were randomised to EACA. Again there was no statistically significant difference between TXA and EACA treatment (MD -0.34 units, 95% CI -0.74 to 0.07 units). Heterogeneity between these trials was not statistically significant (Chi^2 = 0.12, df = 2, P = 0.94; I^2 = 0%).

Blood loss

Six trials of TXA versus EACA involving cardiac surgery reported post-operative blood loss data. These trials included a total of 402 patients, of whom 209 were randomised to TXA and 193 were randomised to EACA. There was no difference between TXA and EACA in the volume of blood lost during the post-operative period (MD -4.36 mls, 95% CI -163.35 to 154.63 mls). Heterogeneity between these trials was statistically significant (Chi^2 = 33.81, df = 5, P <0.00001; I^2 = 85%).

Re-operation for bleeding

Five trials of TXA versus EACA provided data on re-operation for bleeding. These trials included a total of 1853 patients, of whom 922 were randomised to TXA and 931 were randomised to EACA. There was no statistically significant difference between TXA and EACA (RR 1.00, 95% CI 0.73 to 1.39). Heterogeneity between these trials was not statistically significant (Chi^2 = 1.81, df = 3, P = 0.61; I^2 = 0%). The data of the BART study (Fergusson 2008) dominated the results of this analysis (93.4% weight).

Mortality

Five trials of TXA versus EACA provided mortality data. These trials included a total of 1958 patients, of whom 980 were randomised to TXA and 978 were randomised to EACA. There was no statistically significant difference between TXA and EACA (RR 0.93, 95% CI 0.59 to 1.47). Heterogeneity between these trials was not statistically significant ($Chi^2 = 1.43$, df = 3, P = 0.70; $I^2 = 0\%$).The data of the BART study (Fergusson 2008) dominated the results of this analysis (86.8% weight).

Myocardial infarction

Three trials of TXA versus EACA reported data for myocardial infarction. These trials included a total of 1687 patients, of whom 840 were randomised to TXA and 847 were randomised to EACA. There was no statistically significant difference between TXA and EACA (RR 1.33, 95% CI 0.80 to 2.23). Heterogeneity between these trials was not statistically significant ($Chi^2 = 0.62$, df = 2, P = 0.73; $I^2 = 0\%$). The data of the BART study (Fergusson 2008) dominated the results of this analysis (82.9% weight).

Stroke

Three trials of TXA versus EACA reported data for stroke (cerebrovascular accident). These trials included a total of 1658 patients, of whom 820 were randomised to TXA and 838 were randomised to EACA. There was no statistically significant difference between TXA and EACA (RR 1.33, 95% CI 0.78 to 2.29). Heterogeneity between these trials was not statistically significant ($Chi^2 = 0.30$, df = 1, P = 0.58; $I^2 = 0\%$). The data of the BART study (Fergusson 2008) provided 97.1% (weight) of the information for this analysis.

Pulmonary embolism

Three trials of TXA versus EACA reported data for pulmonary embolism. These trials included a total of 284 patients, of whom 150 were randomised to TXA and 134 were randomised to EACA. There was only one reported case of pulmonary embolism, this occurred in EACA treated patients.

Renal failure / dysfunction

Only the BART study (Fergusson 2008) provided data on renal failure / dysfunction in patients treated with either TXA or EACA. The results of the BART study showed that there was no statistically significant difference between TXA and EACA in the rates of patients experiencing renal failure / dysfunction (RR 0.98, 95% CI 0.76 to 1.27).

Hospital length of stay

Only the BART study (Fergusson 2008) hospital length of stay data in patients treated with either TXA or EACA. The results of the BART study showed that there was no statistically significant difference between TXA and EACA in the length of hospital stay (MD -0.64 days, 95% CI -1.82 to 0.54 days).

Aprotinin versus either lysine analogue

Thirty trials of aprotinin versus either TXA or EACA provided data on the number of patients exposed to allogeneic blood transfusion. These trials included a total of 5566 patients, of whom 2407 were randomised to aprotinin and 3159 were randomised to a lysine analogue. The use of aprotinin reduced the need for allogeneic blood transfusion by a relative 10% (RR 0.90, 95% CI 0.81 to 0.99). Heterogeneity between these trials was statistically significant ($Chi^2 = 70.06$, df = 29 ($P < 0.0001$; $I^2 = 59\%$). (When data from Mengistu 2008 were removed, RR was 0.91 (95% CI 0.82 to 1.00).)

In view of the importance of the data on death and myocardial infarction we compared aprotinin with either tranexamic acid or aminocaproic acid. There were nineteen trials that reported on mortality. Of 2115 subjects randomised to aprotinin 71 died, compared with 85 of 3012 randomised to either lysine analogue. The increase in mortality with aprotinin was statistically significant (RR 1.39, 95% CI 1.02 to 1.89). Seventy percent of the statistical weight came from the Bart trial (Fergusson 2008). In contrast, there was no significant increase in the risk of myocardial infarction with aprotinin compared with either lysine analogue (RR 1.11, 95% CI 0.82 to 1.50).

Impact of trial quality

Aprotinin

Of the 108 trials of aprotinin that provided data on the number of patients exposed to allogeneic blood transfusion, 33 trials were assessed as having adequate allocation concealment of treatment schedule. For these 33 trials the use of aprotinin reduced the rate of allogeneic blood transfusion by a relative 36% (RR 0.64, 95% CI 0.53 to 0.79). Heterogeneity between these trials was statistically significant ($Chi^2 = 665.70$, df = 32, $P < 0.00001$; $I^2 = 95\%$). In the 63 trials where there was uncertainty regarding the method of allocation concealment (Unclear), the use of aprotinin reduced the rate of allogeneic blood transfusion by a relative 31% (RR 0.69, 95% CI 0.64 to 0.75). Heterogeneity between these trials was statistically significant ($Chi^2 = 179.31$, df = 62, $P < 0.00001$; $I^2 = 65\%$). In the remaining 12 trials where the method of allocation concealment was assessed as being inadequate (No), the use of aprotinin reduced the rate of allogeneic blood transfusion by a relative 37% (RR 0.63, 95% CI 0.54 to 0.75). Heterogeneity between these trials was not statistically significant ($Chi^2 = 15.50$, df

= 11, P = 0.16; I^2 = 29%). These data indicate the effects of aprotinin were not significantly greater in those studies that reported inferior techniques for concealing the randomisation sequence.

Tranexamic acid

Of the 65 trials of TXA that provided data on the number of patients exposed to allogeneic blood transfusion, 28 were assessed as having adequate allocation concealment of treatment schedule. For these 28 trials the use of TXA reduced the rate of allogeneic blood transfusion by a relative 41% (RR 0.59, 95% CI 0.51 to 0.69). Heterogeneity between these trials was statistically significant (Chi^2 = 41.35, df = 27, P = 0.04; I^2 = 35%). In the 24 trials where there was uncertainty regarding the method of allocation concealment (Unclear), the use of TXA reduced the rate of allogeneic blood transfusion by a relative 47% (RR 0.53, 95% CI 0.37 to 0.76). Heterogeneity between these trials was statistically significant (Chi^2 = 209.62, df = 23, P <0.00001; I^2 = 89%). In the remaining 13 trials where the method of allocation concealment was assessed as being inadequate (No), the use of TXA reduced the rate of allogeneic blood transfusion by a relative 27% (RR 0.73, 95% CI 0.62 to 0.86). Heterogeneity between these trials was not statistically significant (Chi^2 = 16.38, df = 11 (P = 0.13), I^2 = 33%).

Epsilon aminocaproic acid

Of the 16 trials that provided data on the number of patients exposed to allogeneic blood transfusion, five were assessed as having adequate allocation concealment of treatment schedule. For these trials the use of EACA did not statistically significantly reduce the rate of allogeneic blood transfusion (RR 0.82, 95% CI 0.58 to 1.16). Heterogeneity between trials was statistically significant (Chi^2 = 14.35, df = 4, P = 0.006; I^2 = 72%). In the nine trials where there was uncertainty regarding the method of allocation concealment (Unclear), the use of EACA did not statistically significantly reduce the rate of allogeneic blood transfusion (RR 0.68, 95% CI 0.46 to 1.03). Heterogeneity between trials was not statistically significant (Chi^2 = 12.54, df = 8, P = 0.13; I^2 = 36%). In the remaining two trials where the method of allocation concealment was assessed as being inadequate (No), the use of EACA did not statistically significantly reduce the rate of allogeneic blood transfusion (RR 0.93, 95% CI 0.81 to 1.08). Heterogeneity between these trials was not statistically significant (Chi^2 = 0.13, df = 1, P = 0.72; I^2 = 0%).

Aprotinin versus tranexamic acid

Of the 21 trials that compared aprotinin to TXA, four were assessed as having adequate allocation concealment of treatment schedule. For these trials the RR of receiving an allogeneic blood transfusion in those patients treated with aprotinin compared to those patients treated with TXA was 0.80 (95% CI 0.69 to 0.92). Heterogeneity between these trials was not statistically significant (Chi^2 = 3.60, df = 3, P = 0.31; I^2 = 17%). In the 13 trials where there was uncertainty regarding the method of allocation concealment (Unclear), the RR of receiving an allogeneic blood transfusion was statistically significantly different between aprotinin and TXA (RR 0.97, 95% CI 0.88 to 1.07). Heterogeneity between these trials was not statistically significant (Chi^2 = 19.25, df = 12, P = 0.08; I^2 = 38%). (When Mengistu 2008 was removed from the analysis RR was 0.99 (95% CI 0.91 to 1.08). In the remaining four trials where the method of allocation concealment was assessed as being inadequate (No), the RR of receiving an allogeneic blood transfusion was not statistically significantly different between aprotinin treated patients and TXA treated patients (RR 0.93, 95% CI 0.62 to 1.39). Heterogeneity between these trials was statistically significant (Chi^2 = 10.29, df = 3, P = 0.02; I^2 = 71%).

Aprotinin versus epsilon aminocaproic acid

Of the 12 trials of aprotinin versus EACA that were assessed for methodological quality, three were assessed as having adequate allocation concealment. For these trials the RR of receiving an allogeneic blood transfusion in those patients treated with aprotinin compared to those patients treated with EACA was 0.86 (95%CI 0.71 to 1.05). Heterogeneity between these trials was not statistically significant (Chi^2 = 2.75, df = 2, P = 0.25; I^2 = 27%). For eight trials there was uncertainty regarding the method of allocation concealment (Unclear), the RR of receiving an allogeneic blood transfusion was not statistically significantly different between aprotinin and EACA (RR 0.76, 95% CI 0.58 to 0.99). Heterogeneity between these trials was not statistically significant (Chi^2 = 6.19, df = 7, P = 0.52; I^2 = 0%). For one trial the method of allocation concealment was assessed as being inadequate (No).

Tranexamic acid versus epsilon aminocaproic acid

Of the eight trials of TXA versus EACA that were assessed for methodological quality, one trial was assessed as having adequate allocation concealment (Yes). For five trials there was uncertainty regarding the method of allocation concealment (Unclear), and for two trials the method of allocation concealment was assessed as being inadequate (No). There were too few trials to formally assess the impact that methodological quality had on treatment effect.

Aprotinin versus lysine analogues (TXA and EACA combined)

Of the 29 trials that compared aprotinin to the lysine analogues, six were assessed as having adequate allocation concealment of treatment schedule. For these trials the RR of receiving an allogeneic blood transfusion in those patients treated with aprotinin compared to those patients treated with a lysine analogue was 0.82

(95% CI 0.71 to 0.95). Heterogeneity between these trials was not statistically significant (Chi² = 6.44, df = 3, P = 0.27; I² = 22%). In the 18 trials where there was uncertainty regarding the method of allocation concealment (Unclear), the RR of receiving an allogeneic blood transfusion was not statistically significantly different between aprotinin and the lysine analogues (RR 0.95, 95% CI 0.86 to 1.04). Heterogeneity between these trials was not statistically significant (Chi² = 26.77, df = 18, P = 0.08; I² = 33%). (When data from Mengistu 2008 were removed, RR was 0.97 (95% CI 0.89 to 1.06).) In the remaining five trials where the method of allocation concealment was assessed as being inadequate (No), the RR of receiving an allogeneic blood transfusion was not statistically significantly different between aprotinin treated patients and lysine analogue treated patients (RR 0.92, 95% CI 0.67 to 1.28). Heterogeneity between these trials was statistically significant (Chi² = 10.34, df = 4, P = 0.04; I² = 61%).

DISCUSSION

This systematic review of the three anti-fibrinolytic drugs, aprotinin, tranexamic acid (TXA), and epsilon aminocaproic acid (EACA), includes a total of 252 randomised controlled trials (RCTs), which recruited over 25,000 participants. The previous versions of this Cochrane review (Henry 1999; Henry 2007), included a total of 89 trials with 9876 participants and 211 trials with 20,781 participants, respectively. Although the three drugs differ somewhat in their modes of action, the results of this review confirm and strengthen previous findings that they reduce surgical blood loss and exposure to allogeneic red blood cell transfusion to a degree that is both statistically and clinically significant. Importantly, the risk of re-operation necessitated by recurrent or continued bleeding after cardiac surgery was lowered by treatment with aprotinin and a clear trend was also seen with TXA for that outcome. These findings are not new, but this updated review provides additional information regarding two significant questions: how do the drugs compare with each other and to what extent are the clinical benefits offset by adverse effects, in particular vascular occlusion? In addressing these questions the updated review includes data from 49 active comparisons between aprotinin and the lysine analogues, compared with 29 in the previous review (Henry 2007). This updated review also adds to the information about vascular events - capturing 54 more episodes of myocardial infarction than the earlier version.

The analyses of active comparator trials (direct head-to-head comparisons) indicate that aprotinin was slightly more effective than TXA in reducing the need for red cell transfusion in patients undergoing cardiac surgery (RR 0.87, 95% CI 0.76 to 0.99). However, the results of the head-to-head comparison showed that aprotinin was marginally more effective than TXA in reducing post-operative blood loss. In the context of cardiac surgery, aprotinin appeared to be more effective than EACA in reducing the need for red cell transfusion and post-operative blood loss. Our confidence in ascribing an advantage to aprotinin needs to be moderated by evidence of possible publication bias and uncertainty over the comparative dose response relationships.

Mortality appeared to be unaffected by treatment with any of the drugs and there was no evidence that aprotinin, or the lysine analogues, increased the risks of myocardial infarction or other serious thrombosis. These latter results conflict with the findings of recently published observational studies by Mangano et al (Mangano 2006; Mangano 2007) and Karkouti et al (Karkouti 2006), which showed that the use of aprotinin in cardiac surgery was associated with an increase in the incidence of renal failure, myocardial infarction, and all-cause mortality (over five years).

Measures of efficacy: blood loss and need for transfusion

Aprotinin appeared to be the most efficacious of the three drugs in reducing perioperative blood loss, the confidence interval (CI) for the average reduction in blood loss with aprotinin seen in placebo/inactive controlled trials does not overlap with those of either TXA or EACA. This conclusion was supported by the sparser literature from active comparator trials, which found that aprotinin reduced post-operative blood loss to a greater extent than TXA; a similar result was seen in the comparison of aprotinin and EACA. It was notable that the apparent differences between the drugs were only seen in the context of cardiac surgery. There was no advantage of aprotinin over TXA when the drugs were used as an adjunct to orthopaedic procedures.

The three drugs were effective in reducing the proportions of patients who required transfusion with red blood cells. The pooled relative risk (RR) values from placebo/inactive controlled trials were similar. When considering these results it may be relevant that the baseline rates of transfusion differed considerably between the trials of aprotinin and the trials of TXA and EACA. The control-arms of the aprotinin trials had an average transfusion rate of 62%, compared with 44% for the control-arm of the TXA trials and 54% for the control-arms of the EACA trials. A possible explanation for this difference is that aprotinin has been studied more extensively and for a longer period of time than TXA and EACA. It is generally accepted that improvements in surgical technique, advancements in cardiopulmonary bypass technology, the introduction of auto-transfusion procedures and acceptance of lower transfusion thresholds have been responsible for a reduction in the rates of perioperative blood transfusion over time. This time dependant trend was observed in the trials of aprotinin in cardiac surgery. It is also possible that trials of aprotinin included more high-risk patients than trials of the lysine analogues. Such high-risk patients tend to have a greater propensity for blood loss and hence transfusion. Thus, comparisons between drugs based on the placebo/inactive controlled trials of anti-fibrinolytic drugs may be confounded at trial level by differences in patient populations. Publication bias is a further consideration when considering the placebo/inactive controlled studies of these drugs. As in the previous versions of this review, an examination of the generated funnel plots suggested a degree of publication bias (favouring active treatment) in the aprotinin trials (Figure 3), and a similar pattern was also seen with the trials of TXA (Figure 4) and EACA (Figure 5).

Figure 3. Funnel plot of comparison: 1 Aprotinin versus Control (Blood Transfusion & Blood Loss), outcome: 1.1 No. Exposed to Allogeneic Blood.

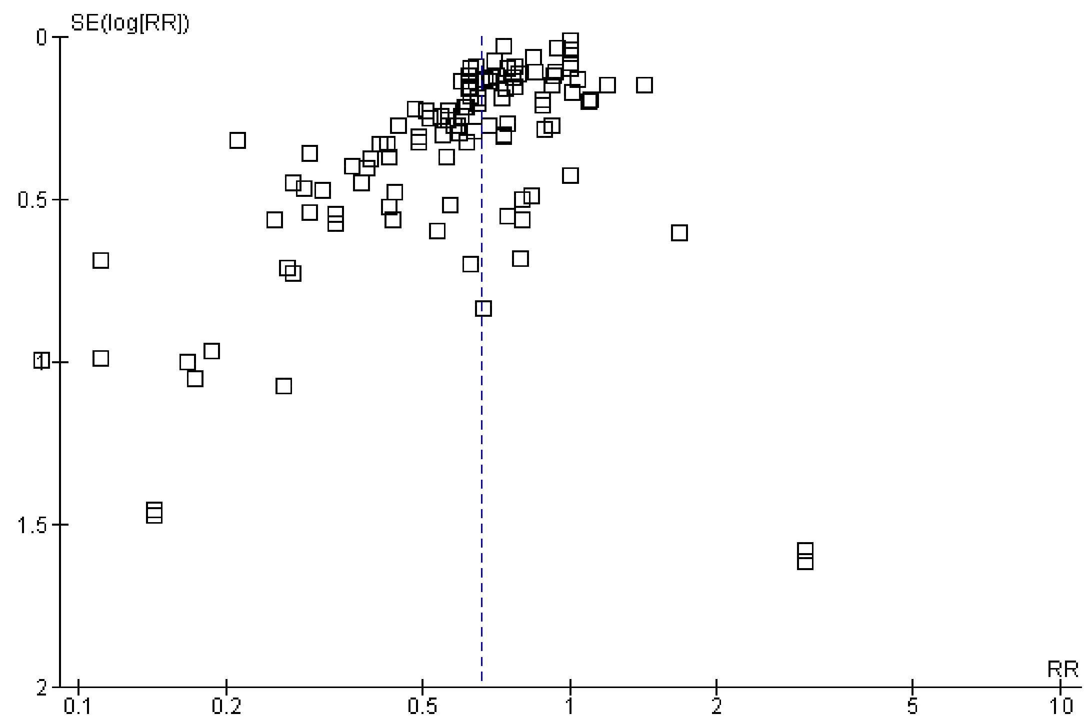


Figure 4. Funnel plot of comparison: 2 Tranexamic Acid versus Control (Blood Transfusion & Blood Loss), outcome: 2.1 No. Exposed to Allogeneic Blood.

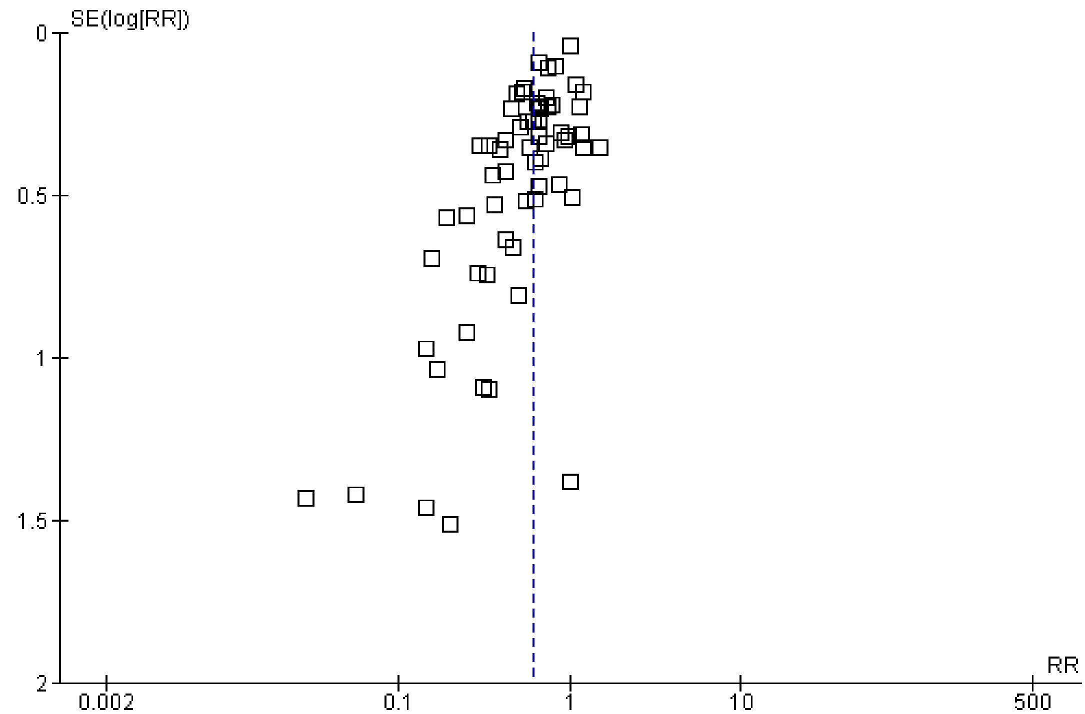
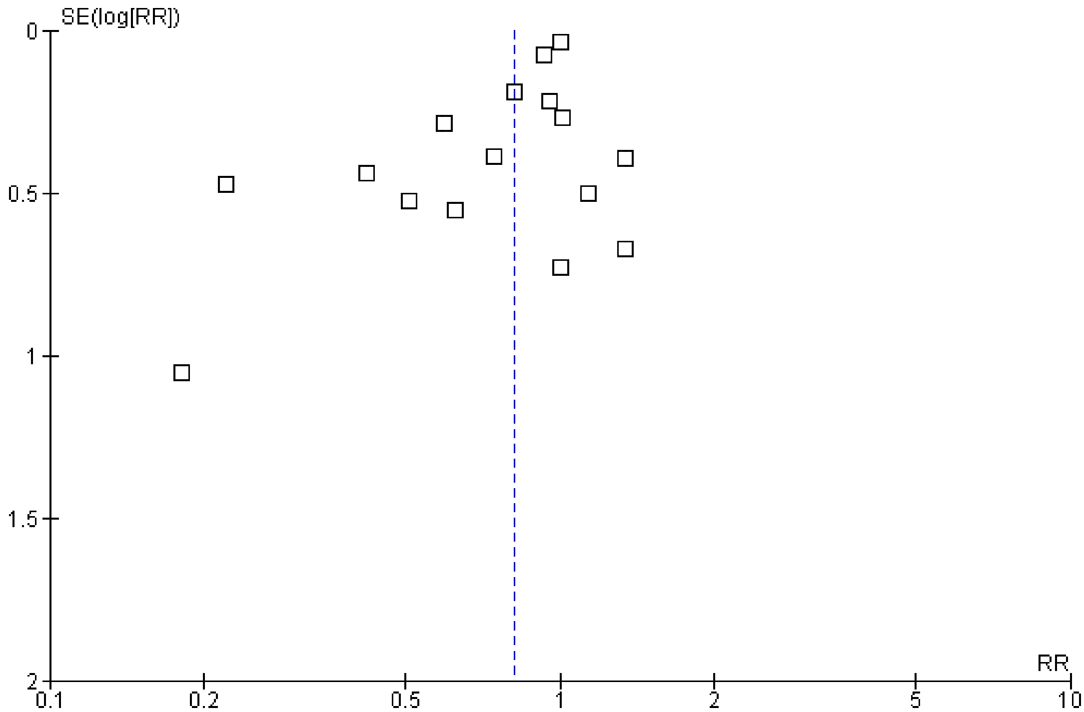


Figure 5. Funnel plot of comparison: 3 Epsilon Aminocaproic Acid versus Control (Blood Transfusion & Blood Loss), outcome: 3.1 No. Exposed to Allogeneic Blood.



In the case of cardiac surgery, when aprotinin was included in pairwise comparisons of blood transfusion requirements with TXA and EACA a small trend in favour of aprotinin was seen in each comparison. When we pooled data on blood transfusions for head-to-head comparisons of aprotinin with either of the lysine analogues the advantage of aprotinin was borderline significant - pooled RR 0.90 (95% CI 0.81 to 0.99). We have previously published a meta-analysis of the comparative trials of aprotinin and lysine analogues in cardiac surgery (Carless 2005). In that study we used a Bayesian meta-analytic approach to determine if TXA and EACA could be considered equivalent (non-inferior) to aprotinin in reducing the rate of allogeneic blood transfusion. Although hampered by the small number and size of the trials, our results showed that for blood transfusion, using a non-inferiority boundary of 20%, the posterior probability that TXA is equivalent to aprotinin was 0.82.

In other words, the updated analyses make us less sure about the equivalence of the lysine analogues and aprotinin when used to reduce the need for red cell transfusion in cardiac surgery. But these conclusions do not take account of two additional factors, dose effects and the possibility of publication bias. As the funnel plots generated from the head-to-head trials of aprotinin and the lysine analogues show there appears to be a gap that should be occupied by small trials favouring the latter drugs (Figure 6; Figure 7; Figure 8; Figure 9). The data are sparse but if this represents non-publication of such trials it could explain some of the apparent advantages of aprotinin seen in the overall analyses. This suggestion was made originally by Beattie 2006 and our updated analysis supports their conclusions. To find evidence of publication bias in the placebo-controlled trials of these drugs is perhaps not surprising, but we thought it less likely to affect the active comparison studies. The commercial interests in the role of aprotinin (an expensive and popular drug) as an adjunct to cardiac surgery may lie behind this. However, it should be noted that none of the reports of the comparative trials mentions commercial sponsorship.

Figure 6. Funnel plot of comparison: 4 Aprotinin versus Tranexamic Acid (Blood Transfusion & Blood Loss), outcome: 4.1 No. Exposed to Allogeneic Blood.

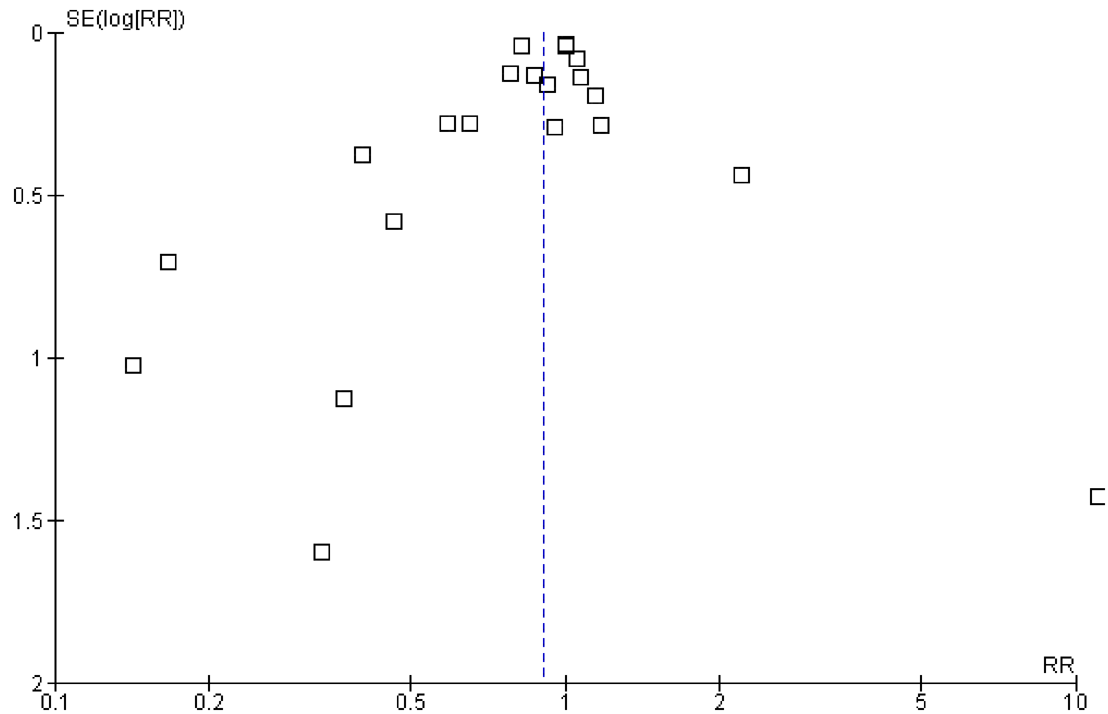


Figure 7. Funnel plot of comparison: 5 Aprotinin versus Epsilon Aminocaproic Acid (Blood Transfusion & Blood Loss), outcome: 5.1 No. Exposed to Allogeneic Blood.

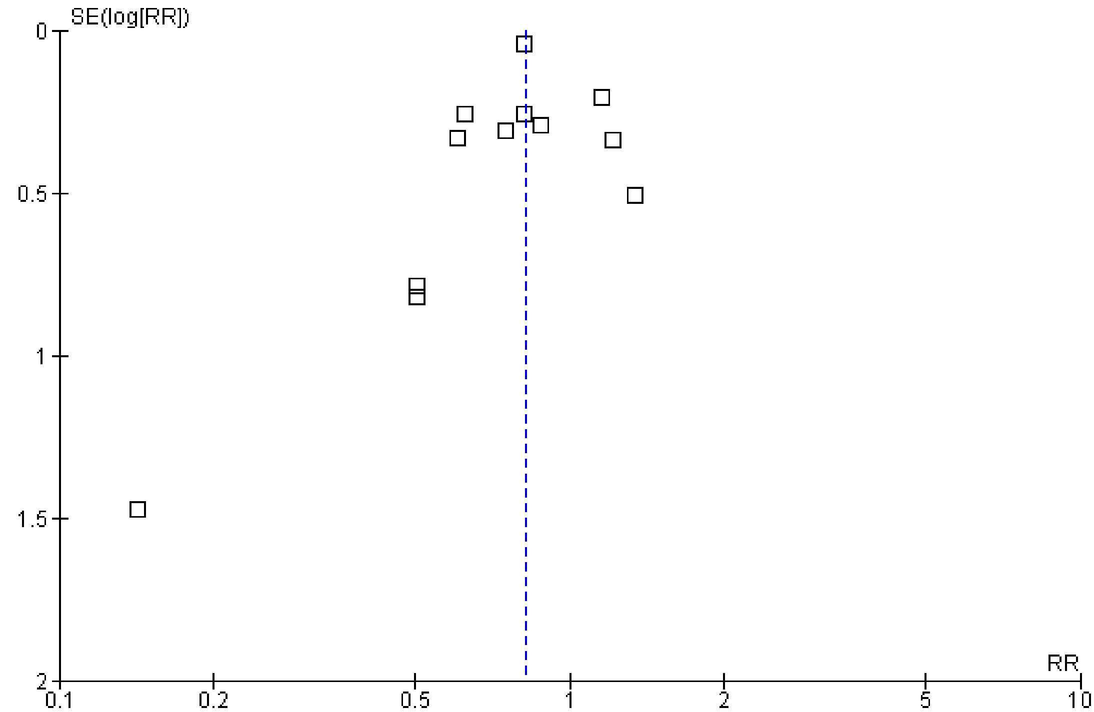


Figure 8. Funnel plot of comparison: 6 Tranexamic Acid versus Epsilon Aminocaproic Acid (Blood Transfusion & Blood Loss), outcome: 6.1 No. Exposed to Allogeneic Blood.

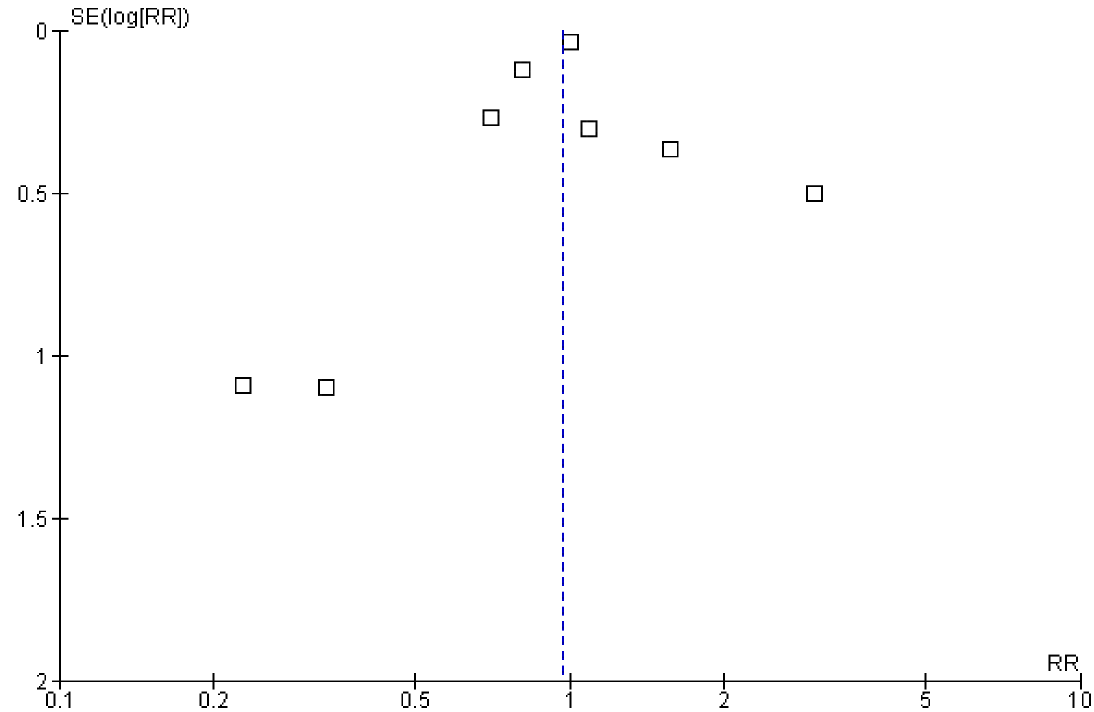
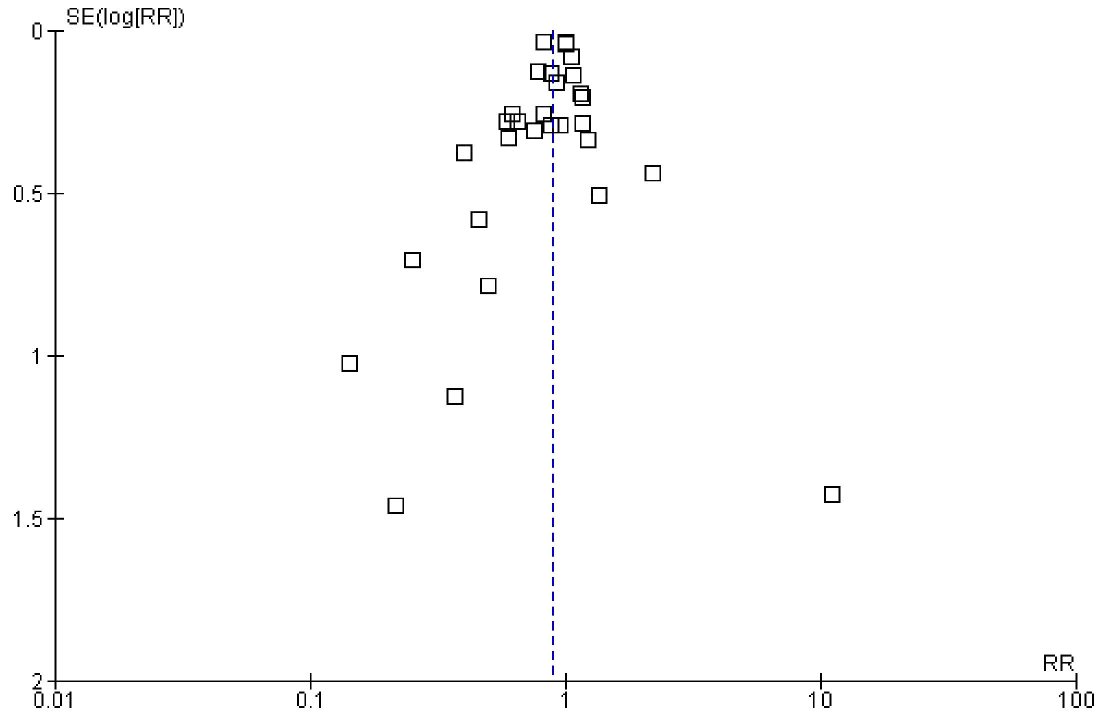


Figure 9. Funnel plot of comparison: 7 Aprotinin versus Lysine Analogues (Blood Transfusion), outcome: 7.1 No. Exposed to Allogeneic Blood.



In making comparisons between the average efficacy of the drugs it is important to consider the possible role of dose as a treatment effect modifier. When the pooled RR values for aprotinin were stratified, both low and high doses reduced the incidence of allogeneic red cell transfusion by around 35%. This was greater than the effect of aprotinin when given only as a priming dose - a RR reduction of 17%. So extending duration of treatment beyond the priming dose may be important. TXA in doses of 2 to 10g and in doses below 2g had a similar effect, reducing allogeneic red cell transfusion by around 30%. There were insufficient data to explore dose effects in the head-to-head trials of aprotinin and TXA.
Analyses of the comparative trials of aprotinin and the lysine analogues in orthopaedic surgery were hampered by sparse data. When the results of placebo/inactive controlled trials were combined TXA appeared to be as effective as aprotinin in reducing the number of patients exposed to allogeneic blood transfusion. Conclusions about the relative efficacy of EACA and aprotinin in orthopaedic surgery were hampered by the small number of trials. Of the fourteen trials of aprotinin eight (57.1%) were published between 2000 and 2006. In comparison, of the 21 trials that compared TXA to placebo-control 16 (76.2%) were published in this time period. As with cardiac surgery, conclusions about the relative efficacy of the drugs may be confounded by changes in surgical technique and transfusion practices that have occurred over time. However, as with the data on blood loss, the apparent advantage of aprotinin over the lysine analogues on the need for blood transfusion observed in cardiac surgery was not seen in orthopaedic surgery.
The analyses of the volumes of red cells transfused were difficult to interpret because of incomplete data in many trials. When all randomised subjects were included in the analyses (which included some who did not receive a transfusion) the average volumes of blood transfused were reduced modestly by all three drugs. When the analysis was confined to individuals who received red cell transfusions the reductions in volume were less marked and a statistically significant treatment effect was observed only for aprotinin. There were insufficient data from head-to-head trials to assess the comparative effectiveness of the three drugs in reducing the volumes of blood transfused.

Clinical significance of avoiding red cell transfusion

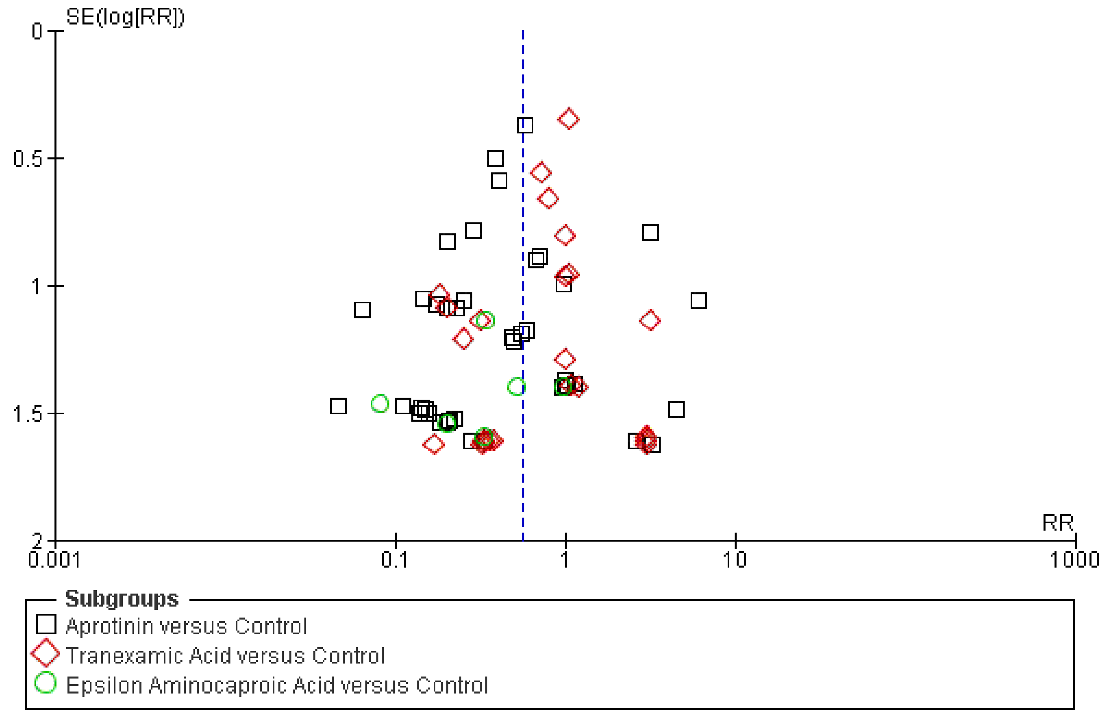
The true value of avoiding allogeneic red cell transfusion remains unclear (Vamvakas 2001). Patients who are concerned about the risks of contracting illness as a result of blood transfusion (or object to transfusion on religious grounds) will be more interested in avoiding it completely, rather than just reducing the volume of transfused blood. The importance of avoiding the need for transfusion depends on the probability of avoiding disease transmission or other adverse effects, in particular immunomodulation thought to be due to transfused white blood cells (Blumberg 1997; Vamvakas 2001). The significance of the latter remains although a number of countries now perform leukocyte depletion, either selectively, or universally, before administering red cell transfusions, despite a lack of convincing evidence that this provides clinical benefits (Vamvakas 2004). The rate of transmission of HIV or viral hepatitis in most developed countries is very low, because of the quality of screening of donated blood (Coyle 1999; Whyte 1997). These broad assumptions do not apply equally in developing countries. Allogeneic red cell transfusion is administered frequently and blood products may be inadequately screened; the prevalence of viral pathogens amongst donors is high (Kimball 1995; McFarland 1997). In these settings there may be much greater clinical value in a range of interventions that diminish or avoid the need for allogeneic blood. However, the costs of the drugs reviewed here are likely to be prohibitive in developing countries.

Most of the red cell transfusion data reviewed here have been collected in the context of major cardiac surgery, where blood loss may be substantial. The applicability of the efficacy data to clinical settings where blood loss is minor is questionable. Anti-fibrinolytic drugs may be used alongside other interventions designed to minimise the need for allogeneic red cell transfusion. A variety of techniques have been employed; most involve the re-infusion of autologous blood either from pre-operative deposit, acute normovolemic haemodilution, or cell salvage. The latter, in most instances involves the re-infusion of red blood cells that have been shed into the operative field. The evidence on the efficacy and safety of these techniques was reviewed extensively by the International Study on Perioperative Transfusion (ISPOT) (Bryson 1998; Forgie 1998; Huet 1999). The literature on re-infusion techniques is generally viewed as being of indifferent quality, because of inadequate randomisation and lack of blinding of outcomes assessment. However, these techniques probably have a modest blood sparing effect. Significantly, the efficacy of autologous re-infusion techniques appears lower when they are used in the context of a rigorous transfusion protocol. This and the growing evidence on the efficacy of transfusion triggers indicates that a more conservative approach to blood transfusion decisions is desirable (Carson 1998; Hebert 1999). This conservative approach, combined with the selective use of anti-fibrinolytic drugs, may offer the best approach for managing the transfusion requirements of participants in high-risk settings such as cardiac surgery.

Other measures of efficacy: need for re-operation due to bleeding

If the significance of avoiding red cell transfusion is unclear the importance of avoiding re-operation is not. Going back to theatre because of continued or recurrent bleeding is a serious development after cardiac surgery and any reduction in the incidence of this event is clinically significant (O'Brien 2002). The updated meta-analysis confirmed that aprotinin reduces the rate of re-operation due to bleeding by about half. This translates into an absolute risk reduction of 2% and a number needed-to-treat of 50 (95% CI 33 to 100). Similar trends were seen with TXA and EACA, but the data were sparse and the differences failed to reach statistical significance. We did not see evidence of publication bias in the data relating to re-operation rates (Figure 10). When aprotinin was compared directly with TXA in head-to-head comparative trials the analysis suggested that aprotinin reduced re-operations by 31%.

Figure 10. Funnel plot of comparison: 7 Adverse Events and Other Outcomes (Active versus Control), outcome: 7.1 Re-operation for bleeding.



Effects of treatment on all cause mortality

Regardless of the type of surgery, when aprotinin was compared with no treatment there was no apparent effect on all-cause mortality (RR 0.81, 95% CI 0.63 to 1.06). In the subset of cardiac surgery trials the result was similar: RR 0.84 (95% CI 0.64 to 1.10). Likewise, when TXA was compared to no treatment the effect on mortality rate in cardiac surgery was not statistically significant and the CI was fairly wide (RR 0.60, 95% CI 0.33 to 1.10). In head to head comparisons there was a trend to higher mortality with aprotinin than either tranexamic acid or aminocaproic acid but the analyses were constrained by the relatively small numbers of outcomes. As there were no qualitative differences between tranexamic acid and aminocaproic acid, and any quantitative differences between these drugs were small, we compared aprotinin with either lysine analogue for the outcomes of mortality and myocardial infarction. The risk of death was higher with aprotinin than with either lysine analogue, although this result was very dependent on the results of the BART trial (Fergusson 2008). There was no significant increase in the risk of myocardial infarction that could explain the higher mortality and indeed there were no other outcome analyses from the head to head trials that could provide an explanation. It is also possible that the difference was due to a benefit of the lysine analogues rather than an adverse effect of aprotinin. In any event this distinction is academic as aprotinin has been withdrawn from world markets and the lysine analogues appear almost equally effective in reducing the need for transfusion with allogeneic blood.

Adverse events and other outcomes

Neither aprotinin nor the lysine analogues appeared to increase the risk of myocardial infarction. In each case the pooled relative risk was close to one. Most data have been collected for aprotinin, which is more often used in cardiac surgery that the lysine analogues. This probably explains the higher rates of myocardial infarction in the placebo-treated subjects in the aprotinin trials (4.5%) than the TXA trials (2.3%). Similarly, the risk of stroke was not increased by any of these drugs; nor was there any apparent increase in the risk of developing other thrombotic events (deep vein thrombosis, pulmonary embolism, 'other thrombosis').
Data aggregated from 28 randomised trials of aprotinin and nine trials of TXA showed that neither drug increased the risk of renal dysfunction compared to control. Although the event rate was slightly higher in aprotinin-treated patients compared to the con-

trol group (2.4% versus 1.5%) the difference was not statistically significant.

Potential sources of bias in this review

In our review we found a large number of small trials. These continue to be published in the literature, even though individually they contribute very little additional information. In the case of aprotinin, redundancy in terms of new information has long since been reached and there is no justification for continuing to perform placebo-controlled trials. Future investigation should involve large trials of the relative efficacy and safety of the different drugs (Hebert 2005). The small size of most of the existing trials raises concerns about the effects of publication bias. The funnel plot of the aprotinin trials reveals possible evidence of this - in the form of a 'missing' population of small negative trials (Figure 3).

The main study outcome used in these trials was a practice variable - the decision to transfuse a patient with allogeneic red cells. Although this requires a degree of subjectivity on the part of clinicians it is probably not a major source of bias in this meta-analysis as around 70% of the trials were assessed as being double-blind, involving the use of an identical placebo.

Sources of heterogeneity

Substantial heterogeneity in trial outcomes was seen. This was seen in the case of aprotinin for blood loss and blood transfusion outcomes. However, it was not apparent in the analyses of more significant clinical outcomes, such as re-operation, myocardial infarction and death. It is therefore possible that the subjective nature of the intermediate outcomes, which require judgement about the degree of blood loss, and the need for transfusion, contributed to the between study heterogeneity. Despite this heterogeneity we have little doubt about the existence of a treatment benefit with these drugs. The variation for blood transfusion variables was in terms of the size, not the direction, of effect.

We considered a number of other factors that might explain variation in the size of the treatment effect for blood loss and rates of transfusion. In the case of transfusion, we stratified the data by the clinical setting, operation type, the concomitant use of clinical transfusion thresholds (transfusion triggers), and trial methodological quality. In the case of blood loss, we stratified the data by the type surgery performed and the period in which blood loss was assessed (that is, intra-operative and/or post-operative blood loss). Basically, none of these provided an adequate explanation for the degree of heterogeneity seen in these studies. Although effect size varied somewhat with dose, considerable heterogeneity was seen within dose strata. Likewise, there was substantial heterogeneity within the trials of aprotinin in cardiac surgery (that is, for intra-and-post-operative blood loss, and the rates of transfusion). For the rates of exposure to allogeneic blood transfusion the adequacy of concealment of treatment allocation was associated with a small variation in treatment effect size, but once again there was heterogeneity within the different strata of methodological quality.

How do the results compare with the observational studies?

The most controversial aspect of this review is the lack of evidence of an increase in the risks of myocardial infarction, stroke, renal dysfunction and death with aprotinin when compared with no treatment. This is in keeping with previous published meta-analyses of the randomised controlled trials of anti-fibrinolytic drugs. In the case of aprotinin this review includes 77% more myocardial infarctions, but only 7% more deaths, than the previous version of this review. The updated data-sets comparing aprotinin with no treatment conflict with those from four recent observational studies (Karkouti 2006; Mangano 2006; Mangano 2007; Schneeweiss 2008). Mangano and colleagues (2007) showed that during five years of follow-up aprotinin-treated patients had a death rate around 1.6 times higher than that of the untreated control group. The adjusted hazard ratio (HR) for all-cause mortality was 1.48 (95% confidence interval 1.19 to 1.85). This study generated considerable scientific debate with calls for the use of aprotinin in cardiac surgery to be abandoned. In 2008 a large pharmaco-epidemiological study by Schneeweiss 2008 confirmed the increased risk of death with aprotinin. These investigators studied the use of aprotinin (33,517 patients) or aminocaproic acid (44,682 patients) on the day coronary bypass surgery was performed. In this non-randomised study they found that 1512 of the 33,517 aprotinin recipients (4.5%) and 1101 of the 44,682 aminocaproic acid recipients (2.5%) died. After adjustment, the estimated risk of death was 64% higher in the aprotinin group than in the aminocaproic acid group (relative risk, 1.64; 95% confidence interval [CI], 1.50 to 1.78). This difference remained statistically significant after a range of analytical procedures including a propensity score matched analysis and an instrumental variable analysis.

The first large observational study to find and adverse effect of aprotinin (Mangano 2006, Mangano 2007) was criticized on several grounds, including the fact that it was based on a multi-centre patient registry, not a true population based cohort, that there were important differences between centres and that a range of selection biases may have influenced the between-drug comparisons. These arguments will not be repeated here as full details are available in the relevant publications (Bidstrup 2006; Body 2006; Ferguson 2007; Levy 2006). Our view is not that the studies of Karkouti 2006; Mangano 2006 and Mangano 2007 were badly done, but that they have inherent limitations, mainly due to their observational nature and selection biases that probably cannot be completely overcome through statistical adjustments by propensity scores and co-variates. These weaknesses were addressed in the larger study performed by Schneeweiss and colleagues (2008), described above. The agreement between these studies adds weight to the claim that aprotinin does indeed increase the chances of death.

In considering the apparently conflicting results of the different study types it is also important to acknowledge weaknesses in the database of randomised trials, in particular under-recording of infrequent events that were not the primary outcomes of the trials. It is important to note that for dichotomous data to be included in our analyses, trial reports had to provide either numeric data, that is the numbers of events that occurred in the treatment and control groups, or where there were no events recorded, the trial report had to clearly state this. So, we have some confidence in the data included in the meta-analyses. However, we acknowledge that under-reporting of uncommon events that were not the primary outcomes of these generally small trials is a potential problem with this literature. In the case of aprotinin our analyses of myocardial infarction were based on data from 37 (49%) out of a total of 76 trials included in the analyses of blood transfusions. These trials were larger than average and included 64% of all participants. Nevertheless, the incomplete data are a potential source of bias in this and the analyses of other vascular outcomes. We are more confident of our analyses of mortality in cardiac surgery where, in the case of aprotinin, data were reported for 60% of all trials and 80% of participants. The most likely effect of under-reporting is to make estimates imprecise, meaning that fairly small changes in mortality or occurrence of thrombotic events might have been missed.

There was a disappointing lack of information in the randomised trials regarding this putative adverse effect of the drug. Only 18 out of 76 trials of aprotinin documented this outcome, so there is a potential for bias due to under-reporting. Based on analysis of 107 events in 4174 individuals the point estimate of the pooled RR with aprotinin (compared with placebo or no treatment) was 1.16 (95% CI 0.79 to 1.70), so we are not confident that we have ruled out a modest increase in risk. On the other hand the suggestion of an increase in risk from Mangano 2006 was based on a total of only 18 events, of which eight occurred in patients treated with aprotinin. Karkouti 2006 carried out a closely matched analysis of 898 individuals who received either aprotinin or TXA. Using a very sensitive measure of renal dysfunction they documented 182 instances, with a higher incidence in aprotinin treated subjects (RR 1.43, 95% CI 1.10 to 1.86).

There was greater agreement when we consider the results of the summary analyses of the head to head trials of aprotinin and lysine analogues and the observational studies described above. The comparison of aprotinin with the combined results of the lysine analogues found a significantly increased risk of death; similar in magnitude to what was found in the observational studies, but no apparent increase in the risk of major thrombotic events. The absence of a no treatment control group from these analyses means that we are unable to say whether the differences in mortality were due to an adverse effect of aprotinin or a protective effect of the lysine analogues. In addition, the meta-analyses for death and myocardial infarction were heavily weighted by the results of the BART trial (Fergusson 2008). These factors limit our ability to draw firm conclusions about the true effects of the drugs. But the summary data now available, and the regulatory action taken against aprotinin, enable us to make some pragmatic recommendations. Despite the possibility that they are inferior to aprotinin in minimising perioperative blood loss and the need for allogeneic red cell transfusion both tranexamic acid and aminocaproic acid appear effective and safe. The experience is greatest with tranexamic acid and confidence in the use of this drug has been strengthened by the recent publication of the CRASH-2 trial (CRASH-2 2010), which found that two doses of tranexamic acid reduced overall mortality when administered soon after major trauma.

Conclusions

Antifibrinolytic drugs are effective in reducing blood loss, the need for allogeneic red cell transfusion, and the need for re-operation due to continued post-operative bleeding (in cardiac surgery). Aprotinin appears more effective than the lysine analogues in minimising peri and post operative blood loss when used as adjunctive therapy in cardiac surgery. Strictly speaking, based on their average effects on the need for red cell transfusion, the lysine analogues do not meet the criteria for being considered equivalent to aprotinin. However, comparisons between the drugs need to take account of the clinical significance of any small advantage of aprotinin, the dose response relationships for each of the drugs, and the possible effects of publication bias, which appears to favour aprotinin. Taking these factors into consideration it may reasonably be concluded that tranexamic acid is as effective as aprotinin, particularly when it is used as an adjunct to non-cardiac surgical procedures. The data for epsilon aminocaproic acid are sparser and as a consequence not so convincing.

The updated meta-analyses of the randomised trials comparing aprotinin with no treatment do not confirm the evidence from observational studies that aprotinin increases the risks of vascular occlusive events and mortality. However, there has been a degree of under-reporting of these adverse events in trials of anti-fibrinolytic drugs. The head to head comparisons of aprotinin and the lysine analogues have yielded results that are closer to those seen in the observational studies and indicate that aprotinin carries an increased risk of death. Consequently, the balance of benefit and harm favours the use of the lysine analogues over aprotinin, and justifies the regulatory action that resulted in the withdrawal of aprotinin from international markets in 2008.

AUTHORS' CONCLUSIONS

Implications for practice

Tranexamic acid and epsilon aminocaproic acid provide worthwhile reductions in blood loss and the need for allogeneic red cell transfusion. Based on the results of randomised trials their efficacy does not appear to be offset by serious adverse effects. The evidence is stronger for tranexamic acid than for epsilon aminocaproic acid.

Implications for research

There is no need for further placebo-controlled trials of anti-fibrinolytic drugs in cardiac surgery. The principal need is for large comparative trials to assess the relative efficacy, safety and cost-effectiveness of the lysine analogues in different surgical procedures.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alajmo 1989

Methods	Patients were randomly divided into two groups according to birth date until an appropriate number of treated patients was reached. Method of blinding and generation of allocation sequences were not described
Participants	34 consecutive patients undergoing cardiac operations were randomly divided into two groups: • Aprotinin group: n = 22, M/F = 12/8, mean (sd) age = 62 (6.6) years • Control group: n = 12, M/F = 7/5, mean (sd) age = 57.8 (16.3) years NB: Possible error in the gender data provided for the aprotinin group
Interventions	• Aprotinin group received 2 million kallikrein inactivation units (KIU) of aprotinin (280 mg) at the start of anaesthesia (Trasylol, Bayer Leverkusen, FRG; 10,000 KIU/ml pure aprotinin with no additives) infused over 20 to 30 minutes. Subsequently, 500,000 KIU/hr (70 mg/hr) of aprotinin was given until the end of the operation. Additionally, 1 million KIU of aprotinin (140 mg) was given via the priming solution of the extracorporeal circuit. • Control group did not receive aprotinin.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss, haemoglobin levels, platelet counts
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	Patients were randomly allocated into two groups according to birth date until an appropriate number of treated patients was reached
Allocation concealment?	No	Inadequate
Blinding? All outcomes	No	

Alderman 1998

Methods	Patients were randomly divided into two groups by random code, generated in blocks with clinical center and stratum. Allocation concealment was not described
Participants	870 patients were randomised into two groups: • Aprotonin group n = 436, M = 87.4%, mean (sd) age = 61.8 (9.1) years • Control group (Placebo) n = 434, M = 86.9%, mean (sd) age = 62.3 (9.1) years

Interventions	• Aprotonin group received a loading dose of 2 million KIU (280 mg), a maintenance dose of 500,000 KIU and a prime dose of 2 million KIU. • No details were described on the placebo used.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss, deaths, myocardial infarction, CABG thrombosis, re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random code generated in blocks
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Alvarez 1995

Methods	The hospital pharmacy made up identical infusions of the study drugs identifiable only by random number. Patients were prospectively randomised into two groups by sealed envelopes. The method used to generate allocation sequences was not described
Participants	100 patients undergoing primary elective cardiac surgery were randomised into one of two groups: • Aprotinin group: n = 49, M/F = 38/11, mean (sd) age = 63.3 (11.0) years • Control group (Placebo): n = 51, M/F = 34/17, mean (sd) age = 62.7 (8.2) years
Interventions	• Aprotinin group received 250,000 kallikrein inactivation units (KIU) of aprotinin added to the prime solution of the cardiopulmonary bypass (CPB) system. Before the start of CPB a further 250,000 KIU of aprotinin, made up to 100 ml with 0.9% saline, was infused intravenously over 30 minutes. • Control group received a placebo of equal volumes of 0.9% saline administered at identical times. NB: Both the intervention and control group were combined with cell salvage
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, patients receiving autotransfusion, blood loss, mortality, myocardial infarctions, re-operation, patients receiving cell salvage
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Alvarez 1995 (*Continued)*

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	No	Inadequate - sealed envelopes were used to conceal treatment allocation
Blinding? All outcomes	Yes	Double blind

Alvarez 2001

Methods	Patients were randomised by a computer-generated random number sequence into either treatment group. All clinical participants were double blinded until the completion of the trial. Placebo and treatment solutions were identical in their appearance and packaging
Participants	55 patients undergoing either elective or urgent cardiac surgery were randomised into one of two groups: • Aprotonin group: n = 26, M/F = 23/3, mean (sd) age = 63 (8) years • Control group (Placebo): n = 29, M/F = 22/7, mean (sd) age = 64 (8) years
Interventions	• Aprotinin group received 250,000 kallikrein inactivation units (KIU) of aprotinin 280mg IV at the time of sternal skin closure. • Control group received a placebo of an equal volume of normal saline solution infused over 20 mins.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, patients receiving autotransfusion, blood loss, mortality, myocardial infarctions, re-operation
Notes	Quality assessment score (Schulz criteria): 7/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random number sequence
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Alvarez 2008

Methods	Patients were allocated according to a computer-generated randomisation sequence. Allocation was concealed using sealed, numbered envelopes
Participants	95 patients undergoing orthopaedic (knee arthroplasty) surgery. Patients were randomly allocated to one of two groups: • Tranexamic acid group: n = 46, M/F = 7/39, mean (sd) age = 71 (9) years • Control group (Placebo): n = 49, M/F = 10/39, mean (sd) age = 72 (7) years
Interventions	• Tranexamic acid group received bolus of 10mg/kg before deflation of tourniquet then infusion of 1mg/kg/hr starting at the end of operation for six hours post-operation. • Control group received saline.
Outcomes	***Outcomes reported:*** Number of patients requiring blood transfusion, blood loss, volume of blood transfused, thrombosis
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random number sequence
Allocation concealment?	No	Inadequate - randomised assignment was sealed in a numbered envelope
Blinding? All outcomes	Yes	Double blind

Amar 2003

Methods	Randomisation of patients in blocks of 20 were done by the Biostatistics Department and the hospital pharmacy using sealed, opaque treatment code envelopes
Participants	69 patients undergoing elective orthopaedic surgery were randomised into one of three groups: • Epsilon aminocaproic acid group: n = 22, M/F = 11/11, mean (sd) age = 53 (18) years • Aprotinin group: n = 23, M/F = 13/10, mean (sd) age = 48 (17) years • Control group (Placebo): n = 24, M/F = 13/11, mean (sd) age = 55 (16) years
Interventions	• Epsilon aminocaproic acid (EACA) group received 150 mg/kg EACA bolus in an equal volume given over 30 minutes followed by an infusion of 15 mg/kg/hr until the end of surgery. • Aprotinin group received a bolus of 2 million KIU (280mg) given over 30 minutes followed by an infusion of 500,000 KIU/hour (70mg/hr) until the end of surgery. • Control group received a placebo of an equal volume of normal saline bolus and infusion.

Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood units - total includes intra-operative & 48 hours post-operative, blood loss - total blood loss = intra-operative & 48 hours post-operative, deep venous thrombosis, pulmonary embolus, hospital length of stay (days), wound infection, thrombocytopenia, Haemoglobin levels (pre-operative & post-operative)
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random numbers
Allocation concealment?	No	Inadequate - sealed opaque treatment coded envelopes were used to conceal treatment allocation
Blinding? All outcomes	Yes	Double blind

Andreasen 2004

Methods	Patients were randomised by a random number sequence. The randomisation schedule was provided in sealed envelopes and preparation of the drug or placebo was carried out just prior to anaesthesia by a staff member not involved in the treatment of the patient
Participants	46 patients undergoing elective coronary surgery. Patients were randomly allocated to one of two groups: • Tranexamic acid group (n = 21), M/F = 18/3, mean age (+/-SD) = 62.3 (9.5) years • Control group (Placebo) (n = 23), M/F = 19/4, mean age (+/-SD) = 63.8 (7.6) years
Interventions	• Tranexamic acid group (TXA) group (Cyklokapron, Phizer Consumer Healthcare) received 1.5g TXA as an IV bolus beginning at the induction of anesthesia, followed by a constant infusion of 200mg/hr until additional 1.5g was given. • Control group received a placebo of 0.9% normal saline solution. NB: Cell salvage - postoperatively shed mediastinal blood was returned in all patients using a closed autotransfusion system
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss, deaths, myocardial Infarctions, CABG thrombosis, renal insufficiency, re-operation for bleeding, cell salvage - autotransfusion 6 hrs, transient ischemic attack (30 day), stroke 30 day
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number sequence
Allocation concealment?	No	Inadequate - used sealed envelopes to conceal treatment allocation
Blinding? All outcomes	Yes	Double blind

Apostolakis 2008

Methods	A randomisation table was used to generate the allocation sequence. No information was provided regarding allocation concealment
Participants	59 patients undergoing elective thoracic surgery. Patients were randomly allocated to one of two groups: • Aprotinin group: n = 29, M/F = 26/3, mean (sd) age = 57.5 (16.3) years • Control group (Placebo): n = 30, M/F = 27/3, mean (sd) age = 58.5 (9.8) years
Interventions	• Aprotinin group, administered immediately after intubation, received a test dose of 1ml then 500,000 KIU intravenously in 50ml of solution over 15 minutes, received the same dose again after thoracotomy closure. • Control group received a placebo of an equal volume of normal saline.
Outcomes	***Outcomes reported:*** Blood loss, volume of transfused blood (units), mortality, re-operation for bleeding, length of hospital stay (days)
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Armellin 2001

Methods	Method of randomisation and allocation concealment were not described
Participants	300 patients undergoing elective cardiac surgery were randomised to one of two groups: • Tranexamic acid group: n = 150, M/F = 71/72, mean (sd) age = 65.7(11.7) years • Control group (Placebo): n = 150, M/F = 90/50, mean (sd) age = 65.9 (12.8) years
Interventions	• Tranexamic acid group (TXA) received 2.5g of TXA before the skin incision with a further 2.5g of TXA added to the CPB prime solution. • Control group received a placebo of an equal dose of saline at the same times as TXA.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss, mortality, myocardial infarction, re-operation for bleeding, hospital length of stay (days), fresh frozen plasma (FFP), platelets (units)
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Arom 1994

Methods	Method of randomisation and allocation concealment were not described
Participants	200 patients undergoing cardiac surgery were randomised to one of two groups: • Epsilon aminocaproic acid group: n = 100, M/F = 70/30, mean age = 60 years • Control group: n = 100, M/F = 71/29, mean age = 55 years
Interventions	• Epsilon aminocaproic acid group received 5g of intravenous EACA just before going on CPB. • Control group did not receive EACA treatment. NB: Both groups received 0.03ug/kg of intravenous desmopressin (DDAVP) after CPB
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), fresh frozen plasma usage (units), platelet usage (units), cryoprecipitate (units), blood loss (ml)
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Arom 1994 (*Continued)*

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Ashraf 1997

Methods	Method of randomisation and allocation concealment were not described
Participants	38 patients undergoing coronary artery bypass graft surgery were randomised to one of two groups: • Aprotinin group: n = 19, M/F = 16/3, median (range) age = 61 (49-72) years • Control group: n = 19, M/F = 15/4, median (range) age = 65 (50-79) years
Interventions	• Aprotinin group received 2 million KIU (280mg) of aprotinin added to the pump prime solution of the extracorporeal circuit. • Control group did not receive aprotinin.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss 24hrs, mortality, re-exploration for bleeding, pro-inflammatory cytokine levels
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Asimakopoulos 2000

Methods	Method of randomisation and allocation concealment not specified
Participants	18 adults undergoing elective coronary artery bypass grafting were randomly allocated to one of two groups: • Aprotinin group: n = 8, M/F = 7/1, mean (sd) age = 59 (3.9) years • Control group: n=10, M/F = 10/0, mean (sd) age = 65 (1.9) years

Interventions	• Aprotinin group received full-dose aprotinin. • Control group did not receive aprotinin.
Outcomes	***Outcomes reported:*** Allogeneic blood (units), blood loss, myocardial infarction, renal failure, re-operation for bleeding, cerebrovascular accident (stroke), hospital length of stay (days)
Notes	Quality assessment score (Schulz criteria): 4/7

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Baele 1992

Methods	Method of randomisation was not described. Allocation concealment was inadequately concealed (sealed envelopes)
Participants	115 consecutive adults undergoing cardiac surgery were randomly allocated to one of two groups: • Aprotinin group: n = 58, M/F = 45/13, mean (sd) age = 61.6 (9.6) years • Control group: n=57, M/F = 41/16, mean (sd) age = 62.9 (10.5) years
Interventions	• Aprotinin group received 2 million kallikrein inactivator units (KIU) before incision, 2 million (KIU) prior to bypass and a continuous infusion of 500,000 KIU/hr for 5 hours. • Control group did not receive aprotinin. NB: Both the intervention and control groups were exposed to pre-operative autologous donation (7 control and 4 intervention patients), acute normovolemic haemodilution (13 patients in each group), and/or cell salvage (data not presented)
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood (units) blood loss, mortality, myocardial infarction, myocardial ischemia, pericarditis, cardiac failure, pneumonia, renal insufficiency, hemiplegia, re-operation, allogeneic + autologous blood usage (units), intensive care unit (ICU) length of stay (hrs), hospital length of stay (days)
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol used

Risk of bias

Item	**Authors' judgement**	**Description**

Baele 1992 (*Continued)*

Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	No	Inadequate - sealed envelopes were used to conceal treatment allocation
Blinding? All outcomes	Unclear	Unclear

Bailey 1994

Methods	Generation of allocation sequences was by a computer generated random number table. One investigator made up all the test solutions; a known volume of sterile 0.9% saline was discarded from 500ml bags and replaced with the same volume of test solution so that all bags contained the same equal volume (500ml). Each set of bags was given a consecutive number. A separate investigator performed all the patient measurements
Participants	100 patients scheduled to undergo primary elective cardiac surgery employing cardiopulmonary bypass were consecutively allocated to one of four groups • Control group (Placebo): n = 25, M/F = 17/8, mean (sd) age = 63 (10) years • Aprotinin group (High dose): n = 25, M/F = 18/7, mean (sd) age = 64 (13) years • Aprotinin group (Prime dose): n = 24, M/F = 17/7, mean (sd) age = 59 (11) years • Aprotinin group (Low dose): n = 26, M/F = 20/6, mean (sd) age = 63 (10) years
Interventions	• Control group received a placebo of an intravenous bolus of 500ml of 0.9% saline at induction of anaesthesia, followed by 500ml of 0.9% saline every hour; a further 500ml of 0.9% saline was added to the pump prime. • Aprotinin (High dose) group received an intravenous bolus of 300ml of 0.9% saline with 200ml of aprotinin (2 million kallikrein inactivator units) at induction of anaesthesia, followed by 450ml of 0.9% saline with 50ml aprotinin (500,000KIU) every hour; a further 300ml of 0.9% saline with 200ml aprotinin (2 million KIU) was added to the pump prime. • Aprotinin (Prime dose) group received an intravenous bolus of 500ml of 0.9% saline at induction of anaesthesia, followed by 500ml of 0.9% saline every hour; a further 300ml of 0.9% saline with 200ml of aprotinin (2 million KIU) was added to the prime pump. • Aprotinin (Low dose) group received an intravenous bolus of 400ml of 0.9% saline with 100ml of aprotinin (1 million KIU) at induction of anaesthesia, followed by 500ml of 0.9% saline every hour; a further 400ml of 0.9% saline with 100ml of aprotinin 1 million KIU) was added to the pump prime.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood (units), fresh frozen plasma usage (units), blood loss
Notes	Quality assessment score (Schulz criteria): 7/7 Transfusion protocol used
Risk of bias	

Item	**Authors' judgement**	**Description**

Adequate sequence generation?	Yes	Generation of allocation sequences was by a computer generated random number table
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Basora 1999

Methods	Method of randomisation and allocation concealment were not described
Participants	59 patients undergoing elective cardiac surgery were randomised to one of three groups: • Control group: n = 21, M/F = 16/5, mean (sd) age = 59.8 (10.3) years • Aprotinin group (Low dose - A2): n = 17, M/F = 12/5, mean (sd) age = 61.2 (13.1) years • Aprotinin group (Low dose - A4): n = 19, M/F = 14/5, mean (sd) age = 60.9 (7.6) years
Interventions	• Control group did not receive aprotinin. • Aprotinin group (Low dose - A2) received 14,286 KIU/kg (2mg/kg) 15 mins before surgery, then a continuous dose of 7,143 KIU/kg/hr (1mg/kg/hr) until the end of surgery. • Aprotinin group (Low dose - A4) received 28,572 KIU/kg (4mg/kg) 15 mins before surgery, then a continuous dose of 7,143 KIU/kg/hr (1mg/kg/hr) until the end of surgery.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss, platelet function
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	No	Single blind

Bennett-Guerrero 1997

Methods	Patients were randomised by means of a computer-generated schedule. Study drug was prepared according to a protocol by hospital pharmacies
Participants	204 patients undergoing repeat cardiac surgery were randomised to one of two groups: • Aprotinin group (High dose): n = 99, M/F = 66/33, mean (sd) age = 62 (14) years • Epsilon aminocaproic acid group: n = 105, M/F = 68/37, mean (sd) age = 63 (12) years

Interventions	• Aprotinin group (High dose) received 2 million KIU (280mg) of aprotinin on skin incision, 500,000 KIU/hr as a continuous infusion for 4 hours on initiation of CPB. An additional 2 million KIU (280mg) was added to the CPB prime solution. Patients received 1ml of the study drug in a blinded manner before the loading dose to test for possible allergy. • Epsilon aminocaproic acid group received 150mg/kg on skin incision, 30mg/kg over 4 hours as a continuous infusion on initiation of CPB. In addition, normal saline solution was added to the CPB prime solution. Patients received 1ml of the study drug in a blinded manner before the loading dose to test for possible allergy. NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of participants exposed to allogeneic blood, allogeneic blood usage (units), fresh frozen plasma usage (units), platelet usage (units), blood loss, re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 7/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Patients were randomised by means of a computer-generated schedule
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Benoni 1996

Methods	Randomisation into blocks of 12 was done by an independent pharmacologist who was not otherwise engaged in the study. Pairs of ampoules, each containing 10ml of either the active substance or the placebo were numbered and packed into envelopes which were opened by the anaesthetist before administration. These ampoules could be identified only by their numbers, and the randomisation code was known only to the independent pharmacologist. The code was not broken until the end of the study and until all data had been corrected and included in the database. Ten patients were excluded from the study after randomisation
Participants	96 patients undergoing total knee arthroplasty were randomly allocated to one of two groups: • Tranexamic acid group: n = 43, M/F = 13/30, mean (sd) age = 76 (7) years • Control group (placebo): n = 43, M/F = 10/33, mean (sd) age = 74 (7) years
Interventions	• TXA group received 10mg/kg of TXA as a slow intravenous injection towards the end of the operation (median time 12 minutes - range 1-40 minutes) before deflation of the limb tourniquet. This dose was repeated after 3 hours from the other ampoule of the pair provided in the envelope. • Control group received a placebo of equal volumes of normal saline solution (0.9%). NB: 15 patients from the placebo group received an extra dose of TXA for severe post-operative

	bleeding, these patients represented the 'placebo-extra' group
Outcomes	***Outcomes reported:*** Number of participants exposed to allogeneic blood, allogeneic blood usage (units), blood loss, deep venous thrombosis, pulmonary embolus, wound haematomas, chest pain, haemoglobin concentrations
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Adequate
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Benoni 2000

Methods	Medication was administered using numbered ampoules and the randomisation was performed by a pharmacist not otherwise engaged in the study
Participants	40 patients undergoing total hip arthroplasty were randomly assigned to one of two groups: • Tranexamic acid group: n = 20, M/F = 6/14, mean (sd) age = 69.5 (10) years • Control group (Placebo): n=20, M/F = 11/8, mean (sd) age = 68 (10) years
Interventions	• Tranexamic acid group received 10mg/kg IV of TXA (Cyklokapron) at the end of the operation and received another 10mg/kg IV 3 hours later. • Control group received corresponding volumes of normal saline (placebo).
Outcomes	***Outcomes reported:*** Number of participants exposed to allogeneic blood, allogeneic blood usage (units), blood loss, amount of pre-operative autologous donated blood (2 units), infection
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate

Benoni 2000 (*Continued)*

Blinding? All outcomes	Yes	Double blind

Benoni 2001

Methods	Method of randomisation was not described. Medication was concealed by a code only known by the hospitals chief pharmacist who was not involved in the study
Participants	40 patients undergoing total hip arthroplasty were randomly assigned to one of two treatments groups: • Tranexamic acid group: n = 20, M/F = 9/9, mean (sd) age = 66 (9.5) years • Control group (Placebo): n = 20, M/F = 10/10, mean (sd) age = 68 (9.4) years
Interventions	• Tranexamic acid group received 100mg/ml of TXA (Cyklokapron), 10mg/kg (maximum 1g) in a slow (5-10 minutes) IV injection immediately before the operation. • Control group received a similar volume of saline as the same times as TXA.
Outcomes	***Outcomes reported:*** Number of participants exposed to allogeneic blood, allogeneic blood usage (units), pulmonary embolus
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate - medication was concealed by a code only known by the hospitals chief pharmacist who was not involved in the study
Blinding? All outcomes	Yes	Double blind

Berenholtz 2009

Methods	Patients were randomised according to a computer-generated randomisation schedule. Allocation was concealed through central (pharmacy) allocation
Participants	182 patients undergoing orthopaedic surgery were randomly allocated to one of two groups: • EACA group: n = 91, M/F = 26/65, mean (sd) age = 55.5 (14.0) years • Control group: n=91, M/F = 29/62, mean (sd) age = 55.4 (15.5) years

Interventions	• EACA group, received 100mg/kg administered immediately after anaesthesia followed by infusion of 10mg/kg/hr continued for 8 hours after surgery. • Control group received saline.
Outcomes	***Outcomes reported:*** Number of patients receiving blood transfusion, volume of blood transfused (units), blood loss, mortality, pulmonary embolism, myocardial infarction, renal failure, stroke, thrombosis, deep vein thrombosis, length of hospital stay (days)
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Patients were randomised according to a computer-generated randomisation schedule
Allocation concealment?	Yes	Adequate - allocation was concealed through central (pharmacy) allocation
Blinding? All outcomes	Yes	Double blind

Bernet 1999

Methods	Random code used for randomisation. Drug solutions were prepared by the hospital pharmacy
Participants	70 patients were randomised to one of two groups: • Tranexamic acid group: n = 28, M/F = 25/3, mean (sd) age = 61.3 (2.86) years • Aprotinin group: n = 28, M/F = 24/4, mean (sd) age = 58.4 (3.76) years
Interventions	• Tranexamic group received 200mL (10g) of TXA administered 20 minutes before sternotomy. Normal saline placebo was given at the same time as aprotinin doses for the purpose of blinding. • Aprotinin group received 200ml (2 million KIU=280mg) of aprotinin administered 20 minutes before sternotomy and 200mL (2 million KIU = 280mg) administered as a continuous infusion of 50ml/hr (500,000 KIU) until closure of the chest.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , fresh frozen plasma (units), platelets (units), blood loss, mortality, myocardial Infarctions, haematocrit levels, stroke, thrombotic complications, re-exploration for bleeding
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used. All patients received ASA until the day of the operation (100mg/day). All patients received cell salvage (Imed 960) - 8 hours post-operatively

Bernet 1999 (*Continued)*

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random code used for randomisation
Allocation concealment?	Unclear	Adequate - drug solutions were prepared by the hospital pharmacy
Blinding? All outcomes	Yes	Double blind

Bert 2008

Methods	A computer-generated randomisation list was used to generate the allocation sequence. No information was provided regarding allocation concealment
Participants	50 patients undergoing elective cardiac surgery were randomised to one of two groups: • Aprotinin group: n = 25, M/F = 20/5, mean (sd) age = 65.7 (10.2) years • Control group: n = 25, M/F = 20/5, mean (sd) age = 67.8 (8.3) years
Interventions	• Aprotinin group received loading dose of 2,000,000 KIU before sternotomy, then continuous infusion of 500,000 KIU until wound closure. • Control group did not receive aprotinin.
Outcomes	***Outcomes reported:*** Blood loss, volume of blood transfused (units), re-operation for bleeding, inflammatory cytokines
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol was not reported

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	A computer-generated randomisation list was used to generate the allocation sequence
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Bidstrup 1989

Methods	The trial drug was provided by the manufacturer (Bayer AG, Leverkusen) in identical case packs, each of 12 bottles identifiable only by the random number. Method of generating allocation sequences was not described
Participants	80 patients undergoing primary aorto-coronary bypass grafting were randomised to either one of two groups: • Aprotinin group: n = 40, M/F = 37/3, mean (sd) age = 58.1 (8.6) years • Control group (Placebo): n = 37, M/F = 32/5; mean (sd) age = 57.7 (8.3) years
Interventions	• Aprotinin group received after induction of anaesthesia, a loading dose of 280mg of aprotinin given intravenously through a central venous cannula over 20 mins, then a continuous infusion of 70mg/hr was begun and maintained until the patient left the operating theatre. In addition to the intravenous infusion, another 280mg of aprotinin was added to the priming volume of the heart lung machine by replacement of an aliquot of the priming volume. • Control group received an equal volume of saline. NB: Both intervention and control received preoperative autologous donation (PAD)
Outcomes	***Outcomes reported:*** Number of participants exposed to allogeneic blood, allogeneic blood usage (units), blood loss (18 -24hrs), mortality
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Bidstrup 1990

Methods	Method of randomisation and allocation concealment were not described
Participants	44 patients undergoing aortocoronary artery bypass graft surgery were randomly allocated to one of two groups: • Aprotinin group: n = 26, M/F = 21/5, mean (sd) age = 59 (8) years • Control group: n = 18, M/F = 15/3, mean (sd) age = 58 (8) years
Interventions	• Aprotinin group received a loading dose of 280mg (2 million KIU) of aprotinin after induction of anaesthesia and a constant infusion of 70mg/hr during the operation. A further 280mg was added to the pump prime. • Control group did not receive aprotinin.

Outcomes	***Outcomes reported:*** Number of participants exposed to allogeneic blood, allogeneic blood usage (units), fresh frozen plasma usage (units), platelets (units), blood loss (18-24hrs), re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Bidstrup 1993

Methods	Patients received aprotinin or placebo (normal saline) from identical bottles supplied by the manufacturer, identifiable only by their random number. Method of randomisation was not described
Participants	96 adult male patients undergoing first-time isolated coronary bypass grafting were randomised to either one of two groups: • Aprotinin group: n = 47, mean (sd) age = 59.1 (7.4) years • Control group (Placebo): n = 49, mean (sd) age = 58.8 (8.5) years NB: Six patients withdrew from the study, four in the aprotinin group and two in the placebo group
Interventions	• Aprotinin group received 280mg of aprotinin (contained in 200ml) as a loading dose before the commencement of bypass. An additional 280mg of aprotinin was added to the prime of the heart-lung machine. A constant infusion of 70mg/hr was maintained during the procedure until skin closure. • Control group (placebo) received identical volumes of normal saline.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss, haemoglobin levels, platelet counts, haemoglobin loss, activated clotting times, adverse events, graft patency, re-operation for bleeding, wound infection
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description

Bidstrup 1993 (*Continued)*

Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Bidstrup 2000

Methods	Patients were allocated to receive either placebo or active treatment in accordance with a previously determined randomization schedule in a double blind fashion. Allocation concealment was adequate, active drug and placebo were contained in identical bottles, identifiable only by a random number
Participants	60 patients undergoing aortocoronary bypass were randomised to one of two groups: • Aprotinin group (High dose): n = 30, M/F = 24/6, mean (sd) age = 63.0 (7.8) years • Control group (Placebo): n = 30, M/F = 27/3, mean (sd) age = 61.7 (6.8) years
Interventions	• Aprotinin group (High dose) received a loading dose 280mg (2 million KIU) of aprotinin over 20 minutes after anaesthesia, 280mg of aprotinin added to the pump prime and a continuous infusion of 70mg/hr until the end of the procedure. • Control group received a placebo of 0.9% normal saline.
Outcomes	***Outcomes reported:*** Number of participants exposed to allogeneic blood, mortality, myocardial infarction, re-operation for bleeding, wound infection, neurologic disturbance, atrial fibrillation/flutter.
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Blauhut 1994

Methods	Method of randomisation and allocation concealment were not described. No exclusions or loss to follow-up reported
Participants	45 patients undergoing cardiopulmonary bypass for coronary surgery were allocated at random to one of three groups: • Aprotinin group: n = 15, M/F = 13/2, mean (sd) age = 64.1 (2.2) years • Tranexamic group: n = 16, M/F = 13/3, mean (sd) age = 62.5 (2.2) years • Control group: n = 14, M/F = 11/3, mean (sd) age = 62.7 (2.6) years
Interventions	• Aprotinin group received a loading dose of 2 million kallikrein inactivator units (KIU) plus a maintenance dose of 500,000 KIU/hr until the patient was transferred to the recovery area of the intensive care unit. In addition, 1 million KIU was added to the oxygenator priming fluid, giving an average total dose of 4.2 million KIU of aprotinin. • Tranexamic (TXA) group received 10mg/kg of TXA beginning 30 minutes before incision of the skin and followed by 1mg/kg/hr for 10 hours after the beginning of the surgical procedures. • Control group did not receive aprotinin or TXA treatment.
Outcomes	***Outcomes reported:*** Number of participants exposed to allogeneic blood, allogeneic blood usage (units), blood loss (24 hrs), mortality, platelet function, coagulation, haematocrit levels
Notes	Quality assessment score (Schulz criteria): 1/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Boldt 1991

Methods	Method of randomisation and allocation concealment were not described. No exclusions or loss to follow-up reported
Participants	30 male patients undergoing elective aortocoronary bypass grafting were randomised to one of three groups: • Cell Salvage group: n = 10, mean (sd) age = 60.4 (7.1) years • Hemofiltration group: n = 10, mean (sd) age = 62.4 (8.6) years • Aprotinin group: n = 10, mean (sd) age = 62.7 (7.8) years • Control group: n = 10, mean (sd) age = 46.6 (16.2) years NB: Control group did not appear to be part of the randomised schedule. Possibly a non-concurrent or historical control group

Interventions	• Cell Salvage group - a cell separator (Cell Saver IV, Hemonetics) was used during and after CPB. • Haemofiltration group had blood concentrated during and after CPB by means of a hemofiltration device (HF-80, Fresenius, Bad Homburg, FRG). • Aprotinin group received an infusion of 2 million kallikrein inactivator units (KIU) before the operation (loading dose) and then as a continuous infusion of 500,000 units/hr until the end of the operation. In addition, 2 million KIU of aprotinin was added to the priming of the heart-lung machine. In addition blood concentration during and after CPB was performed with a hemofiltration device (HF-80, Fresenius, Bad Homburg, FRG) the same as for Group 2. • Control group underwent neurosurgery operations. NB: Only Group 2 and Group 3 were compared.
Outcomes	***Outcomes reported:*** Number of participants exposed to allogeneic blood, allogeneic blood usage (units), blood loss (24hrs)
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used. Study used neurosurgical patients as a control group

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Boldt 1994

Methods	Method of randomisation and allocation concealment were not described
Participants	40 patients undergoing cardiac surgery were randomised to one of two groups: • Aprotinin group (High dose): n = 20, mean (sd) age = 64 (4) years • Control group: n = 20, mean (sd) age = 63 (5) years NB: Gender data were not reported
Interventions	• Aprotinin group (High dose) received 2 million KIU of aprotinin after the induction of anaesthesia, 500,000 KIU/hr of aprotinin as a continuous infusion until the end of the operation, and 2 million KIU was added to the CPB pump prime. • Control group received the same amount of saline solution as aprotinin was administered.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), fresh frozen plasma usage (units), blood loss (24hrs), re-operation for bleeding, haemoglobin levels
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Boylan 1996

Methods	Study agents were prepared by the hospital pharmacy using a randomisation schedule provided in sealed envelopes. The method used to generate allocation sequences was not described
Participants	45 patients undergoing primary, isolated orthotopic liver transplantation were randomised to one of two groups: • Tranexamic acid group: n = 25, mean (sd) age = 49.5 (9.1) years • Control group (Placebo): n = 20, mean (sd) age = 48.8 (9.6) years
Interventions	• Tranexamic acid (TXA) group received a continuous infusion of TXA in normal saline (40mg/kg/hr to a maximum dose of 20g). • Control group (placebo) received an equivalent volume of 0.9% normal saline alone.
Outcomes	Outcomes reported: Allogeneic blood usage (units), fresh frozen plasma usage (units), platelet usage (units), blood loss, mortality, portal vein thrombosis, hepatic thrombosis, hospital length of stay, intensive care unit (ICU) length of stay, overall donor exposure
Notes	Quality assessment score (Schulz criteria):5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	No	Inadequate - randomisation schedule was provided in sealed envelopes
Blinding? All outcomes	Yes	Double blind

Brown 1997

Methods	Method of allocation concealment was not described. Patients were randomised using a computer-generated random number sequence
Participants	91 patients scheduled for elective coronary revascularisation were randomly allocated to one of three groups: • Control group (Placebo): n = 30, M/F = 24/6, mean (sd) age = 59 (7) years • Tranexamic acid group (TXA before CPB): n = 30, M/F = 25/5, mean (sd) age = 61 (9) years • Tranexamic acid group (TXA after CPB): n = 30, M/F = 24/6, mean (sd) age = 62 (10) years
Interventions	• Control group received equivalent volumes of normal saline solution. • Tranexamic acid group received 15mg/kg of TXA before CPB, followed by a TXA infusion of 1mg/kg/hr for 5hrs. • Tranexamic acid group received 15mg/kg of TXA after CPB, followed by a TXA infusion of 1mg/kg/hr for 5hrs.
Outcomes	***Outcomes reported:*** Number of participants exposed to allogeneic blood, haematologic/thromboelastographic/coagulation characteristics, mortality, myocardial infarction, stroke, re-exploration for bleeding, infection
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Adequate - computer-generated random number sequence
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Caglar 2008

Methods	A computer-generated randomisation list was used to generate the allocation sequence. No information was provided regarding allocation concealment
Participants	100 female patients undergoing myomectomy were randomised to one of two groups: • Tranexamic acid group: n = 50, mean (sd) age = 34.2 (5.5) years • Control group: n = 50, mean (sd) age = 36.5 (4.5) years
Interventions	• Tranexamic acid group received bolus of 10mg/kg over 10 minutes 15 minutes before incision, then continuous infusion of 1mg/kg/hr for 10 hours. • Control group received saline.

Caglar 2008 *(Continued)*

Outcomes	***Outcomes reported:*** number of patients exposed to allogeneic blood, blood loss, volume of blood transfused
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated randomisation
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Camarasa 2006

Methods	Randomisation was achieved by computer-generated random numbers. The randomised assignment was sealed in an opaque, numbered envelope which was opened only by the nurse who prepared the solutions. This nurse was the only person who knew the patients study groups and did not participate in any other phase of the trial
Participants	68 patients undergoing total knee replacement were randomised to one of two groups: • Tranexamic acid group: n = 35, M/F = 9/26, mean (range) age = 73 (61-84) years • Epsilon aminocaproic acid group: n = 32, M/F = 4/28, mean (range) age = 73 (59-80) years NB: One patient was excluded from the final analysis
Interventions	• Tranexamic acid group received 10mg/kg of TXA administered over 30 minutes immediately before releasing the tourniquet followed by a continuous intravenous infusion of 10mg/kg for 3 hours. • Epsilon aminocaproic acid group received 100mg/kg of EACA administered over 30 minutes immediately before releasing the tourniquet followed by a continuous intravenous infusion of 1g/hr for 3 hours. NB: Both groups were exposed to cell salvage and pre-operative autologous blood donation (PAD)
Outcomes	***Outcomes reported:*** Number of participants exposed to allogeneic blood, allogeneic blood usage (units), blood loss, deep vein thrombosis
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description

Adequate sequence generation?	Yes	Computer-generated random numbers
Allocation concealment?	No	Inadequate - randomised assignment was sealed in an opaque, numbered envelope
Blinding? All outcomes	Yes	Double blind

Capdevila 1998

Methods	Randomisation was performed using a random number list generated by computer programme. Allocation was adequately concealed (administered fluids were prepared by the hospitals central pharmacy in identical 100-ml bottles)
Participants	23 patients scheduled for orthopaedic surgery of the hip, femur or pelvis for sepsis or malignant tumours were randomly allocated to one of two groups: • Aprotinin group: n = 12, M/F = 7/5, mean (sd) age = 48.6 (17.3) years • Control group (Placebo): n = 11, M/F = 6/5, mean (sd) age = 48.5 (16.3) years
Interventions	• Aprotinin group was administered a bolus of 1 million kallikrein inactivation units (KIU) during a 30 minute injection period, followed by a continuous infusion of 500,000 KIU/hr throughout the duration of surgery. • Control group received identical volumes of saline over the same time periods.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), fresh frozen plasma usage (units), platelet usage (units), blood loss, haemoglobin and haematocrit levels, coagulation and fibrinolytic pathway explorations, allergic reactions
Notes	Quality assessment score (Schulz criteria): 7/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation was performed using a random number list generated by computer programme
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Carrera 1994

Methods	Randomisation and allocation concealment not specified. No exclusions or loss to follow-up reported. [Spanish language]
Participants	102 patients undergoing cardiac surgery were randomly assigned to one of two groups: • Aprotinin group: n = 51, M/F = 20/31, mean (sd) age = 54 (13.1) years • Control group: n = 51, M/F = 21/30, mean (sd) age = 55 (13.0) years
Interventions	• Aprotinin group received 2 million kallikrein inhibiting units (KIU) of aprotinin upon anaesthesia induction, a similar dose in the extracorporeal circulation priming pump, and a maintenance dose of 500,000 KIU/hr until the removal from the operating theatre. • Control group did not receive aprotinin.
Outcomes	***Outcomes reported:*** Number of participants exposed to allogeneic blood, allogeneic blood usage, fresh frozen plasma usage, platelet usage, blood loss, myocardial infarction
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Casas 1995

Methods	Generation of allocation sequences was not specified. Allocation concealment was by sealed envelopes. The pharmacy prepared the encoded infusions
Participants	149 patients scheduled to undergo either coronary artery bypass grafting (CABG), heart valve replacement or annuloplasty, combined valve replacement and CABG, or closure of atrial septal defects, were randomised to one of three groups: • Aprotinin group: n = 48, M/F = 31/17, mean (sd) age = 57 (10) years • Desmopressin group: n = 50, M/F = 33/17, mean (sd) age = 58 (12) years • Control group (Placebo): n = 51, M/F = 31/20, mean (sd) age = 54 (12) years
Interventions	• Aprotinin group received 2 million kallikrein inactivator units (KIU) of aprotinin before anaesthesia (time stage 1) given over 20 to 30 minutes. A dose of 2 million KIU was added to the prime solution of the heart-lung machine (time stage 2). Aprotinin was administered continuously (time stage 3) at 500,000 KIU/hr (50ml/hr) until the end of the operation (from skin incision to skin closure), then patients received 50ml of saline (time stage 4). • Desmopressin group received desmopressin infusions corresponding to 0.3 to 0.4 ug/kg body weight. Desmopressin was infused in 50ml of physiologic saline solution for 20 to 30

	minutes, 15 minutes after protamine administration (time stage 4). In other time phases (1-3) patients received saline solution only. • Control group received a placebo of saline solution during all four stages.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , number of patients exposed to fresh frozen plasma, number of patients exposed to platelets, blood loss (24hrs), re-operation for bleeding, femoral embolism, stroke
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	No	Inadequate - allocation concealment was by sealed envelopes
Blinding? All outcomes	Unclear	Double blind

Casati 1999

Methods	Method ofrandomisation and allocation concealment were not described
Participants	210 patients undergoing cardiac surgery were randomly assigned to one of three groups: • Epsilon aminocaproic group: n = 68, M/F = 54/12, mean (sd) age = 58.7 (10) years • Tranexamic acid group: n = 72, M/F = 57/13, mean (sd) age = 61.9 (9.6) years • Aprotinin group: n= 70, M/F = 54/13, mean (sd) age = 63.6 (9.6) years
Interventions	• EACA group received 5g during 20 minutes after induction of anaesthesia before sternotomy followed by a continuous infusion of 2g/hr until the end of the operation + 2.5g added to the pump prime. • TXA group received 1g over 20 minutes before sternotomy, followed by a continuous infusion of 400mg/hour during operative period and 500mg added to the pump prime. • Aprotinin group received 280mg throughout 20 minutes before sternotomy, followed by a constant infusion of 70mg throughout the operation and 280mg added to the pump prime. NB: All groups were exposed to cell salvage. Pre-operative autologous blood donation use was evenly distributed between groups
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) blood loss, mortality, myocardial infarction, deep venous thrombosis, pulmonary embolus, pre-operative autologous donation of blood, neurological complications, re-operation for surgical bleeding
Notes	Quality assessment score (Schulz criteria): 1/7 Transfusion protocol used

Casati 1999 *(Continued)*

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Casati 2000

Methods	Patients were randomised into treatment groups by means of a computer generated random number sequence. Allocation concealment was not described. Trial was unblinded
Participants	1040 patients undergoing primary elective cardiac operations were randomly assigned to one of two groups: • Tranexamic acid group: n = 522, M/F = 415/107, mean (sd) age = 61 (10) years • Aprotinin group: n = 518, M/F = 412/106, mean (sd) age = 62 (10) years
Interventions	• Tranexamic acid group received 1g over 20 minutes before surgical incision followed by a constant infusion of 400mg/hr during the entire operative period and 500mg was added to the pump prime. • Aprotinin group received 280mg for 20 minutes before surgical incision followed by a constant infusion of 70mg/hr until the end of the operation and 280mg was added to the pump prime. NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss, mortality, myocardial infarction, fresh frozen plasma usage, (units), platelet usage (units), pulmonary embolus
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated random number sequence
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	No	

Casati 2001

Methods	Method of randomisation was not described. Coded infusion syringes were used and prepared by a staff member not directly involved with perioperative clinical treatment
Participants	40 patients undergoing elective cardiac surgery were randomised to one of two groups: • Tranexamic acid group: n = 20, M/F = 15/5, mean (sd) age = 64 (13) years • Control group (Placebo): n = 20, M/F = 17/3, mean (sd) age = 62 (11) years
Interventions	• TXA group (off-pump surgery) received a bolus of 1g of TXA over 20 minutes after the induction of anaesthesia but before skin incision and a continuous infusion of 400mg/hr during the whole surgical period. • Control group received an infusion of saline.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Casati 2002

Methods	Coded infusion syringes were used to conceal which medication was placebo and which was TXA. Method of randomisation was not described
Participants	60 patients undergoing elective thoracic-aorto surgery were randomised to one of two groups: • Tranexamic acid group: n = 30, M/F = 23/6, mean (sd) age = 59 (13) years • Control group (Placebo): n = 30, M/F = 19/10, mean (sd) age = 63 (11) years
Interventions	• Tranexamic acid group received a bolus of TXA 1g in 20 minutes after the induction of anaesthesia but before skin incision and a continuous infusion of 400mg/hr during the whole surgical period and an additional 500mg of TXA was added to the pump prime of CPB. • Control group received an infusion of saline solution.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), number of patients exposed to fresh frozen plasma, number of patients exposed to platelets, blood loss (24hrs), re-operation for bleeding, mortality, myocardial infarction, pulmonary embolus, pre-operative aspirin, pre-operative anticoagulant, stroke, hospital length of stay (days)

Casati 2002 (*Continued)*

Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Casati 2004

Methods	Randomisation was by means of two seperate computer-generated random number sequences. Coded syringes were used to administer medication
Participants	102 patients scheduled for cardiac surgery with either 'on-pump' or 'off-pump' procedures were randomised to one of four groups: • Control group (Placebo) ('Off-pump' surgery): n = 25, M/F = 21/4, mean (sd) age =61 (11) years • Tranexamic acid group ('Off-pump' surgery): n = 26, M/F = 20/6, mean (sd) age = 64 (12) years • Control group (placebo) ('On-pump' surgery): n = 25, M/F = 21/4, mean (sd) age = 60 (9) years • Tranexamic acid group ('On-pump' surgery): n = 26, M/F = 24/2, mean (sd) age = 64 (9) years
Interventions	• Control group ('Off-pump' surgery) received an equivalent volume of saline solution administered as a bolus injection in 20 minutes before skin incision, followed by a continuous infusion of saline until the completion of surgery. • Tranexamic acid group ('Off-pump' surgery) received a bolus injection of 1g of TXA in 20 minutes before skin incision followed by a continuous infusion of 400mg/hr until completion of surgery. • Control group ('On-pump' surgery) received the same treatment as Group 1 plus received an equivalent volume of saline solution added to the CPB pump. • Tranexamic acid ('On-pump' surgery) received the same treatment as Group 2 plus received 500mg of TXA added to the pump prime. NB: 'On-pump' surgery patients (Groups 3 & 4) the remaining blood in the cardiopulmonary bypass (CPB) circuit and that blood aspirated from the surgical field was concentrated with a cell separator and reinfused. For 'Off-pump' surgery patients only in cases of significant intra-operative bleeding was the shed blood concentrated in a cell separator and reinfused. No autotransfusion of shed mediastinal blood was performed during the post-operative period for any group ONCAB-Cell Salvage. Only in cases of significant intra-operative bleeding was the shed blood concentrated in a cell separator and reinfused. No autotransfusion of shed mediastinal blood was performed during the post-operative period

Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), number of patients exposed to fresh frozen plasma, number of participants exposed to platelets, blood loss (24hrs), re-exploration for bleeding, stroke, intra-operative resternotomy, fresh frozen plasma usage (units), platelet usage (units)
Notes	Quality assessment score (Schulz criteria): 7/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random number sequences
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Cicek 1996a

Methods	Method of randomisation and allocation concealment were not described
Participants	75 patients scheduled for elective cardiac operations with cardiopulmonary bypass were randomly assigned to one of three groups: • Aprotinin group (High dose): n = 25, M/F = 22/3, mean (sd) age = 44.9 (18.6) years • Aprotinin group (Post-operative low dose): n = 25, M/F = 19/6, mean (sd) age = 52.9 (12.4) years • Control group: n = 25, M/F = 21/4, mean (sd) age = 46.7 (15) years
Interventions	• Aprotinin group (High dose) received a bolus of 2 million kallikrein inhibiting units (KIU) of aprotinin (280mg), plus a maintenance dose of 500,000 KIU/hr (70mg/hr) until the end of the operation. In addition 2 million KIU (280mg) was added to the oxygenator priming fluid. • Aprotinin group (Post-operative low dose) received a bolus of 2 million KIU (280mg) at the end of the procedure before transfer to the intensive care unit. • Control group did not receive aprotinin.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss, myocardial infarction
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description

Cicek 1996a *(Continued)*

Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Cicek 1996b

Methods	Patients were randomised to receive aprotinin or placebo by means of a random numbers table. Method of allocation concealment was not described
Participants	57 patients undergoing cardiac operations with cardiopulmonary bypass (CPB) were randomly assigned to one of two groups: • Aprotinin group: n = 29, M/F = 21/8, mean (sd) age = 51.6 (15.4) years • Control group (Placebo): n = 28, M/F = 19/9, mean (sd) age = 48.2 (14.2) years
Interventions	• Aprotinin group received a bolus of 2 million kallikrein inhibiting units (KIU) of aprotinin (280mg) infused over 15 minutes when they arrived in intensive care. • Control group received an equal volume of normal saline solution at corresponding times to the aprotinin treated group.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random numbers table
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Cicekcioglu 2006

Methods	Method of randomisation and allocation concealment were not described. Data were collected in a blinded fashion
Participants	44 patients undergoing coronary artery bypass grafting were randomly assigned to one of two groups: • Aprotinin group: n = 24, M/F = 19/5, mean (sd) age = 48.6 (12.1) years

Cicekcioglu 2006 (*Continued)*

	• Control group (Placebo): n = 20, M/F = 18/2, mean (sd) age = 48.3 (9.0) years	
Interventions	• Aprotinin group (low-dose) administered in two equal doses - bolus of 250,000 KIU 5 minutes before skin incision just after induction of anaesthesia, second dose of 250,000 KIU was added to the prime pump. • Control group received saline.	
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, amount of allogeneic blood transfused (units), blood loss, mortality, length of hospital stay, post-operative morbidity	
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Claeys 2007

Methods	Methods of sequence generation and allocation concealment were not described	
Participants	40 patients undergoing orthopaedic (hip) surgery were randomised to one of two groups: • Tranexamic acid group: n = 20, M/F = 5/15, mean (sd) age = 73 (8) years • Control group (Placebo): n = 20, all females, M/F = 7/13, mean (sd) age = 68 (11) years	
Interventions	• Tranexamic acid group received single pre-operative dose of 15mg/kg. • Control group received a placebo of saline.	
Outcomes	***Outcomes reported:*** Number of patients receiving blood transfusions, blood loss, deep vein thrombosis	
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear

Claeys 2007 (*Continued*)

Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Coffey 1995

Methods	Method of randomisation was not described. Pharmacy controlled the randomisation process. Method of allocation concealment was not clear
Participants	30 patients undergoing cardiac surgery were randomised to either one of two groups: • Tranexamic acid group: n = 16, M/F = 5/11, mean age = 63.94 years • Control group (Placebo): n = 14, M/F = 5/9, mean age = 64.75 years
Interventions	• Tranexamic acid group received a loading dose of 10mg/kg of TXA over a period of 30 minutes at the time of skin incision followed by a 1mg/kg/hr infusion over 12 hours. • Control group received an equal volume of saline.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss, mortality
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol not specified

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Cohen 1998

Methods	Patients were randomised by the hospital pharmacy after stratification and blocking in groups of six. The pharmacy supplied bags that contained dipyridamole (DIP), aprotinin (APR) or a saline placebo
Participants	115 patients undergoing cardiac operations for valve replacement or myocardial revascularization, or a combined procedure were randomised to one of two groups: • Aprotinin group: n = 56, M/F = 44/12, mean (sd) age = 63 (9) years • Control group (Placebo): n = 59, M/F = 47/12, mean (sd) age = 61 (8) years

Interventions	• Aprotinin group received a high dose of aprotinin (Full Hammersmith) with a loading dose of 280mg (2 million KIU) plus a pump prime dose of 280mg and a maintenance dose 70mg/hr intra-operatively and continued for 1 hour post-operatively. • Control group received a saline placebo. NB: All patients were administered dipyridamole (DIP) orally (100mg four times daily for three or more doses pre-operatively) and intravenously (at a rate of 0.24mg/kghr beginning before anaesthesia induction and continuing for 1 hour post-operatively). Autologous blood shed into sterile cardiotomy reservoirs from chest drains was autotransfused to the patient when drainage exceeded 150ml during the first 4 hours post-operatively
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss, mortality, myocardial infarction, autologous shed blood transfused, blood loss (24 hrs), renal failure, stroke, intensive care unit length of stay (days), hospital length of stay (days)
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Colwell 2007

Methods	Patients were randomly assigned on the day of surgery to a treatment group in a 1:1 ration from a computer-generated list managed by an interactive voice response system. Aprotinin and placebo were provided to the pharmacy in the same packaging and were dispensed by the randomisation assignment, blinding the patient and staff to the actual treatment group. The primary efficacy analysis was performed on the intention-to-treat population
Participants	359 patients undergoing orthopaedic surgery (hip arthroplasty) were randomised to one of two groups: • Aprotinin group: n = 180, M/F = 61/84, mean (sd) age = 63.4 (12.1) years • Control group: n = 179, M/F = 81/96, mean (sd) age = 64.4 (12.7) years
Interventions	• Aprotinin group - received a test dose of 10,000 KIU, loading dose of 2 million KIU, then 0.5 million KIU per hour until end of surgery. • Control group received saline.
Outcomes	***Outcomes reported:*** Number of patients receiving blood transfusions, volume of blood transfused (units), blood loss, deep vein thrombosis, renal failure, myocardial infarction, stroke, mortality,

	pulmonary embolism	
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated list
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Corbeau 1995

Methods	Method of randomisation and allocation concealment were not described. Two patients were excluded after randomisation. [French language]	
Participants	104 adults undergoing either coronary artery bypass grafting (CABG) or aortic valve replacement (AVR) were randomised to one of three groups: • Aprotinin group: n = 43 [AVR: n = 20, M/F = 13/7, mean (sd) age = 64 (16) years; CABG: n = 23, M/F = 20/3, mean (sd) age = 68 (8) years] • Tranexamic acid group: n = 41 [AVR: n = 19, M/F = 7/12, mean (sd) age = 63 (19) years; CABG: n = 22, M/F = 19/3, mean (sd) age = 62 (9) years • Control group: n = 20 [AVR: n = 10, M/F = 7/3, mean (sd) age = 60 (22) years; CABG: n = 10, M/F = 9/1, mean (sd) age = 66 (3) years]	
Interventions	• Aprotinin group received 2 million kallikrien inactivator units (KIU) of aprotinin (280mg) after induction of anaesthesia, followed by an infusion of 500,000 KIU/hr (70mg/hr) until chest closure, with a supplement to the oxygenator prime of 2 million KIU of aprotinin. • Tranexamic acid group received 15mg/kg of TXA between the injection of heparin (400IU/kg) and the beginning of extracorporeal circulation, plus 15mg/kg after protamine injection (1.3mg/100IU of heparin). • Control group did not receive any antifibrinolytic therapy.	
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss	
Notes	Quality assessment score (Schulz criteria): 1/7 Transfusion protocol used	
Risk of bias		
Item	**Authors' judgement**	**Description**

Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Cosgrove 1992

Methods	Method of randomisation and allocation concealment were not described. All subjects were included in the final analysis
Participants	169 patients undergoing isolated re-operative myocardial revascularisation were randomised to either one of three groups: • Aprotinin group (High dose): n = 57, males (87.7%), mean (sd) age = 60.8 (7.8) years • Aprotinin group (Low dose): n = 56, males (80.4%), mean (sd) age = 61.1 (8.3) years • Control group (Placebo): n = 56, males (87.5%), mean (sd) age = 63.0 (8.8) years
Interventions	• Aprotinin group (High dose) received 70mg of aprotinin in 50ml of 0.9% saline. After induction of anaesthesia, a loading dose of 200ml of aprotinin solution was given intravenously over 20 minutes. Immediately after this, a continuous infusion of 50ml/hr was begun and maintained until the patient left the operating room. An additional 200ml of aprotinin was added to the prime volume of the cardiopulmonary bypass machine. • Aprotinin group (Low dose) received 35mg of aprotinin in 50ml of 0.9% saline solution at corresponding times as Group 1. • Control group received 50ml of saline solution at corresponding times as Group 1.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), mortality, myocardial infarction, re-operation for bleeding, fresh frozen plasma usage (units), platelet usage (units)
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol not specified

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Cvachovec 2001

Methods	Method of randomisation and allocation concealment were not described in the abstract. [Czech Republic]
Participants	42 patients undergoing total hip arthroplasty were randomly allocated to one of two groups: • Aprotinin group (Low dose): n = 20, M/F = 10/10 • Control group: n = 22, M/F = 8/14 NB: No age data were reported
Interventions	• Aprotinin group (Low dose) received 2 million KIU (280mg) of aprotinin started pre-operatively and continued in the course of the first hour of surgery. • Control group did not receive aprotinin.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss
Notes	Foreign language paper Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

D'Ambra 1996

Methods	A separate random code, using blocks of six, was generated for each site by the statistical department of Bayer Incorporated. The study medication for each patient was supplied for each patient in a case pack containing 14 vials. The loading dose vials, pump prime vials, and constant infusion vials were separately identified and packaged within the pack for each patient. Investigators were blinded to the identity and lot number of each case pack
Participants	213 patients undergoing cardiac surgery were enrolled and randomised at the five sites to one of three groups: • Aprotinin group (High dose): n = 65, M/F = 31/34, mean (sd) age = 59.8 (3.1) years • Aprotinin group (Low dose): n = 62, M/F = 33/29, mean (sd) age = 59.2 (3.2) years • Control group (Placebo): n = 64, M/F = 30/34, mean (sd) age = 60.0 (3.1) years NB: Of the 213 patients enrolled and randomised, 212 were included in the safety analysis and 191 were included in a primary analysis of efficacy
Interventions	• Aprotinin group (High dose) received an intravenous loading dose of 280mg of aprotinin (2 million KIU) infused over 20-30 minutes followed by a continuous infusion of 70mg/hr (500, 000 KIU/hr) infused until chest closure. An additional dose of aprotinin equivalent to the loading

	dose was added to the pump prime. • Aprotinin group (Low dose) received a loading dose of 140mg of aprotinin (1 million KIU) infused over 20-30 minutes followed by a continuous infusion of 35mg (250,000 KIU/hr) of aprotinin, infused until chest closure. An additional dose of aprotinin, equivalent to the loading dose, was added to the pump prime. • Control group received equivalent volumes of normal saline solution at corresponding times to the active treatments. NB: Blood conservation measures were used for all groups. These measures included the reinfusion of post-operative mediastinal shed blood (cell salvage) and the pre-operative donation of autologous blood (PAD). Epsilon aminocaproic acid (EACA) and desmopressin (DDAVP) were used to treat active bleeding after the reversal of heparin
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), fresh frozen plasma usage (units), platelet usage (units), mortality, myocardial infarction, re-operation, renal dysfunction, deep vein thrombosis, cardiovascular complications, cerebrovascular accident
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random code generated for each site by the statistical department of Bayer
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

D'Ambrosio 1999

Methods	Method of randomisation and allocation concealment were not described
Participants	60 patients undergoing total hip arthroplasty were randomised into one of four groups: *Comparison 1:* • Aprotinin group: n = 15, M/F = 8/7, mean (sd) age = 61.5 (9.2) years • Control group (Placebo): n = 15, M/F = 9/6, mean (sd) age = 66.7 (7.3) years *Comparison 2:* • Aprotinin group: n = 15, M/F = 7/8, mean (sd) age = 66.6 (9.2) years • Control group (Placebo): n = 15, M/F = 7/8, mean (sd) age = 60.5 (12.9) years
Interventions	*Comparison 1:* • Aprotinin group (epidural + general anaesthesia) received 500,000 KIU of aprotinin administered as a bolus before skin incision and 500,000 KIU continuous infusion until the skin was sutured.

	• Control group (epidural + general anaesthesia) received saline solution 0.9% in same manner as aprotinin. *Comparison 2:* • Aprotinin group (general anaesthesia) 500,000 KIU was administered as a bolus before skin incision and 500,000 KIU continuous until the skin was sutured. • Control group (placebo) (general anaesthesia) saline solution 0.9% in the same manner as aprotinin. NB: All subjects were exposed to pre-operative autologous blood donation and cell savage
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss, allogeneic & autologous blood usage (units)
Notes	Quality assessment score (Schulz criteria): 2/7 No transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Daily 1994

Methods	Method of randomisation was not described. Epsilon-aminocaproic acid (EACA) and placebo were delivered to the operating room in numbered, but otherwise identical vials labelled "study drug"
Participants	40 patients undergoing first-time coronary artery bypass grafting without prior sternotomy were randomised to one of two groups: • Epsilon aminocaproic acid group: n = 21, M/F 14/7, mean (sd) age = 63 (9) years • Control group (Placebo): n = 19, M/F = 18/1, mean (sd) age = 67 (10) years
Interventions	• Epsilon aminocaproic acid group (EACA) received 10g of EACA in 40ml of saline solution given after induction of anaesthesia but before the skin incision. Another 40ml was given after heparin administration in the pump, and a third 40ml dose was given after the administration of protamine. • Control group (Placebo) received equivalent volumes of saline solution. NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss (12/24hrs), myocardial infarction, stroke (cerebrovascular accident), use of shed mediastinal blood
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Dalmau 1999

Methods	Method of randomisation and allocation concealment were not described
Participants	124 patients undergoing orthotopic liver transplantation were randomised to one of three groups: • Epsilon aminocaproic acid group: n = 42 • Tranexamic acid group: n = 42 • Control group (Placebo) group: n = 40 NB: No age or gender data were reported.
Interventions	• Epsilon aminocaproic acid (EACA) group received a continuous infusion of EACA (8g in 480mL normal saline) at 16mg/kg per hour. EACA was infused from induction of anaesthesia to graft reperfusion. • Tranexamic acid group (TXA) received a continuous infusion of TXA (5g in 450mL normal saline) at 10mg/kg per hour. TXA was infused from induction of anaesthesia to graft reperfusion. • Control group received an equal volume infusion of normal saline. Placebo was infused from the induction of anaesthesia to graft reperfusion.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), fresh frozen plasma usage (units), platelet usage (units), thrombotic events, cryoprecipitate (units)
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Dalmau 2000

Methods	Drugs were prepared then randomised to patients using a randomisation schedule provided in sealed envelopes
Participants	132 patients undergoing orthotopic liver transplantation (OLT) were randomly assigned to one of three groups: • Epsilon aminocaproic acid group: n = 42, M/F = 26/16, median (range) age = 56 (32-69) years • Tranexamic acid group: n = 42, M/F = 31/11, median (range) age = 58 (22-69) years • Control group (Placebo): n = 40, M/F = 22/18, median (range) age = 60 (18-67) years
Interventions	• Epsilon aminocaproic acid (EACA) group received a continuous infusion of EACA (8g in 480ml of normal saline) at a rate of 16mg/kg/hr from the induction of anesthesia until the portal vein was unclamped. • Tranexamic acid (TXA) group received a continuous dose infusion of TXA (5g in 450ml of normal saline) at a rate of 16mg/kg/hour from the induction of anaesthesia until the portal vein was unclamped. • Control group received isotonic saline at an equal volume (10ml/kg/hour) from the induction of anaesthesia until the portal vein was unclamped.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , fresh frozen plasma (units), platelets (units), other arterial thrombosis, prophylactic DDAVP treatment, DDAVP treatment for bleeding, EACA treatment (clinical fibrolysis)
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	No	Inadequate - sealed envelopes were used to conceal treatment allocation
Blinding? All outcomes	Yes	Double blind

Dalmau 2004

Methods	Drugs were prepared and then randomised to patients using a randomisation schedule provided in sealed envelopes. Method of randomisation was not described
Participants	127 patients undergoing orthotopic liver transplantation were randomised to one of two groups: • Aprotinin group (Low dose): n = 63, M/F = 45/19, mean (sd) age = 54 (9) years • Tranexamic acid group: n = 64, M/F = 44/19, mean (sd) age = 53 (10) years

Interventions	• Aprotinin group (Low dose) received a bolus of 2 million KIU in 250ml of IV solution in 30 minutes followed by a continuous infusion of 500, 000 KIU/hr. Diluted in normal saline to be administered at a rate of 100ml/hr after the bolus dose. • Tranexamic acid (TXA) group received a bolus of 250ml of normal saline in 30 minutes followed by a continuous infusion of TXA at a dose of 10mg/kg/hr. Diluted in normal saline to be administered at a rate of 100ml/hour after the bolus dose.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), fresh frozen plasma (units), platelets (units), mortality, myocardial infarction, DDAVP pre-operative administration, EACA intra-operative administration, any thrombosis, re-operation for bleeding, renal failure
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	No	Inadequate - sealed envelopes were used to conceal treatment allocation
Blinding? All outcomes	Yes	Double blind

Defraigne 2000

Methods	Randomisation was accomplished using a random number table. Sealed envelopes were used to conceal treatment allocation
Participants	200 patients undergoing cardiac surgery were randomly allocated to one of four groups: • Aprotinin group: n = 50, M/F = 34/16, mean (sd) age = 62.8 (13.4) years • Control group: n = 50, M/F = 36/14, mean (sd) age = 64.2 (11.3) years • Aprotinin group: n = 50, M/F = 35/15, mean (sd) age = 64 (13.4) years • Control group: n = 50, M/F = 34/16, mean (sd) age = 60.1 (12.7) years
Interventions	• Aprotinin group (Heparin coated CPB circuit with aprotinin administration - HCO-A) received a loading dose of 280mg (2 million KIU) before surgery and 280mg in the pump prime and a continuous infusion of 500, 000 KIU/hour IV. • Control group (Heparin coated CPB circuit without aprotinin - HCO). • Aprotinin group (Uncoated CPB circuit with aprotinin) received a loading dose of 280mg (2 million KIU) of aprotinin before surgery and 280mg in the prime solution and continuous infusion of 500,000 KIU/hour IV. • Control group (Uncoated CPB circuit without aprotinin administration).
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), fresh frozen plasma usage (units), platelet usage (units), blood loss

Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table
Allocation concealment?	No	Inadequate - sealed envelopes were used to conceal treatment allocation
Blinding? All outcomes	No	Single blind

Del Rossi 1989

Methods	Method of randomisation and allocation concealment were not described
Participants	350 patients undergoing elective coronary artery bypass surgery, repair of myocardial aneurysms, valve replacement or combined procedures were randomly assigned to one of two groups: • Epsilon aminocaproic acid group: n = 170, M/F = 132/38, mean (sd) age males = 58.9 (2.1) years; mean (sd) age females = 61.6 (2.8) years • Control group (Placebo): n = 180, M/F = 144/66, mean (sd) age males = 59.8 (5.6) years; mean (sd) age females = 60.2 (4.2) years
Interventions	• Epsilon aminocaproic acid group received an initial priming dose of 5g of EACA prior to skin incision, followed by a continuous infusion of 1g/hr over the next 6 to 8 hours. • Control group received saline solution in the same fashion.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss (24hrs), mortality, myocardial infarction, re-operation for bleeding, stroke, graft failure
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Deleuze 1991

Methods	Pharmaceutical company supplied the study drugs in identical bottles, identifiable only by number. The method of generating allocation sequences was not described. [French]
Participants	60 coronary patients undergoing at least two aorto-coronary bypass grafts for the first time were randomised to one of two groups: • Aprotinin group: n = 30, M/F = 24/6, mean (sd) age = 60.3 (8.0) years • Control group (Placebo): n = 30, M/F = 25/5, mean (sd) age = 61.3 (8.0) years
Interventions	• Aprotinin group received 4 flasks (200ml) of aprotinin intravenously, after the induction of anaesthesia, over 30 minutes via a central venous catheter, then a continuous infusion of aprotinin at 50ml/hr until the end of surgery. A further 4 flasks were administered via the extracorporeal circulation circuit. • Control group received the equivalent volume of physiological serum over the same time periods. NB: One active flask contained 70mg (500,000 KIU) of aprotinin in 50mls of physiological serum. One placebo flask contained an equivalent quantity of physiological serum
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss (48 hrs), re-operation
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used French article - translated

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Demeyere 2006

Methods	Method of sequence generation and allocation concealment were not described. [Poster presentation]
Participants	60 patients undergoing cardiac surgery were randomised to one of three groups: • Aprotinin group: n=20 • Tranexamic acid group: n = 20 • Control group: n = 20 NB: Demographic data were not reported.
Interventions	• Aprotinin group (High dose) received 280mg loading dose, 70mg/hr infusion rate and 280mg in the pump prime.

	• Tranexamic acid group received 100mg loading dose then 1mg/kg/hr infusion. • Control group received saline.
Outcomes	***Outcomes reported:*** Transfusion of blood products, blood loss, re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol not reported

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Desai 2009

Methods	Methods of sequence generation and allocation concealment were unclear
Participants	75 patients undergoing cardiac surgery were randomised to one of two groups: • Aprotinin group: n = 38 • Control group: n = 37 NB: Demographic data were not reported.
Interventions	• Aprotinin group (full-dose) 10,000 KIU test dose, 2 million KIU via central line and 500,000 KIU/hr IV until the end of surgery. • Control group received saline.
Outcomes	***Outcomes reported:*** Number of patients receiving blood transfusion, blood loss, myocardial infarction, renal failure, mortality, re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear

Blinding? All outcomes	Yes	Double blind

Dietrich 1990

Methods	Method of randomisation was not described. Aprotinin and placebo were provided by the manufacturer (Bayer AG, Leverkusen, FRG) in identical packages, each containing 12 bottles that could only be identified by the random number. One patient from the aprotinin trial arm was excluded from the final analysis
Participants	40 patients scheduled for elective primary myocardial revascularisation were randomised to one of two groups: • Aprotinin group: n = 20, mean (sd) age = 58 (10) years • Control group (Placebo): n = 20, mean (sd) age = 55 (8) years NB: Gender data were not reported.
Interventions	• Aprotinin group received a loading dose of 2 million KIU (280mg) of aprotinin after induction of anaesthesia and before surgery, over a 15 minute period followed by a continuous infusion of 500,000 KIU/hr administered by infusion pump for the entire duration of surgery. An additional bolus of 2 million KIU of aprotinin was added to the pump prime of the heart-lung machine. • Control group received an equal volume of saline solution.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic whole blood usage (ml/units), fresh frozen plasma usage (units), platelet usage (units), blood loss, re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Dietrich 1992

Methods	Method of randomisation and allocation concealment were not described. No exclusions reported
Participants	1784 adult patients undergoing primary coronary artery bypass grafting, valve replacement (or combined procedures), and cardiac reoperations, were randomly assigned to one of two groups: • Aprotinin group: n = 902, M/F = 667/239, mean (sd) age = 60 (10) years • Control group: n = 882, M/F = 653/229, mean (sd) age = 59 (11) years
Interventions	• Aprotinin group received a loading dose of 2 million KIU of aprotinin after induction of anaesthesia and before surgery, over a 15-minute period, followed by a continuous infusion of 500, 000 KIU/hr administered by an infusion pump during the entire course of surgery. An additional bolus of 2 million KIU of aprotinin was added to the pump prime of the heart-lung machine. • Control group received no aprotinin. NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage, blood loss (36 hrs), mortality, intensive care unit length of stay (days), re-operation, renal failure, hypotension
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Dietrich 1995

Methods	Patients were independently randomised, using a table of random numbers, to either aprotinin or control group. Aprotinin and placebo were provided by the manufacturer (Bayer AG, Leverkusen, Germany) in identical packages each containing 14 bottles, that could only be identified by the random number. No loss to follow-up reported
Participants	30 male patients scheduled for elective primary coronary revascularisation were randomly assigned to one of two groups: • Aprotinin group: n = 15, mean (sd) age = 62.93 (6.77) years • Control group (Placebo): n = 15, mean (sd) age = 62.07 (10.01) years
Interventions	• Aprotinin group received a loading dose of 2 million KIU (280mg) of aprotinin over a 15-minute period at the start of surgery, followed by a continuous infusion of 500,000 KIU/hr throughout the course of surgery. An additional bolus of 2 million KIU was added to the prime of the heart-lung machine.

	• Control group received an equal volume of saline. NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss, complications, re-operation, mortality
Notes	Quality assessment score (Schulz criteria): 7/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Table of random numbers
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Dietrich 2008

Methods	Computer-generated randomisation list and central allocation were used
Participants	220 patients undergoing cardiac surgery were randomly allocated to one of two groups: • Aprotinin group: n = 110, M/F = 82/28, mean (sd) age= 67.3 (10.6) years • Tranexamic acid group (n = 110), M/F = 72/38, mean (sd) age = 69.8 (10.3) years
Interventions	• Aprotonin group received a 1ml test dose, then 1 million KIU IV over 10 minutes, then continuous infusion of 500,000 KIU/hr for the duration of surgery, additional 2 million KIU added to CPB circuit priming fluid. • Tranexamic acid group received a 2g bolus dose, followed by a continuous infusion of 1g/hr, additional bolus added to CPB circuit priming fluid.
Outcomes	***Outcomes reported:*** Number of patients receiving blood transfusion, volume of blood transfused (units), mortality, renal failure, length of hospital stay (days)
Notes	Quality assessment score (Schulz criteria): 7/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated randomisation list
Allocation concealment?	Yes	Adequate

Dietrich 2008 (*Continued)*

Blinding? All outcomes	Yes	Double blind

Dignan 2001

Methods	Study drug was administered by the anesthesiologist as an infusion in a blinded fashion. Allocation concealment was not described
Participants	200 participants undergoing elective cardiac surgery were randomly assigned to one of two groups: • Aprotinin group (Low dose): n = 101, M/F = 75/26, mean (range) age = 62.8 (35-80) years • Control group (Placebo): n = 99, M/F = 77/22, mean (range) age = 65.2 (40-81) years
Interventions	• Aprotinin group received 1 million KIU of aprotinin in total (140mg) - 500,000KIU before skin incision and 500,000 KIU during the initiation of CPB. • Control group received the same volume of normal saline.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic whole blood usage (units/mls), fresh frozen plasma usage (units), platelet usage (units), blood loss, re-operation for bleeding, acute renal failure, stroke
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Diprose 2005

Methods	Computer generated random numbers determined patient allocation to one of three treatment groups. Sealed envelopes were used to conceal treatment allocation
Participants	186 patients undergoing elective cardiac surgery were randomly assigned to one of three groups: • Aprotinin group (High dose): n = 63, M/F = 52/8, median (interquartile range) age = 62 (55-69) years • Tranexamic acid group: n = 62, M/F = 49/11, median (interquartile range) age = 65 (58.5-73.5) years • Control group (Placebo): n = 61, M/F = 52/8, median (interquartile range) age = 65(60-70) years

Interventions	• Aprotinin group received 2 million KIU (280mg) in 200ml volume at the start of surgery, 2 million KIU of aprotinin was added to the pump prime, and a continuous infusion of 500,000 KIU/hr was given throughout the operation. • Tranexamic acid group received 5g in 200ml normal saline, 200ml of normal saline added to the pump prime, and a continuous infusion of 50ml/hour of normal saline throughout the operation. • Control group received normal saline as an IV bolus into the pump prime and a continuous infusion of 50ml/hour of normal saline per hour throughout the operation. NB: All groups received intra-operative cell salvage (Compact A; Dideco, Sorin Biomedica, Italy) and each group received a test dose of 5ml of study solution
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss, mortality, myocardial infarction, re-operation for bleeding, renal failure, respiratory failure
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated random numbers determined patient allocation
Allocation concealment?	No	Inadequate
Blinding? All outcomes	Yes	Double blind

Dorman 2008

Methods	Method of sequence generation and allocation concealment were not described
Participants	60 patients undergoing cardiac surgery were randomly allocated to one of two groups: • Aprotinin group: n = 30, M/F = 25/5, mean (SEM) age = 62.0 (2.0) years • Epsilon aminocaproic acid group: n = 30, M/F = 20/10, mean (SEM) age = 60.0 (2.0) years
Interventions	• Aprotonin group received 1 million KIU IV at the start of surgery with an additional 1 million KIU in the CPB circuit, and a continuous infusion of 250,000 KIU per hour until the end of surgery. • Epsilon aminocaproic acid group received 5g IV concurrent with systemic heparinization and an additional 5g in the CPB circuit, and another 5g administered IV immediately after discontinuation of CPB.
Outcomes	***Outcomes reported:*** Number of patients receiving blood transfusion, volume blood transfused (units), blood loss

Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Dryden 1997

Methods	Method of randomisation was not described. The "study drug" was mixed by independent Intensive Care Unit (ICU) personnel
Participants	41 patients undergoing re-operative cardiac valve surgery were randomised to one of two groups: • Tranexamic acid group: n = 22, M/F = 9/13, mean (sd) age = 63 (12.6) years • Control group (Placebo): n = 19, M/F = 8/11, mean (sd) age = 64 (18) years
Interventions	• Tranexamic acid group received 10g of TXA in 500ml of normal saline infused after the induction of anaesthesia as an intravenous bolus over 30 minutes prior to skin incision. • Control group received normal saline solution in the same volume.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (mls), blood loss, total platelets transfused, total plasma transfused, mortality, hospital length of stay (days), hospital complications, re-operation for active bleeding
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	No	Single blind

Eberle 1998

Methods	Different treatment solutions were identical in appearance. Method of randomisation was not described
Participants	40 patients undergoing cardiac surgery were randomised to one of three groups: • Epsilon aminocaproic acid group: n = 20, mean (sd) age = 61(10) years • Aprotinin group: n = 20, mean (sd) age = 60 (10) years • Non-randomised historical control group: n = 10, mean (sd) age = 57 (14) years NB: No gender data were reported.
Interventions	• Epsilon aminocaproic acid group received a test dose of 1 mL followed after 10 minutes by a loading dose of 200mL of solution given over 30 minutes. EACA was infused continuously at a rate of 50ml/hour until the start of CPB. EACA-10g both as loading and pump prime dose at 2. 5g/hour as an infusion. • Aprotinin group received the same volume regimen as EACA. 2 million KIU (280mg) for loading and pump prime followed by an infusion of 500,000 KIU/hour (70mg/hr) from CPB weaning until 4 hours after heparin reversal. • Control group did not receive either EACA or aprotinin treatment. NB: Both EACA and aprotinin groups received cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss, myocardial Infarction
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Ehrlich 1998

Methods	Each bottle of aprotinin provided by the pharmaceutical company was placed in a box with bottles of normal saline solution. These bottles were indistinguishable from one another. An assistant, who was only involved in randomisation of the medication, arranged these bottles into 50 pairs. Each pair consisted of two bottles of aprotinin or two bottles of saline solution. Each of these pairs was randomly assigned a number from 1 to 50. Each patient was randomly assigned a number and then given the corresponding bottles. After the study was completed, the randomisation code was broken and the data were analysed
Participants	50 patients undergoing thoracic aortic operations with the use of profound hypothermic circulatory arrest were randomly assigned to one of two groups:

	• Aprotinin group: n = 25, M/F = 9/16, mean (range) age = 70 (58-80) years • Control group (Placebo): n = 25, M/F = 7/18, mean (range) age = 70 (60-78) years
Interventions	• Aprotinin group received 1 million KIU of aprotinin (140mg) before the onset of cardiopulmonary bypass. • Control group received an equal volume of 0.9% saline solution as a placebo.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss, mortality (30-day), myocardial infarction, renal dysfunction/renal failure, re-operation for bleeding, neurological deficit, stroke
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Ekback 2000

Methods	Method of randomisation and allocation concealment were not described
Participants	40 patients undergoing elective adult surgery and were randomised to one of two groups: • Tranexamic acid group: n = 20, M/F = 9/11, mean (sd) age = 66.4 (9.0) years • Control group (Placebo): n = 20, M/F = 11/9, mean (sd) age = 65.6 (8.8) years
Interventions	• Tranexamic acid group received a bolus dose of 10mg/kg before surgical incision. A continuous infusion of 1.0mg/kg/hr during 10 hours was then started immediately after the first bolus dose. A second bolus dose of 1.0mg/kg was given three hours later to counteract potential dilutive effects of intra-operative autotransfusion. • Control group received physiological saline as a placebo. NB: All study participants underwent pre-operative autologous blood donation (2 units autologous blood donated) on two occasions within a four week period. Both trial arms were equally exposed to cell salvage
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss, deep vein thrombosis
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Ekback 2000 *(Continued)*

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Ellis 2001

Methods	Randomisation was carried out using a computer generated randomisation table. Allocation concealment was not described
Participants	30 patients were randomly assigned to one of three groups: • Tranexamic acid group: n = 10, M/F = 4/6, mean (sd) age = 71(5) years • Desmopressin group: n = 10, M/F = 2/8, mean (sd) age = 72 (6) years • Control group (Placebo): n = 10, M/F = 3/7, mean (sd) age = 72 (8) years
Interventions	• Tranexamic acid group received TXA 30 minutes before deflating the limb tourniquet an IV bolus dose (15mg/kg) administered over a 30 minute period, thereafter a constant IV infusion of TXA (10mg/kg/hr) was administered until 12 hours after final deflation of the limb tourniquet. • Desmopressin group 30 minutes before deflating the limb tourniquet an IV bolus dose of DDAVP (0.3micrograms/kg) was infused over a 30 minute period, thereafter a constant IV infusion of saline was administered until 12 hours after final deflation of the limb tourniquet. • Control group received an equal volume of saline.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogenic blood usage (units) , hospital length of stay (days)
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation was carried out using a computer generated randomisation table
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Engel 2001

Methods	Method of randomisation and allocation concealment was not described
Participants	36 patients were randomised to one of three groups: • Tranexamic acid group: n = 12, M/F = 4/8, mean (sd) age = 71 (9) years • Aprotinin group: n = 12, M/F = 3/9, mean (sd) age = 71 (9) years • Control group: n = 12, M/F = 4/8, mean (sd) age = 66 (11) years
Interventions	• Tranexamic acid group received 15mg/kg of TXA followed by a repeat dose of 10mg/kg after 3 hours. • Aprotinin group received 1 million KIU (140mg) of aprotinin immediately before deflating the tourniquet followed by an infusion of 500,000 KIU per hour for 4 hours. • Control group received no antifibrinolytic treatment.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss, deep vein thrombosis
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	No	Unblinded

Englberger 2002a

Methods	Bottles of aprotinin and saline (placebo solution) were numbered continuously. Blinding of bottles was performed by personal otherwise not involved in the study. Method of randomisation was not described
Participants	47 patients undergoing elective 'off-pump' cardiac surgery were randomly allocated to one of two groups: • Aprotonin group (Low dose): n = 22, M/F = 16/6, mean (sd) age = 63.9 (10.8) years • Control group (Placebo): n = 25, M/F = 19/6, mean (sd) age = 66.4 (9.0) years
Interventions	• Aprotonin group received a loading dose of 2 million KIU (280mg) of aprotinin at the beginning of surgery followed by a continuous infusion of 500,000 KIU/hr throughout surgery (70mg/hr). • Control group received the same volume of saline solution.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, number of patients exposed to fresh frozen plasma, blood loss, mortality, myocardial infarction, re-operation for bleeding, number

	of patients exposed to autotransfusion, volume of blood autotransfused, hospital length of stay (days), neurological deficit, renal dysfunction
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Englberger 2002b

Methods	Method of randomisation and allocation concealment were not described
Participants	29 patients undergoing elective cardiac surgery were randomly allocated to one of two groups: • Aprotinin group (Low dose - pump prime): n = 15, M/F = 13/2, mean (sd) age = 60.3 (10) years • Control group: n = 14, M/F = 10/4, mean (sd) age = 61.5 (7.5) years
Interventions	• Aprotonin group received 2 million KIU of aprotinin (280mg) added to the pump prime only. • Control group - treatment details were not reported. NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , number of patients exposed to fresh frozen plasma, fresh frozen plasma usage (units), blood loss, mortality, myocardial infarction, re-operation for bleeding, neurological deficit, renal dysfunction, hospital length of stay (days), number of patients exposed to autotransfusion, volume of blood autotransfused
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear

Blinding? All outcomes	Unclear	Unclear

Fauli 2005

Methods	Method of randomisation was not described. All patients received pre-prepared infusions of similar volume and appearance provided by the pharmaceutical company
Participants	60 patients undergoing cardiac surgery were randomised to one of three groups: • Aprotinin group (High dose): n = 20, M/F = 15/5, mean (sd) age = 52.5 (10.1) years • Aprotinin group (Low dose): n = 20, M/F = 17/3, mean (sd) age = 57.7 (4.6) years • Control group (Placebo): n = 20, M/F = 14/6, mean (sd) age = 56.5 (6.5) years
Interventions	• Aprotinin group (High dose) received a loading dose of 280mg of aprotinin, followed by a continuous infusion of 70mg/hr of aprotinin until closure of sternotomy, and 280mg of aprotinin was added to the pump prime. • Aprotinin group (Low dose) received 280mg of aprotinin added to the pump prime. • Control group (Placebo) received the same volume of saline.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss (24hrs), hospital length of stay (days)
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Feindt 1994

Methods	Method of randomisation and allocation concealment were not described
Participants	20 patients undergoing aortocoronary bypass surgery were randomly allocated to one of two groups: • Aprotinin group (High-dose): n = 10, M/F = NR, mean (sd) age = 62.3 (1.2) years • Control group (Placebo): n = 10, M/F = NR, mean (sd) age = 66.4 (2.4) years
Interventions	• Aprotonin group received high-dose (2 million units kallikrein inhibitor at the induction of anaesthesia, 2 million units added to the priming volume of the heart-lung machine and 500,000 U/h during the operation).

	• Control group - treatment details were not reported.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood transfusion, post-operative blood loss, mortality, parameters of thrombin activation and fibrinolysis
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind - study was described as being double blind

Fergusson 2008

Methods	The research pharmacist at each centre randomly assigned patients to receive one of three antifibrinolytic agents with the use of a voice-activated automated centralised program. An independent biostatistician generated the randomisation scheme using a computer-generated randomisation list. Researchers, patients, members of the clinical teams, and members of the data and safety monitoring committee were all unaware of study-group assignment
Participants	2331 high-risk cardiac surgical patients were randomly allocated to one of three groups: • Aprotinin group: n = 781, M/F = 543/238, mean (sd) age = 67.0 (10.8) years • Tranexamic acid group: n = 770, M/F = 562/208, mean (sd) age = 66.9 (11.4) years • Epsilon aminocaproic acid: n = 780, M/F = 569/211, mean (sd) age = 66.6 (10.8) years
Interventions	• Aprotonin group received high-dose aprotinin with a test dose of 40,000 KIU administered during a 10 minute period after the insertion of a central venous line and induction of anaesthesia. In the absence of of anaphylaxis, the remainder of the loading dose (1.96 million KIU), after which a maintenance infusion of 500,000 KIU per hour was initiated and maintained during surgery. An additional dose of 2 million KIU was added to the cardiopulmonary-bypass circuit. • Tranexamic acid group received a 30mg/kg loading dose, a 16mg/kg maintenance dose, then 2 mg/kg added to the bypass circuit. • Epsilon aminocaproic acid group received a 10g loading dose, then a 2g maintenance infusion.
Outcomes	***Outcomes reported:*** Number of patients transfused allogeneic blood, massive post-operative bleeding, re-operation for bleeding, myocardial infarction, stroke, mortality, renal failure, length of stay (days).
Notes	Quality assessment score (Schulz criteria): 7/7 Transfusion protocol used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated randomisation list
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Findlay 2001

Methods	Method of randomisation and allocation concealment were not described
Participants	63 patients undergoing orthotopic liver transplantation were randomised to one of two groups: • Aprotinin group: n = 33, mean (sd) age = 50 (9) years • Control group (Placebo): n = 30, mean (sd) age = 52 (10) years NB: Gender data were not reported.
Interventions	• Aprotinin group received a loading dose of 1 million KIU over 30 minutes (after a test dose of 10,000 KIU) followed by an infusion of 250,000 KIU/hr until skin closure. • Control group received an equivalent infusion of normal saline. NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), fresh frozen plasma usage (units), platelet usage (units), mortality, re-operation for bleeding, hepatic artery thrombosis, hospital length of stay (days), intensive care unit length of stay (hours)
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Fraedrich 1989

Methods	Method of randomisation and allocation concealment were not described
Participants	80 male patients undergoing primary coronary bypass surgery were randomised to one of two groups: • Aprotinin group: n =40, mean age = 60.6 years • Control group: n = 40, mean age = 58.2 years NB: Four patients, two from the intervention and two from the control group were excluded. Aprotinin group excluded two patients: one allergic reaction, one severe cardiac failure. Control group excluded two patients: one surgical bleeding, one lethal cardiac failure
Interventions	• Aprotinin group received a loading dose of 280mg of aprotinin prior to sternotomy, followed by a continuous intravenous infusion of 70mg/hr until skin closure. An additional 280mg of aprotinin was added to the prime volume of the membrane oxygenator. • Control group was not treated with aprotinin.
Outcomes	***Outcomes reported:*** Allogeneic blood usage, plasma usage, blood loss, volume of re-transfused mediastinal blood
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol not specified

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	No	Single blind

Garcia-Enguita 1998

Methods	Method of randomisation and allocation concealment were not described. [Abstract only]
Participants	30 patients undergoing elective orthopaedic surgery were randomly allocated to one of two groups: • Aprotinin group (Low dose): n = 15 • Control group (Placebo): n = 15 NB: Gender and age data were reported.
Interventions	• Aprotinin group received a loading dose of 2 million KIU (280mg) of aprotinin before the induction of anaesthesia administered over 30 minutes followed by 500,000 KIU/hr for the duration of surgery. • Control group received 200ml of normal saline over 30 minutes followed by 50mL/hr of saline.
Outcomes	***Outcomes reported:*** Allogenic blood usage (units), blood loss.

Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol was not used	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Garcia-Huete 1997

Methods	Method of randomisation and allocation concealment were not described
Participants	80 consecutive patients undergoing elective orthotopic liver transplantation were randomised to one of two groups: • Aprotinin group: n = 39, M/F = 24/15, mean (range) age = 50 (15-64) years • Control group (Placebo): n = 41, M/F = 27/14, mean (range) age = 50 (17-65) years
Interventions	• Aprotinin group received an initial dose of 2 million kallikrein inactivator units (KIU) of aprotinin in the induction phase of anaesthesia followed by an infusion of 500,000 KIU/hr of aprotinin until the end of the procedure. • Control group received an equal volume of saline solution.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , mortality, allergic reactions, re-operation for bleeding, re-transplantation
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Garneti 2004

Methods	Patients were randomised using a list of random numbers. Allocation concealment was not described
Participants	50 patients undergoing total hip arthroplasty were randomised to one of two groups: • Tranexamic acid group: n = 25), mean (sd) age = 69.6 (11.99) years • Control group (Placebo): n = 25, mean (sd) age = 67.6 (11.4) years
Interventions	• Tranexamic acid group received 10mg/kg of intravenous TXA as a bolus at time of anaesthesia. • Control group received a similar volume of normal saline as a bolus at time of anaesthesia.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss (48hrs), deep vein thrombosis, pulmonary embolus
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol not specified

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	List of random numbers
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Gherli 1992

Methods	Method of randomisation and allocation concealment were not described.[Italian]
Participants	31 patients undergoing cardiopulmonary bypass were randomly divided into one of three groups: • Aprotinin group (High dose): n = 9, M/F = 7/2, mean (range) age = 61.5 (44-71) years • Aprotinin group (Low dose): n = 9, M/F = 8/1, mean (range) age = 58.2 (47-71) years • Control group: n = 13, M/F = 10/3, mean (range) age = 60.4 (52-66) years
Interventions	• Aprotinin group (High dose) received 2 million kallikrein inactivator units (KIU) of aprotinin over 15 minutes, followed by a continuous infusion of 1 million KIU/hr of aprotinin. An additional 2 million KIU of aprotinin was added to the pump prime. • Aprotinin group (Low dose) received 1 million kallikrein inactivator units (KIU) of aprotinin over 15 minutes, followed by a continuous infusion of 500,000 KIU/hr of aprotinin. An additional 1 million KIU of aprotinin was added to the pump prime. • Control group did not receive aprotinin.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss, myocardial infarction, renal failure, blood products used, haemoglobin levels

Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Gill 2009

Methods	Patients were allocated according to a computer-generated randomisation schedule
Participants	10 patients undergoing orthopaedic (hip) surgery were randomised to one of two groups: • Tranexamic acid group: n = 5, mean (range) age = 66.6 (53-83) years • Control group (Placebo): n = 5, mean (range) age = 61.4 (36-73) years
Interventions	• Tranexamic acid group received 10mg/kg bolus before anaesthesia then 1mg/kg/hr at start of surgery until wound closure. • Control group (placebo) received saline.
Outcomes	***Outcomes reported:*** Number of patients receiving blood transfusion, blood loss, volume blood transfused (units)
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated randomisation schedule
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Golanski 2000

Methods	Method of randomisation and allocation concealment were not described. [Polish]
Participants	54 patients undergoing elective cardiac surgery were randomly allocated to one of two groups: • Aprotinin group (Low dose): n = 30, M/F = 29/1, mean (sd) age = 56.2 (10.5) years • Control group: n = 24, M/F = 22/2, mean (sd) age = 54.7 (8.1) years
Interventions	• Aprotinin group received an infusion of 3 million kallikrein inactivator units (KIU) of aprotinin intra-operatively. • Control did not receive aprotinin.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss, mortality, myocardial infarction
Notes	Quality assessment score (Schulz criteria): 0/7

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Good 2003

Methods	Coded ampoules of TXA or saline placebo prepared by the drug company were randomised in blocks of 10 (five saline, five TXA) by means of computer generated numbers. Four patients were withdrawn from the final analysis before the randomisation code was broken
Participants	55 patients undergoing total knee replacement surgery were randomised to one of two groups: • Tranexamic acid group: n = 27, M/F = 9/18, median (IQR) age = 72 (46-83) years • Control group (Placebo): n = 24, M/F = 6/18, median (IQR) age = 72 (50-84) years
Interventions	• Tranexamic acid group received 10mg/kg of intravenous TXA at the end of the surgical procedure, just before the release of the tourniquet (maximum dose of 1000mg). The dose of TXA was repeated after 3 hours. • Control group received saline placebo solution at corresponding times as the TXA group.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss, deep vein thrombosis, infection
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Good 2003 (*Continued)*

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated numbers
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Gott 1998

Methods	Method of randomisation and allocation concealment were not described
Participants	400 cardiac surgery patients were randomly allocated to one of three groups: • Aprotinin group: n = 109 • Control/standard: n = 112 • Leukocyte depletion: n= 112 • Heparin-bonded circuitry: n = 67 NB: No demographic data were reported.
Interventions	• Aprotonin group received low-dose - standard treatment plus a half-Hammersmith aprotonin protocol. • Control - standard treatment. • Leukocyte depletion - based on the standard CPB protocol with addition of leukocyte filtration of arterial line and cardioplegia delivery line. • Heparin-bonded circuitry, membrane oxygenator and a centrifugal pump.
Outcomes	***Outcomes reported:*** Total amount of allogeneic blood transfused (units), mortality, length of hospital stay, renal dysfunction, lung function
Notes	Quality assessment score (Schulz criteria): 0/7 Transfusion protocol not used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Green 1995

Methods	Study was described as an open label randomised controlled trial conducted in two phases. Patients were assigned to groups by means of computer generated table of random numbers
Participants	84 consecutive patients undergoing primary coronary artery bypass graft surgery or re-operations were randomly assigned to one of two groups: • Aprotinin group: n = 48, M/F = 39/9, mean (sd) age = 62 (9) years • Control group: n = 36, M/F = 31/5, mean (sd) age = 63 (8) years Two aprotinin dose regimens were studied: • Dosage level 1 - Aprotinin group: n = 24, M/F = 20/4, mean (sd) age = 64 (8) years • Dosage level 1 - Control group: n = 18, M/F 16/2, mean (sd) age = 63 (8) years • Dosage level 2 - Aprotinin group: n = 24, M/F=19/5, mean (sd) age = 60 (9) years • Dosage level 2 - Control group: n = 18, M/F=15/3, mean (sd) age = 64 (8) years
Interventions	• Phase 1, patients assigned to recombinant (r) aprotinin (treatment group) received 2mg/kg (14,300 kallikrein inactivation units/kg) as an intravenous bolus given in 20 minutes after the induction of anaesthesia, an intravenous infusion of 0.5mg/kg/hr until the patient left the operating room, and 1 mg/kg added to each litre of lactated Ringers solution for priming of the membrane oxygenator. • Phase 2, each dose was doubled. Studies of dosage level 1 were performed in Chicago (42 patients) and studies of dosage level 2 were conducted both in Chicago (26 patients) and in Temple, Texas (16 patients). Patients were stratified according to centre, surgeon, and type of surgery. The study also compared patients who underwent primary operations (n = 60) with those patients who underwent re-operations (n = 24) NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss, overall erythrocyte loss, autotransfusion device erythrocytes, myocardial infarction, mortality, renal function (BUN + creatinine levels), pre-operative and post-operative haemoglobin levels
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Patients were assigned to groups by means of computer generated table of random numbers
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	No	

Greilich 2001

Methods	Method of randomisation and allocation concealment were not described
Participants	72 patients undergoing elective cardiac surgery were randomised to one of three groups: • Epsilon aminocaproic acid group: n = 23, mean (sd) age = 63 (8) years • Aprotinin group: n =24, mean (sd) age = 64 (9) years • Control group (Placebo) (n = 25), mean (sd) age = 62 (7) years
Interventions	• Epsilon aminocaproic acid group received 100mg/kg loading dose, 5g added to the pump prime, and 30mg/kg/hr as a continuous infusion. • Aprotinin group received 2 million KIU of aprotinin added to the pump prime, and 500, 000 KIU/hr (70mg/hour) as a continuous infusion. • Control group received 200ml normal saline as a loading dose, 200ml of normal saline added to the pump prime, and 50ml/hr of saline as a continuous infusion.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss, intensive care unit length of stay (days), mechanical ventilation (hours)
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Greilich 2003

Methods	Method of randomisation and allocation concealment were not described
Participants	60 male patients undergoing cardiac surgery were randomised to one of three groups: • Aprotinin group (High dose): n = 20, mean (sd) age = 64 (9) years • Epsilon aminocaproic acid (n = 20), mean (sd) age = 62 (9) years • Control group (Placebo) (n = 20), mean (sd) age = 63 (8) years
Interventions	• Aprotinin group (High dose) received 2 million KIU (280mg) of aprotinin as a loading dose and a continuous infusion of 500,000 KIU/hr of aprotinin. An additional 2 million KIU (280mg) of aprotinin was added to the pump prime solution. • Epsilon aminocaproic acid group received 100mg/kg of EACA as a loading dose and a continuous infusion of 30mg/kg/hr. An additional 5g of EACA was added to the pump prime. • Control group (placebo) received normal saline in equivalent volumes. NB: All groups were exposed to cell salvage.

Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), platelet usage (units), blood loss, plasma levels of Interleukin-6 and Interleukin-8 during and after CPB
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Greilich 2004

Methods	Method of randomisation and allocation concealment were not described
Participants	36 male patients undergoing cardiac surgery were randomised to one of three groups: • Aprotinin group (High dose): n = 12, mean (sd) age = 62 (8) years • Epsilon aminocaproic acid group: n = 12, mean (sd) age = 64 (9) years • Control group (Placebo): n = 12, mean (sd) age = 65 (8) years
Interventions	• Aprotinin group (High dose) received a loading dose of 2 million KIU (280mg) of aprotinin and a continuous infusion of 500,000 KIU/hr. An additional 2 million KIU of aprotinin was added to the pump prime. • Epsilon aminocaproic acid group received a loading dose of 100mg/kg of EACA and a continuous infusion of 30mg/kg/hr. An additional 5g of EACA was added to the pump prime. • Control group received normal saline solution using similar volumes as aprotinin and EACA treatments.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss (24hrs), biochemical markers of plasmin activity (D-dimer), biochemical markers of platelet (CD62P), activation, biochemical markers of leukocyte (CD11b) activation, biochemical markers of leukocyte-platelet conjugate formation
Notes	Quality assessment score (Schulz criteria):3/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear

Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Greilich 2009

Methods	A table of random numbers was used to generate the allocation sequence. Central (pharmacy) allocation was used
Participants	78 male patients undergoing cardiac surgery were randomised to one of three groups: • Aprotonin group: n = 26, mean (sd) age = 65 (9) years • EACA group: n = 25, mean (sd) age = 62 (8) years • Control group (Placebo): n = 27, mean (sd) age = 62 (7) years
Interventions	• Aprotonin group received full-dose - loading dose 2 million KIU over 15 minutes plus 2 million added to pump prime and infusion of 500,000 KIU/hr until patient arrival at ICU. • EACA group - high dose - 100mg/kg initial loading dose, 5g in pump prime solution, 30mg/kg/hr. • Control group received saline.
Outcomes	***Outcomes reported:*** Number of patients transfused allogeneic blood, mortality, stroke, myocardial infarction, renal failure, length of hospital stay (days)
Notes	Quality assessment score (Schulz criteria):7/7 Transfusion protocol was used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A table of random numbers was used to generate the allocation sequence
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Groh 1993

Methods	Method of randomisation and allocation concealment was not described
Participants	20 patients undergoing orthotopic liver transplantation were randomised to one of two groups: • Aprotinin group: n = 9, mean (range) age = 51 (28-66) years • Control group (Placebo): n = 9, mean (range) age = 49 (31-59) years NB: Two patients were excluded from the final analysis

Interventions	• Aprotinin group received a loading dose of 2 million KIU of aprotinin after the induction of anaesthesia, followed by a continuous infusion of 500,000 KIU/hr of aprotinin until the end of the procedure. • Control group received an unspecified placebo. NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), fresh frozen plasma usage (units), platelet usage (units)
Notes	Quality assessment score (Schulz criteria):3/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Harder 1991

Methods	Method of randomisation was not described. The randomisation code was only known by the hospital pharmacy. Allocation concealment was by means of coded vials collected from the hospital pharmacy in the morning before the operation. No exclusions were reported
Participants	80 male patients scheduled for elective coronary artery bypass grafting with cardiopulmonary bypass were randomised to one of two groups: • Aprotinin group:n = 40, mean (sd) age = 57.6 (8.8) years • Control group (Placebo): n = 40, mean (sd) age = 57.0 (8.8) years
Interventions	• Aprotinin group received a bolus of 200ml (2 million KIU) of aprotinin just after the Swan-Ganz pulmonary artery catheter was introduced, followed by a continuous infusion of 500,000 KIU/hr (50ml) via an infusion pump. An additional 2 million KIU of aprotinin was added to the pump prime. The total amount of aprotinin delivered by infusion was 4 million KIU before and during bypass. • Control group received saline solution in equivalent volumes.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Hardy 1993

Methods	Randomisation was performed by the pharmacy department with each successive block of four patients being randomised (random allocation of two patients to Group A and two patients to Group C). Method used to generate allocation sequences was not described
Participants	44 patients scheduled for repeat myocardial revascularisation, repeat value surgery, or a combined procedure (primary or repeat) were randomised to one of two groups: • Aprotinin group: n = 22, M/F = 16/6, mean (sd) age = 62 (9) years • Control group (Placebo): n = 19, M/F = 12/12, mean (sd) age = 58 (11) years NB: Three patients in the control group were excluded: one patient died in the operating room and one died upon arrival in the ICU. The third patient was excluded when the surgeon proceeded to a single valve replacement instead of the planned combined procedure
Interventions	• Aprotinin group received a bolus of 200,000 KIU of aprotinin after the induction of anaesthesia, but before skin incision, over a period of 20 minutes, followed by an infusion of 100, 000 KIU/hr during the entire surgical procedure and in the intensive care unit (ICU), for a total dose of 1 million KIU. • Control group received an equal volume of sodium chloride 0.9% throughout surgery and recovery.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , fresh frozen plasma usage (units), platelet usage (units), mortality, re-exploration for bleeding
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate

Blinding? All outcomes	Yes	Double blind

Hardy 1997

Methods	Each successive block of four patients was randomised by the Department of Pharmacy (random allocation of two patients to the treatment group and two patients to the control group). Method used to generate allocation sequences was not described
Participants	52 patients undergoing primary or repeat myocardial revascularisation, or repeat valve surgery were randomised to one of two groups: • Aprotinin group: n = 26, M/F = 15/11, mean (sd) age = 59 (11) years • Control group (placebo) (n = 26), M/F = 19/7, mean (sd) age = 59 (10) years
Interventions	• Aprotinin group received 1 million KIU of aprotinin added to the priming solution of the cardiopulmonary bypass circuit. • Control group (placebo) received an equal volume of sodium chloride 0.9% added to the priming solution of the cardiopulmonary bypass circuit.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), re-operation, blood loss, haemoglobin concentrations, coagulation factors
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Hardy 1998

Methods	Study participants were randomised by the pharmacy department. Each successive block of nine patients were randomised to ensure a comparable number of patients in all groups and a similar distribution of patients over time. All bags were coded by the Department of Pharmacy and identical volumes of solution were infused
Participants	134 patients undergoing scheduled elective coronary artery bypass graft surgery were randomised to one of three groups: • Control group (Placebo): n = 45, M/F = 38/7 • Tranexamic acid group: n = 43, M/F = 27/16

	• Epsilon aminocaproic acid group: n = 46, M/F = 35/11 NB: Age data were not reported
Interventions	• Control group (placebo) received a bolus plus an infusion of placebo solution (0.9% normal saline solution). • Tranexamic acid group received a 10g bolus of TXA over 20 minutes, followed by a placebo infusion. The placebo consisted of 0.9% normal saline solution. • Epsilon aminocaproic acid group received a 15g bolus over 20 minutes, followed by an infusion of 1g/hr.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), fresh frozen plasma usage (units), platelet usage (units), blood loss, mortality, myocardial infarction, cerebrovascular accident, re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Adequate
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Harley 2002

Methods	Method of randomisation and allocation concealment were not described
Participants	35 patients undergoing elective orthopaedic surgery were randomised to one of two groups: • Epsilon aminocaproic acid group: n = 26, M/F = 10/16, mean (sd) age = 69 (11) years • Control group (Placebo): n = 29, M/F = 11/18, mean (sd) age = 69 (10) years
Interventions	• Epsilon aminocaproic acid group received a loading dose of 150mg/kg administered as a bolus dose over 20 minutes on the patients arrival in OR. An hourly EACA infusion of 12.5mg/kg was subsequently administered for an additional 5 hours. • Control group received a placebo of saline solution
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss, deep vein thrombosis, pulmonary embolus
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Harmon 2004

Methods	A computer-generated randomisation sequence was used to allocate patients. The sequence was concealed (numbered containers) until treatment was assigned
Participants	36 patients undergoing cardiac surgery were randomised to one of two groups: • Aprotinin group (High dose): n = 17, M/F = 17/3, mean (sd) age = 63.4 (5.4) years • Control group (Placebo): n = 18, M/F = 14/4, mean (sd) age = 60.1 (9.5) years NB: One patient was excluded from the final analysis
Interventions	• Aprotinin group (High dose) received a loading dose of 2 million KIU (280mg) of aprotinin after the induction of anaesthesia and a continuous infusion of 500,000 KIU/hr of aprotinin during surgery. An additional 2 million KIU was added to the CPB circuit prime. • Control group (placebo) receive an unspecified solution.
Outcomes	***Outcomes reported:*** Cognitive deficit, number of patients exposed to allogeneic blood, blood loss, hospital length of stay (days), serious adverse events
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated randomisation
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	No	Single blind

Havel 1992

Methods	Patients were randomly allocated to receive the test compound or a placebo by use of sealed envelopes. Method of randomisation was not described
Participants	20 male patients undergoing orthotopic heart transplantation were randomised to one of two groups: • Aprotinin group (Low dose): n = 10 • Control group (Placebo): n = 10 NB: Demographic data not reported.
Interventions	• Aprotinin group received 280mg of aprotinin over 20 minutes after anaesthesia prior to surgery. In addition 280mg was added to the priming volume of the heart lung machine. • Control group received a corresponding volume of normal saline solution.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss (24hrs)
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol not specified

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	No	Inadequate - used sealed envelopes to conceal treatment allocation
Blinding? All outcomes	Yes	Double blind

Havel 1994

Methods	Method used to generate random sequences was not described. Bottles of aprotinin and placebo were indistinguishable from each other. The preparation of each patient was individually packaged with 12 bottles each; each individual bottle, as well as the carton, was marked with a label carrying the patient number (the randomisation number). Each study package contained a total of 12 bottles, of which eight carried the label "Infusion" and four the label "Pump"
Participants	45 male patients undergoing cardiac surgery were randomised to one of three groups: • Aprotinin group (High dose): n = 15, mean (sd) age = 60 (8) years • Aprotinin group (Low dose): n = 15, mean (sd) age = 59 (8) years • Control group (Placebo): n = 15, mean (sd) age = 60 (9) years
Interventions	• Aprotinin group (High dose) received 2 million KIU of aprotinin as a bolus over 30 minutes after the institution of anaesthesia but before skin incision, followed by a continuous infusion of 2 million KIU/hr of aprotinin over 4 hours, and an additional 2 million KIU of aprotinin was added to the pump prime.

	• Aprotinin group (Low dose) received 2 million KIU of aprotinin added to the pump prime only. • Control group received 0.9% saline solution.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss, graft patency rates
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol not used

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Hayashida 1997

Methods	Patients were randomised by means of computer-generated randomisation table. Method of allocation concealment was not described
Participants	167 patients undergoing primary isolated coronary artery bypass graft surgery were randomised to one of three groups: • Aprotinin group (Minimal dose): n = 55, M/F = 43/12, mean (sd) age = 64.4 (8.8) years • Aprotinin group (Low dose): n = 55, M/F = 35/20, mean (sd) age = 63.2 (8.2) years • Control group: n = 57, M/F = 41/16, mean (sd) age = 61.2 (9.8) years
Interventions	• Aprotinin group (Minimal dose) received 1 million KIU of aprotinin in the cardiopulmonary bypass priming solution. • Aprotinin group (Low dose) received 30,000 KIU/kg of aprotinin in the priming solution and a continuous infusion of aprotinin at a rate of 7,500 KIU/kg every hour during cardiopulmonary bypass. The mean dose of aprotinin in the low dose group was 2.7 million KIU (range 1.4 million KIU to 4.0 million KIU). • Control group received no aprotinin treatment. NB: All groups were exposed to pre-operative autologous blood donation (PAD)
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), fresh frozen plasma usage (units), all blood product requirements (units), blood loss, mortality, myocardial infarction, allergic reaction, parameters of clotting and fibrinolysis, renal function, early graft pattency rates
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated randomisation table
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	No	Single blind

Hayes 1996

Methods	Method of randomisation and allocation concealment were not described
Participants	40 patients scheduled for total hip replacement surgery were randomly allocated to one of two groups: • Aprotinin group: n = 20, M/F = 8/12, mean (sd) age = 70.0 (7.9) years • Control group: n = 20, M/F = 7/13, mean (sd) age = 72.9 (10.3) years
Interventions	• Aprotinin group received 2 million KIU of aprotinin intravenously over 20 minutes prior to surgical incision. • Control group received an equal volume of infusion consisting of 0.9% normal saline.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss, haemoglobin levels, coagulation parameters, complications
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Hei 2005

Methods	Method of randomisation and allocation concealment were not described. [Chinese language]
Participants	40 patients with severe hepatitis undergoing liver transplantation were randomly assigned to one of two groups: • Aprotinin group: n = 20 • Control group (Placebo): n = 20 Demographic data: M/F = 38/2, age range = 31-67 years.
Interventions	• Aprotinin group received a continuous infusion of 400,000 KIU of aprotinin commenced at the induction of anaesthesia and ceased at the end of surgery. • Control group received normal saline at the same volumes as the aprotinin regimen.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), fresh frozen plasma usage, platelet usage, blood loss
Notes	Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Hekmat 2004

Methods	Randomisation was based on a computer-generated code and sealed in sequentially numbered, opaque envelopes
Participants	120 patients undergoing elective cardiac surgery were randomly assigned to one of two groups: • Aprotinin group (High dose): n = 60, M/F = 51/9, mean (sd) age = 63 (8) years • Tranexamic acid group: n = 60, M/F = 51/7, mean (sd) age = 63 (8) years
Interventions	• Aprotinin group (High dose - "Full Hammersmith" regimen) received a loading dose of 2 million kallikrein inactivation units (KIU) of aprotinin, 2 million KIU of aprotinin added to the CPB pump prime, and a continuous infusion of 500,000 KIU/hr during CPB. • Tranexamic acid group received 500mg of TXA as a loading dose, 500mg added to the CPB pump prime, and 1g was given post CPB (a total of 2g of TXA). NB: Cell Salvage was used during surgery in both groups using a cell saver (Brat2, Cobe Cardiovascular Inc, Arvada, CO.)
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), fresh frozen plasma usage (units), platelet usage (units), blood loss, mortality, myocardial Infarction, hospital length of stay (days), intensive care unit length of stay (days), intubation time (hours), number of patients requiring Intra-aortic balloon pump (IABP) therapy

Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated code
Allocation concealment?	No	Inadequate - sealed envelopes
Blinding? All outcomes	Yes	Double blind

Hendrice 1995

Methods	Method of randomisation and allocation concealment were not described
Participants	26 patients undergoing primary coronary artery bypass surgery were randomly allocated to one of two groups: • Aprotinin group: n = 12, mean (sd) age = 59.8 (7.9) years • Control group: n = 14, mean (sd) age = 58.1 (17.3) years Nb: Gender data not provided.
Interventions	• Aprotinin group received a loading dose of 2 million kallikrein inactivation units (KIU) of aprotinin over a period of 30 minutes, followed by an infusion of 500,000 KIU until the end of surgery. A supplement of 2 million KIU of aprotinin was administered to the priming of the extracorporeal circuit. • Control group did not receive aprotinin.
Outcomes	***Outcomes reported:*** Allogeneic blood usage, blood loss (24 hrs), haemoglobin levels, coagulation factors
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol not specified

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Hiipala 1995

Methods	Concealment of treatment allocation was by means of a ticket drawn from an envelope containing an equal number of treatment and placebo tickets. The method used to generate allocation sequences was not described
Participants	29 patients undergoing total knee arthroplasty were randomly allocated to one of two groups: • Tranexamic acid group: n = 15, M/F = 2/13, mean (range) age = 70 (56-82) years • Control group (Placebo): n = 13, M/F = 3/10, mean (range) age = 70 (63-78) years
Interventions	• Tranexamic acid group received a bolus of 15mg/kg of TXA 2-5 minutes before deflation of limb tourniquet. • Control group received an equal volume of sodium chloride solution (0.9%).
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss, myocardial infarction, deep vein thrombosis, pulmonary embolus, minor non-thromboembolic complications
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	No	Inadequate
Blinding? All outcomes	Yes	Double blind

Hiipala 1997

Methods	A ticket indicating the group was drawn and enclosed in an envelope. The envelopes were opened after the study was completed. Injection syringes were prepared by a person outside the surgical team
Participants	75 patients scheduled for 77 total knee arthroplasties were randomly allocated to one of two groups: • Tranexamic acid group: n = 39, M/F = 4/35, mean (sd) age = 70 (7) years • Control group (Placebo): n = 38, M/F = 8/30, mean (sd) age = 69 (5) years NB: Three patients were excluded from the final analysis for miscellaneous reasons
Interventions	• Tranexamic acid group received 15mg/kg of TXA before the removal of the limb tourniquet, followed by two 10mg/kg additional doses. • Control group received equal volumes of normal saline.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss, mortality, deep vein thrombosis, pulmonary embolus, non-thrombotic complications.

Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	No	Inadequate
Blinding? All outcomes	Yes	Double blind

Hill 1998

Methods	Patients were randomised according to a computer-generated sequence. Method of allocation concealment was not described
Participants	20 adult patients scheduled for first-time myocardial revascularisation were randomly assigned to one of two groups: • Aprotinin group: n = 10, mean (sd) age = 64 (7.9) years • Control group: n = 10, mean (sd) age = 62 (7.9) years NB: Gender data not reported.
Interventions	• Aprotinin group received 280mg of aprotinin (2 million KIU) intravenously as a loading dose followed by 70mg (500,000 KIU) of aprotinin per hour as a constant intravenous infusion until chest closure. In addition 280mg of aprotinin (2 million KIU) was added to the "pump prime". • Control group did not receive aprotinin.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), interleukin-10 (IL-10) levels
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol not specified

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated sequence
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Horrow 1990

Methods	Patients were randomised using a random number table. Sealed envelopes ensured that only the pharmacist, who prepared the encoded infusions, knew whether a patient received drug or placebo
Participants	49 patients undergoing cardiac surgery were randomised to one of two groups: • Tranexamic acid group: n = 18, mean (sd) age = 66 (10) • Control group (Placebo): n = 20, mean (sd) age = 62 (9) years
Interventions	• Tranexamic acid group received a 10mg/kg infusion of TXA over a 20-minute period followed by an infusion of 1mg/kg for 10 hours. • Control group received equivalent infusions of saline (100ml total volume). NB: Both groups received cell salvage.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), number of participants exposed to fresh frozen plasma, number of participants exposed to platelets, blood loss (12 hrs), deep vein thrombosis, pulmonary embolus, stroke, number of patients receiving cell salvage, volume of cell salvage autotransfused
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol not specified

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table
Allocation concealment?	No	Inadequate
Blinding? All outcomes	Yes	Double blind

Horrow 1991

Methods	A table of random numbers determined patient allocation to one of four groups. Coded infusion bags and sealed envelopes prepared by a pharmacist not involved in the study provided double blinded conditions
Participants	163 adult patients undergoing coronary revascularisation, valve replacement, both procedures, or repair of atrial septal defect, were randomly allocated to one of four groups: • Control group (Placebo): n = 44, mean (sd) age = 64 (10) years • Tranexamic acid group: n = 37, mean (sd) age = 65 (11) years • Desmopressin group: n = 38, mean (sd) age = 63 (11) years • Tranexamic acid + Desmopressin group: n = 40, mean (sd) age = 63 (9) years NB: Gender data were not reported.
Interventions	• Control group received saline solutions. • Tranexamic acid group received tranexamic acid beginning after induction of anaesthesia but before skin incision (loading dose - 10mg/kg over 30 minutes) followed by a 12 hour infusion of 1mg/kg/hr.

	• Desmopressin group received desmopressin acetate (0.3ug/kg over 20 minutes) beginning after extracorporeal circulation following completion of protamine infusion. • Tranexamic acid + Desmopressin group received both tranexamic acid and desmopressin in an identical fashion to groups 2 and 3. NB: All patients received cell salvaged autologous blood if available
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , fresh frozen plasma usage (units), platelet usage (units), blood loss (12hrs), myocardial infarction, stroke, deep venous thrombosis, re-operation for bleeding, rash, ventricular dysfunction, pulmonary oedema, ventricular tachycardia
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Table of random numbers
Allocation concealment?	No	Inadequate
Blinding? All outcomes	No	Single blind

Horrow 1995

Methods	Coded infusion bags for both loading and infusion doses and sealed envelopes prepared by a pharmacist provided allocation concealment. Randomisation was determined by a table of random numbers
Participants	148 patients undergoing elective cardiac operations were randomised to one of six groups: • Control group (Placebo): n = 27, M/F = 23/4, mean (sd) age = 63 (10.4) years • Tranexamic acid group (Quarter dose): n = 24; M/F = 18/6; mean (sd) age = 67 (9.8) years • Tranexamic acid group (Half dose): n = 22, M/F = 19/3, mean (sd) age = 61 (9.4) years • Tranexamic acid group (Whole dose): n = 21, M/F = 18/3, mean (sd) age = 66 (9.2) years • Tranexamic acid group (Double dose): n = 27, M/F = 22/5, mean (sd) age = 63 (10.4) years • Tranexamic acid group (Fourfold dose): n = 27, M/F = 21/6, mean (sd) age = 65 (10.4) years
Interventions	• Control group received saline infusions. • Tranexamic acid group (Quarter dose) received a loading dose of 2.5mg/kg of TXA after the induction of anaesthesia over a period of 30 minutes followed by a 12 hour continuous infusion of 0.25mg/kg/hr of TXA. • Tranexamic acid group (Half dose) received a loading dose of 5.0mg/kg of TXA after the induction of anaesthesia over a period of 30 minutes followed by a 12 hour continuous infusion of 0.5mg/kg/hr of TXA. • Tranexamic acid group (Whole dose) received a loading dose of 10mg/kg of TXA after the induction of anaesthesia over a period of 30 minutes followed by a 12 hour continuous infusion

	of 1.0mg/kg/hr of TXA. • Tranexamic acid group (Double dose) received a loading dose of 20mg/kg of TXA after the induction of anaesthesia over a period of 30 minutes followed by a 12 hour continuous infusion of 2.0mg/kg/hr of TXA. • Tranexamic acid group (Fourfold dose) received a loading dose of 40mg/kg of TXA after the induction of anaesthesia over a period of 30 minutes followed by a 12 hour continuous infusion of 4.0mg/kg/hr of TXA. NB: All groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , number of patients exposed to fresh frozen plasma, number of patients exposed to platelets, blood loss (12 hrs), mortality, hypotension
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Table of random numbers
Allocation concealment?	No	Inadequate
Blinding? All outcomes	Yes	Double blind

Husted 2003

Methods	Randomisation was performed by computer. The drugs were packed in numbered envelopes by a person not connected with the surgical procedure and handled by the anaesthetist. The randomisation code was not broken until the study was completed
Participants	40 patients undergoing primary total hip arthroplasty were randomised to one of two groups: • Tranexamic acid group: n = 20, M/F = 7/13, mean age = 65 years • Control group (Placebo): n = 20, M/F = 6/14, mean age = 67 years
Interventions	• Tranexamic acid group received a bolus dose of 10mg/kg of TXA (maximum 1g) during 10 minutes about 15 minutes before the incision, followed by a continuous infusion of 1mg/kg/hr dissolved in 1 litre of saline for 10 hours (maximum 1g over 10 hours). • Control group received saline as a bolus injection of 20ml about 15 minutes before the operation followed by a continuous infusion of 1 litre of saline during 10 hours.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss, deep vein thrombosis, pulmonary embolus, infection, haemoglobin levels
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Husted 2003 *(Continued)*

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation was performed by computer
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Ickx 2006

Methods	Method of randomisation and allocation concealment were not described
Participants	51 patients undergoing primary liver transplantation were randomised to one of two groups: • Aprotinin group (Low dose): n = 24, M/F = 20/4, mean (sd) age = 50 (10) years • Tranexamic acid group (n = 27), M/F = 25/2, mean (sd) age = 53 (7) years
Interventions	• Aprotinin group (Low dose) received 280mg of aprotinin as a slow bolus over 30 minutes followed by a continuous infusion of 70mg/hr. The infusion was initiated during the anhepatic phase, 30 minutes before the expected reperfusion time, and maintained until 2 hours after reperfusion. • Tranexamic acid group received a slow bolus of 40mg/kg of TXA over 30 minutes followed by a continuous infusion at a rate of 40mg/kg/hr. The infusion was initiated during the anhepatic phase, 30 minutes before the expected reperfusion time, and maintained until 2 hours after reperfusion.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, number of patients exposed to fresh frozen plasma, number of patients exposed to platelets, allogeneic blood usage (units), mortality, hospital length of stay (days), intensive care unit length of stay (days)
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Isetta 1993

Methods	Method of randomisation and allocation concealment were not described. Exclusions or loss to follow-up were not reported. [Abstract]
Participants	240 patients undergoing cardiac surgery were randomised to one of four groups: • Tranexamic acid group: n = 70 • Aprotinin group (Low dose): n = 70 • Aprotinin group (High dose): n = 70 • Control group: n = 70 NB: Demographic data were not reported.
Interventions	• Tranexamic acid group received 15mg/kg of TXA before the injection of heparin prior to cardiopulmonary bypass (CPB). • Aprotinin group (Low dose) received 500,000 KIU of aprotinin during 20 minutes after induction, followed by a continuous infusion of 500,000 KIU/hr until the end of CPB. • Aprotinin group (High dose) received 2 million KIU of aprotinin over a 45 minute period after induction followed by a continuous infusion of 500,000 KIU/hr until the end of CPB, the priming volume of the CPB circuit included 2 million KIU of aprotinin. • Control group received no antifibrinolytic treatment. NB: All groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss, haematocrit values
Notes	Quality assessment score (Schulz criteria): 0/7 (Abstract) Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Jamieson 1997

Methods	Method of randomisation and allocation concealment were not described
Participants	50 patients undergoing re-operative cardiac surgery were randomised to one of two groups: • Aprotinin group (High dose): n = 24, M/F = 11/13, median (range) age = 54 (34-77) years • Control group (Placebo): n = 36, M/F = 12/12, median (range) age = 53 (28-78) years
Interventions	• Aprotinin group (High dose) received a loading dose of 280mg of aprotinin infused after induction of anaesthesia, 280mg in the cardiopulmonary prime solution, and 70mg/hr of aprotinin for a period of 6 hours. • Control group received a placebo of normal saline.

	NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), fresh frozen plasma usage (units), platelet usage (units), blood loss, mortality, hospital length of stay (days), total blood products transfused
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Jansen 1999

Methods	Randomisation was performed using a computer-generated random number list. Method of allocation concealment was not described
Participants	42 patients undergoing unilateral bicondylar cemented total knee arthroplasty were randomised to one of two groups: • Tranexamic acid group: n = 21, M/F = 5/16, mean (range) age = 70.7 (62-80) years • Control group (Placebo) (n = 21), M/F = 3/18, mean (range) age = 71.0 (64-84) years
Interventions	• Tranexamic acid group received 15mg/kg of intravenous TXA before inflation of the tourniquet and surgery and repeated every 8 hours for 3 days. • Control group received an equivalent volume of normal saline.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss, deep venous thrombosis
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation was performed using a computer-generated random number list
Allocation concealment?	Unclear	Unclear

Blinding? All outcomes	Yes	Double blind

Janssens 1994

Methods	Method of randomisation and allocation concealment were not described
Participants	40 patients undergoing primary total hip replacement were randomised to one of two groups: • Aprotinin group: n = 20, M/F = 10/10, mean (sd) age = 64.9 (13.2) years • Control group (Placebo): n = 20, mean (sd) age = 65.3 (15.3) years
Interventions	• Aprotinin group received a bolus injection of 2 million KIU of aprotinin over 30 minutes after the induction of anaesthesia, followed by an infusion of 500,000 KIU/hr until the end of surgery with a maximum dose of 3.5 million KIU of aprotinin. • Control group received the same volume of normal saline according to the same protocol as aprotinin.
Outcomes	***Outcomes reported:*** Blood loss, number of patients exposed to allogeneic/autologous blood, allogeneic blood usage (units), autologous blood usage (units), hospital length of stay (days), deep vein thrombosis
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Jares 2003

Methods	Method of randomisation and allocation concealment were not described
Participants	47 patients undergoing 'off pump' coronary artery bypass graft surgery were randomised to one of two groups: • Tranexamic acid group: n = 22, M/F = 20/2 • Control group: n = 25, M/F = 15/10 NB: No age data were reported.
Interventions	• Tranexamic acid group received 1g of TXA 10 minutes before surgical incision followed by a continuous infusion at a rate of 200mg/hr until the end of the procedure.

Jares 2003 *(Continued)*

	• Control group did not receive antifibrinolytic treatment.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss, pulmonary embolus, aspirin use <5 days, re-operation for bleeding, stroke
Notes	Quality assessment score (Schulz criteria): 1/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	No	No blinding

Jeserschek 2003

Methods	Method of randomisation and allocation concealment were not described
Participants	18 patients undergoing elective orthopaedic surgery were randomised to one of two groups: • Aprotinin group (Low dose): n = 9, M/F = 3/6, mean (sd) age = 67 (12.0) years • Control group (Placebo): n = 9, M/F = 5/4, mean (sd) age = 72.7 (7.8) years
Interventions	• Aprotinin group (Low dose) received at the begining of the operation 1 million KIU of aprotinin (140mg) as a loading dose followed by a continuous infusion of 500,000 KIU/hr. • Control group received the same volume of normal saline. NB: Both groups were exposed to intra-operative cell salvage
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol not used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear

Blinding? All outcomes	Yes	Double blind

Jimenez 2007

Methods	Patients were assigned to treatment group by independent pharmacists using a list of pseudo-randomised numbers to receive coded infusions of either TXA or placebo. The cose was revealed once recruitment, data collection, and laboratory analyses were completed
Participants	50 patients undergoing cardiac surgery were randomised to one of two groups: • Tranexamic acid group: n = 24, M/F = 12/12, mean (95%CI) age = 66 (63-70) years • Control group (Placebo): n = 26, M/F = 15/11, mean (95% CI) age = 67 (62-71) years
Interventions	• Tranexamic acid group received 2g before and after surgery. • Control group received saline.
Outcomes	***Outcomes reported:*** Number of patients receiving blood transfusion, volume of blood transfused (units), blood loss, mortality, hospital length of stay, mechanical ventilation hours, inflammatory response, d-dimer levels
Notes	Quality assessment score (Schulz criteria): 7/7 Use of a transfusion protocol was not reported.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomised number list
Allocation concealment?	Yes	Adeaquate
Blinding? All outcomes	Yes	Double blind

Johansson 2005

Methods	Patients were randomised by computer in blocks of 10. Coded ampoules were prepared by the pharmaceutical company. All personnel and patients were blinded as to the treatment until the randomisation code was broken which took place after all patients had been evaluated
Participants	119 patients undergoing total hip arthroplasty were randomised to one of two groups: • Tranexamic acid group: n = 47, M/F = 25/22, mean (sd) age = 69 (7) years • Control group (Placebo): n = 53, M/F = 28/25, mean (sd) age = 68 (8) years NB: Before the randomisation code was broken 19 patients were excluded due to violation of the study protocol

Interventions	• Tranexamic acid group received a bolus infusion of 15mg/kg of TXA mixed in 100ml of normal saline immediately before the start of the operation. • Control group received normal saline.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss, deep vein thrombosis
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer randomisation
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Kahveci 1996

Methods	Method of randomisation and allocation concealment were not described. [Turkish language]
Participants	28 patients undergoing coronary artery bypass surgery or cardiac valvular surgery were randomised to one of two groups: • Aprotinin group (Low dose): n = 14, M/F = 6/8, mean (sd) age = 45.5 (12.8) years • Control group: n = 14, M/F = 8/6, mean (sd) age = 48 (10.5) years
Interventions	• Aprotinin group (Low dose) received a bolus of 2 million KIU of aprotinin (280 mg) before the induction of anaesthesia followed by a continuous infusion of 500,000 KIU/hr. • Control group did not receive aprotinin.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), fresh frozen plasma usage (units), blood loss
Notes	Transfusion protocol not used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear

Kahveci 1996 (*Continued*)

Blinding? All outcomes	Unclear	Unclear

Kalangos 1994

Methods	Method of randomisation and allocation concealment were not described. No exclusions were reported
Participants	165 adult patients undergoing elective primary aortocoronary bypass operations were randomised to one of three groups: • Aprotinin group (High dose): n = 55, M/F = 47/8, mean (sd) age = 58.2 (5.6) years • Aprotinin group (Low dose): n = 55, M/F = 44/11, mean (sd) age = 57.7 (6.6) years • Control (Placebo): n = 55, M/F = 49/6, mean (sd) age = 60.5 (6.8) years
Interventions	• Aprotinin group (High dose) received an intravenous bolus of 2 million KIU of aprotinin at induction of anaesthesia. Another 2 million KIU of aprotinin was added to the pump prime volume. A continuous infusion of 500,000 KIU/hr of aprotinin was maintained until the end of the operation. • Aprotinin group (Low dose) received 25,000 KIU/kg added to the pump prime solution (mean dosage 1.78 million KIU; range 1.375 million KIU to 2.3 million KIU) and saline was administered at all other corresponding times. • Control group received identical volumes of saline at all corresponding times.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss, myocardial infarction, creatine phosphokinase - myocardial band (CK-MB) levels
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Karski 1995

Methods	Randomisation was performed by the pharmacy department. The method used to generate allocation sequences was not described
Participants	150 patients undergoing cardiac operations were randomised to one of three groups: • Tranexamic acid group (TA-10): n = 50, mean (sd) age = 59 (21.2) years • Tranexamic acid group (TA-20): n = 50, mean (sd) age = 63 (7.0) years • Control group (Placebo): n = 50, mean (sd) age = 58 (14.1) years NB: Gender data were not reported.
Interventions	• Tranexamic acid group (TA-10) received an infusion of 10g of TXA intravenously over 20 minutes after induction of anaesthesia and a placebo infusion (0.9% normal saline) over the subsequent 5 hours. • Tranexamic acid group (TA-20) received 10g of TXA over 20 minutes and then a further 10g infused over 5 hours. • Control group received a placebo bolus (0.9% normal saline) and a placebo infusion (0.9% normal saline) over 5 hours. NB: All groups were exposed to cell salvage (autotransfusion). Patients with defined 'excessive bleeding' were treated with 10-40g of intravenous epsilon aminocaproic acid (EACA) or desmopressin (DDAVP)
Outcomes	Outcomes reported: Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	No	Single blind

Karski 2005

Methods	A computer-generated randomisation code in blocks of four was used to assign patients to treatment or control in a double-blinded fashion. The hospital pharmacy prepared identical bags of solution
Participants	312 patients undergoing cardiac surgery were randomised to one of two groups: • Tranexamic acid group: n = 147, M/F = 128/19, mean (sd) age = 59.9 (8.9) years • Control group (Placebo): n = 165, M/F = 147/18, mean (sd) age = 60 (8.3) years
Interventions	• Tranexamic acid group received 100mg/kg of TXA in 100ml solution over 20 minutes after the induction of anaesthesia.

	• Control group received 5% dextrose.
Outcomes	***Outcomes reported:*** Number of patinets exposed to allogeneic blood, number of patients exposed to fresh frozen plasma, number of patients exposed to platelets, mortality, myocardial infarction, stroke, cardiac arrest, atrial fibrillation
Notes	Quality assessment score (Schulz criteria): 7/7 Transfusion protocol not specified NB: Open-labeled tranexamic acid was administered to 4 patients in the TXA group and 24 patients in the control group

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated randomisation code
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Kaspar 1997

Methods	Study infusions were prepared by the hospital pharmacy using a computer generated randomisation schedule
Participants	32 consecutive patients undergoing orthotopic liver transplantation were randomly allocated to one of two groups: • Tranexamic acid group: n = 16 • Control group (Placebo): n = 16 NB: Demographic data were not reported.
Interventions	• Tranexamic acid group received a continuous small dose infusion of TXA (1g in 500ml of normal saline) at a dose of 2mg/kg/hr. • Control group received an equal volume of normal saline. NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), fresh frozen plasma (units), platelets (units), mortality, hepatic arterial thrombosis, epsilon aminocaproic acid 'rescue', cryoprecipitate
Notes	Quality assessment score (Schulz criteria): 7/7 Transfusion protocol not specified

Risk of bias

Item	**Authors' judgement**	**Description**

Adequate sequence generation?	Yes	Computer generated randomisation schedule
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Katoh 1997

Methods	Method of randomisation and allocation concealment were not described
Participants	93 patients undergoing either coronary artery bypass grafting or heart valve operations were randomly divided into one of three groups: • Tranexamic acid group (TA-1): n = 31, M/F = 22/9, mean (sd) age = 63.7 (8.3) years • Tranexamic acid group (TA-2): n = 31, M/F = 21/10, mean (sd) age = 62.9 (9.5) years • Control group: n = 31, M/F = 22/9, mean (sd) age = 64.7 (11.7) years
Interventions	• Tranexamic acid group (TA-1) received an infusion of tranexamic acid (TXA) of 100mg/kg intravenously (IV) over 20 minutes soon after induction of anaesthesia and before cardiopulmonary bypass (CPB). • Tranexamic acid group (TA-2) received a 100mg/kg dose of TXA intravenously (IV) over 20 minutes soon after induction of anaesthesia and before CPB, and an additional dose of 50mg/kg infused IV over 20 minutes soon after being weaned from CPB. • Control group did not receive tranexamic acid.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss, mortality, myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Katsaros 1996

Methods	Method of randomisation was not described. Allocation concealment was by coded infusions. One patient was eliminated from the study due to improper data collection
Participants	211 patients scheduled for open heart operations were randomised to one of two groups: • Tranexamic acid group: n = 104, M/F = 68/36, mean (sd) age = 65 (9.3) years • Control group (Placebo): n = 106, M/F = 80/26, mean (sd) age = 63 (12.3) years
Interventions	• Tranexamic acid group received 10g of TXA (diluted to 250ml with normal saline solution) intravenously over 20 minutes. No incision was made until the completion of the infusions. • Control group received 250ml of normal saline solution. NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, bood loss (24hrs), mortality, myocardial infarctions, deep vein thrombosis, pulmonary embolus, re-operation for bleeding, cerebrovascular accident, renal failure, central nervous system complications
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Katzel 1998

Methods	Method of randomisation and allocation concealment were not described. [German language]
Participants	24 male patients undergoing thoracic surgery for malignant lung disease were randomised to one of two groups: • Aprotinin group (Low dose): n = 12, mean (sd) age = 57.1 (8.2) years • Control group (Placebo): n = 12, mean (sd) age = 59.4 (9.0) years
Interventions	• Aprotinin group (Low dose) received a bolus of 280mg of aprotinin (2 million KIU) followed by 500,000 KIU of aprotinin during surgery until 1 hour after surgery. • Control group was infused with isotonic saline.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss, transient ischaemic attack

Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Kazemi 2010

Methods	Methods of sequence generation and allocation concealment were not described
Participants	64 patients undergoing orthopaedic surgery were randomised to one of two groups: • Tranexamic acid group: n = 32, M/F = 23/9, mean (sd) age = 46.6 (16.2) years • Control group: n = 32, M/F = 20/12, mean (sd) age = 45.4 (17.2) years
Interventions	• Tranexamic acid group received 15mg/kg given five minutes pre-operatively. • Control group received saline.
Outcomes	***Outcomes reported:*** Volume of blood transfused (units), blood loss, deep vein thrombosis, length of stay (days)
Notes	Transfusion protocol was used.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Kikura 2006

Methods	Method of randomisation and allocation concealment were not described
Participants	100 patients undergoing cardiac surgery were randomised to one of two groups: • Epsilon aminocaproic acid: n = 50, M/F = 38/12, mean (sd) age = 63 (10) years • Control group (Placebo): n = 50, M/F = 40/10, mean (sd) age = 62 (11) years
Interventions	• Epsilon aminocaproic acid group received 100mg/kg of EACA as a loading dose over 20-30 minutes, after endotracheal intubation, followed by a continuous infusion of 1g/hr of EACA during the operation, and a loading dose of 10g given into the CPB circuit prime solution. The infusion was discontinued on completion of surgery. • Control group (placebo) received identical appearing normal saline in identical volumes at the same times as EACA treatment. NB: Both groups were exposed to intra-operative cell salvage
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , number of patients exposed to fresh frozen plasma, number of patients exposed to platelets, blood loss (24hrs)
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Kipfer 2003

Methods	Method of randomisation and allocation concealment were not described
Participants	30 adult patients undergoing elective cardiac surgery were randomised into one of two groups: • Aprotinin group (Low dose): n = 15, M/F = 12/3, mean (sd) age = 62.3 (7) years • Control group: n = 15, M/F = 12/3, mean (sd) age = 61.3 (7) years
Interventions	• Aprotinin group (Low dose - pump prime) received 2 million KIU (280mg) of aprotinin added to the prime volume of the CPB. • Control group did not receive aprotonin.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss, fresh frozen plasma, myocardial infarction, mortality, myocardial infarction, retransfused mediastinal shed blood, re-operation for bleeding, renal dysfunction, neurological deficit, hospital length of stay (days)

Kipfer 2003 *(Continued)*

Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Klein 1998

Methods	Method of randomisation and allocation concealment were not described
Participants	109 patients undergoing elective cardiac surgery were randomised to one of three groups: • Aprotinin group (High dose + ASA): n = 40), M/F = 33/7, mean (sd) age = 64.0 (6.3) years • Aprotinin group (High dose): n = 38, M/F = 34/4, mean (sd) age = 62.1 (7.3) years • Control group (Placebo): n = 31, M/F = 28/3, mean (sd) age = 63.0 (9.3) years
Interventions	• Aprotinin group (High dose + ASA) received a loading dose of 2 million KIU (280mg) followed by a continuous infusion of 500,000 KIU/hr until chest closure for a 6 hour maximum period. In addition, 2 million KIU of aprotinin was added to the pump prime. Patients underwent a minimum 10-day run-in period on ASA (100mg/day) until surgery. • Aprotinin group (High dose) received a loading dose of 2 million KIU (280mg) followed by a continuous infusion of 500,000 KIU/hr until chest closure for a 6 hour maximum period. In addition, 2 million KIU of aprotinin was added to the pump prime. • Control group received an unspecified placebo.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss, fresh frozen plasma, myocardial infarction
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear

Blinding? All outcomes	Yes	Double blind

Kluger 2003

Methods	Patients underwent permuted block randomisation using random number tables. All patients received four syringes, labelled A,B,C,and D. Patients, clinicians, and investigators were all blinded to group allocation
Participants	90 patients undergoing cardiac surgery were randomised to one of three groups: • Epsilon aminocaproic acid group (Post-heparin): n = 30, M/F = 24/6, mean (sd) age = 65 (8.1) years • Epsilon aminocaproic acid group (Pre-incision): n = 28, M/F = 23/5, mean (sd) age = 66 (8.1) years • Control group (Placebo): n = 30, M/F = 22/8, mean (sd) age = 67 (6.5) years NB: Two patients were excluded from the final analysis.
Interventions	• Epsilon aminocaproic acid group (Post-heparin) received an initial bolus of normal saline prior to skin incision, followed by a normal saline infusion. Three minutes after heparin administration patients received a bolus of 150mg/kg of EACA over 10 minutes and then an infusion of 15mg/kg/hr. • Epsilon aminocaproic acid group (Pre-incision) received a bolus of 150mg/kg of EACA over 10 minutes after the induction of anaesthesia but before skin incision, followed by an infusion of 15mg/kg/hr. Three minutes after heparin administration, to maintain blinding, this group received a bolus of normal saline over 10 minutes, followed by a resumption of the EACA infusion until the termination of CPB. • Control group received normal saline boluses and infusions throughout. NB: All groups were exposed to acute normovolaemic haemodilution (ANH)
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, number of patients exposed to fresh frozen plasma and platelets, mortality, myocardial infarction, re-operation for bleeding, stroke.
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Koster 2004

Methods	Allocation of patients was blinded to the surgeon. Method of randomisation was not described
Participants	200 patients undergoing elective cardiac surgery were randomised to one of two groups: • Aprotinin group (Low dose + heparin): n = 100, M/F = 56/44, mean (sd) age = 64 (15) years • Control group (Heparin alone): n = 100, M/F = 57/43, mean (sd) age = 66 (17) years
Interventions	• Aprotinin group (Low dose + heparin) received a bolus of 1 million KIU of aprotinin immediately before initiation of CPB and a continuous infusion of 250,000 KIU/hr during the period of CPB. In addition, 1 million KIU of aprotinin was added to the CPB pump prime. • Control group received standard care without aprotinin treatment. NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), fresh frozen plasma, blood loss, duration of ventilation (hours)
Notes	Quality assessment score (Schulz criteria): 0/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	No	Single blind

Kratzer 1997

Methods	Method of randomisation was by means of a random number generator. Method used to conceal treatment allocation was not described. [German language]
Participants	18 patients undergoing orthotopic liver transplantation were randomised to one of two groups: • Aprotinin group: n = 9, mean age 47.9 years • Control group (Placebo): n = 9, mean age 49.4 years NB: Gender data were not reported.
Interventions	• Aprotinin group received an intravenous bolus of 2 million KIU (280mg) of aprotinin at induction of anaesthesia and a continuous infusion of 500,000 KIU/hr of aprotinin until the end of the operation. • Control group received physiological saline solution.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), coagulation parameters, blood loss
Notes	Transfusion protocol used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Kreisler 2005

Methods	Randomisation was accomplished through the use of a computer-generated table of random numbers. Method used to conceal treatment allocation was not described
Participants	71 patients undergoing cardiac surgery were randomised to one of three groups: • Epsilon aminocaproic acid: n = 22, M/F = 17/5, mean (sd) age = 63.4 (7.2) years • Heparin-coated CPB circuit: n = 20, 17/3, mean (sd) age = 59.6 (10.4) years • Control group (Placebo): n = 25, M/F = 17/8, mean (sd) age = 61.4 (8.8) years
Interventions	• Epsilon aminocaproic acid group received non-heparin coated circuits and EACA. A loading dose of 75mg/kg of EACA was given over 10 minutes after the induction of anaesthesia and prior to skin incision followed by a maintenance infusion of EACA of 12.5mg/kg/hr continued for 2 hours after the arrival of the patient in the intensive care unit. An additional 5g of EACA was added to the CPB priming fluid. • Heparin coated (bonded) CPB circuit group were treated with tip-to-tip heparin-coated CPB circuits, including the cardiotomy reservoir, arterial filter, aortic and venous cannulas, and a placebo infusion of normal saline. • Control group received non-heparin coated circuits and a 0.9% normal saline load and maintenance infusion given in the same manner as EACA-treated patients. NB: All groups were exposed to cell savage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, number of patients exposed to platelets, hospital length of stay (days), intensive care length of stay (hours), cell saver volume autotransfused
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated table of random numbers
Allocation concealment?	Unclear	Unclear

Blinding? All outcomes	Yes	Double blind

Kuepper 2003

Methods	Group assignment was by sealed envelopes. Sealed envelopes were opened after induction of anaesthesia by the unblinded investigator who was not part of the operating team
Participants	120 patients undergoing elective cardiac surgery were randomised to one of two groups: • Aprotinin group (Low dose): n = 60, M/F = 40/20, mean (sd) age = 65.5 (7.8) years • Control group: n = 59, M/F = 40/19, mean (sd) age = 65.6 (8.8) years
Interventions	• Aprotonin group (Low dose) received a single loading dose of 2 million KIU (280mg) of aprotinin given after the induction of anaesthesia but before skin incision. • Control group did not receive aprotinin.
Outcomes	Outcomes reported: Allogeneic blood usage (units), blood loss, fresh frozen plasma, platelets (units), mortality
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion threshold for RBC not reported

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	No	Inadequate
Blinding? All outcomes	No	Single blind

Kuitunen 2005

Methods	Study drugs were prepared by the hospital pharmacy. Randomisation was carried out using closed envelopes
Participants	60 patients undergoing primary coronary artery bypass graft surgery were randomised to one of three groups: • Aprotinin group (High dose): n = 20, mean (sd) age = 61 (8.9) years • Tranexamic acid group: n = 20, mean (sd) age = 63 (8.9) years • Control group (Placebo): n = 20, mean (sd) age = 65 (8.9) years
Interventions	• Aprotinin group (High dose) received 2 million KIU (280mg) of aprotinin after the induction of anaesthesia, followed by an infusion of 500,000 KIU/hr (70mg/hr) until the end of surgery. In addition, 2 million KIU (280mg) of aprotinin was added to the pump prime of the

	CPB circuit. • Tranexamic acid group received 15mg/kg after the induction of anaesthesia, followed by an infusion of 15mg/kg until the end of surgery. In addition, 15mg/kg was added to the pump prime of the CPB circuit. • Control group received normal saline. NB: All groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, number of patients exposed to fresh frozen plasma, number of participants exposed to platelets, blood loss (16hrs), mortality, myocardial infarction, re-operation for bleeding, stroke
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	Closed envelopes
Allocation concealment?	No	Inadequate
Blinding? All outcomes	Yes	Double blind

Kuitunen 2006

Methods	Method of randomisation and allocation concealment were not described
Participants	30 patients undergoing elective primary cardiac surgery were randomised to one of two groups: • Tranexamic acid group: n = 15, M/F = 12/3, mean (sd) age = 57 (16) years • Control group: n = 15, M/F = 11/4, mean (sd) age = 61 (11) years
Interventions	• Tranexamic acid group received 1g after administration of 15ml/kg of 6% HES in the immediate post-operative period. • Control group received saline after administration of 15ml/kg of 6% HES in the immediate post-operative period.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood transfusion, number of patients exposed to fresh frozen plasma and platelets, blood loss (24hrs), re-operation for bleeding
Notes	Transfusion protocol used.

Risk of bias

Item	Authors' judgement	Description

Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Kunt 2005

Methods	Method of randomisation and allocation concealment were not described
Participants	86 patients undergoing routine cardiac surgery were randomised to one of two groups: • Aprotinin group: n = 40, M/F = 30/10, mean (sd) age = 63 (12) years • Control group: n = 46, mean (sd) age = 60 (7) years
Interventions	• Aprotinin group received 500,000 KIU (70mg) of aprotinin in the pump prime only. • Control group received "no aprotinin."
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss (24 hrs), mortality, hospital length of stay (days), intensive care unit length of stay (hours), re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol not used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Kyriss 2001

Methods	Randomisation carried out using a computer-generated random list. Allocation concealment not specified
Participants	38 patients undergoing elective thoracic surgery were randomised to one of two groups: • Aprotinin group (Low dose): n = 18, M/F = 12/6, mean age = 51.8 years • Control group (Placebo): n =20, M/F = 12/8, mean age = 50.8 years
Interventions	• Aprotonin group (Low dose) received a test dose of 10,000 KIU during induction of anaesthesia followed by an initial bolus dose of 2 million KIU (280mg) of aprotinin over 20 minutes and a continuous infusion of 500,000 KIU/hr during the surgical procedure. • Control group received a corresponding volume of saline solution.

Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss, fresh frozen plasma, blood loss, mortality, blood loss, re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 5/7 No transfusion protocol

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random list
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Landymore 1997

Methods	Method of randomisation was not described. The study drugs were prepared by pharmacy, given an identification number, and then sent to the operating room
Participants	148 patients undergoing primary myocardial revascularisation were randomised to one of three groups: • Aprotinin group (Low dose): n = 48 • Epsilon-aminocaproic acid group: n = 44 • Tranexamic acid group: n = 56 • Control group: n = 50 (not included in randomisation process) NB: Demographic data were not reported.
Interventions	• Aprotinin group (Low dose) received a loading dose of 200,000 KIU of aprotinin administered before cardiopulmonary bypass (CPB), followed by a maintenance dose of 200,000 KIU/hr of aprotinin continued until the termination of CPB. • Epsilon-aminocaproic acid group received a loading dose of 5g administered before CPB, followed by a maintenance dose of 1g/hr of EACA continued until the termination of CPB. • Tranexamic acid group received a loading dose of 10mg/kg of TXA administered before CPB, followed by a maintenance dose of 1mg/kg/hr of TXA continued until the termination of CPB. • Control group did not receive antifibrinolytic treatment.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss, thrombosis, deep vein thrombosis, pulmonary embolus
Notes	Quality assessment score (Schulz criteria):2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Lass 1995

Methods	Method of randomisation and allocation concealment were not described. Four aprotinin (7.8%) and eight control (14.5%) patients were excluded from the final analysis
Participants	110 male patients undergoing elective primary coronary bypass surgery were randomised to one of two groups: • Aprotinin group (High dose): n = 55 • Control (Placebo): n = 55 NB: Demographic data were not reported.
Interventions	• Aprotinin group (High dose) received 2 million KIU of aprotinin as a loading dose before sternotomy followed by an infusion of 500,000 KIU/hr until the end of surgery. An additional 2 million KIU was added to the priming volume. • Control group received saline solution as a matching placebo in identical form by the same administration scheme.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , graft patency, blood loss, mortality, myocardial infarction, acute heart failure, post-operative complications, re-operation
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Later 2009

Methods	Allocated according to a computer-generated randomisation sequence, allocation concealed by use of sealed, opaque envelopes
Participants	298 patients undergoing cardiac surgery were randomised to one of three groups: • Aprotonin group: n = 96, M/F = 73/23, mean (sd) age = 66.5 (10.7) years • Tranexamic acid group: n = 99, M/F = 73/26, mean (sd) age = 64.1 (13.0) years • Control group: n = 103, M/F = 68/35, mean (sd) age = 65 (11.2) years
Interventions	• Aporinin group (high dose) received 2 million KIU pre-CPB, 2 million KIU at pump prime, and 500,000 KIU/hr during CPB. • Tranexamic acid group received 1g loading dose, 500mg added to CBP system prime, and a continuous infusion of 400mg/hr. • Control group received saline.
Outcomes	***Outcomes reported:*** Number of patienst exposed to allogeneic blood, myocardial infarction, renal failure, hospital length of stay (days), re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Computer-generated randomisation sequence
Allocation concealment?	No	Inadequate - sealed envelopes
Blinding? All outcomes	Yes	Double blind

Laub 1994

Methods	Method of randomisation and allocation concealment were not described
Participants	47 patients undergoing isolated coronary revascularisation were randomised to one of two groups: • Aprotinin group: n = 16, M/F = 12/4, mean (sd) age = 65.3 (11.2) years • Control group (Placebo): n = 16, M/F = 13/3, mean (sd) age = 63.6 (10) years NB: The study group consisted of 32 patients in total. Fifteen of the originally enrolled patients were not included in the final analysis due to: adverse reactions while receiving the study medication (n = 2), inability to obtain or a technically inadequate CT scan (n = 7), refusal to come for follow-up examinations (n = 4), or died (n = 2)
Interventions	• Aprotinin group received 500 KIU of aprotinin as a test dose after the induction of anaesthesia, followed by 2 million KIU (280mg) of aprotinin as a bolus. An infusion of 0.5 million KIU of aprotinin was commenced after the bolus was given and 2 million KIU of aprotinin was added to the pump prime. • Control group received an identical volume of placebo.

	NB: Autologous blood salvage with reinfusion of washed RBCs was used for all patients. Shed mediastinal and pleural blood was filtered and reinfused using an autotransfusion system
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, volume of allogeneic blood transfused, blood loss, volume of platelets and fresh frozen plasma, re-operation for bleeding, post-operative Hb levels, graft occlusions, any blood product usage, haematologic variables, coagulation profiles, renal function
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Lavee 1993

Methods	Method of randomisation and allocation concealment were not described
Participants	30 patients undergoing various cardiopulmonary bypass procedures were randomised to one of two groups: • Aprotinin group (Low dose): n = 15, M/F = 13/2, mean (sd) age = 62 (11) years • Control group (Placebo): n = 11, M/F = 11/4, mean (sd) age = 60 (9) years
Interventions	• Aprotinin group received 2 million KIU of aprotinin added to the priming volume of the oxygenator. No additional aprotinin doses were given to the patients. • Control group received an equivalent volume of placebo solution (saline solution 0.9%) added to the priming volume of the oxygenator.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss (24hrs), platelets (units), platelet aggregation
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear

Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Leijdekkers 2006

Methods	Patients were randomised to receive either placebo or aprotinin using a standard randomisation list stored in the pharmacy department, only to be opened after the study was closed for inclusion
Participants	35 patients undergoing cardiac surgery were randomised to one of two groups: • Aprotonin group: n = 16, M/F = 14/2, mean (sd) age = 68 (9.5) years • Control group: n = 19, M/F = 14/5, mean (sd) age = 68 (6.8) years
Interventions	• Aporinin group received 2 million KIU starting dose followed by 500,000 KIU/hr during surgery. • Control group received saline.
Outcomes	***Outocmes reported:*** Volume blood transfused (units), blood loss, mortality, re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 7/7 Transfusion protocol used.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation list
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Lemay 2004

Methods	Method of randomisation was not described. Study drugs were prepared by the hospital pharmacist. Patient caregivers and the investigator collecting the data were blinded to the solution used
Participants	40 patients undergoing total hip replacement were randomised to one of two groups: • Tranexamic acid group: n = 20, M/F = 12/8, mean (sd) age = 59.7 (10.3) years • Control group (Placebo): n = 19, M/F = 13/6, mean (sd) age = 53.6 (12.8) years NB: One patient was excluded from the final analysis.

Interventions	• Tranexamic acid group received TXA immediately before surgery. After a test dose of 1ml of TXA, patients received a dose of 10mg/kg of intravenous TXA followed by an infusion of TXA of 1mg/kg/hr until skin closure. • Control group received an equivalent volume of physiologic saline. NB: Pre-operative autologous donation of 3 units was offered to all patients
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss, deep vein thrombosis, changes in haemoglobin levels
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Lemmer 1994

Methods	Metho used to generate allocation sequences was not described. Aprotinin and an identically appearing placebo was supplied by Bayer AG, Leverkusen, Germany. Enrolled patients were stratified as to whether they were undergoing primary procedures (n = 151 patients: Lemmer_1) or repeat procedures (n = 65 patients: Lemmer_2)
Participants	151 patients undergoing isolated primary coronary artery bypass graft operations were randomised to one of two groups: • Aprotinin group: n = 74, M/F = 51/16, mean age = 64 years • Control group (Placebo): n = 74, M/F = 61/13, mean age = 62 years 65 patients undergoing repeat coronary artery bypass graft operations were randomised to one of two groups: • Aprotinin group (High dose): n = 29, M/F = 21/2, mean age = 66 years • Control group (Placebo): n = 36, M/F = 29/3, mean age = 65 years
Interventions	• Aprotinin group received a loading dose of 280mg of aprotinin followed by a continuous infusion of 70mg/hr, and 280mg of aprotinin was added to the oxygenator prime solution. The continuous infusion was discontinued on the patients' arrival to the intensive care unit. • Control group received identical volumes of 0.9% sodium chloride solution. NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , fresh frozen plasma (units), platelets (units), blood loss, mortality,

	myocardial infarction, re-operation for bleeding, allergic reactions, renal failure, renal failure + dialysis
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used. Of the 151 patients undergoing primary CABG, 141 (74 in the aprotinin treated group and 67 in the placebo treated group) fulfilled the criteria for efficacy analysis. Patients were eliminated from efficacy analysis before the random code was broken. Of the 65 patients undergoing repeat CABG surgery 55 (23 in the aprotinin treated group and 32 in the placebo treated group) fulfilled the criteria for efficacy analysis. Patients were eliminated from efficacy analysis before the random code was broken

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Lemmer 1996

Methods	Method of randomisation and allocation concealment were not described
Participants	704 first time coronary artery bypass grafting patients were randomised to one of four groups: • Control group (Placebo): n = 178, M/F = 151/27, mean (sd) age = 62.5 (10.67) years • Aprotinin group (High dose): n = 173, M/F = 145/28, mean (sd) age = 61.3 (10.5) years • Aprotinin group (Low dose): n = 180, M/F = 155/25, mean (sd) age = 61.7 (10.7) years • Aprotinin group (Pump prime dose): n = 173, M/F = 151/22, mean (sd) age = 62.1 (10.5) years
Interventions	• Control group received equivalent volumes of 0.9% sodium chloride at the same time periods. • Aprotinin group (High dose) received a loading dose of 280mg of aprotinin, a continuous infusion dose of 70mg/hr until the end of the operation, and 280mg of aprotinin was added to the pump prime solution. • Aprotinin group (Low dose) received a loading dose of 140mg of aprotinin, a continuous infusion dose of 35mg/hr until the end of the operation, and 140mg of aprotinin was added to the pump prime solution. • Aprotinin group (Pump prime dose) received a loading dose of placebo (0.9% sodium chloride), a continuous infusion of placebo until the end of the operation, and 280mg of aprotinin was added to the pump prime. NB: All groups were exposed to cell salvage autotransfusion.

Lemmer 1996 (*Continued)*

Outcomes	***Outcomes reported:*** Total blood product exposures per patient, number of patients exposed to allogeneic blood, allogeneic blood usage (units), platelet (units), fresh frozen plasma (units), cryo-precipitate (units), blood loss, re-operation for diffuse bleeding, myocardial infarction
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Lemmer˙1 1994

Methods	Refer to Lemmer 1994
Participants	151 patients undergoing isolated primary coronary artery bypass graft operations were randomised to one of two groups: • Aprotinin group: n = 74, M/F = 51/16, mean age = 64 years • Control group (Placebo): n = 74, M/F = 61/13, mean age = 62 years
Interventions	• Aprotinin group received a loading dose of 280mg of aprotinin followed by a continuous infusion of 70mg/hr, and 280mg of aprotinin was added to the oxygenator prime solution. The continuous infusion was discontinued on the patients' arrival to the intensive care unit. • Control group received identical volumes of 0.9% sodium chloride solution. NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , fresh frozen plasma (units), platelets (units), blood loss, mortality, myocardial infarction, re-operation for bleeding, allergic reactions, renal failure, renal failure + dialysis
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used. Of the 151 patients undergoing primary CABG, 141 (74 in the aprotinin treated group and 67 in the placebo treated group) fulfilled the criteria for efficacy analysis. Patients were eliminated from efficacy analysis before the random code was broken

Risk of bias

Item	Authors' judgement	Description

Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Lemmer˙2 1994

Methods	Refer to Lemmer 1994
Participants	65 patients undergoing repeat coronary artery bypass graft operations were randomised to one of two groups: • Aprotinin group (High dose): n = 29, M/F = 21/2, mean age = 66 years • Control group (Placebo): n = 36, M/F = 29/3, mean age = 65 years
Interventions	• Aprotinin group (High dose) received a loading dose of 280mg of aprotinin followed by a continuous infusion of 70mg/hr, and 280mg of aprotinin was added to the oxygenator prime solution. The continuous infusion was discontinued on the patients arrival to the intensive care unit. • Control group received an identical volume of 0.9% sodium chloride solution. NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), fresh frozen plasma (units), platelets (units), blood loss, mortality, myocardial infarction, re-operation for bleeding.
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used. Of the 65 patients undergoing repeat CABG surgery 55 (23 in the aprotinin treated group and 32 in the placebo treated group) fulfilled the criteria for efficacy analysis. Patients were eliminated from efficacy analysis before the random code was broken

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Yes

Lentschener 1997

Methods	Generation of allocation sequences was by means of computer-generated random codes. Method of allocation concealment was not described
Participants	97 patients scheduled for elective liver resection performed through subcostal incision were randomly assigned to one of two groups: • Aprotinin group: n = 48, M/F = 23/24, mean (sd) age = 53 (15) years • Control group (Placebo): n = 49, M/F = 26/21, mean (sd) age = 54 (15) years
Interventions	• Aprotinin group received a loading dose of 2 million KIU over 20 minutes after the induction of anaesthesia, followed by a continuous infusion of 500,000 KIU/hr administered by infusion pump until skin closure. An additional bolus of 500,000 KIU of aprotinin was infused for every three units of RBC transfused. • Control group received equivalent volumes of the placebo (0.9% saline solution) at the respective times.
Outcomes	***Outcomes reported:*** Blood loss, number of patients exposed to allogeneic blood transfusion, fresh frozen plasma transfused, platelet units transfused
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random codes
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Lentschener 1999

Methods	Patients were randomised in a double blind fashion by using a computer generated random code. Randomisation was both stratified by the number of fused levels and blocked in groups of four before the induction of anesthesia. Allocation concealment was not described
Participants	72 patients undergoing posterior lumbar spine fusion were randomly assigned to one of two groups: • Aprotinin group: n = 35, M/F = 18/17, mean (sd) age = 46 (9) years • Control group (Placebo): n = 37, M/F = 19/18, mean (sd) age = 51 (11) years
Interventions	• Aprotinin group received a loading dose of 2 million KIU (280mg) over 20 minutes after induction of anaesthesia, followed by a continuous infusion of 500,000 KIU/hr administered by infusion pump until skin closure. An additional bolus of 500,000 KIU of aprotinin was infused every three units of RBC transfused. • Control group received equivalent volumes of the placebo (0.9% saline solution) at the respective times.

Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood (units), autologous transfusion, blood loss (24hrs), post-operative total autologous units (total)
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated random code
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Levy 1995

Methods	Method of randomisation and allocation concealment were not described. Eleven medical centres participated. Study performed efficacy and safety analysis. Exclusions defined by protocol
Participants	287 patients undergoing repeat coronary artery bypass graft surgery were randomly assigned to one of four groups: • Aprotinin group (High dose): n = 73 (safety analysis), n = 61 (efficacy analysis), M/F = 55/6; mean (sd) age = 64 (7.8) years • Aprotinin group (Low dose): n = 70 (safety analysis), n = 59 (efficacy analysis), M/F = 52/7; mean (sd) age = 65+/-7.7 years • Aprotinin group (Pump-prime): n = 72 (safety analysis), n = 68 (efficacy analysis), M/F = 62/6; mean (sd) age = 66 (8.2) years • Control group (Placebo): n = 72 (safety analysis), n = 65 (efficacy analysis), M/F = 59/6; mean (sd) age = 64 (8.0) years
Interventions	• Aprotinin group (High dose) received a loading dose of 2 million KIU of aprotinin, plus an additional 2 million KIU was added to the cardiopulmonary bypass (CPB) circuit prime, followed by a continuous infusion of 500,000 KIU/hr during surgery. • Aprotinin group (Low dose) received a loading dose of 1 million KIU of aprotinin, plus 1 million KIU was added to the CPB circuit prime, followed by a continuous infusion of 250,000 KIU/hr during surgery. • Aprotinin group (Pump-prime) received 2 million KIU of aprotinin added to the CPB circuit prime. • Control group received equivalent volumes of 0.9% sodium chloride. NB: All groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , fresh frozen plasma usage (units), platelet usage (units), blood loss

Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Li 2005

Methods	Method of randomisation and allocation concealment were not described
Participants	70 patients undergoing elective cardiac surgery were randomised to one of four groups: • Control group: n = 10, M/F = 9/1, mean (sd) age = 59 (9) years • Platelet-rich plasmapheresis + acute normovolaemic haemodilution + cell salvage group: n = 20, M/F = 17/3, mean (sd) age = 59 (6) years • Aprotinin group: n = 22, M/F = 9/1, mean (sd) age = 61 (7) years • Combined group: n = 18, M/F = 16/2, mean (sd) age 62 (8) years
Interventions	• Control received standard care with no active intervention. • PRP+ ANH + CS group: After the induction of anaesthesia, blood was withdrawn via the 9-French central venous catheter at a rate of 35-45ml/min and collected in the 125mL centrifugal bowl of an autotransfusion unit (Cell Saver 5, Haemonetics Corp., Braintree, MA). No systemic heparin was administered at this time but calcium in the blood was sequested with citrate by mixing the blood and ACD (adenosine, citrate, dextrose) agent (Perfect, Beijing, China) at a volume ratio of 8:1. The withdrawn blood volume was replaced with a mixing (1:2) of plasma substitute (Gelofusion) and crystalloid (Lactate Ringer Injection) at a volume ratio of 1:2-3 to maintain a steady PCWP. The withdrawn blood was centrifuged at 2400 rpm to separate the RBC's from the plasma and platelets. After removing the RBC's the plasma was continuously centrifuged at 2400 rpm to separate the PRP from the platelet-poor plasma. An average of 30 minutes and three to four passes were required to complete blood withdrawal and separation of the PRP and PPP. A volume of blood was withdrawn to obtain approximately 300ml of PRP from each study patient. In addition, the autotransfusion device at the same machine (Cell saver 5, Haemonetics Corp., Braintree, MA) was also used to retrieve RBC's that were lost throughout the course of the operation. Saline (0.9% NaCl) was used to irrigate all the sponges with blood in the surgical field and then suctioned to the cell saver for further washing. Autologous RBC's both obtained during initial blood withdrawal and obtained via the autotransfusion device during the operation were reinfused as necessary. After reversal of heparin, the autologous PPP and PRP were reinfused back to the patients as were any remaining autologous RBC's. • Aprotinin group (High dose) received a loading dose of 2 million KIU before CPB and 2 million KIU added to the pump prime and a continuous infusion of 1 million KIU/hr administered until skin closure or until a total dose of 5 million KIU was achieved.

	• Combined group (PRP + ANH +CS + Aprotinin) received treatment combining interventions of Group 2 and Group 3.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , number of patients receiving fresh frozen plasma, number of patients receiving platelets, blood loss
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Liu 1993

Methods	Allocation sequences were generated by a computer generated random list. The trial drug and placebo were supplied in identical packs. Exclusions or loss to follow-up were reported
Participants	40 patients undergoing elective myocardial revascularisation were randomised to one of two groups: • Aprotinin group: n = 20, M/F = 13/7, mean (sd) age = 64.7 (2.0) years • Control group (Placebo): n = 20, M/F = 17/3, mean (sd) age = 66.7 (1.3) years
Interventions	• Aprotinin group received a loading dose of 1 million KIU of aprotinin intravenously after the induction of anaesthesia, 1 million KIU in the priming volume of the heart-lung machine and 250,000 KIU/hr after the loading dose to the end of skin closure, or up to 1 million KIU of aprotinin if the operation exceeded 4 hours in duration. • Control group received a corresponding volume of placebo (substance used was not specified). NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , fresh frozen plasma, blood loss, total post-operative autotransfusion from the chest drainage, mortality, re-operation for bleeding, allergic reaction, hospital length of stay (days)
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol not specified

Risk of bias

Item	Authors' judgement	Description

Liu 1993 *(Continued)*

Adequate sequence generation?	Yes	Allocation sequences were generated by a computer generated random list
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Liu 1998

Methods	Method of randomisation and allocation concealment were not described
Participants	60 patients undergoing open heart surgery were randomly assigned to one of three groups: • Epsilon aminocaproic group: n = 20, mean (sd) age = 65 (9) years • Epsilon aminocaproic + platelet-rich plasmapheresis group: n = 20, mean (sd) age = 67 (12) years • Control group: n = 20, mean (sd) age = 64 (11) years NB: Gender data were not reported.
Interventions	• Epsilon aminocaproic acid group received 150mg/kg before CPB. • Epsilon aminocaproic + platelet-rich plasmapheresis group received 150mg/kg of EACA before CPB and platelet-rich plasma (PRP) at 10ml/kg salvaged from each patient with a plasma saver before CPB which was then reinfused. PRP was reinfused at the end of CPB after protamine administration. • Control group received standard care.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), fresh frozen plasma usage (units), platelets usage (units), blood loss
Notes	Quality assessment score (Schulz criteria): 0/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Llau 1998

Methods	Method of randomisation and allocation concealment were not described. [Abstract]
Participants	20 patients undergoing elective orthopaedic surgery were randomly allocated to one of two groups: • Aprotinin group (Low dose): n = 10, mean (sd) age = 68 (8) years • Control group (Placebo): n = 10, mean (sd) age = 67 (7) years
Interventions	• Aprotinin group (Low dose) received 2 million KIU of aprotinin 30 minutes immediately after the induction of anaesthesia. • Control group received normal saline in the same volume and time as aprotinin, immediately after the induction of anaesthesia.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss, deep vein thrombosis, change in haematocrit levels - baseline to 24 hrs post-operative, change in haemoglobin levels - baseline to 24 hrs post-operative
Notes	Transfusion protocol used.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Locatelli 1990

Methods	Method of randomisation and allocation concealment were not described. [Italian language]
Participants	38 patients undergoing myocardial revascularisation were randomly allocated to one of three groups: • Aprotinin group (High dose): n = 12 • Aprotinin group (Low dose): n = 13 • Control group: n = 13 NB: Demographic data were not reported.
Interventions	• Aprotinin group (High dose) received a loading dose of 2 million KIU of aprotinin previous to median sternotomy, followed by a continuous infusion of 500,000 KIU/hr until the end of the operation. An additional 2 million KIU of aprotinin was added to the pump prime. • Aprotinin group (Low dose) received a continuous infusion of 500,000 KIU/hr of aprotinin until the end of the operation. • Control group did not receive aprotinin. NB: All groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss (28 hrs), adverse reactions

Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Luo 1998

Methods	Method of randomisation and allocation concealment were not described
Participants	20 patients undergoing cardiac surgery were randomised to one of two groups: • Aprotonin group: n = 10, M/F = 7/3, mean (sd) age = 36.9 (15.97) years • Control group: n = 10, M/F = 7/3, mean (sd) age = 42.8 (13.31) years
Interventions	• Aprotinin group received 3 million KIU of aprotinin. • Control group did not receive aprotinin. no intervention.
Outcomes	***Outcomes reported:*** volume of blood transfused, duration of CPB.
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol not reported.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Maccario 1994

Methods	Method of randomisation and allocation concealment were not described. [Italian language]
Participants	99 patients undergoing coronary artery bypass graft surgery and valvular cardiac surgery were randomised to one of three groups: • Aprotinin group (High dose): n = 33, mean (sd) age = 64.0 (8.51) years • Aprotinin group (Low dose): n = 33, mean (sd) age = 63.5 (8.37) years • Control group: n = 33, mean (sd) age = 62.9 (9.7) years NB: Gender data were not reported.
Interventions	• Aprotinin group (High dose) received a loading dose of 2 million KIU of aprotinin intravenously (IV) over a period of 30 minutes, followed by 500,000 KIU/hr until the termination of the operation. An additional 2 million KIU was added to pump prime. • Aprotinin group (Low dose) received 2 million KIU added to the pump prime. • Control group did not receive aprotinin. NB: All groups were exposed to acute normovolemic haemodilution and cell salvage
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss (24hrs), allergic reactions
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used. Four patients were excluded from the study due to surgical bleeding (one from the control group, one from the high-dose aprotinin group, and two from the low-dose aprotinin group). One patient from the low-dose aprotinin group died and was excluded from analysis

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	No	Single blind

MacGillivray 2010

Methods	Tranexamic acid or placebo for infusion was prepared by the institution's pharmacy in two identical 50mL bags (identified only by random number) with the constituents unknown to the administering anesthesiologist or surgeon. Method of randomisation was not described
Participants	60 patients undergoing orthopaedic (knee) surgery were randomised to one of three groups: • Tranexamic acid group #1: n = 20, M/F = 7/13, mean (sd) age = 62 (4.3) years • Tranexamic acid group #2: n = 20, M/F = 8/12, mean (sd) age = 65 (4.3) years • Control group: n = 20, M/F = 5/15, mean (sd) age = 66 (7.3) years

Interventions	• Tranexamic acid group #1 received two doses of 10mg/kg. Patients received the first infusion over 10 minutes before deflation of the first tourniquet and the second (over 10 minutes) 3 hours after the first. • Tranexamic acid group #2 received two doses of 15mg/kg. Patients received the first infusion over 10 minutes before deflation of the first tourniquet and the second (over 10 minutes) 3 hours after the first. • Control group received normal saline. Patients received the first infusion of saline over 10 minutes before deflation of the first tourniquet and the second (over 10 minutes) 3 hours after the first. NB: Patients received re-infusion of autotransfused blood from the intra-articular drains
Outcomes	***Outcomes reported:*** number of patients exposed to allogeneic blood transfusion, blood loss, number of allogeneic units transfused, adverse events
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Maddali 2007

Methods	A computer-generated randomisation code was used to allocate participants. Allocation was concealed by using sequentially-numbered, sealed opaque envelopes
Participants	222 patients undergoing cardiac surgery were randomised to one of two groups: • Tranexamic acid group: n = 111, M/F = 80/31, mean (sd) age = 57.1 (8.9) years • Control group: n = 111, M/F = 72/38, mean (sd) age = 58.2 (8.3) years
Interventions	• Tranexamic acid group received loading dose of 10mg/kg before incision, then a continuous infusion of 1mg/kg/hr until end of CPB. • Control group received saline.
Outcomes	***Outcomes reported:*** Volume blood transfused, blood loss, mortality, stroke, re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Maddali 2007 (*Continued)*

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated randomisation code
Allocation concealment?	No	Inadequate - sealed envelopes
Blinding? All outcomes	Yes	Double blind

Maineri 2000

Methods	Method of randomisation and allocation concealment were not described
Participants	48 patients undergoing elective cardiac surgery were randomised to one of two groups: • Epsilon aminocaproic acid group: n = 24, mean (sd) age = 59.9 (10) years • Tranexamic acid group (n = 24), mean (sd) age = 64.2 (9) years NB: Gender data were not reported.
Interventions	• Epsilon aminocaproic acid group received 10g of EACA as a standard dose in 30 minutes following the induction of anaesthesia, and a maintenance infusion of 2g/hr was given throughout the operation. • Tranexamic acid group received a loading dose of 20mg/kg of TXA given in 60 minutes, followed by a maintenance infusion of 2mg/kg/hr.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss, pulmonary embolus, post -operative Hct, stroke
Notes	Quality assessment score (Schulz criteria): 0/7 Transfusion protocol used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Mansour 2004

Methods	Randomisation of patients was performed with the help of a computer -generated random number sequence programme. To ensure proper blinding the three studied solutions were prepared by the pharmacy as bottles
Participants	60 patients undergoing elective cardiac surgery (off pump CABG) were randomly assigned to one of three groups: • Aprotinin group: n = 20, M/F = 1/5, mean (sd) age = 56.4 (9.1) years • Tranexamic acid group: n = 20, M/F = 17/3, mean (sd) age = 57.5 (8.4) years • Control group (Placebo): n = 20, M/F = 19/1, mean (sd) age = 57.7 (8.4) years
Interventions	• Aprotinin group received 2 million KIU of aprotinin after skin incision, followed by a continuous infusion of 3 million KIU throughout surgery at a rate of 500,000 KIU/hr. • Tranexamic acid group received 1.5g of TXA (15mg/kg) after skin incision followed by a continuous infusion of 1g throughout surgery at a rate of 2mg/kg/hr. • Control group received normal saline at the same time and volumes as aprotinin and TXA. NB: Loading dose was administered over 20 minutes in all groups. Infusion dose was infused at a rate of 50ml/hr in all groups
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , fresh frozen plasma usage (units), platelet usage (units), blood loss (24hrs), myocardial infarction, number of patients exposed to fresh frozen plasma, number of patients exposed to platelets, re-operation for bleeding, renal dysfunction, hospital length of stay (days), renal dysfunction, neurological deficit
Notes	Quality assessment score (Schulz criteria): 7/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer -generated random number sequence programme
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Marcel 1996

Methods	Patients were randomised by a computer program. Method of allocation concealment was not described
Participants	44 consecutive patients undergoing orthotopic liver transplantation were randomised to one of two groups: • Aprotinin group: n = 21 • Control group (Placebo): n = 23

Marcel 1996 (*Continued*)

	NB: Demographic data were not reported.
Interventions	• Aprotinin group received 200,000 KIU per hour via an intravenous infusion which was started immediately after the induction of anaesthesia. • Control group received normal saline.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), fresh frozen plasma usage (units), platelet usage (units), blood loss (24hrs)
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomised by a computer program
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Mehr-Aein 2007

Methods	Method of randomisation was not reported. Concealment of allocation was achieved by using pharmacy prepared coded infusion syringes
Participants	66 patients undergoing cardiac surgery were randomised to one of two groups: • Tranexamic acid group: n = 33, mean (sd) age = 44 (10) years • Control group: n = 33, mean (sd) age = 45 (10) years NDB: Gender data were not reported.
Interventions	• Tranexamic acid group received loading dose of 15mg/kg at beginning of surgery, same dose before infusion of heparin at end of surgery, and again after protamine infusion. • Control group received saline.
Outcomes	***Outcomes reported:*** Number of patient exposed to allogeneic blood transfusion, volume of blood transfused (units), blood loss, re-operation for bleeding, mortality, myocardial infarction, renal failure, length of hospital stay (days)
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description

Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Mengistu 2008

Methods	Method of randomisation and allocation concealment were not described
Participants	50 patients undergoing cardiac surgery were randomised to one of two groups: • Aprotinin group: n = 25, M/F = 20/5, mean (sd) age = 69 (9) years • Tranexamic acid group: n = 25, M/F = 18/7, mean (sd) age = 70 (9) years
Interventions	• Aprotinin group received 2 million KIU pre-CPB, 2 million KIU at pump prime, and 500, 000 KIU/hr until arrival at ICU. • Tranexamic group received 2g administered after induction of anaesthesia and 6mg/kg/hr given continuously until arrival at ICU, and 1g added to CBP system prime.
Outcomes	***Outcomes reported:*** number of patients exposed to allogeneic blood transfusion, volume of allogeneic blood transfused, blood loss
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	No	Single blind

Menichetti 1996

Methods	Method of randomisation and allocation concealment were not described
Participants	96 consecutive patients undergoing coronary artery bypass surgery were randomised to one of four groups: • Aprotinin group: n = 24, M/F = 12/12, mean (sd) age = 60.4 (5.1) years • Epsilon aminocaproic acid group: n = 24, M/F = 14/10, mean (sd) age = 56.6 (6.7) years • Tranexamic acid group: n = 24, M/F = 12/12, mean (sd) age = 55.2 (8.6) years • Control group: n = 24, M/F = 13/11, mean (sd) age = 61.0 (9.7) years

Interventions	• Aprotinin group received a loading dose of 2 million KIU of aprotinin followed by a continuous infusion of 500,000 KIU/hr. An additional 2 million KIU of aprotinin was added to the CPB prime solution. • Epsilon aminocaproic acid group received 80mg bolus of EACA intravenously and after 30 minutes a continuous infusion of 30 mg/kg of EACA. An additional 80mg/kg of EACA was added to the CPB prime solution. • Tranexamic acid group received a 10mg/kg bolus of TXA followed by a continuous infusion of 3mg/kg/hr. An additional 10mg/kg of TXA was added to the CPB prime solution. • Control group received usual care.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss (24hrs), re-operation for bleeding, haemoglobin levels, activated clotting times (ACT), prothrombin times, activated partial thromboplastin times (APTT), plasminogen levels, factor VIII levels, TAT complex/values
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Misfeld 1998

Methods	Method of randomisation and allocation concealment were not described
Participants	42 patients undergoing elective cardiac surgery were randomised to one of three groups: • Aprotinin group: n = 14, M/F = 14/0, mean (sd) age = 63 (6) years • Tranexamic acid group: n = 14, M/F = 14/0, mean (sd) age = 56 (7) years • Control group: n = 14, M/F = 11/3, mean (sd) age = 59 (10) years
Interventions	• Aprotinin group received a test dose of 30,000 KIU at anesthesia induction and 1 million KIU of aprotinin was added to the pump prime. After protamine administration further aprotinin was administered in a dose of 200,000 KIU/hr for another 5 hours. • Tranexamic acid group received 10mg/kg as a bolus after heparinization followed by a continuous intravenous infusion of 1mg/kg/hr over 10 hours. • Control treatment was not specified.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss (6 hrs), mortality, change in haemoglobin levels - baseline to 24 hrs post-operative

Misfeld 1998 (*Continued)*

Notes	Quality assessment score (Schulz criteria): 1/7 Transfusion protocol used	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	No	Single blind

Mohr 1992

Methods	Method of randomisation and allocation concealment were not described. No loss to follow-up reported
Participants	50 patients undergoing primary coronary artery bypass graft surgery (CABG), repeat CABG, valve replacement, or valve replacement + CABG surgery were randomised to one of three groups: • Aprotinin group (High dose): n = 17, M/F = 14/3, mean (sd) age = 58 (10) years • Aprotinin group (Low dose): n = 17, M/F = 14/3, mean (sd) age = 62 (10) years • Control group (Placebo): n = 16, M/F = 11/5, mean (sd) age = 63 (11) years
Interventions	• Aprotinin group (High dose) received a loading dose of 2 million KIU of aprotinin for 20 minutes before sternotomy. An additional 2 million KIU of aprotinin was added to the priming volume of the bubble oxygenator, and a continuous infusion of 500,000 KIU/hr was given after the loading dose throughout surgery until skin closure or a total of 6 million KIU of aprotinin was achieved. • Aprotinin group (Low dose) received placebo (saline 0.9%) as a loading dose, 2 million KIU of aprotinin in the pump prime, and placebo in the continuous infusion phase. • Control group received equal volumes of placebo solution (0.9% saline) at the respective times.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss (24hrs), re-operation for bleeding, post-operative platelet counts, platelet aggregation evaluation by scanning electron microscopy
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear

Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Mongan 1998

Methods	Patients were randomised using a computer-generated random sequence. Method used to conceal treatment allocation was not described
Participants	150 patients undergoing primary coronary artery bypass graft surgery were randomised to one of two groups: • Aprotinin group (High dose): n = 75, M/F = 61/14, mean (sd) age = 62 (10) years • Tranexamic acid (n = 75), M/F = 59/16, mean (sd) age = 61 (11) years
Interventions	• Aprotinin group (High dose) received a loading dose of 2 million KIU (280mg in 200ml) administered before skin incision and a continuous infusion of 500,000 KIU/hr (3 million KIU in 300ml) limited to the subsequent 6 hours. An additional 2 million KIU (280mg in 200ml) was added to the pump prime. • Tranexamic acid group received a loading dose of 1g (15mg/kg) administered before skin incision and a continuous infusion of 1g infused at 50ml/hr (2mg/kg/hr in 300ml) limited to the subsequent 6 hours. Normal saline solution (300ml) was added to the pump prime.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , mortality, myocardial infarction, re-operation for bleeding, stroke
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random sequence
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Moran 2000

Methods	Patients were randomly assigned by a computer-generated code. Method used to conceal treatment allocation was not described
Participants	42 patients undergoing coronary artery bypass surgery were randomised to one of three groups: • Aprotinin group (High dose): n = 12, M/F = 11/1, mean (sd) age = 58.0 (8.4) years

	• Aprotinin group (Low dose): n = 12, M/F = 12/4, mean (sd) age = 59.6 (10.7) years • Control group (placebo) (n = 14), M/F = 11/3, mean (sd) age = 59.7 (8.6) years NB: Four patients were excluded from the final efficacy analysis. All 42 patients were included in the safety analysis
Interventions	• Aprotinin group (High dose) received a total dose of 6 million KIU (840mg) of aprotinin. Prior to anaesthesia 2 million KIU (280mg) of aprotinin was administered and another 2 million KIU (280mg) was added to the pump prime. An additional 2 million KIU (280mg) was administered after the completion of CPB. • Aprotinin group (Low dose) received a total dose of 4 million KIU (560mg) of aprotinin. Prior to anaesthesia 2 million KIU (280mg) of aprotinin was administered and another 2 million KIU (280mg) was added to the pump prime. • Control group received 600ml of normal saline solution.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss (24hrs), mortality, myocardial infarction, re-operation for bleeding, stroke
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated code
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Murkin 1994

Methods	Method of allocation concealment was not described. Randomisation was by means of computer-generated random code
Participants	54 patients undergoing first-time coronary artery bypass or valvular heart operations requiring cardiopulmonary bypass (CPB) were randomised to one of two groups: • Aprotinin group: n = 29, M/F = 22/7, mean (sd) age = 62 (9.7) years • Control group (Placebo): n = 25, M/F = 16/9, mean (sd) age = 65.8 (7.5) years NB: Three of the 57 enrolled patients were deemed ineligible because of cancellation of the operation (n = 2) and non-use of CPB (n = 1). All 54 remaining patients were included for analysis
Interventions	• Aprotinin group received 2 million KIU of aprotinin (200ml) as a loading dose including an initial 5 ml dose given after establishment of full monitoring and anaesthesia, 2 million KIU of aprotinin was added to the CPB pump prime, and a continuous infusion of 500,000 KIU/hr of aprotinin was given throughout the operation and for 1 hour after the patient had returned to the intensive care unit (ICU). The maximum dose of aprotinin was 7 million KIU.

	• Control group received equal volumes of placebo (substance not specified). NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), fresh frozen plasma usage (units), platelet usage (units), blood loss (36hrs), myocardial infarction, pulmonary embolic events, hospital length of stay (days)
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random code
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Murkin 1995

Methods	Randomisation was by means of computer generated codes. Method of allocation concealment was not described
Participants	53 consecutive patients undergoing revision total hip arthroplasty or primary bilateral total hip arthroplasty were randomly assigned to one of two groups: • Aprotinin group: n = 29, M/F = 9/20, mean (sd) age = 66.9 (15) years • Control group (Placebo): n = 24, M/F = 11/13, mean (sd) age = 65.5 (16.6) years
Interventions	• Aprotinin group received 2 million KIU (200ml) of aprotinin over 15 minutes followed by an infusion of 500,000 KIU (50ml) per hour. Those patients weighing less than 60kg and more than 80kg received a loading dose of 2.8ml/kg (10,000 KIU/ml) and an infusion of 0.7ml/kg/hr. • Control group received an equivalent volume of 0.9% saline.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss, cerebrovascular accident, deep vein thrombosis, hospital length of stay (days).
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated codes

Murkin 1995 (*Continued*)

Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Murkin 2000

Methods	Labels on all medication vials were the same except for the patient executive number. Patients were stratified on the basis of whether or not pre-operative autologous blood donations had been made
Participants	301 undergoing elective primary unilateral total hip replacement were randomised to one of four groups: • Aprotinin group (Low dose): n = 69, M/F = 34/35, mean age = 63.7 years • Aprotinin group (Medium dose): n = 68, M/F = 27/41, mean age = 65.5 years • Aprotinin group (High dose): n = 75, M/F = 46/29, mean age = 63.4 years • Control group (Placebo): n = 68, M/F = 32/36, mean age = 63.2 years
Interventions	• Aprotinin group (Low dose) received a loading dose of 500,000 KIU (70mg) of aprotinin. • Aprotinin group (Medium dose) received a loading dose of 1 million KIU (140mg) of aprotinin and a continuous infusion of 250,000 KIU/hr. • Aprotinin group (High dose) received a loading dose of 2 million KIU (280mg) of aprotinin and a continuous infusion of 500,000 KIU/hr. • Control group received an unspecified placebo. NB: Epsilon aminocaproic acid and desmopressin were used if deemed necessary. Data regarding the use of these two drugs to minimise blood loss were not reported. All groups used pre-operative autologous donation
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss, myocardial infarction, mortality, deep venous thrombosis, pre-operative autologous blood donation
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Murphy 2006

Methods	Allocation was generated by a card system and concealed in sealed, opaque envelopes
Participants	100 off-pump coronary artery bypass grafting surgical patients were randomly allocated to one of two groups: • Tranexamic acid group: n = 50, M/F = 42/8, mean (sd) age = 64.9 (7.0) years • Control group (Placebo): n = 50, M/F = 37/13, mean (sd) age = 65.8 (8.7) years
Interventions	• Tranexamic acid group received 2g as an intravenous bolus before sternotomy. • Control group received a bolus of normal saline. NB: All patients underwent peri-operative cell salvage with autotransfusion of washed salvaged red blood cells at the completion of the operative procedure
Outcomes	***Outcomes reported:*** number of patients exposed to allogeneic blood transfusion, blood loss, mortality, stroke, renal dysfunction, myocardial infarction, length of stay
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	No	Inadequate - sealed envelopes
Blinding? All outcomes	Yes	Double blind

Niskanen 2005

Methods	Patients were randomised into two groups by an envelope method in a double-blind manner. The randomisation and preparation of the drug were done in the absence of other personnel by two anaesthesia nurses not engaged in the study. The code was broken after the last patient had been treated
Participants	40 patients undergoing cemented hip arthroplasty were randomised to one of two groups: • Tranexamic acid group: n = 19, M/F = 6/13, mean (sd) age = 66 (9.1) years • Control group (Placebo): n = 20, M/F = 7/13, mean (sd) age = 65 (8.2) years NB: One patient was excluded from the final analysis.
Interventions	• Tranexamic acid group received 10mg/kg of intravenous TXA over 5-10 minutes, immediately before the operation. The next two doses were given 8 hours and 16 hours after the first injection. • Control group received corresponding doses of saline.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), deep vein thrombosis

Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Norman 2009

Methods	Patients were allocated according to a randomisation schedule based on study accession number. Pharmacy controlled allocation
Participants	20 undergoing extrapleural pneumonectomy for mesothelioma were randomised to one of two groups: • Aprotinin group: n = 11, M/F = 0/9, mean (sd) age = 63.5 (6.2) years • Control group (Placebo): n = 9, M/F = 8/3, mean (sd) age = 62 (7.6) years
Interventions	• Aprotinin group (High dose) received a loading dose of 2 million KIU infused over 1 hour, followed by maintenance infusion of 500,000 KIU/hr until ICU admission. • Control group received a saline placebo.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood transfusion, blood loss, mortality
Notes	Quality assessment score (Schulz criteria): 7/7 Use of transfusion protocol not reported

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation schedule based on study accession number
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Nurözler 2008

Methods	Patients were allocated according to a list of random treatment codes. Method used to conceal treatment allocation was not described
Participants	51 undergoing cardiac surgery were randomised to one of two groups: • Aprotinin group: n = 25, M/F = 19/6, mean (sd) age = 63.1 (8.8) years • Control group (Placebo): n = 26, M/F = 18/8, mean (sd) age = 64.6 (6.7) years
Interventions	• Aprotinin group (low dose) received bolus 1 million KIU infused over 30 minutes, then continuous infusion of 500,000 KIU/hr until end of surgery. • Control group received a saline placebo.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood transfusion, volume blood transfused (units), blood loss, re-operation for bleeding, myocardial infarction, stroke, length of hospital stay (days)
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol used

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	List of random treatment codes
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Nuttall 2000

Methods	Patients were randomly assigned by a computer-generated random number sequence. Method used to conceal treatment allocation was not described
Participants	168 patients undergoing cardiac surgery were randomised to one of four groups: • Aprotinin group (High dose): n = 40, M/F = 28/12, median (range) age = 70.5 (45-86) years • Tranexamic acid group: n = 45, M/F = 31/14, median (range) age = 71 (43-83) years • Tranexamic acid + acute normovolaemic haemodilution (ANH) group: n = 32, M/F = 28/4, median (range) age = 67.5 (42-91) years • Control group (Placebo): n = 43, M/F = 35/8, median (range) age = 63 (29-83) years NB: Eight patients were excluded from the final analysis.
Interventions	• Aprotinin group (High dose) received a test dose of 1.4mg (1ml) followed by a loading dose of 280mg of aprotinin over 20-30 minutes. In addition, patients received a continuous infusion of 70mg/hr (50ml/hr) of aprotinin and 280mg (200ml) was added to the pump prime. • Tranexamic acid group received a loading dose of 10mg/kg and a continuous infusion of 1mg/kg/hr commenced after central venous cannulation and continued for 2 hours into treatment in intensive care. • Tranexamic acid + ANH group received a loading dose of 10mg/kg and a continuous

	infusion of 1mg/kg/hr commenced after central venous cannulation and continued for 2 hours into treatment in intensive care. In addition, patients received intra-operative autologous blood (12.5% of whole blood volume withdrawn before CPB and within 10 mins after central venous cannulation). • Control group received a normal saline infusion.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), mortality, re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random number sequence
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Okita 1996

Methods	Method of randomisation and allocation concealment were not described
Participants	60 patients undergoing aortic surgery under deep hypothermic circulatory arrest were randomly allocated to one of two groups: • Aprotinin group: n = 39, M/F = 26/13, mean (sd) age = 63.5 (8.9) years • Control group: n = 21, M/F = 16/5, mean (sd) age = 67.9 (9.4) years
Interventions	• Aprotinin group received 2 million KIU of aprotinin administered in the pump prime only. • Control group did not receive aprotinin.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage, blood loss (24 hrs), mortality, myocardial infarction, stroke, renal failure, respiratory failure + pneumonia.
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol not specified

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear

Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Orpen 2006

Methods	A pharmacist not involved with the study carried out randomisation in the pharmacy by a sealed envelope method and prepared the contents of the administered solution. The operating team was blinded to the contents of the administered solution for every patient although allowance was made for the code to be broken should an adverse drug reaction occur
Participants	30 patients undergoing total knee arthroplasty were randomised to one of two groups: • Tranexamic acid group: n = 15, M/F = 8/7, mean (95%CI) age = 73 (70-78) years • Control group: n = 14, M/F = 3/11, mean (95%CI) age = 69 (63-74) years NB: One patient was excluded from the final analysis.
Interventions	• Tranexamic acid group received 15mg/kg of TXA intravenously at the time that cement mixing commenced. • Control group received an equivalent volume of normal saline given intravenously at the time that cement mixing commenced.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss, deep vein thrombosis, change in haemoglobin levels
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Palmer 2003

Methods	A computer generated randomisation schedule was used to randomly assign patients into the treatment groups. The vials used for each group were only identifiable by the patient study number
Participants	95 patients undergoing elective neurological surgery were divided into two subsets: Meningioma subset: n = 56 • Aprotinin group: n = 30, M/F = 7/23, mean (sd) age = 58.4 (13.0) years

	• Control group (Placebo): n = 26, M/F = 9/17, mean (sd) age = 58.5 (2.8) years Vestibular Schwannoma subset: n = 39 • Aprotinin group: n = 17, M/F =11/6, mean (sd) age = 48.6 (10.9) years • Control group (Placebo): n = 17, M/F = 11/16, mean (sd) age = 54.1 (12.0) years
Interventions	• Aprotinin group (Low dose) received a loading dose of 30,000 KIU/kg of aprotinin infused over 15-20 minutes administered before the start of surgery and followed by a continuous infusion of 10,000 KIU/kg/hr until the patient was transferred to the Intensive Care Unit. • Control group received 0.9% sodium chloride solution.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss, mortality (7-day & 30-day)
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated randomisation schedule
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Parvizi 2007

Methods	Patients were allocated according to a computer-generated randomisation list. Adequacy of allocation concealment was unclear
Participants	162 undergoing cardiac surgery were randomised to one of two groups: • Aprotinin group: n = 81), M/F = 49/32, mean (sd) age = 52.6 (13.8) years • Control group (Placebo): n = 81, M/F = 49/32, mean (sd) age = 54.1 (11.4) years
Interventions	• Aprotinin group received 500,000 KIU infused before and 500,000 KIU during CPB. • Control group received a saline placebo.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood transfusion, volume of blood transfused, blood loss, myocardial infarction, re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated randomisation list
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Penta de Peppo 1995

Methods	Method of randomisation and allocation concealment were not described
Participants	60 consecutive patients undergoing elective open-heart surgery were randomised to one of four groups: • Control group: n = 15, M/F = 13/2, mean (sd) age = 63 (7) years • Epsilon aminocaproic acid group: n = 15, M/F = 13/2, mean (sd) age = 62 (7) years • Tranexamic acid group: n = 15, M/F = 12/3, mean (sd) age = 60 (12) years • Aprotinin group (High dose): n = 15, M/F = 12/3, mean (sd) age = 64 (10) years
Interventions	• Control group received no antifibrinolytic treatment. • Epsilon aminocaproic acid group received 10g of EACA intravenously (IV) at the induction of anaesthesia followed by an infusion of 2g/hr for 5 hours. • Tranexamic acid group received 10mg/kg of TXA IV within 30 minutes after the induction of anaesthesia, followed by an infusion of 1mg/kg per hour for 10 hours. • Aprotinin group (High dose) received 2 million KIU of aprotinin IV at the induction of anaesthesia followed by an infusion of 500,000 KIU/hr during surgery and 2 million KIU of aprotinin added to the extracorporeal circuit. NB: All groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss, re-operation for bleeding,
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Petsatodis 2006

Methods	Patients were randomised using an envelope technique. Method of allocation concealment was not described
Participants	50 patients undergoing total hip arthroplasty were randomised to one of two groups: • Aprotinin group: n = 25, mean (sd) age = 58.4 (12.5) years • Control group (Placebo): n = 25, mean (sd) age = 59.6 (10.9) years
Interventions	• Aprotinin group received a bolus of 20,000 KIU/kg of aprotinin at the time of anaesthesia followed by an infusion of 50,000 KIU/hr. • Control group received normal saline in the same volumes.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss, deep vein thrombosis
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol not used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Inadequate - sealed envelopes
Blinding? All outcomes	Yes	Double blind

Pinosky 1997

Methods	Method of randomisation and allocation concealment were not described
Participants	59 patients undergoing cardiac surgery were randomly assigned to one of three groups: • Epsilon aminocaproic acid group: n = 20, M/F = 12/8, mean (sd) age = 62.6 (9.4) years • Tranexamic acid group: n = 20, M/F = 12/18, mean (sd) age = 62.6 (9.4) years • Control group (Placebo): n = 19, M/F = 15/4, mean (sd) age = 60.6 (10.9) years
Interventions	• Epsilon aminocaproic acid group received an intravenous loading dose of 150mg/kg and a continuous infusion of 10mg/kg/hr for 6 hours. EACA was given immediately following the induction of anaesthesia. • Tranexamic acid group received a loading dose of 15mg/kg followed by a continuous infusion of 1mg/kg/hr for 6 hours. TXA was given immediately following the induction of anaesthesia. • Control group received a bolus of normal saline and a continuous infusion of normal saline for 6 hours. NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss, aspirin use, number of patients exposed to platelets and fresh frozen plasma

Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Pleym 2003

Methods	Randomisation was by mean of a computer programme. Study medications were delivered in identical 50mL syringes
Participants	79 patients undergoing elective cardiac surgery were randomised to one of two groups: • Tranexamic acid group: n = 40, M/F = 34/6, mean (sd) age = 63.6 (9.9) years • Control group (Placebo): n = 39, M/F = 32/7, mean (sd) age = 62 (9.2) years
Interventions	• Tranexamic acid group received 30mg/kg of TXA as a bolus injection given over 5 minutes immediately before the start of CPB. • Control group received a bolus injection of the corresponding volume of 0.9% sodium chloride solution given 5 minutes immediately before the start of CPB. NB: Both groups were exposed to post-operative cell salvage, tranexamic acid, and desmopressin
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss, re-operation for bleeding, fresh frozen plasma usage (units), platelet usage (units), pulmonary embolus, retransfused mediastinal shed blood, post-operative TXA, post-operative DDAVP, ASA 75mg/day, ASA 160mg/day
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer programme
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Porte 2000

Methods	The trial drug was provided double-blind by the manufacturer in blocks of 12 identical case packs. Each case pack contained all bottles for one patient, identifiable only by the sequence number. Each block of 12 case packs contained four packs of each dosage group, randomly assigned to the sequence numbers 1 to 12. Patients received the next available case pack of each block. Centres were provided with sealed cards with the randomisation codes to enable an individual patient's code to be broken in an emergency. A separate set of the sealed randomisation cards was kept at the Central Data Centre. At the end of the study all cards with randomisation codes were sent to the Central Data Centre
Participants	141 patients undergoing orthotopic liver transplantation were randomised to one of three groups: • Aprotinin group (High dose): n = 46, M/F = 34/12, median (range) age = 52 (18-66) years • Aprotinin group (Low dose): n = 43, M/F = 34/19, median (range) age = 49 (18-69) years • Control group (Placebo): n = 48, M/F = 36/12, median (range) age = 53 (19-68) years NB: Four patients were excluded from the final analysis.
Interventions	• Aprotinin group (High dose) received a loading dose of 2 million KIU (280mg) of aprotinin over 20 minutes before and during the induction of anaesthesia, followed by a continuous infusion of 1 million KIU/hr (140mg/hr) until 2 hours after graft reperfusion. An additional dose of 1 million KIU was administered 30 minutes before graft reperfusion. • Aprotinin group (Low dose) received a loading dose of 2 million KIU (280mg) of aprotinin over 20 minutes before and during the induction of anaesthesia, followed by a continuous infusion of 500,000 KIU/hr until 2 hours after graft reperfusion. • Control group received 0.9% normal saline in an identical time schedule and volume.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss, number of patients exposed to platelets and cryoprecipitate
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Poston 2006

Methods	Study drug or placebo was delivered to the operating room in unlabeled bottles to maintain blinding. Method of randomisation was not specified
Participants	70 patients undergoing 'off-pump' coronary artery bypass graft surgery were randomised to one of two groups: • Aprotinin group (Low dose): n = 29

	• Control group (Placebo): n = 31 NB: Demographic data were not reported.
Interventions	• Aprotinin group (Low dose) received 10,000 KIU of aprotinin as a test dose followed by 2 million KIU (280mg) of aprotinin as a bolus before sternotomy, and 500,000 KIU/hr (70mg/hr) of aprotinin as a continuous infusion until the end of surgery. • Control group received normal saline. NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), fresh frozen plasma usage (units), platelet usage (units), myocardial infarction, deep vein thrombosis, stroke, hospital length of stay (days), Intensive Care Unit length of stay (days)
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Prendergast˙1 1996

Methods	Method of randomisation and allocation concealment were not described
Participants	38 patients undergoing primary sternotomy for heart transplantation were randomised to one of two groups: • Aprotinin group: n = 18, M/F = 15/3, mean (sd) age = 45.4 (10.2) years • Control group: n = 20, M/F = 14/6, mean (sd) age = 49.3 (6.7) years
Interventions	• Aprotinin group received 200ml of aprotinin as a loading dose intravenously followed by a continuous infusion of aprotinin of 50ml/hr until the end of the operation. In addition, 200ml of aprotinin was added to the cardiopulmonary bypass circuit. • Control group did not receive aprotinin. NB: Precise dose of aprotinin (KIU or mg) was not reported.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss (24hrs), haemoglobin levels, creatinine levels
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol not specified

Prendergast˙1 1996 (*Continued)*

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Prendergast˙2 1996

Methods	Method of randomisation and allocation concealment were not described
Participants	32 patients undergoing re-operative heart transplantation were randomised to one of two groups: • Aprotinin group: n = 16, M/F = 14/2, mean (sd) age = 54.4 (6.9) years • Control group: n = 16, M/F = 13/3, mean (sd) age = 55 (10.6) years
Interventions	• Aprotinin received a 200ml loading dose of aprotinin intravenously followed by a continuous infusion of 50ml/hr until the end of the operation. In addition, 200ml of aprotinin was added to the cardiopulmonary bypass circuit. • Control group received no aprotinin. NB: Precise dose of aprotinin (KIU or mg) was not reported.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss (24 hrs), haemoglobin levels, creatinine levels
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol not specified

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Pugh 1995

Methods	Method of randomisation and allocation concealment were not described
Participants	75 patients scheduled for routine primary cardiac surgery were randomly allocated to one of three groups: • Control group: n = 23, M/F = 16/7, mean (sd) age (+/-SD) = 66 (9.3) years • Tranexamic acid group: n = 22, M/F = 17/5, mean (sd) age = 58 (10) years • Aprotinin group: n = 21, M/F = 15/6, mean (sd) age = 62 (9.7) years NB: Nine patients were withdrawn from the trial: two from the control group, three from the tranexamic acid group, and four from the aprotinin group
Interventions	• Control group received neither trial drug nor placebo preparation. • Tranexamic acid group received 2.5g of TXA before skin incision, with a further 2.5g of TXA added to the cardiopulmonary bypass (CPB) solution. • Aprotinin group received 1 million KIU of aprotinin before skin incision, with a further 1 million KIU added to the priming solution.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , number of patinets exposed to fresh frozen plasma, blood loss, re-operation for bleeding.
Notes	Quality assessment score (Schulz criteria): 1/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Ranaboldo 1997

Methods	Allocation concealment was by the use of identical coded bottles containing active drug or placebo. The method of randomisation was not described
Participants	136 patients undergoing elective aortic surgery were randomised to one of two groups: • Aprotinin group: n = 66, M/F = 55/11, median age = 68 years • Control group (Placebo) group: n = 62, M/F = 45/17, median age = 70 years NB: Eight patients were excluded from the final analysis. Four deaths occurred within 7 days of surgery (two in each group). Four patients were found at operation not to be suitable for the planned reconstructive surgery
Interventions	• Aprotinin group received 2 million KIU of aprotinin as a loading dose over a 20 minute period, followed by a maintenance infusion of 500,000 KIU/hr. • Control group received equal volumes of 0.9% normal saline.

Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss (24hrs), mortality (30 day), myocardial infarction, stroke, pulmonary embolus, deep vein thrombosis, chest infection, hepatitis, sepsis, renal failure, urinary tract infection
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Rao 1999

Methods	Method of randomisation and allocation concealment were not described
Participants	30 patients undergoing elective cardiac surgery were randomised to one of two groups: • Epsilon aminocaproic acid group: n = 15, M/F = 13/2, mean age = 53 years • Control group: n = 15, M/F = 13/2, mean age = 55 years
Interventions	• Epsilon aminocaproic acid group received 100mg/kg of EACA as a loading dose slowly after the induction of anaesthesia and a continuous infusion of EACA at 1g/hr for a further 6 hours. • Control group received no EACA treatment.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss (24 hrs), myocardial infarction, fresh frozen plasma usage (units), platelet usage (units), ASA treatment until surgery (185mg), ASA treatment until surgery (375mg), stroke, re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 0/7 Transfusion protocol not used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear

Blinding? All outcomes	Unclear	Unclear

Ray 1997

Methods	Method of randomisation and allocation concealment were not described
Participants	106 patients undergoing aortic or mitral valve replacement or both were randomly assigned to one of two groups: • Aprotinin group: n = 54, M/F = 35/19, median age = 54 years • Control group (Placebo): n = 52, M/F = 28/24, median age = 58 years
Interventions	• Aprotinin group received 2 million KIU of aprotinin (280mg) over 20 minutes after the induction of anaesthesia followed by 500,000 KIU/hr (70mg/hr) until the patient was returned to the post-operative ward. In addition, 2 million KIU (280mg) was added to the oxygenator prime. • Control group received an equivalent volume of normal saline. NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, re-operation, platelet usage (units), fresh frozen plasma usage (units)
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Ray 1999

Methods	Method of randomisation and allocation concealment were not described
Participants	150 patients in elective adult cardiac surgery were randomly assigned to one of three groups: • Aprotinin group (High dose): n = 50 • Aprotinin group (Low dose): n = 50 • Control group (Placebo): n = 50 NB: Gender or age data were not reported.

Interventions	• Aprotinin group (High dose) received a loading dose of 2 million KIU over 20 minutes after the induction of anaesthesia followed by 500,000 KIU/hr (70mg/hr) until the patient was returned to the post-operative ward. In addition, 2 million KIU (280mg) was added to the pump prime. • Aprotinin group (Low dose) received a loading dose of 140mg (1 million KIU) infused over 20 minutes after the induction of anaesthesia and a pump prime dose of 140mg (1 million KIU). • Control group received a volume of saline solution equivalent to the volume admitted in the low dose aprotinin.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol not used

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Ray 2001

Methods	Method of randomisation and allocation concealment were not described
Participants	100 patients undergoing elective cardiac surgery were randomly assigned to one of two groups: • Epsilon aminocaproic acid group: n = 51 • Aprotinin group: n = 49 NB: Gender or age data were not reported.
Interventions	• Epsilon aminocaproic acid group received a test dose of 250mg at least 10 minutes before the loading dose of 5g given over a 20 minute period after the induction of anaesthesia and 1.25g/hr continuous infusion until 4 hours after bypass. In addition, 5g of EACA was added to the pump prime before cross clamping. • Aprotinin group received a test dose of 10,000 KIU before the loading dose (1 million KIU) given over a 20 minute period after the induction of anaesthesia and 1 million KIU was added to the pump prime.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, re-operation for bleeding, aspirin use within 10 days, Intensive Care Unit length of stay (hours), neurologic events
Notes	Quality assessment score (Schulz criteria): 1/7 Transfusion protocol was not used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	No	Single blind

Ray 2005

Methods	Method of randomisation and allocation concealment were not described. Allocation of the randomised drug was performed by a nurse not otherwise connected with the study
Participants	45 patients undergoing elective primary total hip arthroplasty were randomly allocated to one of three groups: • Aprotinin group: n = 15, mean (interquartile range) age = 69 (58-74) years • Epsilon aminocaproic acid group: n = 15, mean (interquartile range) age = 72 (59-77) years • Control group (Placebo): n = 15, mean (interquartile range) age = 72 (59-77) years
Interventions	• Aprotinin group received a 10,000 KIU test dose of aprotinin followed by a bolus of 2 million KIU given over 30 minutes after the induction of anaesthesia followed by a continuous infusion of 500,000 KIU/hr for 3 hours. • Epsilon aminocaproic acid group received 10g of EACA in 250mL of IV saline given over 30 minutes after the induction of anaesthesia followed by 5g in 250mL of IV saline over 3 hours. • Control group received normal saline in the same manner as the other trial arms.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss (24hrs), deep vein thrombosis, pre-operative apirin use
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol not used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Rhydderch 1993

Methods	Methods of sequence generation and allocation concealment were unclear
Participants	43 undergoing cardiac surgery were randomised to one of two groups: • Aprotinin group (n = 20), M/F = 14/6, mean (SD) age = 42 (15) years • Control group (placebo) (n = 23), M/F = 15/8, mean (SD) age = 37 (17) years
Interventions	• Aprotinin group received 2 million KIU added to the pump prime. • Control group received a saline placebo.
Outcomes	***Outcomes reported:*** Volume blood transfused, re-operation for bleeding.
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Rocha 1994

Methods	Method of randomisation and allocation concealment were not described
Participants	109 of 122 eligible patients scheduled for coronary artery bypass graft surgery, valvular surgery, or mixed cardiac surgery were randomised to one of four groups: • Aprotinin group: n = 28, M/F = 16/12, mean (sd) age = 58.9 (10.0) years • Desmopressin group: n = 25, M/F = 14/11, mean (sd) age = 56.6 (8.8) years • Desmopressin group: n = 28, M/F = 20/8, mean (sd) age = 57.3 (7.6) years • Control group: n = 28, M/F = 22/6, mean (sd) age = 56.3 (10.1) years
Interventions	• Aprotinin group received a bolus infusion of 2 million KIU of aprotinin within 30 minutes after the induction of anaesthesia followed by a continuous infusion of 500,000 KIU/hr of aprotinin until the patient left the operating room. In addition, a bolus of 2 million KIU of aprotinin was added to the pump prime by replacement of crystalloid. • Desmopressin group received 0.3ug/kg of desmopressin (DDAVP) in 50ml of saline solution over a period of 20 minutes, given intravenously on completion of cardiopulmonary bypass (CPB) and immediately after administration of protamine. • Desmopressin group received two doses of DDAVP (2 x 0.3ug/ml) and an additional dose 6 hours after surgery. • Control group did not receive aprotinin or DDAVP.

Rocha 1994 *(Continued)*

Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage, blood loss (72hrs), mortality, thrombosis	
Notes	Quality assessment score (Schulz criteria): 1/7 Transfusion protocol not used	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	No	Single blind

Rodrigus 1996

Methods	Method of randomisation and allocation concealment were not described
Participants	99 adult patients undergoing elective primary coronary artery bypass graft, or valvular surgery, with cardiopulmonary bypass were randomised to one of two groups: • Aprotinin group: n = 46, M/F = 39/7, mean (sd) age = 60.4 (8.8) years • Control group (Placebo): n = 47, M/F = 34/13, mean (sd) age = 59 (7.8) years NB: Six of the 99 patients randomised were excluded from the study. Ninety-three patients remained in the study for analysis
Interventions	• Aprotinin group received aprotinin as an infusion of 2 million KIU in 200ml of normal saline after induction, followed by a continuous infusion of 500,000 KIU/hr and 2 million KIU in the priming volume of the extracorporeal circuit. • Control group received the same volume of normal saline.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), fresh frozen plasma usage (units), platelet usage (units), blood loss (24hrs), mortality, myocardial infarction [definite & possible], re-operation for bleeding, atrial fibrillation
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol not specified

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear

Blinding? All outcomes	Yes	Double blind

Rossi 1997

Methods	Method of randomisation and allocation concealment were not described
Participants	43 patients scheduled for elective primary myocardial revascularisation were randomly allocated to one of two groups: • Aprotinin group: n = 21, mean (sd) age = 58 (8) years • Control group (n = 22), mean (sd) age = 56 (12) years NB: Gender data were not reported.
Interventions	• Aprotinin group received 2 million KIU of aprotinin in the cardiopulmonary bypass prime. • Control group did not receive aprotinin. NB: Both groups were exposed to acute normovolaemic haemodilution (ANH)
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss (24hrs), re-operation for bleeding, side effects
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Royston 1987

Methods	Patients were randomly allocated to receive test compound by means of sealed envelopes. Method of randomisation was not described
Participants	22 patients undergoing repeat cardiac surgery through previous median sternotomy wound were randomised to one of two groups: • Aprotinin group: n = 11, mean (sd) age = 53 (15) years • Control group: n = 11, mean (sd) age = 57 (13) years NB: Gender data were not reported.

Interventions	• Aprotinin group received a loading dose of 280mg of aprotinin via central venous access over 20 minutes before the opening of the previous median sternotomy wound, followed by a continuous infusion of 70mg/hr until skin closure at the end of the operation. An additional 280mg of aprotinin was added to the prime volume of the oxygenator. • Control group did not receive aprotinin. NB: Both groups were exposed to acute normovolaemic haemodilution (ANH)
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss (24hrs), mortality, total haemoglobin loss, time for wound closure (mins), platelet counts.
Notes	Quality assessment score (Schulz criteria):3/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	No	Inadequate - sealed envelopes
Blinding? All outcomes	Unclear	Unclear

Sadeghi 2007

Methods	Patients were randomised using a random number technique. The correct treatment option was assured by means of coded infusion syringes prepared by hospital pharmacy not involved otherwise in the study
Participants	67 undergoing orthopaedic surgery for hip fractures were randomised to one of two groups: • Tranexamic acid group: n = 32, M/F = 17/15, mean (sd) age = 51.81 (25.7) years • Control group (Placebo): n = 35, M/F = 24/11, mean (sd) age = 44.4 (26.16) years
Interventions	• Tranexamic acid group received a bolus of 15mg/kg at the beginning of surgery. • Control group received saline solution.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood transfusion, mortality, blood loss, volume blood transfused (units), length of hospital stay (days)
Notes	Quality assessment score (Schulz criteria):7/7 Transfusion protocol not used

Risk of bias

Item	Authors' judgement	Description

Sadeghi 2007 (*Continued)*

Adequate sequence generation?	Yes	Random number technique
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Samama 2002

Methods	Centres were provided with sealed envelopes with the randomisation codes to enable an individual patient's code to be broken in an emergency. A separate set of sealed randomisation tables were kept at the central data centre. To maintain masking, all patients received identical volumes of solution and an identical number of bottles for the identical dose and for the continuous infusion, regardless of treatment group
Participants	58 patients undergoing elective orthopaedic surgery were randomised to one of three groups: • Aprotinin group (High dose): n = 18, mean (sd) age = 44 (17) years • Aprotinin group (Low dose): n = 22, mean (sd) age = 48 (19) years • Control group (Placebo): n = 18, mean (sd) age = 44 (22) years NB: Gender data were not reported.
Interventions	• Aprotinin group (High dose) received a loading dose of 4 million KIU (560mg) given over 20 minutes before and during the induction of anaesthesia followed by a continuous infusion of 1 million KIU until skin closure. • Aprotinin group (Low dose) received a loading dose of 2 million KIU (280mg) given over 20 minutes before and during the induction of anaesthesia followed by a continuous infusion of 500, 000 KIU until skin closure. • Control group received saline in an identical time schedule and volume.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss, deep vein thrombosis, pulmonary embolus, trauma cases, cell salvage used, autologous transfusion
Notes	Quality assessment score (Schulz criteria):6/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation codes
Allocation concealment?	No	Inadequate - sealed envelopes
Blinding? All outcomes	Yes	Double blind

Santamaria 2000

Methods	Method of randomisation and allocation concealment were not described
Participants	84 patients undergoing elective coronary artery bypass graft surgery were randomly allocated to one of two groups: • Aprotinin group (High dose): n = 28, M/F = 27/1, mean (range) age = 58 (38-78) years • Aprotinin group (Low dose): n = 28, M/F = 24/4, mean (range) age = 61 (40-75) years • Control group (Placebo): n = 28, M/F = 24/4, mean (range) age = 59 (41-76) years
Interventions	• Aprotinin group (High dose) received a bolus of 2 million KIU as a loading dose followed by a continuous infusion of 500,000 KIU/hr during CPB. In addition, 2 million KIU (280mg) of aprotinin was added to the pump prime. • Aprotonin group (Low dose - pump prime only) received a bolus of saline as a loading dose followed by a continuous infusion of saline during CPB. Two million KIU (280mg) of aprotinin was added to the prime solution. • Control group received a bolus of saline. Saline was added to the priming solution and a continuous infusion of saline was administered during CPB.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss, myocardial infarction, stroke, hypertension, A-V block
Notes	Quality assessment score (Schulz criteria):4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Santos 2006

Methods	Groups were randomised by means of sequentially numbered sealed envelopes opened by a nurse in the operating room. Only the nurse, who prepared the infusions, knew whether a patient received drug or placebo. Study drugs were delivered in identical volumes. Staff in the operating room and in the intensive care unit were not aware of the treatment
Participants	65 patients undergoing primary coronary artery bypass graft surgery were randomised to one of two groups: • Tranexamic acid group: n = 29, M/F = 18/11, mean (sd) age = 62 (9.2) years • Control group (placebo) (n = 31), M/F = 25/6, mean (sd) age = 59 (8.7) years NB: Five patients were excluded from the final analysis.

Interventions	• Tranexamic acid group received a loading dose of 10mg/kg of TXA before skin incision, followed by a continuous infusion of 1mg/kg/hr for 5 hours. • Control group received a bolus of normal saline solution in an identical syringe and a continuous infusion of normal saline for 5 hours.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , fresh frozen plasma usage (units), blood loss, mortality, re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	No	Inadequate - sealed envelopes
Blinding? All outcomes	Yes	Double blind

Schmartz 2003

Methods	Sixty patients were divided into three groups by means of computerised randomisation. Allocation concealment was not specified
Participants	60 male patients undergoing primary elective cardiac surgery were randomised to one of three groups: • Aprotinin group (High dose): n = 20, mean (sd) age = 62 (9) years • Aprotinin group (Low dose): n = 20, mean (sd) age = 59 (11) years • Control group (Placebo): n = 20, mean (sd) age = 61 (11) years
Interventions	• Aprotonin group (High dose) received a loading dose of 2 million KIU (280mg) followed by a continuous infusion of 500,000 KIU/hr. In addition, 2 million KIU (280mg) of aprotinin was added to the pump prime. • Aprotinin group (Low dose) received a loading dose of 1 million KIU (140mg) followed by a continuous infusion of 250,000 KIU/hr. In addition, 1 million KIU (140mg) of aprotinin was added to the pump prime. • Control group received an unspecified placebo.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood markers of inflammation during and after CPB
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol not used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computerised randomisation
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blinding

Schweizer 2000

Methods	Concealment of treatment allocation was not described. Patients were allocated randomly in a double-blind manner. Method of randomisation was not described
Participants	60 patients undergoing elective coronary artery bypass graft surgery, aortic valve replacement and mitral valve replacement and repair were randomised to one of two groups: • Aprotinin group (Low dose): n = 28), M/F = 21/7, mean (range) age = 66 (35-85) years • Control group (Placebo): n = 29, M/F = 21/8, mean (range) age = 64 (33-81) years
Interventions	• Aprotinin group (Low dose) received a mean dose of 4.1 million KIU of aprotinin, consisting of a loading dose of 280mg (2 million KIU) over 30 minutes, 140mg (1 million KIU) added to the pump prime and a continuous infusion of 500,000 KIU/hr from the start of surgery until skin closure. • Control group received a similar volume of normal saline.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss, mortality, myocardial infarction, re-operation for bleeding
Notes	Quality assessment score (Schulz criteria):3/7 Transfusion protocol used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Shore-Lesserson 1996

Methods	Patients were randomly assigned to treatment or placebo by computer generated table. The pharmacist who prepared the infusions knew whether the patient received active treatment or placebo in the event of an adverse response
Participants	31 patients undergoing repeat open heart surgery were randomised to one of two groups: • Tranexamic acid group: n = 17, M/F = 10/7, mean (sd) age = 68 (13) years • Control group (Placebo): n = 13, M/F = 10/3, mean (sd) age = 63 (6) years NB: One patient from the placebo group was withdrawn from the study due to excessive post-operative bleeding and requiring intra-aortic balloon counter pulsation
Interventions	• Tranexamic acid group received an initial dose of TXA, 20mg/kg over 20 minutes, followed by a continuous infusion of 2mg/kg/hr. This infusion was terminated at the completion of the surgical procedure. • Control group received an equal volume of saline. NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage, fresh frozen plasma usage, platelet usage, blood loss, mortality, myocardial infarction, pulmonary complications, re-operation, renal impairment, cerebral ischemia, embolic stroke
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated table
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Sorin 1999

Methods	Method of randomisation and allocation concealment were not described. [Abstract]
Participants	42 patients undergoing total knee replacement were randomly assigned to one of two groups: • Tranexamic acid group: n = 21 • Control group (Placebo): n = 21 NB: Demographic data were not reported.
Interventions	• Tranexamic acid group received 15mg/kg of TXA 30 minutes before surgery and subsequently every 8 hours over the following 3 days. • Control group received an equal volume of saline.

Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss, deep vein thrombosis	
Notes	Transfusion protocol used	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Speekenbrink 1995

Methods	Method of randomisation and allocation concealment were not described	
Participants	60 patients scheduled for elective primary coronary artery bypass grafting were randomly assigned to one of four groups: • Aprotinin group: n = 15, M/F = 13/2, mean (sd) age = 62 (10) years • Tranexamic acid group: n = 15, M/F = 14/1, mean (sd) age = 61 (11) years • Dipyridamole group: n = 15, M/F = 13/2, mean (sd) age = 60 (9) years • Control group: n = 15, M/F = 14/1, mean (sd) age = 57 (12) years	
Interventions	• Aprotinin group received single dose of 2 million KIU of aprotinin added to the pump prime. • Tranexamic acid group received a bolus of 10mg/kg over 20 minutes and continued at a rate of 1mg/kg up to total dose of 1,000 mg. • Dipyridamole (Persantin) group received 100mg four times a day (oral), 36 hours before the operation. After induction of anaesthesia treatment was continued with intravenous dipyridamole at a rate of 0.24mg/kg/hr for 24 hours. • Control group received usual care.	
Outcomes	Outcomes reported: Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , fresh frozen plasma usage (units), blood loss (6hrs), myocardial infarction, haemorrhage from chest	
Notes	Quality assessment score (Schulz criteria): 1/7 Transfusion protocol not specified	
Risk of bias		
Item	**Authors' judgement**	**Description**

Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Speekenbrink 1996

Methods	Study medications were supplied in boxes containing 12 bottles with 50mL solution. The randomisation code was kept by supplied. The codes were broken after data acquisition were complete and verified
Participants	115 patients scheduled for elective coronary artery bypass graft surgery were randomised to one of three groups: • Control group (Placebo): n = 37, M/F = 29/8, mean (sd) age = 57 (8) years • Aprotinin group (Low dose): n = 37, M/F = 33/4, mean (sd) age = 62 (9) years • Aprotinin group (High dose): n = 38, M/F = 30/8, mean (sd) age = 62 (9) years
Interventions	• Control group received equivalent volumes of normal saline. • Aprotinin group (Low dose) received 500,000 KIU of aprotinin in the prime solution. • Aprotinin group (High dose) received 2 million KIU of aprotinin over 30 minutes followed by an infusion of 500,000 KIU/hr. In addition, 500,000 KIU of aprotinin was added to the prime solution.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss (24hrs), mortality, myocardial infarction, renal failure, re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used Three patients were excluded from the final analysis: Two from the placebo group (one for excessive postoperative bleeding caused by a broken suture and one for a small left ventricular aneurysm requiring resection), one from the high dose aprotinin group who had dense pericardial adhesions resembling those found in reoperation

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Stammers 1997

Methods	Method of randomisation was not described. All drugs were drawn up by a pharmacist and placed in a 500mL glass bottle which was labelled with the patient's name, registration number and date. No other clinician knew of the treatment received by the patient
Participants	20 patients undergoing first time coronary artery bypass grafting were randomly assigned to one of two groups: • Aprotinin group: n = 8, M/F = 6/2, mean (sd) age = 66.3 (5.8) years • Control group (Placebo): n = 12, M/F = 10/2, mean (sd) age = 63.9 (9.2) years
Interventions	• Aprotinin group received a loading dose of 2 million KIU (280mg) of aprotinin administered intravenously immediately following the induction of anaesthesia, 2 million KIU of aprotinin placed in the priming volume of the extracorporeal circuit, and a constant infusion of 500,000 KIU/hr (70mg/hr) until chest closure. • Control group received an equal volume of saline administered in the same manner.
Outcomes	***Outcomes reported:*** Allogeneic blood usage, Intensive care ventilator time (hrs), renal failure, neurological injury, hospital length of stay (days), blood loss (24hrs)
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Stewart 2001

Methods	Randomisation using numbers chosen randomly from a computer generated table. Study drug and placebo bottles were identifiable only by the random number
Participants	30 patients undergoing elective orthognathic surgery (maxillary Le Fort I and mandibular sagittal split osteotomies) were randomised to one of two groups: • Aprotinin group (Low dose): n = 15 • Control group (Placebo): n = 15 NB: Gender and age data were not reported.
Interventions	• Aprotinin group (Low dose) received a loading dose of 280mg (2 million KIU) given after the induction of anaesthesia and before the operation started for over 20 minutes, followed by a continuous infusion at a rate of 500,000 KIU/hr was infused until the end of the procedure. • Control group received normal saline at the same time and volumes as aprotinin.

Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated table
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Swart 1994

Methods	Method of randomisation was not described. Intervention and placebo solutions were supplied by Bayer AG (Germany)
Participants	50 patients undergoing primary coronary artery bypass surgery and 50 patients undergoing valve surgery were randomised to one of two groups: • Aprotinin group: n = 49, M/F = 33/16, mean (range) age = 53.1 (18-78) years • Control group (Placebo) (n = 49), M/F = 32/17, mean (range) age = 51.6 (18-76) years
Interventions	• Aprotinin group received 2 million KIU of aprotinin at the start of the operation, infused over a period of 30 minutes followed by a continuous infusion of aprotinin at 500,000 KIU/hr for 4 hours or until the end of the operation. In addition, 2 million KIU was added to the priming solution of the extracorporeal circuit. • Control group received similar volumes of saline.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss (48hrs), mortality, biochemistry and haematology values
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate

Blinding? All outcomes	Yes	Double blind

Tabuchi 1994

Methods	Method of randomisation was not described. The study solution was prepared by the pharmacy department according to a randomised code, which was kept blind to all clinicians and investigators until all data were obtained
Participants	40 patients undergoing elective coronary artery bypass grafting were randomised to one of two groups: • Aprotinin group: n = 19, mean (sd) age = 60.9 (8.7) years • Control group (Placebo): n = 17, mean (sd) age = 60.2 (8.6) years NB: Gender data were not reported. Four patients were excluded from the final analysis; three from the placebo group for surgical bleeding requiring repeat thoracotomy, and one from the aprotinin group for haemothorax
Interventions	• Aprotinin group received 325mg of aspirin orally 10 hours before operation and 2 million KIU of aprotinin (280mg) added to the pump prime solution. • Control group received 325mg of aspirin orally 10 hours before operation and 200ml of placebo solution.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , fresh frozen plasma usage (units), platelet usage (units), re-operation for bleeding, haemothorax
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Taggart 2003

Methods	A pre-determined randomisation scheme was generated by the pharmaceutical company supplying the trial drug. Sealed code break cards were available if necessary. The study was analysed on an intention-to-treat (ITT) basis and included those patients who received open-label aprotinin

Taggart 2003 (*Continued)*

Participants	74 patients undergoing cardiac surgery with total arterial grafting were randomised to one of two groups: • Aprotinin group (High dose): n = 37, M/F = 33/3, mean (sd) age = 60 (8) years • Control group (Placebo): n = 34, M/F = 32/2, mean (sd) age = 61 (8) years NB: Four patients were excluded from the final analysis.
Interventions	• Aprotinin group (High dose) received a 5mL (1.4mg/mL) test dose of aprotinin after the induction of anaesthesia and before sternotomy. The remaining 195mL of the loading dose was administered over 20-30 minutes using an infusion pump. After the completion of the loading dose, a maintenance infusion of 50ml/hr was continued for 4 hours. A further 200mL was added to the pump prime of the bypass circuit. • Control group received an unspecified solution.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , number of participants exposed to fresh frozen plasma and platelets, blood loss, myocardial infarction, re-operation for bleeding, hospital length of stay
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol used NB: Nine patients in the control group (placebo) received open-label aprotinin whilst two patients in the aprotinin group received open-label aprotinin

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	No	Single blind

Taghaddomi 2009

Methods	Table of random numbers was used to generate the allocation sequence. An independent anesthesiologist prepared coded infusions with tranexamic acid and placebo and was not directly involved in the clinical treatment of randomised patients. Both operating room staff and the intensive care unit staff were blinded regarding the study group
Participants	100 patients undergoing cardiac surgery were randomised to one of two groups: • Tranexamic acid group: n = 50, M/F = 38/12, mean (sd) age = 54.7 (10.9) years • Control group (Placebo): n = 50, M/F = 34/16, mean (sd) age = 60.3 (10.2) years
Interventions	• Tranexamic acid group received a bolus of 1g was given 20 minutes before incision then a maintenance dose of 400mg/hr during the entire surgical procedure. • Control group received normal saline.

Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood transfusion, blood loss, stroke, renal failure, myocardial infarction
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Table of random numbers
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Tanaka 2001

Methods	Ampoules containing either tranexamic acid or placebo were numbered and placed in envelopes at random by a pharmacologist
Participants	99 patients undergoing elective knee arthroplasty were randomised to one of four groups: • Control group (Placebo): n = 26, M/F = 9/17, mean (range) age = 65 (58-70) years • Tranexamic acid group (Pre-operative TXA): n = 24, M/F = 7/17, mean (range) age = 65 (59-70) years • Tranexamic acid group (Intra-operative TXA): n = 22, M/F = 7/15, mean (range) age = 65 (60-71) years • Tranexamic acid group (Pre-and-intra-operative TXA): n = 27, M/F = 8/19, mean (range) age = 65 (59-69) years
Interventions	• Control group received saline twice, 10 minutes before surgery and on deflation of the tourniquet. • Tranexamic acid group (Pre-operative TXA) received 20mg/kg of TXA 10 minutes before surgery and saline 10 minutes before the deflation of the tourniquet. • Tranexamic acid group (Intra-operative TXA) received saline 10 minutes before surgery and 20mg/kg of TXA 10 minutes before deflation of the tourniquet. • Tranexamic acid group (Pre-and-intra-operative TXA) received 10mg of TXA 10 minutes before surgery and 10mg/kg 10 minutes before deflation of the tourniquet.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , blood loss
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol not used

Risk of bias

Tanaka 2001 (*Continued)*

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Tassani 2000

Methods	Study performed in a double blind, placebo controlled manner. Method of randomisation and allocation concealment were not described
Participants	20 patients undergoing elective cardiac surgery were randomly assigned to one of two groups: • Aprotinin group: n = 10 • Control group (Placebo): n = 10 NB: Gender and age data were not reported.
Interventions	• Aprotinin group received a loading dose of 2 million KIU of aprotinin, a priming dose of 2 million KIU, and a continuous infusion of 500,000 KIU/hr during surgery. • Control group received an unspecified placebo.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol not used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Thorpe 1994

Methods	Method of randomisation and allocation concealment were not described
Participants	17 patients undergoing elective knee replacement surgery were randomly allocated to one of two groups: • Aprotinin group: n = 8

	• Control group: n = 9 NB: Demographic data were not reported.
Interventions	• Aprotinin group received 0.5 million KIU of aprotinin over 20 minutes immediately before inflation of the tourniquet, another 0.5 million KIU of aprotinin over 20 minutes before deflation of the tourniquet followed by an infusion of 1 million KIU over the next 2 hours. • Control group did not receive aprotinin.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss, femoral thrombosis
Notes	Quality assessment score (Schulz criteria): 1/7 Transfusion protocol not specified

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Trinh-Duc 1992

Methods	Method of randomisation and allocation concealment were not described. [French language]
Participants	60 patients undergoing cardiac surgery were randomised to one of two groups: • Aprotinin group (High dose): n = 29, M/F = 19/10, mean (sd) age = 54.89 (14.92) years • Epsilon aminocaproic acid group (n = 27), M/F = 20/7, mean (sd) age = 61.07 (10.65) years NB: Four patients were excluded from the final analysis.
Interventions	• Aprotinin group received 2 million KIU (280mg) of aprotinin after the induction of anaesthesia followed by a continuous infusion of 500,000 KIU/hr of aprotinin until skin closure. In addition, 2 million KIU (280mg) of aprotinin was added to the pump prime. • Epsilon aminocaproic acid group received 5g of EACA as a bolus after the induction of anaesthesia followed by a continuous infusion of 2g/hr until skin closure. In addition, 5g of EACA was added to the pump prime. NB: Both groups received cell salvage and acute normovolaemic haemodilution (ANH)
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), fresh frozen plasma usage (units), blood loss (48hrs), mortality, minor stroke, respiratory problems, severe hypotension.
Notes	Transfusion protocol not used

Trinh-Duc 1992 *(Continued)*

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Troianos 1999

Methods	Method of randomisation and allocation concealment were not described
Participants	72 patients undergoing primary coronary artery bypass surgery were randomised to one of two groups: • Epsilon aminocaproic acid group: n = 38, M/F = 27/11, mean (sd) age = 66 (9) years • Control group (Placebo): n = 36, M/F = 24/12, mean (sd) age = 65 (9) years
Interventions	• Epsilon aminocaproic acid group received a bolus dose of 0.5ml/kg of EACA administered immediately after systemic heparization (125mg/kg), and an infusion of EACA commenced at 0.05ml/kg/hr (12.5mg/kg/hr) and continued until after the administration of protamine and before the patient left the operating room. • Control group received saline solution.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), number of patients exposed to fresh frozen plasma and platelets, blood loss (6hrs & 48hrs), re-exploration for bleeding, haemoglobin loss
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Turkoz 2001

Methods	Method of randomisation and allocation concealment were not described
Participants	30 patients undergoing elective cardiac surgery were allocated randomly to one of three groups: • Aprotonin group (High dose): n = 10, M/F = 9/1, mean (sd) age = 60.2 (3.4) years • Methylprednisolone group: n = 10, M/F = 8/2, mean (sd) age = 58.3 (3.0) years • Control group: n = 10, M/F = 9/1, mean (sd) age = 63.8 (1.9) years
Interventions	• Aprotinin group (High dose) received a loading dose of 280mg (2 million KIU) of aprotinin followed by a continuous infusion of 70mg/hr (500,000 KIU/hr) administered during the operation. In addition, 280mg (2million KIU) of aprotinin was added to the pump prime. • Methylprednisolone group received 30mg/kg of methylprednisolone intravenously 5 minutes before surgery. • Control group received standard care.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss.
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Uozaki 2001

Methods	Method of randomisation and allocation concealment were not described
Participants	14 patients undergoing elective cardiac surgery were allocated to one of two groups: • Tranexamic acid group: n = 14, M/F = 5/1, mean (sd) age = 72.3 (4.1) years • Control group: n = 7, M/F = 3/3, mean (sd) age = 63.3 (5.3) years
Interventions	• Tranexamic acid group received 50mg/kg of intravenous TXA before skin incision and after the start of CPB. • Control group did not receive TXA treatment.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss (24hrs), re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 0/7 Transfusion protocol not used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Urban 2001

Methods	Patients were randomised by means of a random number generator. Method used to conceal treatment allocation was not described
Participants	60 patients undergoing complex reconstructive spinal surgery were randomised to one of three groups: • Aprotinin group: n = 20, mean (sd) age = 47.2 years • Epsilon aminocaproic acid group: n = 17, mean (sd) age = 46.6 years • Control group: n = 18, mean (sd) age = 47.3 years NB: Gender data were not reported. Five patients were excluded from the final analysis
Interventions	• Aprotinin group received 1 million KIU of aprotinin as a loading dose over 30 minutes followed by 250,000 KIU/hr. • Epsilon aminocaproic acid group received a 5g loading dose over 30 minutes followed by 15mg/kg/hr. • Control group received no antifibrinolytic treatment. NB: All groups were exposed to cell salvage and pre-operative autologous blood donation (PAD)
Outcomes	***Outcomes reported:*** Allogeneic & autologous blood usage (units), blood loss, respiratory complications
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number generator
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Utada 1997

Methods	Method of randomisation and allocation concealment were not described. [Japanese language]
Participants	21 patients undergoing primary total hip replacement were randomised to one of two groups: • Aprotinin group (Low dose): n = 11, M/F = 1/10, mean (sd) age = 63 (11) years • Control group (Placebo): n = 10, M/F = 2/8, mean (sd) age = 64 (5) years
Interventions	• Aprotinin group (Low dose) received 2 million KIU (280mg) of aprotinin as a continuous infusion throughout the surgical procedure. • Control group received normal saline solution.
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), blood loss, changes in haemoglobin levels
Notes	Transfusion protocol not used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Van der Linden 2005

Methods	Random assignment was conducted using unmasked envelopes, each containing a card indicating treatment with aprotinin or placebo. A nurse, assigned to another department of the hospital was responsible for the preparation of placebo and treatment solutions, which were identical in appearance and packing
Participants	75 patients scheduled for urgent or acute isolated coronary artery bypass graft surgery were randomised to one of two groups: • Aprotinin group (High dose): n = 37, M/F = 31/6, mean (sd) age = 66.4 (10) years • Control group (Placebo): n = 38, M/F = 25/13, mean (sd) age = 68.3 (10) years
Interventions	• Aprotinin group (High dose) received a 1 ml test dose of aprotinin after the induction of anaesthesia then received 2 million KIU (280 mg) of aprotinin as a bolus before the start of surgery. Another 2 million KIU of aprotinin was added to the pump prime and a continuous infusion of 500,000 KIU/hr was infused during surgery. • Control group received an equal volume of saline solution at the same time periods as the aprotinin regimen.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), fresh frozen plasma usage (units), platelets usage (units), mortality, myocardial infarction, stroke, atrial fibrillation, number of patients receiving TXA treatment

Van der Linden 2005 (*Continued)*

Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	No	Inadequate - sealed envelopes
Blinding? All outcomes	Yes	Double blind

Van Oeveren 1987

Methods	Method of randomisation and allocation concealment were not described	
Participants	22 patients undergoing coronary artery bypass graft surgery were randomised to one of two groups: • Aprotinin group: n = 11, mean (sd) age = 56.2 (3.9) years • Control group: n = 11, mean (sd) age = 57.5 (5.1) years	
Interventions	• Aprotinin group received an infusion of 2 million KIU (280mg) of aprotinin over 20-30 minutes and a continuous infusion of 500,000 KIU/hr until the end of the operation. In addition, for each litre of transfused whole blood given during the operation, an additional 500,000 KIU of aprotinin was administered by a separate bolus infusion. • Control group did not receive aprotinin.	
Outcomes	***Outcomes reported:*** Allogeneic blood usage, blood loss, biochemical markers.	
Notes	Quality assessment score (Schulz criteria): 0/7 Transfusion protocol not used	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Vander-Salm 1996

Methods	Random assignment was by means of a random number table and drug preparation was performed by the hospital pharmacy
Participants	103 patients undergoing coronary artery bypass graft surgery or valvular surgery were randomly assigned to one of two groups: • Epsilon aminocaproic acid group: n = 51, M/F = 35/16, mean (sd) age = 64.7 (12.1) years • Control group (Placebo): n = 52, M/F = 40/12, mean (sd) age = 64.2 (12.4) years
Interventions	• Epsilon aminocaproic acid group received 10mg of EACA intravenously before skin incision, 10g of EACA after heparin administration, and 10g of EACA at discontinuation of cardiopulmonary bypass (CPB) but before protamine administration. • Control group received saline solution in the same volumes and with the same timing as the EACA treated group.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), number of patients exposed to fresh frozen plasma, blood loss (12hrs & 24hrs), mortality, cerebrovascular accident, re-operation for bleeding
Notes	Quality assessment score (Schulz criteria): 7/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Vanek 2005

Methods	An envelope method with random numbers was used to randomise patients. An independent pharmacologist not directly involved in the clinical treatment of randomised patients prepared coded infusions with the study drug and placebo
Participants	91 patients undergoing cardiac surgery were randomised to one of three groups: • Tranexamic acid group: n = 32, M/F = 16/16, mean (95% CI) age = 68.4 (64.6-72.2) years • Aprotinin group: n = 29, M/F = 20/9, mean (95% CI) age = 67.3 (64.2-70.4) years • Control group: n = 30, M/F = 22/8, mean (95% CI) age = 68.9 (65.8-72.0) years
Interventions	• Tranexamic acid group received 1g TXA before skin incision and a continuous infusion of 200mg/hr during the whole surgical procedure. • Aprotinin group received 1 million KIU of aprotinin before skin incision and a continuous infusion of 250,000 KIU/hr during the whole surgical procedure. • Control group received normal saline 0.9% before skin incision and a continuous infusion

	during the whole surgical procedure.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss, number of patients exposed to fresh frozen plasma
Notes	Quality assessment score (Schulz criteria): 6/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random numbers
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Vedrinne 1992

Methods	Method of randomisation and allocation concealment were not described
Participants	90 consecutive patients undergoing cardiac surgery were randomly allocated to one of three groups: • Aprotinin group: n = 30, M/F = 23/7, mean (sd) age = 58 (8) years • Auto-transfusion group: n = 30, M/F = 20/10, mean (sd) age = 57 (7) years • Control group: n = 30, M/F = 24/6, mean (sd) age = 59 (10) years
Interventions	• Aprotinin group received 2 million KIU of aprotinin at the induction of anaesthesia infused over 20-30 minutes (10,000 KIU/ml of pure aprotinin without additives) followed by a continuous infusion of 500,000 KIU/hr of aprotinin administered throughout the operation. In addition, 2 million KIU of aprotinin was added to the priming solution of the extracorporeal circuit. • Auto-transfusion group had 400 ml of autologous blood withdrawn into citrate-phosphate-dextrose during electrocardiographic and haemodynamic monitoring. Blood was withdrawn after the induction of anaesthesia and before skin incision. Withdrawn blood was concomitantly replaced by 500ml of 4% albumin. Autologous blood was kept at room temperature (18-20 degrees) and was transfused after the completion of cardiopulmonary bypass, but before the patients were transferred to the Intensive Care Unit (ICU). • Control group patients underwent routine management without autologous transfusion or aprotinin treatment.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), number of patients exposed to fresh frozen plasma and platelets, blood loss (6hrs & 48hrs), re-operation for bleeding, haemoglobin loss
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Veien 2002

Methods	Patients were randomised using a computer generated randomisation table to treatment groups. Method of allocation concealment was not described
Participants	30 patients undergoing elective orthopaedic surgery were randomly assigned to one of two groups: • Tranexamic acid group: n = 15, M/F = 4/11, mean (sd) age = 70.5 (9.5) years • Control group: n = 15, M/F = 1/14, mean (sd) age = 69.5 (9.0) years
Interventions	• Tranexamic acid group received 10mg/kg of TXA administered just before the release of the tourniquet, and 10mg/kg of TXA given 3 hours later in the recovery room. Although a maximum of 1g was given each time. • Control group received standard care without TXA treatment. NB: All groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), cell salvage autologous blood returned, thrombo-embolic events
Notes	Quality assessment score (Schulz criteria):3/7 Transfusion protocol used

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Computer generated randomisation table
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Wei 2006

Methods	Method of allocation concealment and randomisation were not described
Participants	112 patients undergoing 'off-pump' coronary artery bypass graft surgery were randomised to one of two groups: • Aprotinin group: n = 36, M/F = 28/8, mean (sd) age = 61.4 (7.5) years • Tranexamic acid group: n = 36, M/F = 28/8, mean (sd) age = 62.8 (7.9) years • Control group (Placebo): n = 40, M/F = 32/8, mean (sd) age = 60.7 (8.0) years
Interventions	• Aprontinin group received 1 million KIU loading dose at beginning of surgery, followed by continuous infusion of 500000 KIU per hour during surgery. • Tranexamic acid group received a loading dose of 0.75g of TXA over 20 minutes at the beginning of surgery followed by a continuous infusion of 0.25g/hr throughout surgery. • Control group received the same volume of saline solution.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units) , fresh frozen plasma usage (units), number of patients exposed to fresh frozen plasma, blood loss (24hrs), hospital length of stay (days), Intensive Care Unit length of stay (days)
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used Results for aprotinin versus control and TXA versus control - reported in separate publications

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Wendel 1995

Methods	Method of randomisation was not described. Aprotinin and placebo were provided by the manufacturer in identical bottles that differed only in the random numbers on their labels
Participants	40 patients undergoing aorto-coronary artery bypass graft surgery were randomised to one of two groups: • Aprotinin group: n = 20, mean (sd) age = 62.4 (7.4) years • Control group (Placebo): n = 20, mean (sd) age = 60.6 (7.7) years NB: Gender data were not reported.
Interventions	• Aprotinin group received 30,000 KIU/kg of aprotinin as a loading dose over 20 minutes, followed by a continuous infusion of 7,000 KIU/kg/per/hr. In addition, 30,000 KIU/kg of aprotinin was added to the priming solution after 5 minutes of extracorporeal circulation (ECC). • Control group received physiologic saline solution.

Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss, myocardial infarction, infarctional biomarkers
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol not specified

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Wong 2000

Methods	The randomisation and preparation of study drugs was performed by the hospitals department of pharmacy. There was no attempt to stratify the randomisation process
Participants	80 patients undergoing elective cardiac surgery were randomised to one of two groups: • Tranexamic acid group: n = 40, mean (sd) age = 66.0 (10.9) years • Aprotinin group (High dose): n = 40, mean (sd) age = 65.4 (8.6) years NB: Gender data were not reported.
Interventions	• Tranexamic acid group received a bolus of 10g of TXA over 20 minutes after the induction of anaesthesia and before skin incision. Normal saline 0.9% was used during the other time periods similar to the aprotinin regimen. A test dose of 1mL was given. • Aprotinin group (High dose) received an infusion of 2 million KIU (280mg) of aprotinin infused over 20 minutes after the induction of anaesthesia and before skin incision, followed by a continuous infusion of 500,000 KIU/hr administered throughout the operation until skin closure. In addition, 2 million KIU (280mg) was added to the pump prime. NB: Both groups were exposed to cell salvage.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss (24hrs), myocardial infarction, mortality, fresh frozen plasma usage, platelet usage (units), re-operation for bleeding, stroke
Notes	Quality assessment score (Schulz criteria): 5/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description

Wong 2000 *(Continued)*

Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Wong 2008

Methods	A computer-generated randomisation list was used for sequence generation. The randomisation schedule was kept inaccessible throughout the study period. Patient assignments were placed into sequentially numbered opaque sealed envelopes. A research pharmacist, not involved with care of the patient prepared the placebo and treatment medications that were identical in appearance. The research personnel, anaesthesiologists, surgeons, and operating room staff were blinded to the randomisation
Participants	151 patients undergoing orthopaedic (spinal) surgery were randomised to one of two groups: • Tranexamic acid group: n = 73, M/F = 21/52, mean (sds) age = 56.8 (16.2) years • Control group (Placebo): n = 74, M/F = 26/48, mean (sd) age = 50.0 (16.2) years
Interventions	• Tranexamic acid group received a bolus of 10mg/kg IV, then maintenance infusion of 1mg/kg/hr until skin closure. • Control group received the same volume of saline solution.
Outcomes	***Outcomes reported:*** number of patients exposed to allogeneic blood transfusion, blood loss, volume blood transfused (units), deep vein thrombosis
Notes	Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated randomisation list
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind

Wu 2006

Methods	Method of randomisation was not described. Sealed envelopes were used to conceal treatment allocation
Participants	217 patients undergoing liver tumor resection were randomised to one of two groups: • Tranexamic acid group: n = 106, M/F = 77/29, mean (range) age = 62 (22-88) years • Control group (Placebo): n = 108, M/F = 80/28, mean (range) age = 57 (28-84) years NB: Three patients were excluded from the final analysis.
Interventions	• Tranexamic acid group received 500mg of intravenous TXA administered just before the operation, then received 250mg of intravenous TXA every 6 hours for 3 days. • Control group group received a similar volume of normal saline at the same time intervals as the TXA drug regimen.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss, hospital length of stay (days), wound infection
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	No	Inadequate - sealed envelopes
Blinding? All outcomes	Yes	Double blind

Yamasaki 2004

Methods	Randomisation was carried out by a person not involved in the operation using a ticket drawn from an envelope containing an equal number of tranexamic acid and placebo tickets
Participants	40 patients undergoing cementless total hip arthroplasty were randomised to one of two groups: • Tranexamic acid group: n = 20, M/F = 19/1, mean (sd) age = 55.5 (14.2) years • Control group: n = 20, M/F = 18/2, mean (sd) age = 61.2 (6.9) years
Interventions	• Tranexamic acid group received 1,000mg of TXA administered intravenously 5 minutes before the start of the operation. • Control group did not receive TXA treatment. NB: Both groups received pre-operatively donated autologous blood (PAD)
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, blood loss (24hrs), thrombo-embolic events

Yamasaki 2004 (*Continued)*

Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol not used	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Adequate
Allocation concealment?	No	Inadequate
Blinding? All outcomes	Unclear	Unclear

Yassen 1993

Methods	Method of randomisation and allocation concealment were not described	
Participants	20 patients undergoing orthotopic liver transplantation were randomly allocated to one of two groups: • Tranexamic acid group: n = 10, M/F = 5/5, mean (sd) age = 44.8 (12.2) years • Control group (Placebo): n = 10, M/F = 4/6, mean (sd) age = 49.6 (14.2) years	
Interventions	• Tranexamic acid group received 10mg/kg loading dose of TXA at the start of the anhepatic phase of the operation, followed by an infusion of 3mg/kg/hr until the patient was transferred to the Intensive Care Unit (ICU). • Control group received a similar volume of normal saline as a bolus followed by an infusion. NB: Both groups were exposed to cell salvage.	
Outcomes	***Outcomes reported:*** Allogeneic blood usage (units), fresh frozen plasma usage (units), platelets usage (units), blood loss, any thrombosis	
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Zabeeda 2002

Methods	Method of randomisation and allocation concealment were not described. The surgeon was blinded with respect to whether tranexamic acid or placebo was infused
Participants	50 patients undergoing coronary artery bypass graft surgery were randomised to one of two groups: • Tranexamic acid group: n = 25, M/F = 20/5, mean (sd) age = 65.6 (9) years • Control group (Placebo): n = 25, M/F = 18/7, mean (sd) age = 65 (13) years
Interventions	• Tranexamic acid group received 10mg/kg of TXA for more than 15 minutes in a volume of 10ml after the induction of anaesthesia followed by a continuous infusion of 1mg/kg/hr in a volume of 10ml for the duration of the procedure. • Control group received a 10ml bolus of 0.9% saline solution followed by a continuous infusion of saline (10ml/hr).
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage (units), blood loss (24hrs), stroke, mediastinal infection, pre-operative aspirin use
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind

Zhang 2007

Methods	Methods of sequence generation and allocation concealment were not described. [Chinese language]
Participants	102 patients undergoing orthopaedic knee surgery were randomised to one of two groups: • Tranexamic acid group: n = 51 • Control group (Placebo): n = 51 NB: Randomised subjects were aged between 59-77 years of age. Gender: M/F = 43/59
Interventions	• Tranexamic acid group received 1g in 250ml saline IV infused before deflation of tourniquet, then IV administration of 1g 3 hours later. • Control group received saline.
Outcomes	***Outcomes reported:*** Volume blood transfused (units), blood loss, deep vein thrombosis
Notes	Use of transfusion protocol is not reported

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Zohar 2004

Methods	Patients were randomly allocated to treatment groups using a computer generated randomisation table. Method used to conceal treatment allocation was not described
Participants	40 patients undergoing total knee replacement were randomised to one of two groups: • Tranexamic acid group: n = 20, M/F = 6/14, mean (sd) age = 73 (8) years • Control group: n = 20, M/F = 7/13, mean (sd) age = 73 (7) years
Interventions	• Tranexamic acid group received 15mg/kg of TXA as an intravenous bolus 30 minutes before the limb tourniquet was deflated administered over 30 minutes. Thereafter a constant infusion of 10mg/kg/hr was administered until 12 hours after final deflation of the limb tourniquet. • Control group received usual care with no TXA treatment.
Outcomes	***Outcomes reported:*** Number of patients exposed to allogeneic blood, allogeneic blood usage, blood loss (12hrs), thrombo-embolic events (30-day), hospital length of stay (days)
Notes	Quality assessment score (Schulz criteria): 1/7 Transfusion protocol used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated randomisation table
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Fejer 1998	Study was excluded on the basis there was uncertainty regarding the age of study participants. As the study involved thoracolumbar transpedicular (TLT) fixation of the spine for spondylolisthesis subjects less than 18 years of age may have been included
Langdown 2000	Study did not report the number of patients randomised to each trial arm rather reported the total number of patients randomised. Study was excluded on the basis there was uncertainty regarding the number of patients in each trial arm
Montesano 1996	Abstract refers to patients as being randomly selected but methods section of paper states study was retrospective. Study was excluded on the basis there was uncertainty regarding trial design
Zufferey 2010	Patients undergoing surgery for hip fractures - not elective

Characteristics of ongoing studies *[ordered by study ID]*

Myles 2008

Trial name or title	ATACAS trial
Methods	Multi-centre, randomised, blinded 2x2 factorial trial.
Participants	N=4600, patients undergoing elective CABG surgery.
Interventions	Patients will be allocated to one of four groups (1) Aspirin (2) Tranexamic acid (3) Tranexamic acid plus aspirin (4) Placebo
Outcomes	Mortality Myocardial infarction Stroke Pulmonary embolism Renal failure Bowel infarction Re-operation for bleeding Blood transfusion
Starting date	
Contact information	
Notes	

Verma 2010

Trial name or title	
Methods	Single-centre, randomised, double-blinded control study
Participants	Patient undergoing corrective spinal surgery.
Interventions	Patients will be allocated to one of three groups (1) Tranexamic acid (2) EACA (3) Saline
Outcomes	Perioperative blood loss Renal failure
Starting date	
Contact information	
Notes	ClinicalTrials.gov ID: NCT00958581

DATA AND ANALYSES

Comparison 1. Aprotinin versus Control (Blood Transfusion & Blood Loss)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. Exposed to Allogeneic Blood	108	11172	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.60, 0.72]
2 No. Exposed to Allogeneic Blood - Type of Surgery	108	11172	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.60, 0.72]
2.1 Cardiac surgery	84	9497	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.63, 0.73]
2.2 Orthopaedic surgery	15	1146	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.52, 0.89]
2.3 Thoracic surgery	3	78	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.14, 0.59]
2.4 Vascular surgery	2	188	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.97, 1.03]
2.5 Liver surgery	2	177	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.37, 0.90]
2.6 Neuro surgery	1	56	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.40, 1.35]
2.7 Orthognathic surgery	1	30	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.02, 0.77]
3 No. Exposed to Allogeneic Blood - Transfusion Protocol	108	11172	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.60, 0.72]
3.1 Transfusion Protocol	87	9974	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.59, 0.71]
3.2 No Transfusion Protocol	21	1198	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.61, 0.84]
4 No. Exposed to Allogeneic Blood - Dose	107	12116	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.62, 0.73]
4.1 Prime Dose	16	1251	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.71, 0.96]
4.2 Low Dose	50	3601	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.55, 0.77]
4.3 High Dose	61	7264	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.61, 0.71]
5 No. Exposed to Allogeneic Blood - Dose (Cardiac Surgery)	83	10423	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.65, 0.74]
5.1 Prime Dose	15	1191	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.69, 0.96]
5.2 Low Dose	29	2372	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.60, 0.80]
5.3 High Dose	58	6860	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.62, 0.72]
6 Trial Methodological Quality - Allocation Concealment	108	11172	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.60, 0.72]
6.1 Allocation concealment - Yes	33	2755	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.53, 0.79]
6.2 Allocation concealment - Unclear	63	7489	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.64, 0.75]
6.3 Allocation concealment - No	12	928	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.54, 0.75]
7 Units of Allogeneic Blood Transfused - Transfused Patients	40	3563	Mean Difference (IV, Random, 95% CI)	-0.98 [-1.29, -0.66]
8 Units of Allogeneic Blood Transfused - All Patients	74	7820	Mean Difference (IV, Random, 95% CI)	-1.02 [-1.26, -0.79]
9 Blood loss - Intra-operative	16	883	Mean Difference (IV, Random, 95% CI)	-191.87 [-280.45, -103.28]
9.1 Cardiac surgery	7	470	Mean Difference (IV, Random, 95% CI)	-148.18 [-240.21, -56.14]
9.2 Orthopaedic surgery	5	201	Mean Difference (IV, Random, 95% CI)	-151.05 [-317.63, 15.52]

9.3 Thoracic surgery	2	40	Mean Difference (IV, Random, 95% CI)	-577.06 [-893.71, -260.41]
9.4 Liver surgery	2	137	Mean Difference (IV, Random, 95% CI)	-1200.40 [-2943.39, 542.59]
9.5 Vascular surgery	1	35	Mean Difference (IV, Random, 95% CI)	-102.00 [-1004.32, 796.32]
10 Blood loss - Post-operative	87	7896	Mean Difference (IV, Random, 95% CI)	-345.88 [-383.47, -308.29]
10.1 Cardiac surgery	75	7371	Mean Difference (IV, Random, 95% CI)	-369.62 [-408.95, -330.29]
10.2 Orthopaedic surgery	7	318	Mean Difference (IV, Random, 95% CI)	-113.58 [-223.69, -3.46]
10.3 Thoracic surgery	2	83	Mean Difference (IV, Random, 95% CI)	-359.31 [-460.15, -258.48]
10.4 Orthognathic surgery	1	30	Mean Difference (IV, Random, 95% CI)	-513.0 [-717.21, -308.79]
10.5 Liver surgery	1	44	Mean Difference (IV, Random, 95% CI)	-105.0 [-194.36, -15.64]
10.6 Vascular surgery	1	50	Mean Difference (IV, Random, 95% CI)	-203.00 [-404.93, -1.07]
11 Blood loss - Post-operative - Dose (Cardiac Surgery)	75	8181	Mean Difference (IV, Random, 95% CI)	-367.69 [-403.50, -331.87]
11.1 Prime Dose	15	1158	Mean Difference (IV, Random, 95% CI)	-343.08 [-458.13, -228.04]
11.2 Low Dose	24	2038	Mean Difference (IV, Random, 95% CI)	-274.58 [-316.48, -232.67]
11.3 High Dose	52	4985	Mean Difference (IV, Random, 95% CI)	-418.59 [-470.96, -366.22]
12 Blood loss - Total	17	1789	Mean Difference (IV, Random, 95% CI)	-415.95 [-520.38, -311.51]
12.1 Cardiac surgery	7	1359	Mean Difference (IV, Random, 95% CI)	-448.86 [-612.82, -284.91]
12.2 Orthopaedic surgery	10	430	Mean Difference (IV, Random, 95% CI)	-399.09 [-562.81, -235.37]

Comparison 2. Tranexamic Acid versus Control (Blood Transfusion & Blood Loss)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. Exposed to Allogeneic Blood	65	4842	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.53, 0.70]
2 No. Exposed to Allogeneic Blood - Type of Surgery	65	4842	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.53, 0.70]
2.1 Cardiac surgery	34	3006	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.57, 0.81]
2.2 Orthopaedic surgery	27	1381	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.39, 0.62]
2.3 Liver surgery	2	296	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.4 Vascular surgery	1	59	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.33, 0.96]
2.5 Gynaecological surgery	1	100	Risk Ratio (M-H, Random, 95% CI)	1.5 [0.75, 3.01]

3 No. Exposed to Allogeneic Blood - Transfusion Protocol	65	4842	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.53, 0.70]
3.1 Transfusion Protocol	56	4125	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.48, 0.67]
3.2 No Transfusion Protocol	9	717	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.61, 0.96]
4 No. Exposed to Allogeneic Blood - Dose (Cardiac Surgery)	36	3191	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.58, 0.80]
4.1 Total dose < 2.0 grams	19	1123	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.58, 0.84]
4.2 Total dose 2.0 - 10.0 grams	18	2068	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.52, 0.86]
5 Trial Methodological Quality - Allocation Concealment	65	4842	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.53, 0.70]
5.1 Allocation concealment - Yes	28	2110	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.51, 0.69]
5.2 Allocation concealment - Unclear	24	1503	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.37, 0.76]
5.3 Allocation concealment - No	13	1229	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.62, 0.86]
6 Units Allogeneic Blood Transfused - Transfused Patients	13	481	Mean Difference (IV, Random, 95% CI)	-0.34 [-0.80, 0.11]
7 Units of Allogeneic Blood Transfused - All Patients	23	1814	Mean Difference (IV, Random, 95% CI)	-0.87 [-1.20, -0.53]
8 Blood loss - Intra-operative	17	1173	Mean Difference (IV, Random, 95% CI)	-121.41 [-180.19, -62.63]
8.1 Cardiac surgery	4	244	Mean Difference (IV, Random, 95% CI)	-166.76 [-331.24, -2.27]
8.2 Orthopaedic surgery	12	829	Mean Difference (IV, Random, 95% CI)	-115.52 [-187.88, -43.16]
8.3 Gynaecological surgery	1	100	Mean Difference (IV, Random, 95% CI)	-164.00 [-366.45, 34.45]
8.4 Head & neck surgery	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
9 Blood loss - Post-operative	35	2501	Mean Difference (IV, Random, 95% CI)	-247.17 [-294.76, -199.58]
9.1 Cardiac surgery	22	1597	Mean Difference (IV, Random, 95% CI)	-272.87 [-328.85, -216.89]
9.2 Orthopaedic surgery	12	804	Mean Difference (IV, Random, 95% CI)	-228.52 [-321.76, -135.27]
9.3 Gynaecological surgery	1	100	Mean Difference (IV, Random, 95% CI)	-63.0 [-118.89, -7.11]
9.4 Head & neck surgery	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
10 Blood loss - Post-operative - Dose (Cardiac Surgery)	22	1597	Mean Difference (IV, Random, 95% CI)	-272.87 [-328.85, -216.89]
10.1 Total dose < 2.0 grams	12	619	Mean Difference (IV, Random, 95% CI)	-245.03 [-329.76, -160.29]
10.2 Total dose 2.0 - 10.0 grams	10	978	Mean Difference (IV, Random, 95% CI)	-297.94 [-364.49, -231.39]
11 Blood loss - Total	28	1712	Mean Difference (IV, Random, 95% CI)	-414.06 [-525.19, -302.92]
11.1 Cardiac surgery	6	391	Mean Difference (IV, Random, 95% CI)	-300.47 [-470.74, -130.21]

11.2 Orthopaedic surgery	20	1201	Mean Difference (IV, Random, 95% CI)	-446.19 [-554.61, -337.78]
11.3 Liver surgery	1	20	Mean Difference (IV, Random, 95% CI)	-6552.0 [-14329.54, 1225.54]
11.4 Gynaecological surgery	1	100	Mean Difference (IV, Random, 95% CI)	-243.0 [-460.02, -25.98]
11.5 Head & neck surgery	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable

Comparison 3. Epsilon Aminocaproic Acid versus Control (Blood Transfusion & Blood Loss)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. Exposed to Allogeneic Blood	16	1035	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.67, 0.99]
2 No. Exposed to Allogeneic Blood - Type of Surgery	16	1035	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.67, 0.99]
2.1 Cardiac Surgery	11	649	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.52, 0.93]
2.2 Orthopaedic Surgery	4	304	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.93, 1.08]
2.3 Liver Surgery	1	82	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.80, 1.08]
3 No. Exposed to Allogeneic Blood - Transfusion Protocol	16	1035	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.67, 0.99]
3.1 Transfusion Protocol	15	1005	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.65, 0.98]
3.2 No Transfusion Protocol	1	30	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.36, 4.97]
4 Trial Methodological Quality - Allocation Concealment	16	1035	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.67, 0.99]
4.1 Allocation concealment - Yes	5	452	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.58, 1.16]
4.2 Allocation concealment - Unclear	9	455	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.46, 1.03]
4.3 Allocation concealment - No	2	128	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.81, 1.08]
5 Units of Allogeneic Blood Transfused - Transfused Patients	3	119	Mean Difference (IV, Random, 95% CI)	0.22 [-0.34, 0.79]
6 Units of Allogeneic Blood Transfused - All Patients	6	432	Mean Difference (IV, Random, 95% CI)	-1.30 [-2.14, -0.45]
7 Blood loss - Intra-operative	5	353	Mean Difference (IV, Random, 95% CI)	-156.63 [-276.92, -36.33]
7.1 Cardiac surgery	2	79	Mean Difference (IV, Random, 95% CI)	-213.58 [-310.03, -117.13]
7.2 Orthopaedic surgery	3	274	Mean Difference (IV, Random, 95% CI)	-40.66 [-236.71, 155.38]
8 Blood loss - Post-operative	14	1174	Mean Difference (IV, Random, 95% CI)	-207.49 [-276.43, -138.54]
8.1 Cardiac surgery	12	946	Mean Difference (IV, Random, 95% CI)	-200.27 [-273.44, -127.09]
8.2 Orthopaedic surgery	2	228	Mean Difference (IV, Random, 95% CI)	-285.06 [-452.73, -117.39]

9 Blood loss - Total	2	92	Mean Difference (IV, Random, 95% CI)	-299.69 [-522.54, -76.84]
9.1 Orthopaedic surgery	2	92	Mean Difference (IV, Random, 95% CI)	-299.69 [-522.54, -76.84]

Comparison 4. Aprotinin versus Tranexamic Acid (Blood Transfusion & Blood Loss)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. Exposed to Allogeneic Blood	21	4185	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 1.01]
2 No. Exposed to Allogeneic Blood - Type of Surgery	21	4185	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 1.01]
2.1 Cardiac surgery	18	3983	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.76, 0.99]
2.2 Liver surgery	2	178	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.91, 1.11]
2.3 Orthopaedic surgery	1	24	Risk Ratio (M-H, Random, 95% CI)	11.00 [0.67, 179.29]
3 No. Exposed to Allogeneic Blood - Transfusion Protocol	21	4185	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 1.01]
3.1 Transfusion Protocol	20	4155	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.01]
3.2 No Transfusion Protocol	1	30	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.67, 1.27]
4 Trial Methodological Quality - Allocation Concealment	21	4185	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 1.01]
4.1 Allocation concealment - Yes	4	1871	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.69, 0.92]
4.2 Allocation concealment - Unclear	13	1832	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.88, 1.07]
4.3 Allocation concealment - No	4	482	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.62, 1.39]
5 Units Allogeneic Blood Transfused - Transfused Patients	6	207	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.44, 0.30]
6 Units Allogeneic Blood Transfused - All Patients	10	992	Mean Difference (IV, Random, 95% CI)	-0.24 [-0.45, -0.04]
7 Blood loss	14	1041	Mean Difference (IV, Random, 95% CI)	-136.44 [-198.40, -74.47]
7.1 Cardiac surgery - Post-operative	13	831	Mean Difference (IV, Random, 95% CI)	-145.81 [-209.99, -81.62]
7.2 Cardiac surgery - Total	1	210	Mean Difference (IV, Random, 95% CI)	6.0 [-171.38, 183.38]

Comparison 5. Aprotinin versus Epsilon Aminocaproic Acid (Blood Transfusion & Blood Loss)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. Exposed to Allogeneic Blood	12	2200	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.76, 0.89]
2 No. Exposed to Allogeneic Blood - Type of Surgery	12	2200	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.76, 0.89]
2.1 Cardiac surgery	10	2125	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.76, 0.89]
2.2 Orthopaedic surgery	2	75	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.48, 1.40]
3 No. Exposed to Allogeneic Blood - Transfusion Protocol	12	2200	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.76, 0.89]
3.1 Transfusion Protocol	9	2014	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.76, 0.89]
3.2 No Transfusion Protocol	3	186	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.47, 1.31]
4 Trial Methodological Quality - Allocation Concealment	12	2200	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.76, 0.89]
4.1 Allocation concealment - Yes	3	1651	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.71, 1.05]
4.2 Allocation concealment - Unclear	8	504	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.58, 0.99]
4.3 Allocation concealment - No	1	45	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.49, 1.55]
5 Units of Allogeneic Blood Transfused - Transfused Patients	2	63	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.63, 0.28]
6 Units of Allogeneic Blood Transfused - All Patients	5	329	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.55, 0.14]
7 Blood loss	8	499	Mean Difference (IV, Random, 95% CI)	-106.01 [-212.50, 0.47]
7.1 Cardiac surgery - Post-operative	7	454	Mean Difference (IV, Random, 95% CI)	-111.43 [-220.64, -2.21]
7.2 Orthopaedic surgery - Total	1	45	Mean Difference (IV, Random, 95% CI)	100.0 [-515.06, 715.06]

Comparison 6. Tranexamic Acid versus Epsilon Aminocaproic Acid (Blood Transfusion & Blood Loss)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. Exposed to Allogeneic Blood	8	2003	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.77, 1.21]
2 No. Exposed to Allogeneic Blood - Type of Surgery	8	2003	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.77, 1.21]
2.1 Cardiac surgery	6	1852	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.79, 1.46]
2.2 Orthopaedic surgery	1	67	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.03, 1.94]
2.3 Liver surgery	1	84	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.64, 1.02]
3 No. Exposed to Allogeneic Blood - Transfusion Protocol	8	2003	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.77, 1.21]
3.1 Transfusion Protocol	8	2003	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.77, 1.21]

4 Trial Methodological Quality - Allocation Concealment	8	2003	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.77, 1.21]
4.1 Allocation concealment - Yes	1	1550	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.93, 1.07]
4.2 Allocation concealment - Unclear	5	302	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.68, 1.98]
4.3 Allocation concealment - No	2	151	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.22, 1.84]
5 Units of Allogeneic Blood Transfused - Transfused Patients	4	133	Mean Difference (IV, Random, 95% CI)	-0.34 [-0.74, 0.07]
6 Units of Allogeneic Blood Transfused - All Patients	3	268	Mean Difference (IV, Random, 95% CI)	-0.28 [-0.59, 0.03]
7 Blood loss	7	469	Mean Difference (IV, Random, 95% CI)	-4.20 [-147.29, 138.89]
7.1 Cardiac surgery - Post-operative	6	402	Mean Difference (IV, Random, 95% CI)	-4.36 [-163.35, 154.63]
7.2 Orthopaedic surgery - Total	1	67	Mean Difference (IV, Random, 95% CI)	-9.0 [-270.16, 252.16]
7.3 Gynaecological surgery - Total	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable

Comparison 7. Aprotinin versus Lysine Analogues (Blood Transfusion)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. Exposed to Allogeneic Blood	29	5566	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 0.99]
2 No. Exposed to Allogeneic Blood - Type of Surgery	29	5469	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.80, 0.98]
2.1 Cardiac surgery	24	5192	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.76, 0.96]
2.2 Orthopaedic surgery	3	99	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.32, 3.48]
2.3 Liver surgery	2	178	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.91, 1.11]
3 No. Exposed to Allogeneic Blood - Transfusion Protocol	29	5429	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.81, 0.98]
3.1 Transfusion Protocol	25	5213	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.80, 0.99]
3.2 No Transfusion Protocol	4	216	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.65, 1.12]
4 Units of Allogeneic Blood Transfused - Transfused Patients	7	251	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.42, 0.21]
5 Units of Allogeneic Blood Transfused - All Patients	14	1254	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.42, -0.09]
6 Trial Methodological Quality - Allocation Concealment	29	5566	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 0.99]
6.1 Allocation concealment - Yes	6	2742	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.71, 0.95]
6.2 Allocation concealment - Unclear	18	2297	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.86, 1.04]

6.3 Allocation concealment - No	5	527	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.67, 1.28]

Comparison 8. Adverse Events and Other Outcomes (Active versus Control)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Re-operation for bleeding	85		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Aprotinin versus Control	61	6117	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.34, 0.62]
1.2 Tranexamic Acid versus Control	27	2386	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.55, 1.17]
1.3 Epsilon Aminocaproic Acid versus Control	8	922	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.11, 0.99]
2 Mortality	92		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Aprotinin versus Control	63	8876	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.63, 1.06]
2.2 Tranexamic Acid versus Control	30	2917	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.33, 1.10]
2.3 Epsilon Aminocaproic Acid versus Control	8	988	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.44, 2.57]
3 Myocardial Infarction (MI)	71		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Aprotinin versus Control	49	7137	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.69, 1.11]
3.2 Tranexamic Acid versus Control	21	2186	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.41, 1.52]
3.3 Epsilon aminocaproic Acid versus Control	7	896	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.48, 1.63]
4 Stroke (CVA)	45		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Aprotinin versus Control	23	3122	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.44, 1.52]
4.2 Tranexamic Acid versus Control	18	2027	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.49, 3.07]
4.3 Epsilon Aminocaproic Acid versus Control	8	936	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.16, 2.36]
5 Deep Vein Thrombosis (DVT)	40		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Aprotinin versus Control	16	1456	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.47, 1.29]
5.2 Tranexamic Acid versus Control	23	1472	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.35, 1.43]
5.3 Epsilon Aminocaproic Acid versus Control	4	304	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.20, 3.03]
6 Pulmonary Embolism (PE)	20		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Aprotinin versus Control	4	585	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.42, 5.29]
6.2 Tranexamic Acid versus Control	14	1006	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.23, 1.99]
6.3 Epsilon Aminocaproic Acid versus Control	3	274	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.06, 2.13]
7 Other Thrombosis	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Aprotinin versus Control	9	736	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.25, 2.15]
7.2 Tranexamic Acid versus Control	9	484	Risk Ratio (M-H, Random, 95% CI)	2.10 [0.49, 8.99]

7.3 Epsilon Aminocaproic Acid versus Control	2	264	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.15, 1.72]
8 Coronary artery graft occlusion	2	728	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.10, 5.67]
8.1 Aprotinin versus Control	2	728	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.10, 5.67]
9 Renal Failure / Dysfunction	34		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Aprotinin versus Control	27	5185	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.79, 1.54]
9.2 Tranexamic Acid versus Control	9	912	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.33, 2.37]
9.3 Epsilon Aminocaproic Acid versus control	2	235	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.14, 1.22]
10 Hospital Length of Stay	31		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 Aprotinin versus Control	23	2017	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.71, 0.20]
10.2 Tranexamic Acid versus Control	10	772	Mean Difference (IV, Random, 95% CI)	-0.34 [-0.82, 0.13]
10.3 Epsilon Aminocaproic Acid versus Control	2	228	Mean Difference (IV, Random, 95% CI)	0.58 [-3.17, 4.33]

Comparison 9. Adverse Events and Other Outcomes (Active versus Active)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Re-operation for bleeding - Aprotinin versus Tranexamic Acid	17	4010	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
2 Re-operation for bleeding - Aprotinin versus Epsilon Aminocaproic Acid	6	2075	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.49, 1.00]
3 Re-operation for bleeding - Tranexamic Acid versus Epsilon Aminocaproic Acid	5	1853	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.73, 1.39]
4 Mortality - Aprotinin versus Tranexamic Acid	17	4130	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.94, 1.93]
5 Mortality - Aprotinin versus Epsilon Aminocaproic Acid	5	1891	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.99, 2.30]
6 Mortality - Tranexamic Acid versus Epsilon Aminocaproic Acid	5	1958	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.59, 1.47]
7 Mortality - Aprotinin versus Lysine Analogues	19	5127	Risk Ratio (M-H, Random, 95% CI)	1.39 [1.02, 1.89]
8 Myocardial Infarction - Aprotinin versus Tranexamic Acid	13	3574	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.71, 1.42]
9 Myocardial Infarction - Aprotinin versus Epsilon Aminocaproic Acid	4	1676	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.90, 2.22]
10 Myocardial Infarction - Tranexamic Acid versus Epsilon Aminocaproic Acid	3	1687	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.80, 2.23]

11 Myocardial infarction - Aprotinin versus Lysine Analogues	15	4466	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.82, 1.50]
12 Stroke (CVA) - Aprotinin versus Tranexamic Acid	6	2030	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.52, 1.47]
13 Stroke (CVA) - Aprotinin versus Epsilon Aminocaproic Acid	2	1578	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.60, 1.85]
14 Stroke (CVA) - Tranexamic Acid versus Epsilon Aminocaproic Acid	3	1658	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.78, 2.29]
15 Deep Vein Thrombosis (DVT) - Aprotinin versus Tranexamic Acid	3	265	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.05, 4.81]
16 Deep Vein Thrombosis (DVT) - Aprotinin versus Epsilon Aminocaproic Acid	4	300	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.51]
17 Deep Vein Thrombosis (DVT) - Tranexamic Acid versus Epsilon Aminocaproic Acid	3	303	Risk Ratio (M-H, Random, 95% CI)	Not estimable
18 Pulmonary Embolism (PE) - Aprotinin versus Tranexamic Acid	2	241	Risk Ratio (M-H, Random, 95% CI)	Not estimable
19 Pulmonary Embolism (PE) - Aprotinin versus Epsilon Aminocaproic Acid	3	270	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.10, 18.42]
20 Pulmonary Embolism (PE) - Tranexamic Acid versus Epsilon Aminocaproic Acid	3	284	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.01, 7.59]
21 Other Thrombosis - Aprotinin versus Tranexamic Acid	3	287	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.10, 2.68]
22 Other Thrombosis - Aprotinin versus Epsilon Aminocaproic Acid	1	92	Risk Ratio (M-H, Random, 95% CI)	Not estimable
23 Other Thrombosis - Tranexamic Acid versus Epsilon Aminocaproic Acid	2	184	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.39, 10.34]
24 Renal Failure / Dysfunction - Aprotinin versus Tranexamic Acid	6	2238	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.79, 1.31]
25 Renal Failure / Dysfunction - Aprotinin versus Epsilon Aminocaproic Acid	2	1595	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.59, 2.99]
26 Renal Failure / Dysfunction - Tranexamic Acid versus Epsilon Aminocaproic Acid	1	1540	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.76, 1.27]
27 Hospital Length of Stay - Aprotinin versus Tranexamic Acid	6	2174	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.92, 0.83]

28 Hospital Length of Stay - Aprotinin versus Epsilon Aminocaproic Acid	2	1605	Mean Difference (IV, Random, 95% CI)	-0.49 [-1.74, 0.77]
29 Hospital Length of Stay - Tranexamic Acid versus Epsilon Aminocaproic Acid	1	1550	Mean Difference (IV, Random, 95% CI)	-0.64 [-1.82, 0.54]

Comparison 10. Adverse Events and Other Outcomes (Active versus Control) - Cardiac Surgery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Re-operation for bleeding	78	8895	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.44, 0.71]
1.1 Aprotinin versus Control	56	5827	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.34, 0.63]
1.2 Tranexamic Acid versus Control	26	2328	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.54, 1.17]
1.3 Epsilon Aminocaproic Acid versus Control	7	740	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.11, 1.17]
2 Mortality	76	11240	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.65, 1.07]
2.1 Aprotinin versus Control	55	8174	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.64, 1.10]
2.2 Tranexamic Acid versus Control	23	2342	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.26, 1.28]
2.3 Epsilon Aminocaproic Acid versus Control	6	724	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.50, 5.43]
3 Myocardial Infarction	65	9472	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.71, 1.09]
3.1 Aprotinin versus Control	46	6658	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.71, 1.14]
3.2 Tranexamic Acid versus Control	19	2100	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.37, 1.47]
3.3 Epsilon Aminocaproic Acid versus Control	6	714	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.48, 1.63]
4 Stroke	38	4850	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.55, 1.63]
4.1 Aprotinin versus Control	18	2127	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.40, 1.67]
4.2 Tranexamic Acid versus Control	17	1969	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.53, 3.91]
4.3 Epsilon Aminocaproic Acid versus Control	7	754	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.16, 3.10]
5 Deep Vein Thrombosis (DVT)	7	1046	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.31, 2.87]
5.1 Aprotinin versus Control	3	624	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.36, 4.58]
5.2 Tranexamic Acid versus Control	4	422	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.04, 3.47]
6 Pulmonary Embolism	7	921	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.14, 2.74]
6.1 Tranexamic Acid versus Control	6	569	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.15]
6.2 Aprotinin versus Control	1	352	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.14, 7.10]
7 Other Thrombosis	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Aprotinin versus Control	4	426	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.11, 3.36]
7.2 Tranexamic Acid versus Control	1	100	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8 Renal Failure / Dysfunction	30	5912	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.71, 1.33]

8.1 Aprotinin versus Control	24	4947	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.76, 1.51]
8.2 Tranexamic Acid versus Control	9	912	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.33, 2.37]
8.3 Epsilon Aminocaproic Acid versus control	1	53	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.11, 1.14]
9 Hospital Length of Stay	19		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Aprotinin versus Control	17	1756	Mean Difference (IV, Random, 95% CI)	-0.22 [-0.73, 0.29]
9.2 Tranexamic Acid versus Control	5	434	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.34, 0.18]

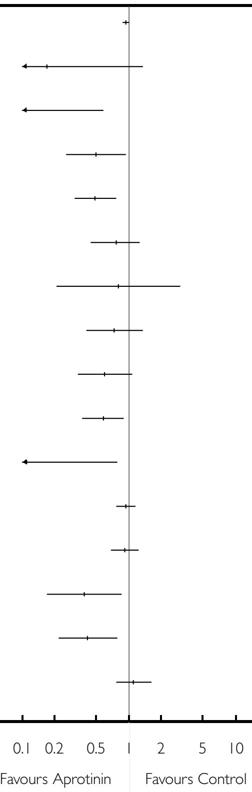
Analysis 1.1. Comparison 1 Aprotinin versus Control (Blood Transfusion & Blood Loss), Outcome 1 No. Exposed to Allogeneic Blood.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 1 Aprotinin versus Control (Blood Transfusion % Blood Loss)

Outcome: 1 No. Exposed to Allogeneic Blood

Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bailey 1994	119/129	25/25		1.6 %	0.94 [0.87, 1.01]
Vanek 2005	1/29	6/30		0.2 %	0.17 [0.02, 1.35]
Mansour 2004	1/20	12/20		0.2 %	0.08 [0.01, 0.58]
Dietrich 1990	7/19	15/20		0.9 %	0.49 [0.26, 0.93]
Cohen 1998	17/56	37/59		1.1 %	0.48 [0.31, 0.75]
Tabuchi 1994	10/19	12/17		1.0 %	0.75 [0.44, 1.26]
Harmon 2004	3/17	4/18		0.3 %	0.79 [0.21, 3.04]
Palmer 2003	11/30	13/26		0.9 %	0.73 [0.40, 1.35]
Poston 2006	10/29	18/31		0.9 %	0.59 [0.33, 1.07]
Bidstrup 2000	13/30	23/30		1.1 %	0.57 [0.36, 0.89]
Stewart 2001	1/15	9/15		0.2 %	0.11 [0.02, 0.77]
Speekenbrink 1996	55/75	29/37		1.5 %	0.94 [0.75, 1.16]
Hardy 1993	17/22	16/19		1.4 %	0.92 [0.68, 1.24]
Murkin 2000	12/212	10/68		0.7 %	0.38 [0.17, 0.85]
Bidstrup 1993	9/43	24/47		0.8 %	0.41 [0.22, 0.78]
Greilich 2009	18/26	17/27		1.2 %	1.10 [0.75, 1.62]



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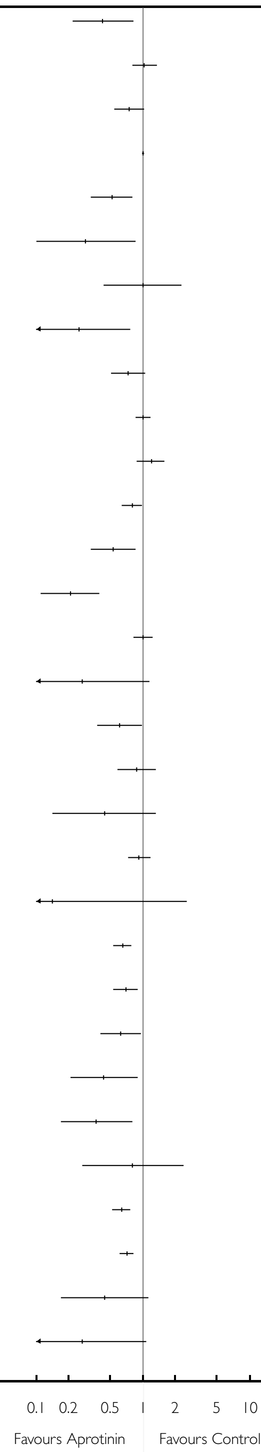
Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lemmer`2 1994	7/23	23/32		0.8 %	0.42 [0.22, 0.82]
Harder 1991	30/40	29/40		1.4 %	1.03 [0.80, 1.34]
Dietrich 1995	11/15	15/15		1.3 %	0.74 [0.54, 1.02]
Ranaboldo 1997	66/66	62/62		1.6 %	1.00 [0.97, 1.03]
Taggart 2003	14/36	26/34		1.1 %	0.51 [0.32, 0.80]
Norman 2009	2/8	8/8		0.5 %	0.29 [0.10, 0.85]
Deleuze 1991	8/30	8/30		0.6 %	1.00 [0.43, 2.31]
Liu 1993	3/20	12/20		0.4 %	0.25 [0.08, 0.75]
Lemmer`1 1994	28/74	35/67		1.2 %	0.72 [0.50, 1.05]
Capdevila 1998	12/12	11/11		1.5 %	1.00 [0.85, 1.17]
D'Ambra 1996	73/127	31/64		1.4 %	1.19 [0.88, 1.59]
Swart 1994	33/49	42/49		1.5 %	0.79 [0.63, 0.98]
Colwell 2007	20/175	39/177		1.1 %	0.52 [0.32, 0.85]
Bidstrup 1989	8/40	35/37		0.9 %	0.21 [0.11, 0.39]
Hardy 1997	23/26	23/26		1.5 %	1.00 [0.82, 1.22]
Englberger 2002a	2/21	8/23		0.3 %	0.27 [0.07, 1.15]
Wendel 1995	10/20	15/18		1.1 %	0.60 [0.37, 0.97]
Jeserschek 2003	7/9	8/9		1.2 %	0.88 [0.58, 1.33]
Maccario 1994	5/61	6/32		0.4 %	0.44 [0.14, 1.32]
Parvizi 2007	48/81	52/81		1.4 %	0.92 [0.72, 1.18]
Penta de Peppo 1995	0/15	3/15		0.1 %	0.14 [0.01, 2.55]
Lemmer 1996	173/487	87/157		1.5 %	0.64 [0.53, 0.77]
Petsatodis 2006	17/25	25/25		1.4 %	0.69 [0.52, 0.90]
Fraedrich 1989	16/38	26/38		1.2 %	0.62 [0.40, 0.95]
Lentschener 1997	8/48	19/49		0.8 %	0.43 [0.21, 0.89]
Ray 1997	7/53	19/52		0.7 %	0.36 [0.17, 0.79]
Kipfer 2003	4/15	5/15		0.4 %	0.80 [0.27, 2.41]
Kalangos 1994	60/110	48/55		1.5 %	0.63 [0.51, 0.76]
Alderman 1998	152/401	213/395		1.5 %	0.70 [0.60, 0.82]
Lentschener 1999	5/35	12/37		0.6 %	0.44 [0.17, 1.12]
Englberger 2002b	2/15	7/14		0.3 %	0.27 [0.07, 1.07]



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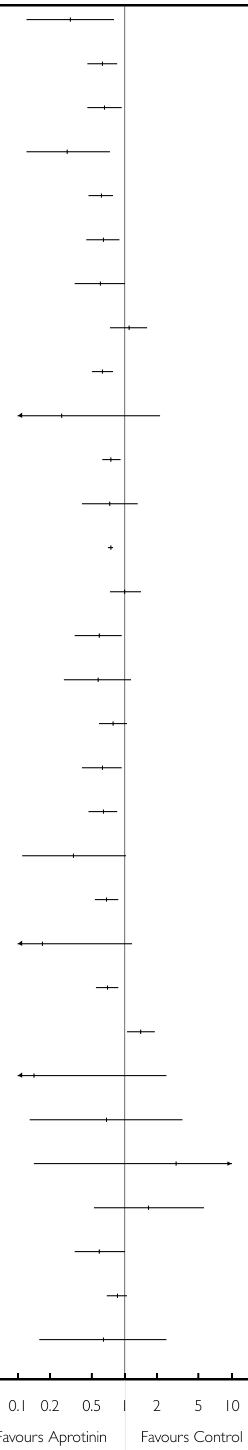
Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Li 2005	5/40	12/30		0.6 %	0.31 [0.12, 0.79]
Lass 1995	25/51	37/47		1.3 %	0.62 [0.45, 0.85]
Bidstrup 1990	15/26	16/18		1.3 %	0.65 [0.45, 0.94]
Gherli 1992	4/18	10/13		0.6 %	0.29 [0.12, 0.72]
Isetta 1993	55/140	46/70		1.4 %	0.60 [0.46, 0.78]
Murkin 1994	16/29	22/25		1.3 %	0.63 [0.44, 0.90]
Cicek 1996b	11/29	18/28		1.0 %	0.59 [0.34, 1.01]
Speekenbrink 1995	12/15	11/15		1.2 %	1.09 [0.73, 1.62]
Cosgrove 1992	55/113	44/56		1.5 %	0.62 [0.49, 0.78]
Rossi 1997	1/21	4/22		0.2 %	0.26 [0.03, 2.16]
Hayashida 1997	66/110	46/57		1.5 %	0.74 [0.61, 0.91]
Desai 2009	12/38	16/37		0.9 %	0.73 [0.40, 1.33]
Dietrich 1992	549/902	730/882		1.6 %	0.74 [0.69, 0.78]
Okita 1996	28/39	15/21		1.3 %	1.01 [0.72, 1.40]
Cicek 1996a	17/50	15/25		1.0 %	0.57 [0.34, 0.94]
Greilich 2001	7/24	13/25		0.8 %	0.56 [0.27, 1.16]
Nurözler 2008	17/25	23/26		1.4 %	0.77 [0.57, 1.04]
Vedrinne 1992	14/30	23/30		1.2 %	0.61 [0.40, 0.94]
Dignan 2001	37/101	58/99		1.3 %	0.63 [0.46, 0.85]
Kyriss 2001	3/18	10/20		0.4 %	0.33 [0.11, 1.02]
Basora 1999	23/36	20/21		1.4 %	0.67 [0.52, 0.87]
Katzel 1998	1/12	6/12		0.2 %	0.17 [0.02, 1.18]
Mohr 1992	23/34	16/16		1.4 %	0.69 [0.54, 0.88]
Rodrigus 1996	36/46	26/47		1.4 %	1.41 [1.05, 1.91]
Llau 1998	0/10	3/10		0.1 %	0.14 [0.01, 2.45]
Ray 2005	2/15	3/15		0.2 %	0.67 [0.13, 3.44]
Boldt 1991	1/10	0/10		0.1 %	3.00 [0.14, 65.90]
Engel 2001	5/12	3/12		0.4 %	1.67 [0.51, 5.46]
Corbeau 1995	15/43	12/20		1.0 %	0.58 [0.34, 1.00]
Rocha 1994	22/28	26/28		1.5 %	0.85 [0.68, 1.05]
Cicekcioglu 2006	3/24	4/20		0.3 %	0.63 [0.16, 2.47]



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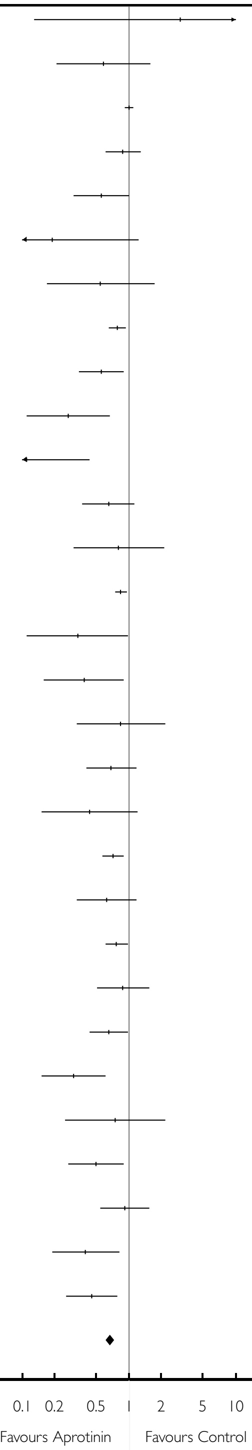
Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
D'Ambrosio 1999	1/30	0/30		0.1 %	3.00 [0.13, 70.83]
Laub 1994	4/16	7/16		0.5 %	0.57 [0.21, 1.58]
Pugh 1995	21/21	23/23		1.6 %	1.00 [0.92, 1.09]
Murkin 1995	18/29	17/24		1.2 %	0.88 [0.60, 1.29]
Cvachovec 2001	8/20	16/22		0.9 %	0.55 [0.30, 1.00]
Thorpe 1994	1/8	6/9		0.2 %	0.19 [0.03, 1.24]
Klein 1998	4/36	6/29		0.4 %	0.54 [0.17, 1.72]
Levy 1995	109/188	49/65		1.5 %	0.77 [0.64, 0.93]
Ray 1999	23/100	21/50		1.1 %	0.55 [0.34, 0.89]
Santamaria 2000	6/56	11/28		0.6 %	0.27 [0.11, 0.66]
Menichetti 1996	2/24	18/24		0.3 %	0.11 [0.03, 0.43]
Locatelli 1990	11/25	9/13		0.9 %	0.64 [0.36, 1.13]
Tassani 2000	4/10	5/10		0.5 %	0.80 [0.30, 2.13]
Carrera 1994	42/51	50/51		1.6 %	0.84 [0.74, 0.96]
Blauhut 1994	3/14	9/14		0.5 %	0.33 [0.11, 0.98]
Green 1995	6/48	12/36		0.6 %	0.38 [0.16, 0.90]
Wei 2006	6/36	8/40		0.5 %	0.83 [0.32, 2.17]
Garcia-Huete 1997	13/39	20/41		1.0 %	0.68 [0.40, 1.18]
Havel 1992	3/10	7/10		0.5 %	0.43 [0.15, 1.20]
Later 2009	48/96	73/103		1.4 %	0.71 [0.56, 0.89]
Alajmo 1989	9/22	8/12		0.9 %	0.61 [0.32, 1.17]
Baele 1992	35/58	45/57		1.4 %	0.76 [0.60, 0.98]
Amar 2003	11/23	13/24		1.0 %	0.88 [0.50, 1.55]
Van der Linden 2005	17/37	27/38		1.2 %	0.65 [0.43, 0.97]
Diprose 2005	8/60	27/60		0.8 %	0.30 [0.15, 0.60]
Alvarez 1995	5/49	7/51		0.5 %	0.74 [0.25, 2.19]
Samama 2002	12/40	11/18		0.9 %	0.49 [0.27, 0.89]
Kuitunen 2005	11/20	12/20		1.0 %	0.92 [0.54, 1.56]
Royston 1987	4/11	11/11		0.7 %	0.39 [0.19, 0.82]
Casas 1995	12/47	29/51		1.0 %	0.45 [0.26, 0.77]
Total (95% CI)	**6259**	**4913**		**100.0 %**	**0.66 [0.60, 0.72]**



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Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 2695 (Aprotinin), 3067 (Control)					
Heterogeneity: Tau^2 = 0.12; Chi^2 = 961.52, df = 107 (P<0.00001); I^2 =89%					
Test for overall effect: Z = 9.54 (P < 0.00001)					

0.1 0.2 0.5 1 2 5 10

Favours Aprotinin Favours Control

Analysis 1.2. Comparison 1 Aprotinin versus Control (Blood Transfusion & Blood Loss), Outcome 2 No. Exposed to Allogeneic Blood - Type of Surgery.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 1 Aprotinin versus Control (Blood Transfusion % Blood Loss)

Outcome: 2 No. Exposed to Allogeneic Blood - Type of Surgery

Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Cardiac surgery					
Alajmo 1989	9/22	8/12		0.9 %	0.61 [0.32, 1.17]
Alderman 1998	152/401	213/395		1.5 %	0.70 [0.60, 0.82]
Alvarez 1995	5/49	7/51		0.5 %	0.74 [0.25, 2.19]
Baele 1992	35/58	45/57		1.4 %	0.76 [0.60, 0.98]
Bailey 1994	119/129	25/25		1.6 %	0.94 [0.87, 1.01]
Basora 1999	23/36	20/21		1.4 %	0.67 [0.52, 0.87]
Bidstrup 1989	8/40	35/37		0.9 %	0.21 [0.11, 0.39]
Bidstrup 1990	15/26	16/18		1.3 %	0.65 [0.45, 0.94]
Bidstrup 1993	9/43	24/47		0.8 %	0.41 [0.22, 0.78]
Bidstrup 2000	13/30	23/30		1.1 %	0.57 [0.36, 0.89]
Blauhut 1994	3/14	9/14		0.5 %	0.33 [0.11, 0.98]

0.1 0.2 0.5 1 2 5 10

Favours Aprotinin Favours Control

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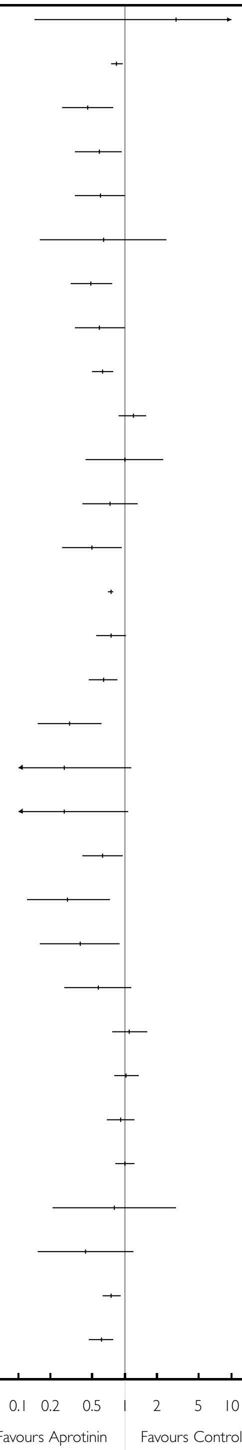
Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Boldt 1991	1/10	0/10		0.1 %	3.00 [0.14, 65.90]
Carrera 1994	42/51	50/51		1.6 %	0.84 [0.74, 0.96]
Casas 1995	12/47	29/51		1.0 %	0.45 [0.26, 0.77]
Cicek 1996a	17/50	15/25		1.0 %	0.57 [0.34, 0.94]
Cicek 1996b	11/29	18/28		1.0 %	0.59 [0.34, 1.01]
Cicekcioglu 2006	3/24	4/20		0.3 %	0.63 [0.16, 2.47]
Cohen 1998	17/56	37/59		1.1 %	0.48 [0.31, 0.75]
Corbeau 1995	15/43	12/20		1.0 %	0.58 [0.34, 1.00]
Cosgrove 1992	55/113	44/56		1.5 %	0.62 [0.49, 0.78]
D'Ambra 1996	73/127	31/64		1.4 %	1.19 [0.88, 1.59]
Deleuze 1991	8/30	8/30		0.6 %	1.00 [0.43, 2.31]
Desai 2009	12/38	16/37		0.9 %	0.73 [0.40, 1.33]
Dietrich 1990	7/19	15/20		0.9 %	0.49 [0.26, 0.93]
Dietrich 1992	549/902	730/882		1.6 %	0.74 [0.69, 0.78]
Dietrich 1995	11/15	15/15		1.3 %	0.74 [0.54, 1.02]
Dignan 2001	37/101	58/99		1.3 %	0.63 [0.46, 0.85]
Diprose 2005	8/60	27/60		0.8 %	0.30 [0.15, 0.60]
Englberger 2002a	2/21	8/23		0.3 %	0.27 [0.07, 1.15]
Englberger 2002b	2/15	7/14		0.3 %	0.27 [0.07, 1.07]
Fraedrich 1989	16/38	26/38		1.2 %	0.62 [0.40, 0.95]
Gherli 1992	4/18	10/13		0.6 %	0.29 [0.12, 0.72]
Green 1995	6/48	12/36		0.6 %	0.38 [0.16, 0.90]
Greilich 2001	7/24	13/25		0.8 %	0.56 [0.27, 1.16]
Greilich 2009	18/26	17/27		1.2 %	1.10 [0.75, 1.62]
Harder 1991	30/40	29/40		1.4 %	1.03 [0.80, 1.34]
Hardy 1993	17/22	16/19		1.4 %	0.92 [0.68, 1.24]
Hardy 1997	23/26	23/26		1.5 %	1.00 [0.82, 1.22]
Harmon 2004	3/17	4/18		0.3 %	0.79 [0.21, 3.04]
Havel 1992	3/10	7/10		0.5 %	0.43 [0.15, 1.20]
Hayashida 1997	66/110	46/57		1.5 %	0.74 [0.61, 0.91]
Isetta 1993	55/140	46/70		1.4 %	0.60 [0.46, 0.78]



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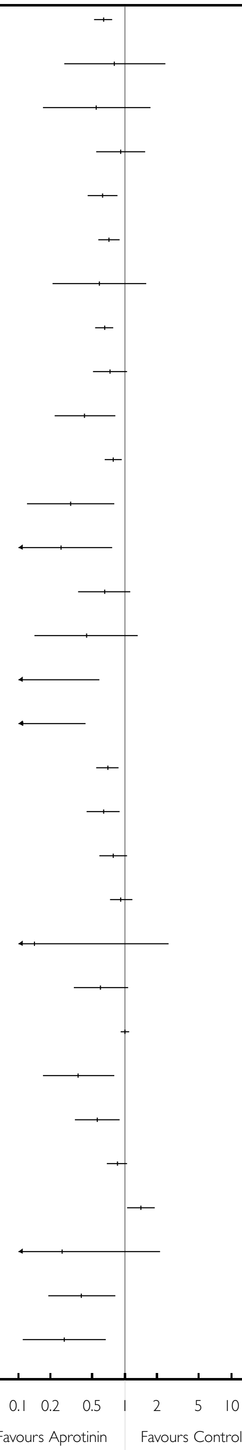
Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Kalangos 1994	60/110	48/55		1.5 %	0.63 [0.51, 0.76]
Kipfer 2003	4/15	5/15		0.4 %	0.80 [0.27, 2.41]
Klein 1998	4/36	6/29		0.4 %	0.54 [0.17, 1.72]
Kuitunen 2005	11/20	12/20		1.0 %	0.92 [0.54, 1.56]
Lass 1995	25/51	37/47		1.3 %	0.62 [0.45, 0.85]
Later 2009	48/96	73/103		1.4 %	0.71 [0.56, 0.89]
Laub 1994	4/16	7/16		0.5 %	0.57 [0.21, 1.58]
Lemmer 1996	173/487	87/157		1.5 %	0.64 [0.53, 0.77]
Lemmer˙1 1994	28/74	35/67		1.2 %	0.72 [0.50, 1.05]
Lemmer˙2 1994	7/23	23/32		0.8 %	0.42 [0.22, 0.82]
Levy 1995	109/188	49/65		1.5 %	0.77 [0.64, 0.93]
Li 2005	5/40	12/30		0.6 %	0.31 [0.12, 0.79]
Liu 1993	3/20	12/20		0.4 %	0.25 [0.08, 0.75]
Locatelli 1990	11/25	9/13		0.9 %	0.64 [0.36, 1.13]
Maccario 1994	5/61	6/32		0.4 %	0.44 [0.14, 1.32]
Mansour 2004	1/20	12/20		0.2 %	0.08 [0.01, 0.58]
Menichetti 1996	2/24	18/24		0.3 %	0.11 [0.03, 0.43]
Mohr 1992	23/34	16/16		1.4 %	0.69 [0.54, 0.88]
Murkin 1994	16/29	22/25		1.3 %	0.63 [0.44, 0.90]
Nurözler 2008	17/25	23/26		1.4 %	0.77 [0.57, 1.04]
Parvizi 2007	48/81	52/81		1.4 %	0.92 [0.72, 1.18]
Penta de Peppo 1995	0/15	3/15		0.1 %	0.14 [0.01, 2.55]
Poston 2006	10/29	18/31		0.9 %	0.59 [0.33, 1.07]
Pugh 1995	21/21	23/23		1.6 %	1.00 [0.92, 1.09]
Ray 1997	7/53	19/52		0.7 %	0.36 [0.17, 0.79]
Ray 1999	23/100	21/50		1.1 %	0.55 [0.34, 0.89]
Rocha 1994	22/28	26/28		1.5 %	0.85 [0.68, 1.05]
Rodrigus 1996	36/46	26/47		1.4 %	1.41 [1.05, 1.91]
Rossi 1997	1/21	4/22		0.2 %	0.26 [0.03, 2.16]
Royston 1987	4/11	11/11		0.7 %	0.39 [0.19, 0.82]
Santamaria 2000	6/56	11/28		0.6 %	0.27 [0.11, 0.66]



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Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Speekenbrink 1995	12/15	11/15		1.2 %	1.09 [0.73, 1.62]
Speekenbrink 1996	55/75	29/37		1.5 %	0.94 [0.75, 1.16]
Swart 1994	33/49	42/49		1.5 %	0.79 [0.63, 0.98]
Tabuchi 1994	10/19	12/17		1.0 %	0.75 [0.44, 1.26]
Taggart 2003	14/36	26/34		1.1 %	0.51 [0.32, 0.80]
Tassani 2000	4/10	5/10		0.5 %	0.80 [0.30, 2.13]
Van der Linden 2005	17/37	27/38		1.2 %	0.65 [0.43, 0.97]
Vanek 2005	1/29	6/30		0.2 %	0.17 [0.02, 1.35]
Vedrinne 1992	14/30	23/30		1.2 %	0.61 [0.40, 0.94]
Wei 2006	6/36	8/40		0.5 %	0.83 [0.32, 2.17]
Wendel 1995	10/20	15/18		1.1 %	0.60 [0.37, 0.97]
Subtotal (95% CI)	**5329**	**4168**		**81.8 %**	**0.68 [0.63, 0.73]**
Total events: 2431 (Aprotinin), 2728 (Control)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 329.48$, df = 83 ($P<0.00001$); $I^2 = 75\%$					
Test for overall effect: Z = 10.18 (P < 0.00001)					
2 Orthopaedic surgery					
Amar 2003	11/23	13/24		1.0 %	0.88 [0.50, 1.55]
Capdevila 1998	12/12	11/11		1.5 %	1.00 [0.85, 1.17]
Colwell 2007	20/175	39/177		1.1 %	0.52 [0.32, 0.85]
Cvachovec 2001	8/20	16/22		0.9 %	0.55 [0.30, 1.00]
D'Ambrosio 1999	1/30	0/30		0.1 %	3.00 [0.13, 70.83]
Engel 2001	5/12	3/12		0.4 %	1.67 [0.51, 5.46]
Jeserschek 2003	7/9	8/9		1.2 %	0.88 [0.58, 1.33]
Lentschener 1999	5/35	12/37		0.6 %	0.44 [0.17, 1.12]
Llau 1998	0/10	3/10		0.1 %	0.14 [0.01, 2.45]
Murkin 1995	18/29	17/24		1.2 %	0.88 [0.60, 1.29]
Murkin 2000	12/212	10/68		0.7 %	0.38 [0.17, 0.85]
Petsatodis 2006	17/25	25/25		1.4 %	0.69 [0.52, 0.90]
Ray 2005	2/15	3/15		0.2 %	0.67 [0.13, 3.44]
Samama 2002	12/40	11/18		0.9 %	0.49 [0.27, 0.89]
Thorpe 1994	1/8	6/9		0.2 %	0.19 [0.03, 1.24]
Subtotal (95% CI)	**655**	**491**		**11.4 %**	**0.68 [0.52, 0.89]**
Total events: 131 (Aprotinin), 177 (Control)					

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Favours Aprotinin Favours Control

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Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau^2 = 0.14; Chi^2 = 45.47, df = 14 (P = 0.00003); I^2 =69%					
Test for overall effect: Z = 2.77 (P = 0.0055)					
3 Thoracic surgery					
Katzel 1998	1/12	6/12		0.2 %	0.17 [0.02, 1.18]
Kyriss 2001	3/18	10/20		0.4 %	0.33 [0.11, 1.02]
Norman 2009	2/8	8/8		0.5 %	0.29 [0.10, 0.85]
Subtotal (95% CI)	**38**	**40**		**1.1 %**	**0.29 [0.14, 0.59]**
Total events: 6 (Aprotinin), 24 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.37, df = 2 (P = 0.83); I^2 =0.0%					
Test for overall effect: Z = 3.41 (P = 0.00066)					
4 Vascular surgery					
Okita 1996	28/39	15/21		1.3 %	1.01 [0.72, 1.40]
Ranaboldo 1997	66/66	62/62		1.6 %	1.00 [0.97, 1.03]
Subtotal (95% CI)	**105**	**83**		**2.9 %**	**1.00 [0.97, 1.03]**
Total events: 94 (Aprotinin), 77 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.01, df = 1 (P = 0.94); I^2 =0.0%					
Test for overall effect: Z = 0.00 (P = 1.0)					
5 Liver surgery					
Garcia-Huete 1997	13/39	20/41		1.0 %	0.68 [0.40, 1.18]
Lentschener 1997	8/48	19/49		0.8 %	0.43 [0.21, 0.89]
Subtotal (95% CI)	**87**	**90**		**1.7 %**	**0.58 [0.37, 0.90]**
Total events: 21 (Aprotinin), 39 (Control)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.03, df = 1 (P = 0.31); I^2 =3%					
Test for overall effect: Z = 2.44 (P = 0.015)					
6 Neuro surgery					
Palmer 2003	11/30	13/26		0.9 %	0.73 [0.40, 1.35]
Subtotal (95% CI)	**30**	**26**		**0.9 %**	**0.73 [0.40, 1.35]**
Total events: 11 (Aprotinin), 13 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.00 (P = 0.32)					
7 Orthognathic surgery					
Stewart 2001	1/15	9/15		0.2 %	0.11 [0.02, 0.77]
Subtotal (95% CI)	**15**	**15**		**0.2 %**	**0.11 [0.02, 0.77]**
Total events: 1 (Aprotinin), 9 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.22 (P = 0.026)					
Total (95% CI)	**6259**	**4913**		**100.0 %**	**0.66 [0.60, 0.72]**
Total events: 2695 (Aprotinin), 3067 (Control)					
Heterogeneity: Tau^2 = 0.12; Chi^2 = 961.52, df = 107 (P<0.00001); I^2 =89%					
Test for overall effect: Z = 9.54 (P < 0.00001)					

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Favours Aprotinin Favours Control

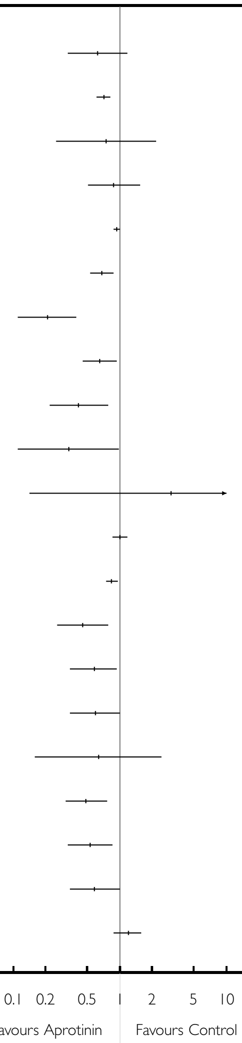
Analysis 1.3. Comparison 1 Aprotinin versus Control (Blood Transfusion & Blood Loss), Outcome 3 No. Exposed to Allogeneic Blood - Transfusion Protocol.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 1 Aprotinin versus Control (Blood Transfusion % Blood Loss)

Outcome: 3 No. Exposed to Allogeneic Blood - Transfusion Protocol

Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Transfusion Protocol					
Alajmo 1989	9/22	8/12		0.9 %	0.61 [0.32, 1.17]
Alderman 1998	152/401	213/395		1.5 %	0.70 [0.60, 0.82]
Alvarez 1995	5/49	7/51		0.5 %	0.74 [0.25, 2.19]
Amar 2003	11/23	13/24		1.0 %	0.88 [0.50, 1.55]
Bailey 1994	119/129	25/25		1.6 %	0.94 [0.87, 1.01]
Basora 1999	23/36	20/21		1.4 %	0.67 [0.52, 0.87]
Bidstrup 1989	8/40	35/37		0.9 %	0.21 [0.11, 0.39]
Bidstrup 1990	15/26	16/18		1.3 %	0.65 [0.45, 0.94]
Bidstrup 1993	9/43	24/47		0.8 %	0.41 [0.22, 0.78]
Blauhut 1994	3/14	9/14		0.5 %	0.33 [0.11, 0.98]
Boldt 1991	1/10	0/10		0.1 %	3.00 [0.14, 65.90]
Capdevila 1998	12/12	11/11		1.5 %	1.00 [0.85, 1.17]
Carrera 1994	42/51	50/51		1.6 %	0.84 [0.74, 0.96]
Casas 1995	12/47	29/51		1.0 %	0.45 [0.26, 0.77]
Cicek 1996a	17/50	15/25		1.0 %	0.57 [0.34, 0.94]
Cicek 1996b	11/29	18/28		1.0 %	0.59 [0.34, 1.01]
Cicekcioglu 2006	3/24	4/20		0.3 %	0.63 [0.16, 2.47]
Cohen 1998	17/56	37/59		1.1 %	0.48 [0.31, 0.75]
Colwell 2007	20/175	39/177		1.1 %	0.52 [0.32, 0.85]
Corbeau 1995	15/43	12/20		1.0 %	0.58 [0.34, 1.00]
D'Ambra 1996	73/127	31/64		1.4 %	1.19 [0.88, 1.59]



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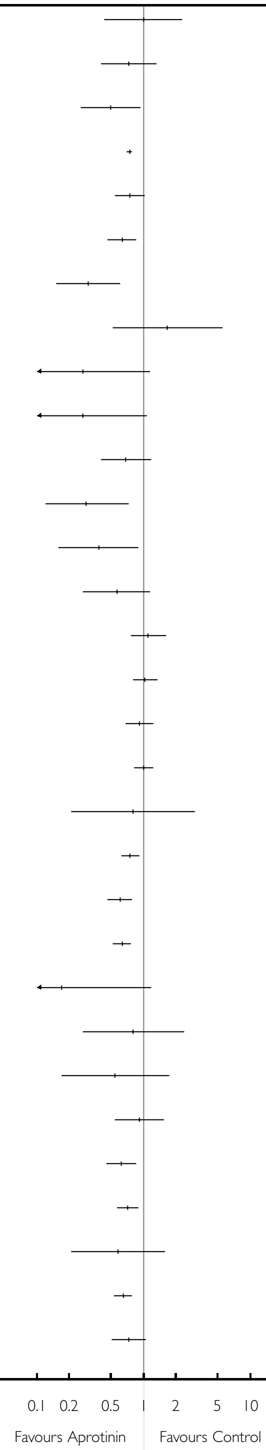
Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Deleuze 1991	8/30	8/30		0.6 %	1.00 [0.43, 2.31]
Desai 2009	12/38	16/37		0.9 %	0.73 [0.40, 1.33]
Dietrich 1990	7/19	15/20		0.9 %	0.49 [0.26, 0.93]
Dietrich 1992	549/902	730/882		1.6 %	0.74 [0.69, 0.78]
Dietrich 1995	11/15	15/15		1.3 %	0.74 [0.54, 1.02]
Dignan 2001	37/101	58/99		1.3 %	0.63 [0.46, 0.85]
Diprose 2005	8/60	27/60		0.8 %	0.30 [0.15, 0.60]
Engel 2001	5/12	3/12		0.4 %	1.67 [0.51, 5.46]
Englberger 2002a	2/21	8/23		0.3 %	0.27 [0.07, 1.15]
Englberger 2002b	2/15	7/14		0.3 %	0.27 [0.07, 1.07]
Garcia-Huete 1997	13/39	20/41		1.0 %	0.68 [0.40, 1.18]
Gherli 1992	4/18	10/13		0.6 %	0.29 [0.12, 0.72]
Green 1995	6/48	12/36		0.6 %	0.38 [0.16, 0.90]
Greilich 2001	7/24	13/25		0.8 %	0.56 [0.27, 1.16]
Greilich 2009	18/26	17/27		1.2 %	1.10 [0.75, 1.62]
Harder 1991	30/40	29/40		1.4 %	1.03 [0.80, 1.34]
Hardy 1993	17/22	16/19		1.4 %	0.92 [0.68, 1.24]
Hardy 1997	23/26	23/26		1.5 %	1.00 [0.82, 1.22]
Harmon 2004	3/17	4/18		0.3 %	0.79 [0.21, 3.04]
Hayashida 1997	66/110	46/57		1.5 %	0.74 [0.61, 0.91]
Isetta 1993	55/140	46/70		1.4 %	0.60 [0.46, 0.78]
Kalangos 1994	60/110	48/55		1.5 %	0.63 [0.51, 0.76]
Katzel 1998	1/12	6/12		0.2 %	0.17 [0.02, 1.18]
Kipfer 2003	4/15	5/15		0.4 %	0.80 [0.27, 2.41]
Klein 1998	4/36	6/29		0.4 %	0.54 [0.17, 1.72]
Kuitunen 2005	11/20	12/20		1.0 %	0.92 [0.54, 1.56]
Lass 1995	25/51	37/47		1.3 %	0.62 [0.45, 0.85]
Later 2009	48/96	73/103		1.4 %	0.71 [0.56, 0.89]
Laub 1994	4/16	7/16		0.5 %	0.57 [0.21, 1.58]
Lemmer 1996	173/487	87/157		1.5 %	0.64 [0.53, 0.77]
Lemmer˙1 1994	28/74	35/67		1.2 %	0.72 [0.50, 1.05]



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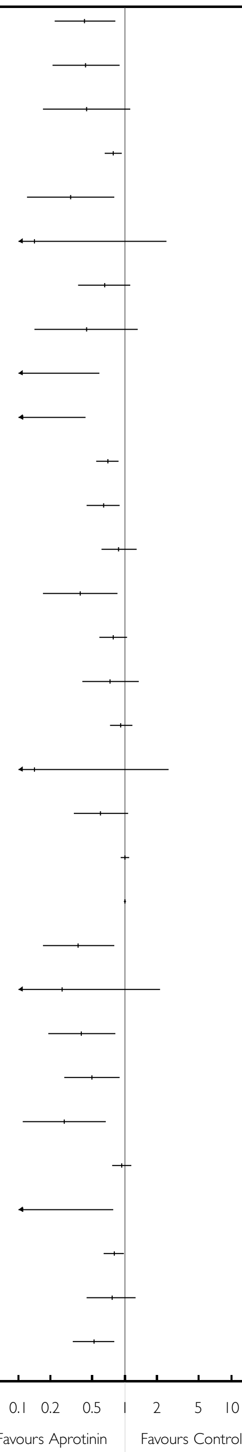
Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lemmer 2 1994	7/23	23/32		0.8 %	0.42 [0.22, 0.82]
Lentschener 1997	8/48	19/49		0.8 %	0.43 [0.21, 0.89]
Lentschener 1999	5/35	12/37		0.6 %	0.44 [0.17, 1.12]
Levy 1995	109/188	49/65		1.5 %	0.77 [0.64, 0.93]
Li 2005	5/40	12/30		0.6 %	0.31 [0.12, 0.79]
Llau 1998	0/10	3/10		0.1 %	0.14 [0.01, 2.45]
Locatelli 1990	11/25	9/13		0.9 %	0.64 [0.36, 1.13]
Maccario 1994	5/61	6/32		0.4 %	0.44 [0.14, 1.32]
Mansour 2004	1/20	12/20		0.2 %	0.08 [0.01, 0.58]
Menichetti 1996	2/24	18/24		0.3 %	0.11 [0.03, 0.43]
Mohr 1992	23/34	16/16		1.4 %	0.69 [0.54, 0.88]
Murkin 1994	16/29	22/25		1.3 %	0.63 [0.44, 0.90]
Murkin 1995	18/29	17/24		1.2 %	0.88 [0.60, 1.29]
Murkin 2000	12/212	10/68		0.7 %	0.38 [0.17, 0.85]
Nurözler 2008	17/25	23/26		1.4 %	0.77 [0.57, 1.04]
Palmer 2003	11/30	13/26		0.9 %	0.73 [0.40, 1.35]
Parvizi 2007	48/81	52/81		1.4 %	0.92 [0.72, 1.18]
Penta de Peppo 1995	0/15	3/15		0.1 %	0.14 [0.01, 2.55]
Poston 2006	10/29	18/31		0.9 %	0.59 [0.33, 1.07]
Pugh 1995	21/21	23/23		1.6 %	1.00 [0.92, 1.09]
Ranaboldo 1997	66/66	62/62		1.6 %	1.00 [0.97, 1.03]
Ray 1997	7/53	19/52		0.7 %	0.36 [0.17, 0.79]
Rossi 1997	1/21	4/22		0.2 %	0.26 [0.03, 2.16]
Royston 1987	4/11	11/11		0.7 %	0.39 [0.19, 0.82]
Samama 2002	12/40	11/18		0.9 %	0.49 [0.27, 0.89]
Santamaria 2000	6/56	11/28		0.6 %	0.27 [0.11, 0.66]
Speekenbrink 1996	55/75	29/37		1.5 %	0.94 [0.75, 1.16]
Stewart 2001	1/15	9/15		0.2 %	0.11 [0.02, 0.77]
Swart 1994	33/49	42/49		1.5 %	0.79 [0.63, 0.98]
Tabuchi 1994	10/19	12/17		1.0 %	0.75 [0.44, 1.26]
Taggart 2003	14/36	26/34		1.1 %	0.51 [0.32, 0.80]



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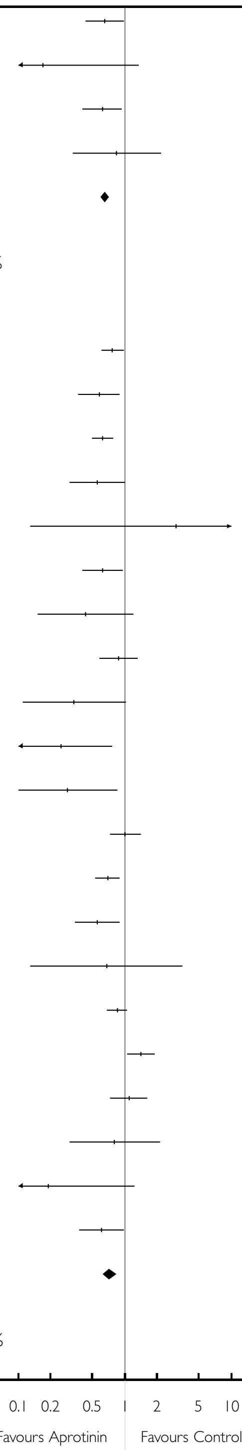
Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Van der Linden 2005	17/37	27/38		1.2 %	0.65 [0.43, 0.97]
Vanek 2005	1/29	6/30		0.2 %	0.17 [0.02, 1.35]
Vedrinne 1992	14/30	23/30		1.2 %	0.61 [0.40, 0.94]
Wei 2006	6/36	8/40		0.5 %	0.83 [0.32, 2.17]
Subtotal (95% CI)	**5599**	**4375**		**81.0 %**	**0.65 [0.59, 0.71]**
Total events: 2394 (Aprotinin), 2715 (Control)					
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 924.12$, df = 86 (P<0.00001); I^2 =91%					
Test for overall effect: Z = 8.72 (P < 0.00001)					
2 No Transfusion Protocol					
Baele 1992	35/58	45/57		1.4 %	0.76 [0.60, 0.98]
Bidstrup 2000	13/30	23/30		1.1 %	0.57 [0.36, 0.89]
Cosgrove 1992	55/113	44/56		1.5 %	0.62 [0.49, 0.78]
Cvachovec 2001	8/20	16/22		0.9 %	0.55 [0.30, 1.00]
D'Ambrosio 1999	1/30	0/30		0.1 %	3.00 [0.13, 70.83]
Fraedrich 1989	16/38	26/38		1.2 %	0.62 [0.40, 0.95]
Havel 1992	3/10	7/10		0.5 %	0.43 [0.15, 1.20]
Jeserschek 2003	7/9	8/9		1.2 %	0.88 [0.58, 1.33]
Kyriss 2001	3/18	10/20		0.4 %	0.33 [0.11, 1.02]
Liu 1993	3/20	12/20		0.4 %	0.25 [0.08, 0.75]
Norman 2009	2/8	8/8		0.5 %	0.29 [0.10, 0.85]
Okita 1996	28/39	15/21		1.3 %	1.01 [0.72, 1.40]
Petsatodis 2006	17/25	25/25		1.4 %	0.69 [0.52, 0.90]
Ray 1999	23/100	21/50		1.1 %	0.55 [0.34, 0.89]
Ray 2005	2/15	3/15		0.2 %	0.67 [0.13, 3.44]
Rocha 1994	22/28	26/28		1.5 %	0.85 [0.68, 1.05]
Rodrigus 1996	36/46	26/47		1.4 %	1.41 [1.05, 1.91]
Speekenbrink 1995	12/15	11/15		1.2 %	1.09 [0.73, 1.62]
Tassani 2000	4/10	5/10		0.5 %	0.80 [0.30, 2.13]
Thorpe 1994	1/8	6/9		0.2 %	0.19 [0.03, 1.24]
Wendel 1995	10/20	15/18		1.1 %	0.60 [0.37, 0.97]
Subtotal (95% CI)	**660**	**538**		**19.0 %**	**0.71 [0.61, 0.84]**
Total events: 301 (Aprotinin), 352 (Control)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 49.74$, df = 20 (P = 0.00024); I^2 =60%					



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Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 4.02 (P = 0.000058)					
Total (95% CI)	**6259**	**4913**		**100.0 %**	**0.66 [0.60, 0.72]**
Total events: 2695 (Aprotinin), 3067 (Control)					
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 961.52$, df = 107 (P<0.00001); I^2 =89%					
Test for overall effect: Z = 9.54 (P < 0.00001)					

0.1 0.2 0.5 1 2 5 10

Favours Aprotinin Favours Control

Analysis 1.4. Comparison 1 Aprotinin versus Control (Blood Transfusion & Blood Loss), Outcome 4 No. Exposed to Allogeneic Blood - Dose.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 1 Aprotinin versus Control (Blood Transfusion % Blood Loss)

Outcome: 4 No. Exposed to Allogeneic Blood - Dose

Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Prime Dose					
Bailey 1994	49/51	25/25		1.4 %	0.97 [0.89, 1.05]
Englberger 2002b	2/15	7/14		0.2 %	0.27 [0.07, 1.07]
Hardy 1997	23/26	23/26		1.3 %	1.00 [0.82, 1.22]
Hayashida 1997	31/55	46/57		1.2 %	0.70 [0.54, 0.91]
Kalangos 1994	31/55	48/55		1.2 %	0.65 [0.50, 0.83]
Kipfer 2003	4/15	5/15		0.4 %	0.80 [0.27, 2.41]
Lemmer 1996	56/159	87/157		1.2 %	0.64 [0.49, 0.82]
Levy 1995	49/68	49/65		1.3 %	0.96 [0.78, 1.17]
Maccario 1994	3/29	6/32		0.3 %	0.55 [0.15, 2.01]
Mohr 1992	15/17	16/16		1.3 %	0.89 [0.72, 1.09]

0.01 0.1 1 10 100

Favours Aprotinin Favours Control

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Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Okita 1996	28/39	15/21		1.1 %	1.01 [0.72, 1.40]
Rossi 1997	1/21	4/22		0.1 %	0.26 [0.03, 2.16]
Santamaria 2000	3/28	11/28		0.3 %	0.27 [0.09, 0.87]
Speekenbrink 1995	12/15	11/15		1.0 %	1.09 [0.73, 1.62]
Speekenbrink 1996	28/37	29/37		1.2 %	0.97 [0.75, 1.24]
Tabuchi 1994	10/19	12/17		0.8 %	0.75 [0.44, 1.26]
Subtotal (95% CI)	**649**	**602**		**14.2 %**	**0.83 [0.71, 0.96]**
Total events: 345 (Aprotinin), 394 (Control)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 59.49$, df = 15 (P<0.00001); I^2 =75%					
Test for overall effect: Z = 2.47 (P = 0.014)					
2 Low Dose					
Alajmo 1989	9/22	8/12		0.7 %	0.61 [0.32, 1.17]
Alvarez 1995	5/49	7/51		0.4 %	0.74 [0.25, 2.19]
Amar 2003	11/23	13/24		0.8 %	0.88 [0.50, 1.55]
Bailey 1994	47/53	25/25		1.3 %	0.90 [0.80, 1.00]
Basora 1999	23/36	20/21		1.2 %	0.67 [0.52, 0.87]
Blauhut 1994	3/14	9/14		0.4 %	0.33 [0.11, 0.98]
Capdevila 1998	12/12	11/11		1.3 %	1.00 [0.85, 1.17]
Cicek 1996a	9/25	15/25		0.7 %	0.60 [0.33, 1.11]
Cicek 1996b	11/29	18/28		0.8 %	0.59 [0.34, 1.01]
Cicekcioglu 2006	3/24	4/20		0.3 %	0.63 [0.16, 2.47]
Cosgrove 1992	29/56	44/56		1.2 %	0.66 [0.49, 0.88]
Cvachovec 2001	8/20	16/22		0.8 %	0.55 [0.30, 1.00]
D'Ambra 1996	32/62	31/64		1.1 %	1.07 [0.75, 1.51]
D'Ambrosio 1999	1/30	0/30		0.1 %	3.00 [0.13, 70.83]
Dignan 2001	37/101	58/99		1.1 %	0.63 [0.46, 0.85]
Engel 2001	5/12	3/12		0.3 %	1.67 [0.51, 5.46]
Englberger 2002a	2/21	8/23		0.2 %	0.27 [0.07, 1.15]
Garcia-Huete 1997	13/39	20/41		0.8 %	0.68 [0.40, 1.18]
Gherli 1992	2/9	10/13		0.3 %	0.29 [0.08, 1.02]
Hardy 1993	17/22	16/19		1.1 %	0.92 [0.68, 1.24]
Havel 1992	3/10	7/10		0.4 %	0.43 [0.15, 1.20]

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Favours Aprotinin Favours Control

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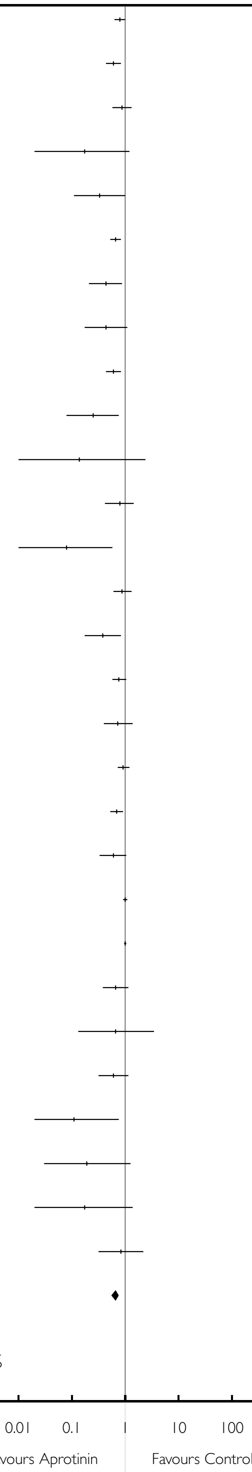
Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Hayashida 1997	35/55	46/57		1.2 %	0.79 [0.62, 1.00]
Isetta 1993	28/70	46/70		1.1 %	0.61 [0.44, 0.85]
Jeserschek 2003	7/9	8/9		1.0 %	0.88 [0.58, 1.33]
Katzel 1998	1/12	6/12		0.1 %	0.17 [0.02, 1.18]
Kyriss 2001	3/18	10/20		0.3 %	0.33 [0.11, 1.02]
Lemmer 1996	62/168	87/157		1.2 %	0.67 [0.52, 0.85]
Lentschener 1997	8/48	19/49		0.6 %	0.43 [0.21, 0.89]
Lentschener 1999	5/35	12/37		0.5 %	0.44 [0.17, 1.12]
Levy 1995	27/59	49/65		1.1 %	0.61 [0.44, 0.83]
Liu 1993	3/20	12/20		0.4 %	0.25 [0.08, 0.75]
Llau 1998	0/10	3/10		0.1 %	0.14 [0.01, 2.45]
Locatelli 1990	7/13	9/13		0.7 %	0.78 [0.42, 1.45]
Mansour 2004	1/20	12/20		0.1 %	0.08 [0.01, 0.58]
Murkin 1995	18/29	17/24		1.0 %	0.88 [0.60, 1.29]
Murkin 2000	12/212	10/68		0.6 %	0.38 [0.17, 0.85]
Nurözler 2008	17/25	23/26		1.1 %	0.77 [0.57, 1.04]
Palmer 2003	11/30	13/26		0.7 %	0.73 [0.40, 1.35]
Parvizi 2007	48/81	52/81		1.2 %	0.92 [0.72, 1.18]
Petsatodis 2006	17/25	25/25		1.2 %	0.69 [0.52, 0.90]
Poston 2006	10/29	18/31		0.8 %	0.59 [0.33, 1.07]
Pugh 1995	21/21	23/23		1.4 %	1.00 [0.92, 1.09]
Ranaboldo 1997	66/66	62/62		1.4 %	1.00 [0.97, 1.03]
Ray 1999	14/50	21/50		0.8 %	0.67 [0.38, 1.16]
Ray 2005	2/15	3/15		0.2 %	0.67 [0.13, 3.44]
Samama 2002	8/22	11/18		0.7 %	0.60 [0.31, 1.16]
Stewart 2001	1/15	9/15		0.1 %	0.11 [0.02, 0.77]
Thorpe 1994	1/8	6/9		0.1 %	0.19 [0.03, 1.24]
Vanek 2005	1/29	6/30		0.1 %	0.17 [0.02, 1.35]
Wei 2006	6/36	8/40		0.4 %	0.83 [0.32, 2.17]
Subtotal (95% CI)	**1899**	**1702**		**35.6 %**	**0.65 [0.55, 0.77]**

Total events: 722 (Aprotinin), 969 (Control)

Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 721.10$, df = 49 (P<0.00001); I^2 =93%



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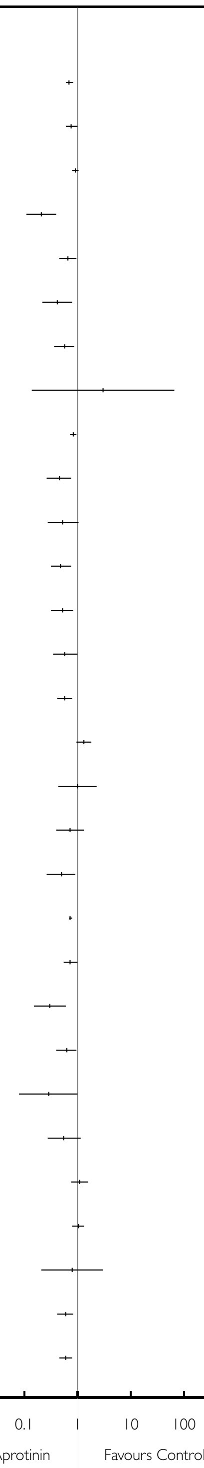
Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 5.01 (P < 0.00001)					
3 High Dose					
Alderman 1998	152/401	213/395		1.3 %	0.70 [0.60, 0.82]
Baele 1992	35/58	45/57		1.2 %	0.76 [0.60, 0.98]
Bailey 1994	23/25	25/25		1.3 %	0.92 [0.80, 1.06]
Bidstrup 1989	8/40	35/37		0.7 %	0.21 [0.11, 0.39]
Bidstrup 1990	15/26	16/18		1.0 %	0.65 [0.45, 0.94]
Bidstrup 1993	9/43	24/47		0.7 %	0.41 [0.22, 0.78]
Bidstrup 2000	13/30	23/30		0.9 %	0.57 [0.36, 0.89]
Boldt 1991	1/10	0/10		0.1 %	3.00 [0.14, 65.90]
Carrera 1994	42/51	50/51		1.3 %	0.84 [0.74, 0.96]
Casas 1995	12/47	29/51		0.8 %	0.45 [0.26, 0.77]
Cicek 1996a	8/25	15/25		0.7 %	0.53 [0.28, 1.03]
Cohen 1998	17/56	37/59		0.9 %	0.48 [0.31, 0.75]
Colwell 2007	20/175	39/177		0.9 %	0.52 [0.32, 0.85]
Corbeau 1995	15/43	12/20		0.8 %	0.58 [0.34, 1.00]
Cosgrove 1992	26/57	44/56		1.1 %	0.58 [0.42, 0.80]
D'Ambra 1996	41/65	31/64		1.1 %	1.30 [0.95, 1.78]
Deleuze 1991	8/30	8/30		0.5 %	1.00 [0.43, 2.31]
Desai 2009	12/38	16/37		0.8 %	0.73 [0.40, 1.33]
Dietrich 1990	7/19	15/20		0.7 %	0.49 [0.26, 0.93]
Dietrich 1992	549/902	730/882		1.4 %	0.74 [0.69, 0.78]
Dietrich 1995	11/15	15/15		1.1 %	0.74 [0.54, 1.02]
Diprose 2005	8/60	27/60		0.6 %	0.30 [0.15, 0.60]
Fraedrich 1989	16/38	26/38		1.0 %	0.62 [0.40, 0.95]
Gherli 1992	2/9	10/13		0.3 %	0.29 [0.08, 1.02]
Greilich 2001	7/24	13/25		0.6 %	0.56 [0.27, 1.16]
Greilich 2009	18/26	17/27		1.0 %	1.10 [0.75, 1.62]
Harder 1991	30/40	29/40		1.2 %	1.03 [0.80, 1.34]
Harmon 2004	3/17	4/18		0.3 %	0.79 [0.21, 3.04]
Isetta 1993	27/70	46/70		1.1 %	0.59 [0.42, 0.83]
Kalangos 1994	29/55	48/55		1.2 %	0.60 [0.46, 0.79]



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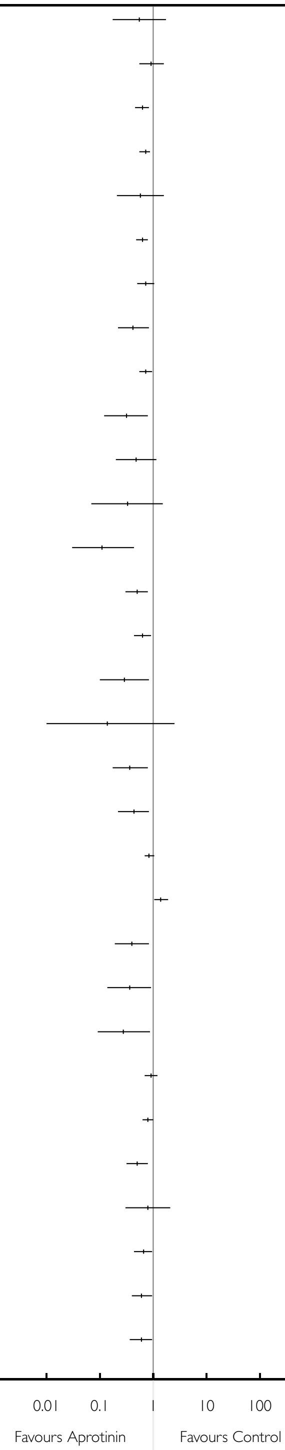
Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Klein 1998	4/36	6/29		0.3 %	0.54 [0.17, 1.72]
Kuitunen 2005	11/20	12/20		0.8 %	0.92 [0.54, 1.56]
Lass 1995	25/51	37/47		1.1 %	0.62 [0.45, 0.85]
Later 2009	48/96	73/103		1.2 %	0.71 [0.56, 0.89]
Laub 1994	4/16	7/16		0.4 %	0.57 [0.21, 1.58]
Lemmer 1996	55/160	87/157		1.2 %	0.62 [0.48, 0.80]
Lemmer˙1 1994	28/74	35/67		1.0 %	0.72 [0.50, 1.05]
Lemmer˙2 1994	7/23	23/32		0.7 %	0.42 [0.22, 0.82]
Levy 1995	33/61	49/65		1.2 %	0.72 [0.55, 0.94]
Li 2005	5/40	12/30		0.5 %	0.31 [0.12, 0.79]
Locatelli 1990	4/12	9/13		0.5 %	0.48 [0.20, 1.16]
Maccario 1994	2/32	6/32		0.2 %	0.33 [0.07, 1.53]
Menichetti 1996	2/24	18/24		0.3 %	0.11 [0.03, 0.43]
Mohr 1992	8/17	16/16		0.9 %	0.49 [0.30, 0.80]
Murkin 1994	16/29	22/25		1.1 %	0.63 [0.44, 0.90]
Norman 2009	2/8	8/8		0.4 %	0.29 [0.10, 0.85]
Penta de Peppo 1995	0/15	3/15		0.1 %	0.14 [0.01, 2.55]
Ray 1997	7/53	19/52		0.6 %	0.36 [0.17, 0.79]
Ray 1999	9/50	21/50		0.7 %	0.43 [0.22, 0.84]
Rocha 1994	22/28	26/28		1.2 %	0.85 [0.68, 1.05]
Rodrigus 1996	36/46	26/47		1.1 %	1.41 [1.05, 1.91]
Royston 1987	4/11	11/11		0.6 %	0.39 [0.19, 0.82]
Samama 2002	4/18	11/18		0.4 %	0.36 [0.14, 0.93]
Santamaria 2000	3/28	11/28		0.3 %	0.27 [0.09, 0.87]
Speekenbrink 1996	27/38	29/37		1.2 %	0.91 [0.70, 1.18]
Swart 1994	33/49	42/49		1.2 %	0.79 [0.63, 0.98]
Taggart 2003	14/36	26/34		0.9 %	0.51 [0.32, 0.80]
Tassani 2000	4/10	5/10		0.4 %	0.80 [0.30, 2.13]
Van der Linden 2005	17/37	27/38		1.0 %	0.65 [0.43, 0.97]
Vedrinne 1992	14/30	23/30		1.0 %	0.61 [0.40, 0.94]
Wendel 1995	10/20	15/18		0.9 %	0.60 [0.37, 0.97]



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Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**3663**	**3601**		**50.2 %**	**0.66 [0.61, 0.71]**
Total events: 1622 (Aprotinin), 2357 (Control)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 173.52$, df = 60 (P<0.00001); I^2 =65%					
Test for overall effect: Z = 10.02 (P < 0.00001)					
Total (95% CI)	**6211**	**5905**		**100.0 %**	**0.67 [0.62, 0.73]**
Total events: 2689 (Aprotinin), 3720 (Control)					
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 1011.26$, df = 126 (P<0.00001); I^2 =88%					
Test for overall effect: Z = 10.19 (P < 0.00001)					

0.01 0.1 1 10 100

Favours Aprotinin Favours Control

Analysis 1.5. Comparison 1 Aprotinin versus Control (Blood Transfusion & Blood Loss), Outcome 5 No. Exposed to Allogeneic Blood - Dose (Cardiac Surgery).

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 1 Aprotinin versus Control (Blood Transfusion % Blood Loss)

Outcome: 5 No. Exposed to Allogeneic Blood - Dose (Cardiac Surgery)

Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Prime Dose					
Bailey 1994	49/51	25/25		1.9 %	0.97 [0.89, 1.05]
Englberger 2002b	2/15	7/14		0.2 %	0.27 [0.07, 1.07]
Hardy 1997	23/26	23/26		1.7 %	1.00 [0.82, 1.22]
Hayashida 1997	31/55	46/57		1.5 %	0.70 [0.54, 0.91]
Kalangos 1994	31/55	48/55		1.6 %	0.65 [0.50, 0.83]
Kipfer 2003	4/15	5/15		0.3 %	0.80 [0.27, 2.41]
Lemmer 1996	56/159	87/157		1.6 %	0.64 [0.49, 0.82]
Levy 1995	49/68	49/65		1.7 %	0.96 [0.78, 1.17]

0.1 0.2 0.5 1 2 5 10

Favours Aprotinin Favours Control

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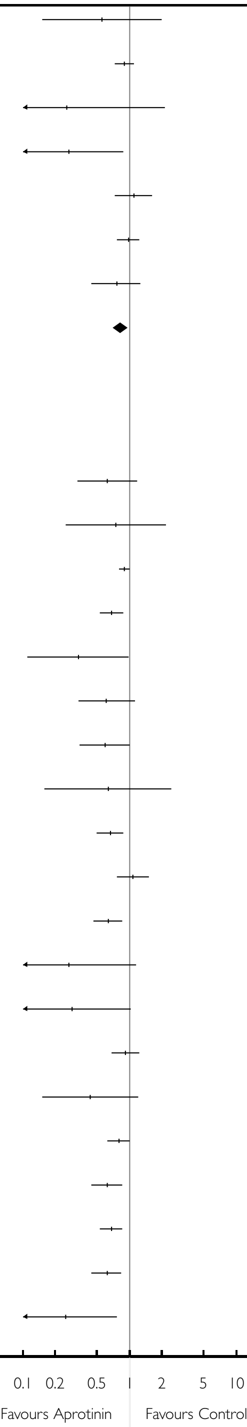
Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Maccario 1994	3/29	6/32		0.2 %	0.55 [0.15, 2.01]
Mohr 1992	15/17	16/16		1.7 %	0.89 [0.72, 1.09]
Rossi 1997	1/21	4/22		0.1 %	0.26 [0.03, 2.16]
Santamaria 2000	3/28	11/28		0.3 %	0.27 [0.09, 0.87]
Speekenbrink 1995	12/15	11/15		1.2 %	1.09 [0.73, 1.62]
Speekenbrink 1996	28/37	29/37		1.6 %	0.97 [0.75, 1.24]
Tabuchi 1994	10/19	12/17		0.9 %	0.75 [0.44, 1.26]
Subtotal (95% CI)	**610**	**581**		**16.4 %**	**0.81 [0.69, 0.96]**
Total events: 317 (Aprotinin), 379 (Control)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 62.42, df = 14 (P<0.00001); I^2 =78%					
Test for overall effect: Z = 2.50 (P = 0.012)					
2 Low Dose					
Alajmo 1989	9/22	8/12		0.7 %	0.61 [0.32, 1.17]
Alvarez 1995	5/49	7/51		0.3 %	0.74 [0.25, 2.19]
Bailey 1994	47/53	25/25		1.9 %	0.90 [0.80, 1.00]
Basora 1999	23/36	20/21		1.5 %	0.67 [0.52, 0.87]
Blauhut 1994	3/14	9/14		0.3 %	0.33 [0.11, 0.98]
Cicek 1996a	9/25	15/25		0.7 %	0.60 [0.33, 1.11]
Cicek 1996b	11/29	18/28		0.9 %	0.59 [0.34, 1.01]
Cicekcioglu 2006	3/24	4/20		0.2 %	0.63 [0.16, 2.47]
Cosgrove 1992	29/56	44/56		1.5 %	0.66 [0.49, 0.88]
D'Ambra 1996	32/62	31/64		1.3 %	1.07 [0.75, 1.51]
Dignan 2001	37/101	58/99		1.4 %	0.63 [0.46, 0.85]
Englberger 2002a	2/21	8/23		0.2 %	0.27 [0.07, 1.15]
Gherli 1992	2/9	10/13		0.2 %	0.29 [0.08, 1.02]
Hardy 1993	17/22	16/19		1.4 %	0.92 [0.68, 1.24]
Havel 1992	3/10	7/10		0.3 %	0.43 [0.15, 1.20]
Hayashida 1997	35/55	46/57		1.6 %	0.79 [0.62, 1.00]
Isetta 1993	28/70	46/70		1.3 %	0.61 [0.44, 0.85]
Lemmer 1996	62/168	87/157		1.6 %	0.67 [0.52, 0.85]
Levy 1995	27/59	49/65		1.4 %	0.61 [0.44, 0.83]
Liu 1993	3/20	12/20		0.3 %	0.25 [0.08, 0.75]



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Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Locatelli 1990	7/13	9/13		0.7 %	0.78 [0.42, 1.45]
Mansour 2004	1/20	12/20		0.1 %	0.08 [0.01, 0.58]
Nurözler 2008	17/25	23/26		1.4 %	0.77 [0.57, 1.04]
Parvizi 2007	48/81	52/81		1.6 %	0.92 [0.72, 1.18]
Poston 2006	10/29	18/31		0.8 %	0.59 [0.33, 1.07]
Pugh 1995	21/21	23/23		1.9 %	1.00 [0.92, 1.09]
Ray 1999	14/50	21/50		0.8 %	0.67 [0.38, 1.16]
Vanek 2005	1/29	6/30		0.1 %	0.17 [0.02, 1.35]
Wei 2006	6/36	8/40		0.4 %	0.83 [0.32, 2.17]
Subtotal (95% CI)	**1209**	**1163**		**27.1 %**	**0.69 [0.60, 0.80]**
Total events: 512 (Aprotinin), 692 (Control)					
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 125.74$, df = 28 (P<0.00001); I^2 =78%					
Test for overall effect: Z = 4.99 (P < 0.00001)					
3 High Dose					
Alderman 1998	152/401	213/395		1.8 %	0.70 [0.60, 0.82]
Baele 1992	35/58	45/57		1.6 %	0.76 [0.60, 0.98]
Bailey 1994	23/25	25/25		1.8 %	0.92 [0.80, 1.06]
Bidstrup 1989	8/40	35/37		0.7 %	0.21 [0.11, 0.39]
Bidstrup 1990	15/26	16/18		1.2 %	0.65 [0.45, 0.94]
Bidstrup 1993	9/43	24/47		0.7 %	0.41 [0.22, 0.78]
Bidstrup 2000	13/30	23/30		1.0 %	0.57 [0.36, 0.89]
Boldt 1991	1/10	0/10		0.0 %	3.00 [0.14, 65.90]
Carrera 1994	42/51	50/51		1.9 %	0.84 [0.74, 0.96]
Casas 1995	12/47	29/51		0.9 %	0.45 [0.26, 0.77]
Cicek 1996a	8/25	15/25		0.7 %	0.53 [0.28, 1.03]
Cohen 1998	17/56	37/59		1.1 %	0.48 [0.31, 0.75]
Corbeau 1995	15/43	12/20		0.9 %	0.58 [0.34, 1.00]
Cosgrove 1992	26/57	44/56		1.4 %	0.58 [0.42, 0.80]
D'Ambra 1996	41/65	31/64		1.4 %	1.30 [0.95, 1.78]
Deleuze 1991	8/30	8/30		0.5 %	1.00 [0.43, 2.31]
Desai 2009	12/38	16/37		0.8 %	0.73 [0.40, 1.33]
Dietrich 1990	7/19	15/20		0.7 %	0.49 [0.26, 0.93]

0.1 0.2 0.5 1 2 5 10

Favours Aprotinin Favours Control

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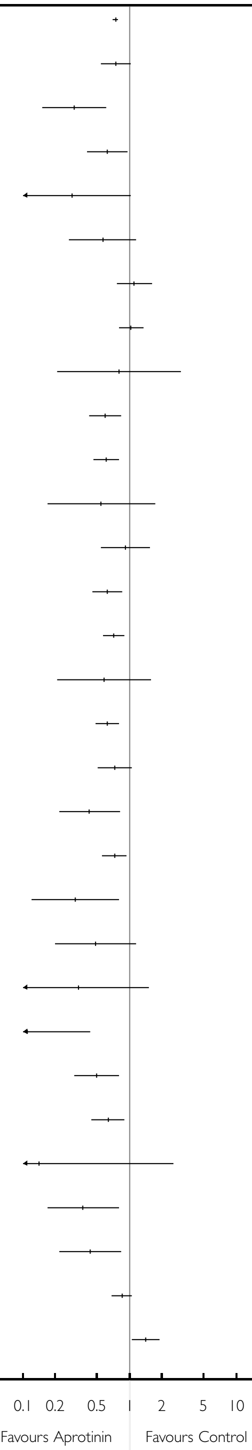
Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Dietrich 1992	549/902	730/882		2.0 %	0.74 [0.69, 0.78]
Dietrich 1995	11/15	15/15		1.4 %	0.74 [0.54, 1.02]
Diprose 2005	8/60	27/60		0.6 %	0.30 [0.15, 0.60]
Fraedrich 1989	16/38	26/38		1.1 %	0.62 [0.40, 0.95]
Gherli 1992	2/9	10/13		0.2 %	0.29 [0.08, 1.02]
Greilich 2001	7/24	13/25		0.6 %	0.56 [0.27, 1.16]
Greilich 2009	18/26	17/27		1.2 %	1.10 [0.75, 1.62]
Harder 1991	30/40	29/40		1.5 %	1.03 [0.80, 1.34]
Harmon 2004	3/17	4/18		0.2 %	0.79 [0.21, 3.04]
Isetta 1993	27/70	46/70		1.3 %	0.59 [0.42, 0.83]
Kalangos 1994	29/55	48/55		1.5 %	0.60 [0.46, 0.79]
Klein 1998	4/36	6/29		0.3 %	0.54 [0.17, 1.72]
Kuitunen 2005	11/20	12/20		0.9 %	0.92 [0.54, 1.56]
Lass 1995	25/51	37/47		1.4 %	0.62 [0.45, 0.85]
Later 2009	48/96	73/103		1.6 %	0.71 [0.56, 0.89]
Laub 1994	4/16	7/16		0.4 %	0.57 [0.21, 1.58]
Lemmer 1996	55/160	87/157		1.5 %	0.62 [0.48, 0.80]
Lemmer˙1 1994	28/74	35/67		1.2 %	0.72 [0.50, 1.05]
Lemmer˙2 1994	7/23	23/32		0.7 %	0.42 [0.22, 0.82]
Levy 1995	33/61	49/65		1.5 %	0.72 [0.55, 0.94]
Li 2005	5/40	12/30		0.4 %	0.31 [0.12, 0.79]
Locatelli 1990	4/12	9/13		0.4 %	0.48 [0.20, 1.16]
Maccario 1994	2/32	6/32		0.2 %	0.33 [0.07, 1.53]
Menichetti 1996	2/24	18/24		0.2 %	0.11 [0.03, 0.43]
Mohr 1992	8/17	16/16		0.9 %	0.49 [0.30, 0.80]
Murkin 1994	16/29	22/25		1.3 %	0.63 [0.44, 0.90]
Penta de Peppo 1995	0/15	3/15		0.1 %	0.14 [0.01, 2.55]
Ray 1997	7/53	19/52		0.5 %	0.36 [0.17, 0.79]
Ray 1999	9/50	21/50		0.7 %	0.43 [0.22, 0.84]
Rocha 1994	22/28	26/28		1.6 %	0.85 [0.68, 1.05]
Rodrigus 1996	36/46	26/47		1.4 %	1.41 [1.05, 1.91]



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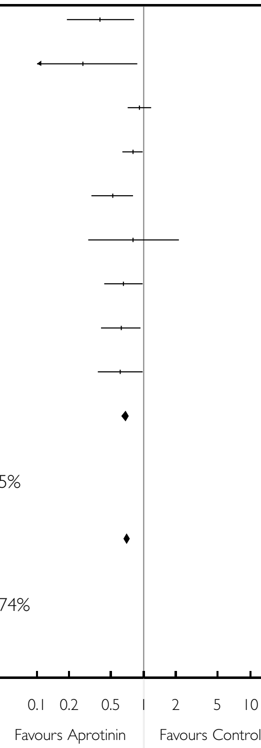
Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Royston 1987	4/11	11/11		0.6 %	0.39 [0.19, 0.82]
Santamaria 2000	3/28	11/28		0.3 %	0.27 [0.09, 0.87]
Speekenbrink 1996	27/38	29/37		1.5 %	0.91 [0.70, 1.18]
Swart 1994	33/49	42/49		1.6 %	0.79 [0.63, 0.98]
Taggart 2003	14/36	26/34		1.0 %	0.51 [0.32, 0.80]
Tassani 2000	4/10	5/10		0.4 %	0.80 [0.30, 2.13]
Van der Linden 2005	17/37	27/38		1.2 %	0.65 [0.43, 0.97]
Vedrinne 1992	14/30	23/30		1.1 %	0.61 [0.40, 0.94]
Wendel 1995	10/20	15/18		1.0 %	0.60 [0.37, 0.97]
Subtotal (95% CI)	**3462**	**3398**		**56.5 %**	**0.67 [0.62, 0.72]**
Total events: 1596 (Aprotinin), 2299 (Control)					
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 164.59$, df = 57 (P<0.00001); I^2 =65%					
Test for overall effect: Z = 9.67 (P < 0.00001)					
Total (95% CI)	**5281**	**5142**		**100.0 %**	**0.69 [0.65, 0.74]**
Total events: 2425 (Aprotinin), 3370 (Control)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 392.72$, df = 101 (P<0.00001); I^2 =74%					
Test for overall effect: Z = 10.73 (P < 0.00001)					



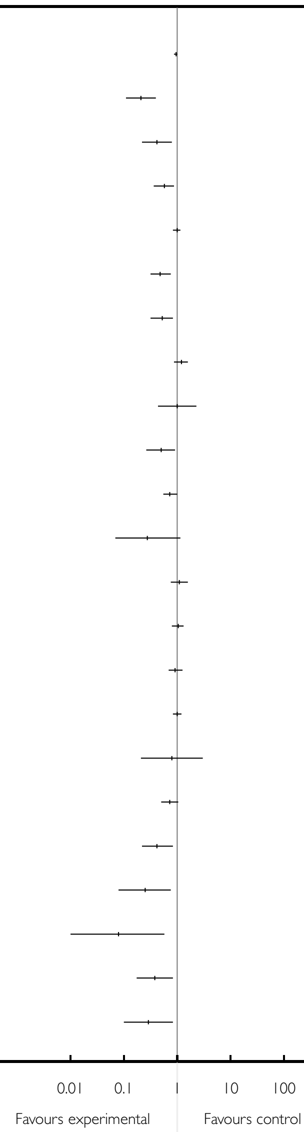
Analysis 1.6. Comparison 1 Aprotinin versus Control (Blood Transfusion & Blood Loss), Outcome 6 Trial Methodological Quality - Allocation Concealment.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 1 Aprotinin versus Control (Blood Transfusion % Blood Loss)

Outcome: 6 Trial Methodological Quality - Allocation Concealment

Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Allocation concealment - Yes					
Bailey 1994	119/129	25/25		1.6 %	0.94 [0.87, 1.01]
Bidstrup 1989	8/40	35/37		0.9 %	0.21 [0.11, 0.39]
Bidstrup 1993	9/43	24/47		0.8 %	0.41 [0.22, 0.78]
Bidstrup 2000	13/30	23/30		1.1 %	0.57 [0.36, 0.89]
Capdevila 1998	12/12	11/11		1.5 %	1.00 [0.85, 1.17]
Cohen 1998	17/56	37/59		1.1 %	0.48 [0.31, 0.75]
Colwell 2007	20/175	39/177		1.1 %	0.52 [0.32, 0.85]
D'Ambra 1996	73/127	31/64		1.4 %	1.19 [0.88, 1.59]
Deleuze 1991	8/30	8/30		0.6 %	1.00 [0.43, 2.31]
Dietrich 1990	7/19	15/20		0.9 %	0.49 [0.26, 0.93]
Dietrich 1995	11/15	15/15		1.3 %	0.74 [0.54, 1.02]
Englberger 2002a	2/21	8/23		0.3 %	0.27 [0.07, 1.15]
Greilich 2009	18/26	17/27		1.2 %	1.10 [0.75, 1.62]
Harder 1991	30/40	29/40		1.4 %	1.03 [0.80, 1.34]
Hardy 1993	17/22	16/19		1.4 %	0.92 [0.68, 1.24]
Hardy 1997	23/26	23/26		1.5 %	1.00 [0.82, 1.22]
Harmon 2004	3/17	4/18		0.3 %	0.79 [0.21, 3.04]
Lemmer 1 1994	28/74	35/67		1.2 %	0.72 [0.50, 1.05]
Lemmer 2 1994	7/23	23/32		0.8 %	0.42 [0.22, 0.82]
Liu 1993	3/20	12/20		0.4 %	0.25 [0.08, 0.75]
Mansour 2004	1/20	12/20		0.2 %	0.08 [0.01, 0.58]
Murkin 2000	12/212	10/68		0.7 %	0.38 [0.17, 0.85]
Norman 2009	2/8	8/8		0.5 %	0.29 [0.10, 0.85]



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Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Palmer 2003	11/30	13/26		0.9 %	0.73 [0.40, 1.35]
Poston 2006	10/29	18/31		0.9 %	0.59 [0.33, 1.07]
Ranaboldo 1997	66/66	62/62		1.6 %	1.00 [0.97, 1.03]
Speekenbrink 1996	55/75	29/37		1.5 %	0.94 [0.75, 1.16]
Stewart 2001	1/15	9/15		0.2 %	0.11 [0.02, 0.77]
Swart 1994	33/49	42/49		1.5 %	0.79 [0.63, 0.98]
Tabuchi 1994	10/19	12/17		1.0 %	0.75 [0.44, 1.26]
Taggart 2003	14/36	26/34		1.1 %	0.51 [0.32, 0.80]
Vanek 2005	1/29	6/30		0.2 %	0.17 [0.02, 1.35]
Wendel 1995	10/20	15/18		1.1 %	0.60 [0.37, 0.97]
Subtotal (95% CI)	**1553**	**1202**		**32.2 %**	**0.64 [0.53, 0.79]**
Total events: 654 (Aprotinin), 692 (Control)					
Heterogeneity: Tau² = 0.25; Chi² = 665.70, df = 32 (P<0.00001); I² =95%					
Test for overall effect: Z = 4.30 (P = 0.000017)					
2 Allocation concealment - Unclear					
Alderman 1998	152/401	213/395		1.5 %	0.70 [0.60, 0.82]
Basora 1999	23/36	20/21		1.4 %	0.67 [0.52, 0.87]
Bidstrup 1990	15/26	16/18		1.3 %	0.65 [0.45, 0.94]
Blauhut 1994	3/14	9/14		0.5 %	0.33 [0.11, 0.98]
Boldt 1991	1/10	0/10		0.1 %	3.00 [0.14, 65.90]
Carrera 1994	42/51	50/51		1.6 %	0.84 [0.74, 0.96]
Cicek 1996a	17/50	15/25		1.0 %	0.57 [0.34, 0.94]
Cicek 1996b	11/29	18/28		1.0 %	0.59 [0.34, 1.01]
Cicekcioglu 2006	3/24	4/20		0.3 %	0.63 [0.16, 2.47]
Corbeau 1995	15/43	12/20		1.0 %	0.58 [0.34, 1.00]
Cosgrove 1992	55/113	44/56		1.5 %	0.62 [0.49, 0.78]
Cvachovec 2001	8/20	16/22		0.9 %	0.55 [0.30, 1.00]
D'Ambrosio 1999	1/30	0/30		0.1 %	3.00 [0.13, 70.83]
Desai 2009	12/38	16/37		0.9 %	0.73 [0.40, 1.33]
Dietrich 1992	549/902	730/882		1.6 %	0.74 [0.69, 0.78]
Dignan 2001	37/101	58/99		1.3 %	0.63 [0.46, 0.85]
Engel 2001	5/12	3/12		0.4 %	1.67 [0.51, 5.46]

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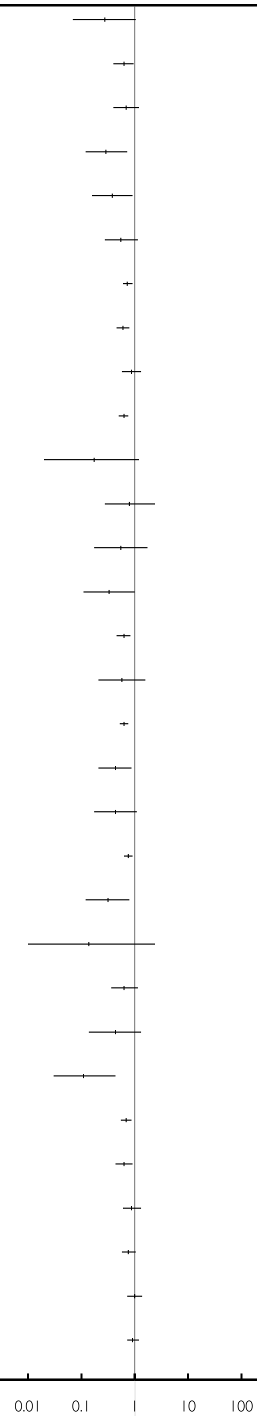
Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Englberger 2002b	2/15	7/14		0.3 %	0.27 [0.07, 1.07]
Fraedrich 1989	16/38	26/38		1.2 %	0.62 [0.40, 0.95]
Garcia-Huete 1997	13/39	20/41		1.0 %	0.68 [0.40, 1.18]
Gherli 1992	4/18	10/13		0.6 %	0.29 [0.12, 0.72]
Green 1995	6/48	12/36		0.6 %	0.38 [0.16, 0.90]
Greilich 2001	7/24	13/25		0.8 %	0.56 [0.27, 1.16]
Hayashida 1997	66/110	46/57		1.5 %	0.74 [0.61, 0.91]
Isetta 1993	55/140	46/70		1.4 %	0.60 [0.46, 0.78]
Jeserschek 2003	7/9	8/9		1.2 %	0.88 [0.58, 1.33]
Kalangos 1994	60/110	48/55		1.5 %	0.63 [0.51, 0.76]
Katzel 1998	1/12	6/12		0.2 %	0.17 [0.02, 1.18]
Kipfer 2003	4/15	5/15		0.4 %	0.80 [0.27, 2.41]
Klein 1998	4/36	6/29		0.4 %	0.54 [0.17, 1.72]
Kyriss 2001	3/18	10/20		0.4 %	0.33 [0.11, 1.02]
Lass 1995	25/51	37/47		1.3 %	0.62 [0.45, 0.85]
Laub 1994	4/16	7/16		0.5 %	0.57 [0.21, 1.58]
Lemmer 1996	173/487	87/157		1.5 %	0.64 [0.53, 0.77]
Lentschener 1997	8/48	19/49		0.8 %	0.43 [0.21, 0.89]
Lentschener 1999	5/35	12/37		0.6 %	0.44 [0.17, 1.12]
Levy 1995	109/188	49/65		1.5 %	0.77 [0.64, 0.93]
Li 2005	5/40	12/30		0.6 %	0.31 [0.12, 0.79]
Llau 1998	0/10	3/10		0.1 %	0.14 [0.01, 2.45]
Locatelli 1990	11/25	9/13		0.9 %	0.64 [0.36, 1.13]
Maccario 1994	5/61	6/32		0.4 %	0.44 [0.14, 1.32]
Menichetti 1996	2/24	18/24		0.3 %	0.11 [0.03, 0.43]
Mohr 1992	23/34	16/16		1.4 %	0.69 [0.54, 0.88]
Murkin 1994	16/29	22/25		1.3 %	0.63 [0.44, 0.90]
Murkin 1995	18/29	17/24		1.2 %	0.88 [0.60, 1.29]
Nurözler 2008	17/25	23/26		1.4 %	0.77 [0.57, 1.04]
Okita 1996	28/39	15/21		1.3 %	1.01 [0.72, 1.40]
Parvizi 2007	48/81	52/81		1.4 %	0.92 [0.72, 1.18]



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Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Penta de Peppo 1995	0/15	3/15		0.1 %	0.14 [0.01, 2.55]
Petsatodis 2006	17/25	25/25		1.4 %	0.69 [0.52, 0.90]
Pugh 1995	21/21	23/23		1.6 %	1.00 [0.92, 1.09]
Ray 1997	7/53	19/52		0.7 %	0.36 [0.17, 0.79]
Ray 1999	23/100	21/50		1.1 %	0.55 [0.34, 0.89]
Ray 2005	2/15	3/15		0.2 %	0.67 [0.13, 3.44]
Rocha 1994	22/28	26/28		1.5 %	0.85 [0.68, 1.05]
Rodrigus 1996	36/46	26/47		1.4 %	1.41 [1.05, 1.91]
Rossi 1997	1/21	4/22		0.2 %	0.26 [0.03, 2.16]
Santamaria 2000	6/56	11/28		0.6 %	0.27 [0.11, 0.66]
Speekenbrink 1995	12/15	11/15		1.2 %	1.09 [0.73, 1.62]
Tassani 2000	4/10	5/10		0.5 %	0.80 [0.30, 2.13]
Thorpe 1994	1/8	6/9		0.2 %	0.19 [0.03, 1.24]
Vedrinne 1992	14/30	23/30		1.2 %	0.61 [0.40, 0.94]
Wei 2006	6/36	8/40		0.5 %	0.83 [0.32, 2.17]
Subtotal (95% CI)	**4233**	**3256**		**56.5 %**	**0.69 [0.64, 0.75]**
Total events: 1866 (Aprotinin), 2105 (Control)					
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 179.31$, df = 62 (P<0.00001); I^2 =65%					
Test for overall effect: Z = 9.14 (P < 0.00001)					
3 Allocation concealment - No					
Alajmo 1989	9/22	8/12		0.9 %	0.61 [0.32, 1.17]
Alvarez 1995	5/49	7/51		0.5 %	0.74 [0.25, 2.19]
Amar 2003	11/23	13/24		1.0 %	0.88 [0.50, 1.55]
Baele 1992	35/58	45/57		1.4 %	0.76 [0.60, 0.98]
Casas 1995	12/47	29/51		1.0 %	0.45 [0.26, 0.77]
Diprose 2005	8/60	27/60		0.8 %	0.30 [0.15, 0.60]
Havel 1992	3/10	7/10		0.5 %	0.43 [0.15, 1.20]
Kuitunen 2005	11/20	12/20		1.0 %	0.92 [0.54, 1.56]
Later 2009	48/96	73/103		1.4 %	0.71 [0.56, 0.89]
Royston 1987	4/11	11/11		0.7 %	0.39 [0.19, 0.82]
Samama 2002	12/40	11/18		0.9 %	0.49 [0.27, 0.89]
Van der Linden 2005	17/37	27/38		1.2 %	0.65 [0.43, 0.97]

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Study or subgroup	Aprotinin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**473**	**455**		**11.2 %**	**0.63 [0.54, 0.75]**
Total events: 175 (Aprotinin), 270 (Control)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 15.50, df = 11 (P = 0.16); I^2 =29%					
Test for overall effect: Z = 5.22 (P < 0.00001)					
Total (95% CI)	**6259**	**4913**		**100.0 %**	**0.66 [0.60, 0.72]**
Total events: 2695 (Aprotinin), 3067 (Control)					
Heterogeneity: Tau^2 = 0.12; Chi^2 = 961.52, df = 107 (P<0.00001); I^2 =89%					
Test for overall effect: Z = 9.54 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.0, df = 2 (P = 0.0), I^2 =0.0%					

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Favours experimental Favours control

Analysis 1.7. Comparison 1 Aprotinin versus Control (Blood Transfusion & Blood Loss), Outcome 7 Units of Allogeneic Blood Transfused - Transfused Patients.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 1 Aprotinin versus Control (Blood Transfusion % Blood Loss)

Outcome: 7 Units of Allogeneic Blood Transfused - Transfused Patients

Study or subgroup	Aprotinin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Alderman 1998	152	0.99 (1.67)	213	1.92 (2.63)		-0.93 [-1.37, -0.49]
Basora 1999	23	2.11 (1.75)	20	2.4 (1.18)		-0.29 [-1.17, 0.59]
Bidstrup 1990	15	1.39 (0.52)	16	3.04 (1.98)		-1.65 [-2.66, -0.64]
Bidstrup 2000	13	3 (1.74)	23	2.86 (2.08)		0.14 [-1.13, 1.41]
Blauhut 1994	3	1.67 (0.58)	9	2.44 (1.13)		-0.77 [-1.76, 0.22]
Carrera 1994	42	4.25 (1.45)	50	5.51 (2.93)		-1.26 [-2.18, -0.34]
Casas 1995	12	2.54 (1.81)	29	3.25 (1.96)		-0.71 [-1.96, 0.54]
Colwell 2007	20	1.6 (0.5)	39	1.95 (0.89)		-0.35 [-0.71, 0.01]

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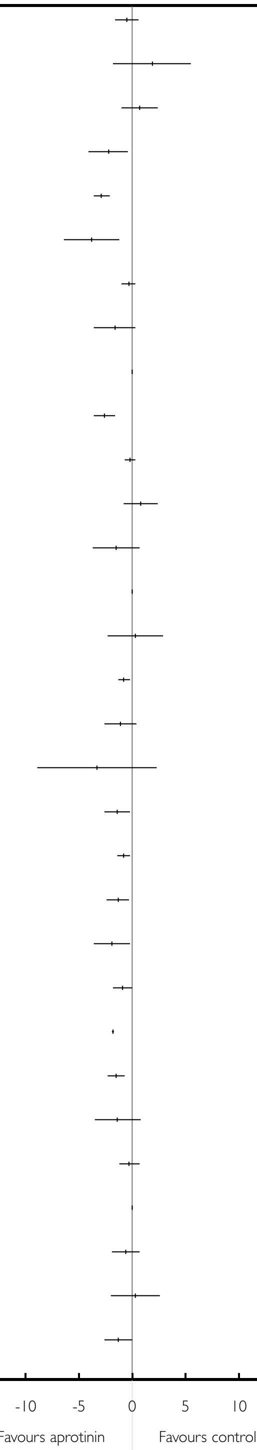
Study or subgroup	Aprotinin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Corbeau 1995	15	2.29 (1.49)	12	2.83 (1.45)		-0.54 [-1.65, 0.57]
Cosgrove 1992	55	7.07 (11.64)	44	5.22 (6.57)		1.85 [-1.79, 5.49]
D'Ambra 1996	73	3.39 (3.58)	31	2.68 (4.2)		0.71 [-0.98, 2.40]
Dietrich 1990	7	1.47 (1.26)	15	3.72 (3.21)		-2.25 [-4.12, -0.38]
Dietrich 1992	549	5.16 (6.17)	730	8.05 (7.67)		-2.89 [-3.65, -2.13]
Dietrich 1995	12	2.75 (1.86)	15	6.53 (4.66)		-3.78 [-6.36, -1.20]
Dignan 2001	37	2.18 (1.77)	58	2.51 (1.3)		-0.33 [-0.99, 0.33]
Diprose 2005	8	2.1 (1.42)	27	3.73 (4.47)		-1.63 [-3.58, 0.32]
Engel 2001	5	1.4 (0.55)	3	2 (0)		0.0 [0.0, 0.0]
Fraedrich 1989	16	1.92 (1.13)	26	4.56 (2.2)		-2.64 [-3.65, -1.63]
Harder 1991	30	2 (1.05)	29	2.21 (0.91)		-0.21 [-0.71, 0.29]
Hardy 1993	17	3.88 (2.58)	16	3.09 (2.18)		0.79 [-0.84, 2.42]
Jeserschek 2003	7	3.71 (1.5)	8	5.25 (2.76)		-1.54 [-3.75, 0.67]
Katzel 1998	1	1 (0)	6	2.67 (1.03)		0.0 [0.0, 0.0]
Klein 1998	4	3 (2)	6	2.67 (2.16)		0.33 [-2.28, 2.94]
Lemmer 1996	173	2.45 (0.82)	87	3.25 (2.56)		-0.80 [-1.35, -0.25]
Lemmer˙1 1994	28	2.91 (3.54)	35	4.02 (1.95)		-1.11 [-2.57, 0.35]
Lemmer˙2 1994	7	1.31 (7.26)	23	4.59 (3.99)		-3.28 [-8.90, 2.34]
Levy 1995	109	2 (2.15)	49	3.4 (4.03)		-1.40 [-2.60, -0.20]
Li 2005	5	0.35 (0.59)	8	1.14 (0.39)		-0.79 [-1.37, -0.21]
Mohr 1992	23	2.09 (1.02)	15	3.44 (1.97)		-1.35 [-2.43, -0.27]
Murkin 1994	16	3.4 (2.4)	22	5.3 (2.81)		-1.90 [-3.56, -0.24]
Murkin 1995	18	2 (0.85)	17	2.9 (1.65)		-0.90 [-1.78, -0.02]
Parvizi 2007	55	2.56 (0.27)	61	4.34 (0.37)		-1.78 [-1.90, -1.66]
Petsatodis 2006	17	2.29 (0.99)	25	3.8 (1.66)		-1.51 [-2.31, -0.71]
Speekenbrink 1995	12	2.91 (1.94)	11	4.27 (3.15)		-1.36 [-3.52, 0.80]
Speekenbrink 1996	55	1.64 (1.13)	29	1.91 (2.57)		-0.27 [-1.25, 0.71]
Stewart 2001	1	2 (0)	9	2.33 (1.12)		0.0 [0.0, 0.0]
Tabuchi 1994	10	2.66 (1.53)	12	3.26 (1.66)		-0.60 [-1.93, 0.73]
Tassani 2000	4	1.5 (1.58)	5	1.2 (1.9)		0.30 [-1.97, 2.57]
Van der Linden 2005	17	2.61 (1.07)	27	3.94 (3.15)		-1.33 [-2.62, -0.04]



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Study or subgroup	Aprotinin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Vedrinne 1992	14	1.78 (0.53)	23	2.43 (1.02)		-0.65 [-1.15, -0.15]
Total (95% CI)	**1680**		**1883**			**-0.98 [-1.29, -0.66]**

Heterogeneity: $Tau^2 = 0.55$; $Chi^2 = 197.82$, df = 36 (P<0.00001); I^2 =82%

Test for overall effect: Z = 6.15 (P < 0.00001)

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Favours aprotinin Favours control

Analysis 1.8. Comparison 1 Aprotinin versus Control (Blood Transfusion & Blood Loss), Outcome 8 Units of Allogeneic Blood Transfused - All Patients.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 1 Aprotinin versus Control (Blood Transfusion % Blood Loss)

Outcome: 8 Units of Allogeneic Blood Transfused - All Patients

Study or subgroup	Aprotinin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Alajmo 1989	22	0.71 (1.33)	11	1.36 (1.62)		-0.65 [-1.76, 0.46]
Alvarez 2001	26	1 (1.8)	29	1.9 (2)		-0.90 [-1.90, 0.10]
Amar 2003	23	1.8 (1.5)	24	1.8 (2.5)		0.0 [-1.17, 1.17]
Apostolakis 2008	29	0 (0)	30	0.03 (0.183)		0.0 [0.0, 0.0]
Basora 1999	23	2.11 (1.75)	212	2.29 (1.26)		-0.18 [-0.92, 0.56]
Bert 2008	25	0.44 (0.77)	25	1.3 (1.34)		-0.86 [-1.47, -0.25]
Bidstrup 1990	26	0.8 (0.8)	18	2.7 (2.1)		-1.90 [-2.92, -0.88]
Bidstrup 2000	30	1.3 (1.88)	30	2.19 (2.19)		-0.89 [-1.92, 0.14]
Blauhut 1994	14	0.36 (0.74)	14	1.57 (1.5)		-1.21 [-2.09, -0.33]
Carrera 1994	51	3.5 (2.1)	51	5.4 (3)		-1.90 [-2.91, -0.89]
Cicek 1996a	50	1.25 (1.22)	25	2.55 (1.09)		-1.30 [-1.84, -0.76]

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Favours Aprotinin Favours Control

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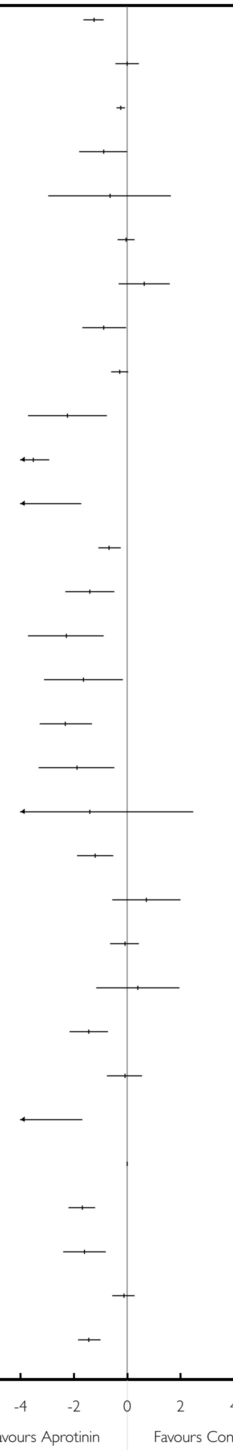
Study or subgroup	Aprotinin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Cicek 1996b	29	0.45 (0.5)	28	1.7 (0.9)		-1.25 [-1.63, -0.87]
Cicekcioglu 2006	24	0.91 (0.75)	20	0.91 (0.76)		0.0 [-0.45, 0.45]
Colwell 2007	175	0.18 (0.52)	177	0.43 (0.91)		-0.25 [-0.40, -0.10]
Corbeau 1995	43	0.8 (1.4)	20	1.7 (1.8)		-0.90 [-1.79, -0.01]
Cosgrove 1992	113	3.44 (8.83)	56	4.1 (6.2)		-0.66 [-2.96, 1.64]
Cvachovec 2001	20	1.58 (0.32)	22	1.63 (0.67)		-0.05 [-0.36, 0.26]
D'Ambra 1996	127	1.95 (3.19)	64	1.3 (3.2)		0.65 [-0.31, 1.61]
Defraigne 2000	100	2.13 (2.57)	100	3.01 (3.28)		-0.88 [-1.70, -0.06]
Desai 2009	38	0.39 (0.64)	37	0.66 (0.78)		-0.27 [-0.59, 0.05]
Dietrich 1990	19	0.54 (1.03)	20	2.79 (3.21)		-2.25 [-3.73, -0.77]
Dietrich 1992	902	3.14 (5.43)	882	6.66 (7.61)		-3.52 [-4.13, -2.91]
Dietrich 1995	15	2.2 (2.01)	15	6.5 (4.66)		-4.30 [-6.87, -1.73]
Dignan 2001	101	0.8 (1.5)	99	1.47 (1.59)		-0.67 [-1.10, -0.24]
Diprose 2005	60	0.28 (0.87)	60	1.68 (3.51)		-1.40 [-2.32, -0.48]
Ehrlich 1998	25	1.2 (2)	25	3.5 (3)		-2.30 [-3.71, -0.89]
Fauli 2005	40	1.55 (1.4)	20	3.2 (3.2)		-1.65 [-3.12, -0.18]
Fraedrich 1989	38	0.81 (1.2)	38	3.12 (2.81)		-2.31 [-3.28, -1.34]
Garcia-Enguita 1998	15	2.3 (2.1)	15	4.2 (1.9)		-1.90 [-3.33, -0.47]
Garcia-Huete 1997	39	13 (8)	41	14.4 (9.7)		-1.40 [-5.29, 2.49]
Golanski 2000	29	1.7 (1.5)	24	2.9 (1)		-1.20 [-1.88, -0.52]
Greilich 2009	26	2.5 (2.7)	27	1.8 (2)		0.70 [-0.58, 1.98]
Harder 1991	40	1.5 (1.26)	40	1.6 (1.26)		-0.10 [-0.65, 0.45]
Hardy 1993	22	3 (2.8)	19	2.6 (2.3)		0.40 [-1.16, 1.96]
Hayashida 1997	110	2.85 (2.22)	57	4.3 (2.26)		-1.45 [-2.17, -0.73]
Hayes 1996	20	1.1 (0.9)	20	1.2 (1.2)		-0.10 [-0.76, 0.56]
Hei 2005	20	2.94 (1.72)	20	7.04 (5.28)		-4.10 [-6.53, -1.67]
Hendrice 1995	12	0 (0)	14	1.35 (0.33)		0.0 [0.0, 0.0]
Hill 1998	10	1.1 (0.47)	10	2.8 (0.66)		-1.70 [-2.20, -1.20]
Janssens 1994	20	1.8 (1.24)	20	3.4 (1.31)		-1.60 [-2.39, -0.81]
Kahveci 1996	14	0.28 (0.45)	14	0.42 (0.64)		-0.14 [-0.55, 0.27]
Kalangos 1994	110	2.87 (0.88)	55	4.3 (1.5)		-1.43 [-1.86, -1.00]



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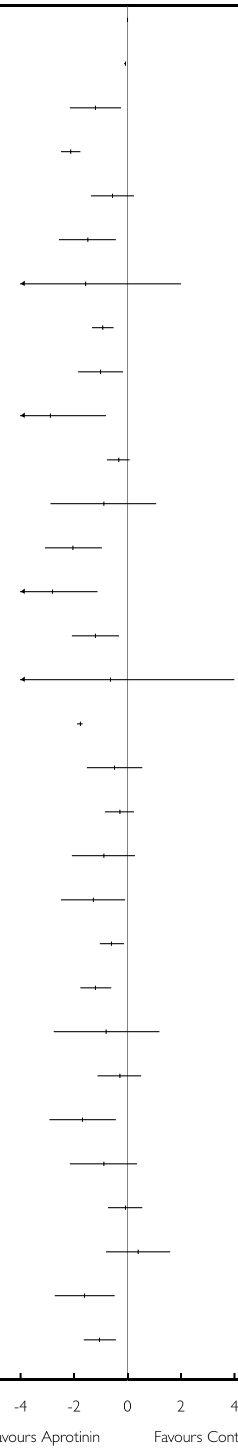
Study or subgroup	Aprotinin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Katzel 1998	12	1 (0)	12	1.3 (1.56)		0.0 [0.0, 0.0]
Koster 2004	100	0.1 (0.05)	100	0.2 (0.1)		-0.10 [-0.12, -0.08]
Kuepper 2003	60	2.1 (1.7)	59	3.3 (3.3)		-1.20 [-2.15, -0.25]
Kunt 2005	40	1.2 (0.52)	46	3.33 (1.13)		-2.13 [-2.49, -1.77]
Laub 1994	16	0.42 (0.68)	16	0.99 (1.47)		-0.57 [-1.36, 0.22]
Lavee 1993	15	2.1 (1.1)	15	3.6 (1.8)		-1.50 [-2.57, -0.43]
Leijdekkers 2006	16	0.44 (0.7)	19	2 (7.9)		-1.56 [-5.13, 2.01]
Lemmer 1996	487	0.87 (1.27)	157	1.8 (2.5)		-0.93 [-1.34, -0.52]
Lemmer˙1 1994	74	1.1 (2.58)	67	2.1 (2.46)		-1.00 [-1.83, -0.17]
Lemmer˙2 1994	23	0.4 (3.84)	32	3.3 (3.96)		-2.90 [-4.98, -0.82]
Maccario 1994	61	0.17 (0.56)	32	0.5 (1.14)		-0.33 [-0.75, 0.09]
Marcel 1996	21	2.1 (2)	23	3 (4.4)		-0.90 [-2.89, 1.09]
Mohr 1992	34	1.41 (1.21)	16	3.44 (1.97)		-2.03 [-3.08, -0.98]
Murkin 1994	29	1.9 (3.23)	25	4.7 (3)		-2.80 [-4.46, -1.14]
Nurözler 2008	25	1.7 (1.4)	26	2.9 (1.8)		-1.20 [-2.08, -0.32]
Okita 1996	39	11.64 (9.07)	21	12.27 (8.5)		-0.63 [-5.25, 3.99]
Parvizi 2007	81	2.56 (0.27)	81	4.34 (0.37)		-1.78 [-1.88, -1.68]
Poston 2006	29	1.8 (2.1)	31	2.3 (2)		-0.50 [-1.54, 0.54]
Prendergast˙1 1996	18	0.2 (0.5)	20	0.5 (1.1)		-0.30 [-0.83, 0.23]
Prendergast˙2 1996	16	1.3 (1.2)	16	2.2 (2.1)		-0.90 [-2.09, 0.29]
Rhydderch 1993	20	2 (1.7)	23	3.3 (2.3)		-1.30 [-2.50, -0.10]
Schmartz 2003	40	1.62 (0.68)	20	2.21 (0.91)		-0.59 [-1.04, -0.14]
Schweizer 2000	26	1.4 (0.7)	28	2.6 (1.4)		-1.20 [-1.78, -0.62]
Speekenbrink 1995	15	2.33 (2.1)	15	3.13 (3.3)		-0.80 [-2.78, 1.18]
Speekenbrink 1996	75	1.2 (1.21)	37	1.5 (2.4)		-0.30 [-1.12, 0.52]
Stammers 1997	8	0.58 (1.19)	12	2.27 (1.67)		-1.69 [-2.94, -0.44]
Tabuchi 1994	19	1.4 (1.74)	17	2.3 (2.06)		-0.90 [-2.15, 0.35]
Turkoz 2001	10	1.9 (0.5)	10	2 (0.9)		-0.10 [-0.74, 0.54]
Utada 1997	11	3.2 (1.4)	10	2.8 (1.4)		0.40 [-0.80, 1.60]
Van der Linden 2005	37	1.2 (1.5)	38	2.8 (3.2)		-1.60 [-2.73, -0.47]
Vedrinne 1992	30	0.83 (0.97)	30	1.86 (1.37)		-1.03 [-1.63, -0.43]



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Study or subgroup	Aprotinin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Wei 2006	36	1.67 (0.56)	40	1.33 (0)		0.0 [0.0, 0.0]
Total (95% CI)	**4198**		**3622**			**-1.02 [-1.26, -0.79]**
Heterogeneity: Tau^2 = 0.77; Chi^2 = 1627.35, df = 69 (P<0.00001); I^2 =96%						
Test for overall effect: Z = 8.41 (P < 0.00001)						

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Favours Aprotinin Favours Control

Analysis 1.9. Comparison 1 Aprotinin versus Control (Blood Transfusion & Blood Loss), Outcome 9 Blood loss - Intra-operative.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 1 Aprotinin versus Control (Blood Transfusion % Blood Loss)

Outcome: 9 Blood loss - Intra-operative

Study or subgroup	Aprotinin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Cardiac surgery							
Desai 2009	38	794 (465)	37	1034 (659)		6.7 %	-240.00 [-498.74, 18.74]
Dietrich 1990	19	363 (159)	20	636 (322)		10.4 %	-273.00 [-431.20, -114.80]
Fauli 2005	40	958.5 (385.12)	20	829 (421)		8.0 %	129.50 [-90.24, 349.24]
Harmon 2004	17	568 (355)	18	840 (296)		8.1 %	-272.00 [-489.20, -54.80]
Hendrice 1995	12	225 (121)	14	401 (207)		11.8 %	-176.00 [-304.24, -47.76]
Koster 2004	100	261 (107)	100	355 (127)		15.3 %	-94.00 [-126.55, -61.45]
Leijdekkers 2006	16	2362 (1340)	19	2466 (1370)		0.9 %	-104.00 [-1004.32, 796.32]
Subtotal (95% CI)	**242**		**228**			**61.1 %**	**-148.18 [-240.21, -56.14]**
Heterogeneity: Tau^2 = 6875.87; Chi^2 = 13.63, df = 6 (P = 0.03); I^2 =56%							
Test for overall effect: Z = 3.16 (P = 0.0016)							
2 Orthopaedic surgery							
Amar 2003	23	1200 (1000)	24	1000 (900)		2.3 %	200.00 [-344.67, 744.67]

-1000 -500 0 500 1000

Favours Aprotinin Favours Control

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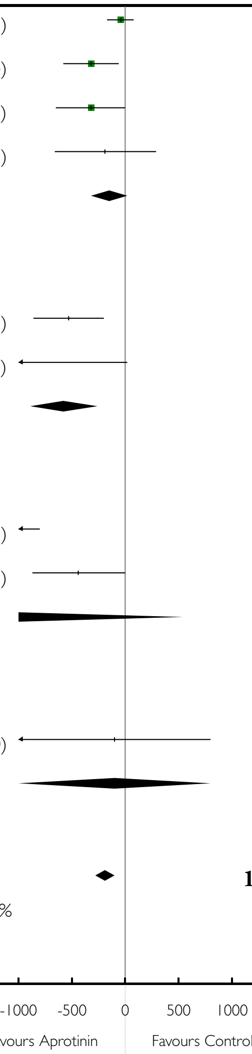
Study or subgroup	Aprotinin N	Aprotinin Mean(SD)	Control N	Control Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hayes 1996	20	725 (150)	20	768 (235)		12.0 %	-43.00 [-165.18, 79.18]
Janssens 1994	20	793 (332)	20	1113 (494)		6.6 %	-320.00 [-580.85, -59.15]
Murkin 1995	29	996 (436.2)	24	1318 (710.35)		5.0 %	-322.00 [-647.53, 3.53]
Utada 1997	11	1573 (462)	10	1760 (623)		2.9 %	-187.00 [-659.90, 285.90]
Subtotal (95% CI)	**103**		**98**			**28.8 %**	**-151.05 [-317.63, 15.52]**
Heterogeneity: $Tau^2 = 13580.14$; $Chi^2 = 6.62$, df = 4 (P = 0.16); I^2 =40%							
Test for overall effect: Z = 1.78 (P = 0.076)							
3 Thoracic surgery							
Katzel 1998	12	324 (159)	12	856 (563)		4.9 %	-532.00 [-863.00, -201.00]
Norman 2009	8	769 (630.4)	8	1832 (1436.39)		0.6 %	-1063.00 [-2149.99, 23.99]
Subtotal (95% CI)	**20**		**20**			**5.5 %**	**-577.06 [-893.71, -260.41]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.84$, df = 1 (P = 0.36); I^2 =0.0%							
Test for overall effect: Z = 3.57 (P = 0.00035)							
4 Liver surgery							
Hei 2005	20	3107 (1281)	20	5342 (3013)		0.4 %	-2235.00 [-3669.87, -800.13]
Lentschener 1997	48	1217 (966)	49	1653 (1221)		3.2 %	-436.00 [-873.67, 1.67]
Subtotal (95% CI)	**68**		**69**			**3.6 %**	**-1200.40 [-2943.39, 542.59]**
Heterogeneity: $Tau^2 = 1325289.21$; $Chi^2 = 5.52$, df = 1 (P = 0.02); I^2 =82%							
Test for overall effect: Z = 1.35 (P = 0.18)							
5 Vascular surgery							
Leijdekkers 2006	16	2362 (1340)	19	2466 (1370)		0.9 %	-104.00 [-1004.32, 796.32]
Subtotal (95% CI)	**16**		**19**			**0.9 %**	**-104.00 [-1004.32, 796.32]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.23 (P = 0.82)							
Total (95% CI)	**449**		**434**			**100.0 %**	**-191.87 [-280.45, -103.28]**
Heterogeneity: $Tau^2 = 13085.01$; $Chi^2 = 40.04$, df = 16 (P = 0.00077); I^2 =60%							
Test for overall effect: Z = 4.24 (P = 0.000022)							



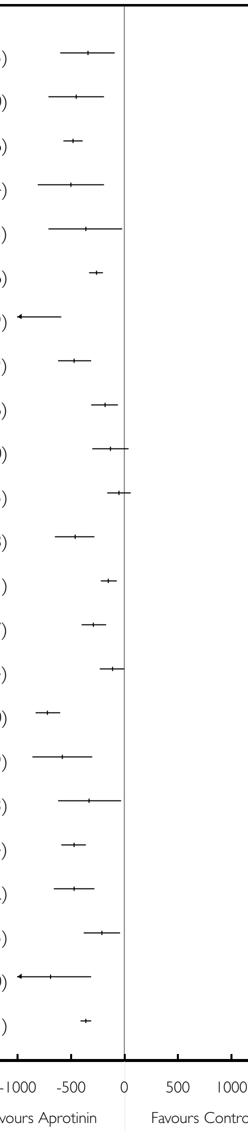
Analysis 1.10. Comparison 1 Aprotinin versus Control (Blood Transfusion & Blood Loss), Outcome 10 Blood loss - Post-operative.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 1 Aprotinin versus Control (Blood Transfusion % Blood Loss)

Outcome: 10 Blood loss - Post-operative

Study or subgroup	Aprotinin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Cardiac surgery							
Alajmo 1989	22	486 (220)	11	830 (405)		0.9 %	-344.00 [-600.38, -87.62]
Alvarez 2001	26	890 (430)	29	1340 (560)		0.9 %	-450.00 [-712.41, -187.59]
Asimakopoulos 2000	8	371 (62)	10	848 (126)		1.6 %	-477.00 [-566.13, -387.87]
Baele 1992	58	699 (429)	57	1198 (1124)		0.8 %	-499.00 [-810.98, -187.02]
Basora 1999	36	498.15 (372.58)	21	863.1 (755.5)		0.7 %	-364.95 [-710.24, -19.66]
Bidstrup 1989	40	309 (133)	37	573 (166)		1.6 %	-264.00 [-331.53, -196.47]
Bidstrup 1990	26	352 (138)	18	1393 (979)		0.5 %	-1041.00 [-1496.37, -585.63]
Bidstrup 2000	30	368.7 (164.3)	30	837.3 (404.9)		1.3 %	-468.60 [-624.96, -312.24]
Blauhut 1994	14	269 (142.18)	14	453 (192.56)		1.4 %	-184.00 [-309.38, -58.62]
Boldt 1991	10	260 (160)	10	390 (230)		1.2 %	-130.00 [-303.65, 43.65]
Boldt 1994	20	465 (195)	20	515 (155)		1.5 %	-50.00 [-159.17, 59.17]
Carrera 1994	51	431.8 (343)	51	895.2 (568)		1.2 %	-463.40 [-645.51, -281.29]
Cicek 1996a	50	265 (165.68)	25	411 (151)		1.6 %	-146.00 [-220.92, -71.08]
Cicek 1996b	29	410.5 (174.8)	28	696.2 (247.7)		1.5 %	-285.70 [-397.35, -174.05]
Cicekcioglu 2006	24	547.8 (170.6)	20	660.6 (213.4)		1.5 %	-112.80 [-228.58, 2.98]
Cohen 1998	56	780 (262)	59	1497 (360)		1.5 %	-717.00 [-831.66, -602.34]
Corbeau 1995	43	834 (448)	20	1416 (559)		0.9 %	-582.00 [-861.19, -302.81]
Cosgrove 1992	113	792.35 (1269.74)	56	1121 (683)		0.8 %	-328.65 [-623.28, -34.02]
Defraigne 2000	100	587 (328.82)	100	1060.5 (503.84)		1.5 %	-473.50 [-591.42, -355.58]
Deleuze 1991	30	380 (125)	30	852 (522)		1.2 %	-472.00 [-664.07, -279.93]
Desai 2009	38	603 (330)	37	810 (415)		1.3 %	-207.00 [-376.97, -37.03]
Dietrich 1990	19	738 (411)	20	1431 (760)		0.6 %	-693.00 [-1073.91, -312.09]
Dietrich 1992	902	678 (419)	882	1037 (671)		1.6 %	-359.00 [-411.04, -306.96]



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Study or subgroup	Aprotinin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Dietrich 1995	15	597 (312.4)	15	1496 (785.51)		0.5 %	-899.00 [-1326.80, -471.20]
Dignan 2001	99	455 (298.5)	99	689 (298.5)		1.6 %	-234.00 [-317.16, -150.84]
Englberger 2002b	15	850 (231)	14	1227 (582)		0.7 %	-377.00 [-703.51, -50.49]
Fauli 2005	40	526 (675.83)	20	1157 (783)		0.6 %	-631.00 [-1033.02, -228.98]
Feindt 1994	10	279 (29)	10	664 (108)		1.6 %	-385.00 [-454.31, -315.69]
Fraedrich 1989	38	652 (382)	38	1204 (705)		1.0 %	-552.00 [-806.94, -297.06]
Gherli 1992	18	280 (145.09)	13	660 (185)		1.4 %	-380.00 [-500.86, -259.14]
Golanski 2000	29	660 (221)	24	1215 (587)		1.0 %	-555.00 [-803.24, -306.76]
Greilich 2009	26	685 (505)	27	1002 (627)		0.8 %	-317.00 [-622.96, -11.04]
Hardy 1993	22	565 (589)	19	631 (423)		0.8 %	-66.00 [-377.05, 245.05]
Harmon 2004	17	520 (287)	18	769 (303)		1.2 %	-249.00 [-444.46, -53.54]
Hayashida 1997	110	391.5 (167.32)	57	535 (294.44)		1.6 %	-143.50 [-226.09, -60.91]
Hendrice 1995	12	328 (84)	14	699 (261)		1.4 %	-371.00 [-515.74, -226.26]
Kalangos 1994	110	752 (159.15)	55	1378 (375)		1.5 %	-626.00 [-729.47, -522.53]
Kipfer 2003	15	964 (355)	15	1193 (526)		0.8 %	-229.00 [-550.14, 92.14]
Klein 1998	36	597 (266)	29	772 (299)		1.4 %	-175.00 [-314.26, -35.74]
Koster 2004	100	564 (425)	100	744 (497)		1.4 %	-180.00 [-308.17, -51.83]
Kuepper 2003	60	608 (336)	59	1115 (1106)		0.8 %	-507.00 [-801.74, -212.26]
Kuitunen 2005	20	540 (259.4)	20	995 (281.7)		1.3 %	-455.00 [-622.83, -287.17]
Kunt 2005	40	188 (51.5)	46	818 (243.8)		1.6 %	-630.00 [-702.24, -557.76]
Laub 1994	16	722 (304)	16	1540 (800)		0.5 %	-818.00 [-1237.34, -398.66]
Lavee 1993	15	487 (121)	15	752 (404)		1.1 %	-265.00 [-478.42, -51.58]
Lemmer 1996	487	831.52 (650.03)	157	1286 (651.56)		1.5 %	-454.48 [-571.61, -337.35]
Lemmer`1 1994	74	855 (671)	67	1503 (671.2)		1.1 %	-648.00 [-869.82, -426.18]
Lemmer`2 1994	23	1225 (1563.44)	32	1979 (1600.88)		0.2 %	-754.00 [-1600.11, 92.11]
Levy 1995	188	1132.02 (1083.18)	65	1700 (1128.72)		0.8 %	-567.98 [-883.05, -252.91]
Li 2005	40	304.3 (105.64)	30	610.67 (193.37)		1.6 %	-306.37 [-382.92, -229.82]
Locatelli 1990	25	323.55 (136.42)	13	524.6 (147.47)		1.5 %	-201.05 [-297.41, -104.69]
Maccario 1994	61	387.21 (169.4)	32	621 (255.87)		1.5 %	-233.79 [-332.11, -135.47]
Menichetti 1996	24	298 (140)	24	811 (600)		1.0 %	-513.00 [-759.49, -266.51]
Misfeld 1998	14	290 (110)	14	760 (320)		1.2 %	-470.00 [-647.25, -292.75]

-1000 -500 0 500 1000

Favours Aprotinin Favours Control

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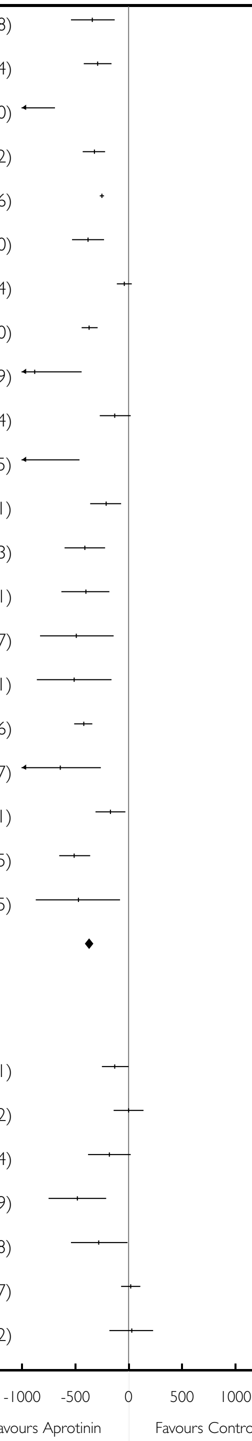
Study or subgroup	Aprotinin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Mohr 1992	34	442 (129.14)	16	780 (408)		1.1 %	-338.00 [-542.57, -133.43]
Moran 2000	24	162 (123.17)	14	450 (224)		1.4 %	-288.00 [-415.26, -160.74]
Murkin 1994	29	1409.7 (1251.51)	25	2765.8 (1240)		0.3 %	-1356.10 [-2022.24, -689.96]
Nurözler 2008	25	423 (178)	26	748 (212)		1.5 %	-325.00 [-432.28, -217.72]
Parvizi 2007	81	555 (56)	81	805 (76)		1.7 %	-250.00 [-270.56, -229.44]
Penta de Peppo 1995	15	344 (106)	15	724 (280)		1.3 %	-380.00 [-531.51, -228.49]
Prendergast 1 1996	18	510 (105)	20	550 (124)		1.6 %	-40.00 [-112.84, 32.84]
Prendergast 2 1996	16	526 (95)	16	894 (120)		1.6 %	-368.00 [-442.99, -293.01]
Rodrigus 1996	45	1051 (944)	46	1933 (1189)		0.5 %	-882.00 [-1322.60, -441.40]
Rossi 1997	21	446 (155)	22	573 (304)		1.4 %	-127.00 [-270.29, 16.29]
Royston 1987	11	286 (159.2)	11	1509 (1286.85)		0.2 %	-1223.00 [-1989.26, -456.74]
Santamaria 2000	56	558 (301.64)	28	772 (336.1)		1.3 %	-214.00 [-361.44, -66.56]
Schweizer 2000	26	775 (314)	28	1185 (403)		1.2 %	-410.00 [-601.96, -218.04]
Speekenbrink 1995	15	270 (174)	15	674 (411)		1.1 %	-404.00 [-629.86, -178.14]
Speekenbrink 1996	75	581.95 (381.94)	37	1068 (1047)		0.7 %	-486.05 [-834.31, -137.79]
Stammers 1997	8	435.1 (169.6)	12	944 (585.1)		0.7 %	-508.90 [-860.19, -157.61]
Tabuchi 1994	19	416 (67)	17	841 (156)		1.6 %	-425.00 [-505.04, -344.96]
Tassani 2000	10	648 (202.4)	10	1284 (578.7)		0.6 %	-636.00 [-1015.98, -256.02]
Turkoz 2001	10	510 (139.14)	10	680 (183.41)		1.4 %	-170.00 [-312.69, -27.31]
Vedrinne 1992	30	328 (153.36)	30	834 (372.45)		1.4 %	-506.00 [-650.13, -361.87]
Wendel 1995	20	878.9 (438)	18	1353.6 (746.5)		0.6 %	-474.70 [-869.38, -80.02]
Subtotal (95% CI)	**4132**		**3239**			**85.5 %**	**-369.62 [-408.95, -330.29]**
Heterogeneity: $Tau^2 = 19799.20$; $Chi^2 = 513.91$, df = 74 ($P<0.00001$); $I^2 = 86\%$							
Test for overall effect: Z = 18.42 ($P < 0.00001$)							
2 Orthopaedic surgery							
Cvachovec 2001	20	379 (162)	22	505 (251)		1.4 %	-126.00 [-252.65, 0.65]
Hayes 1996	20	432 (270)	20	432 (162)		1.4 %	0.0 [-138.00, 138.00]
Janssens 1994	20	653 (306)	20	830 (334)		1.2 %	-177.00 [-375.52, 21.52]
Lentschener 1999	35	812 (411)	37	1295 (719)		0.9 %	-483.00 [-751.72, -214.28]
Murkin 1995	29	502 (333.88)	24	778 (578.08)		0.9 %	-276.00 [-537.26, -14.74]
Petsatodis 2006	25	451.2 (161.9)	25	434 (169.7)		1.5 %	17.20 [-74.74, 109.14]
Utada 1997	11	412 (243)	10	387 (242)		1.1 %	25.00 [-182.65, 232.65]



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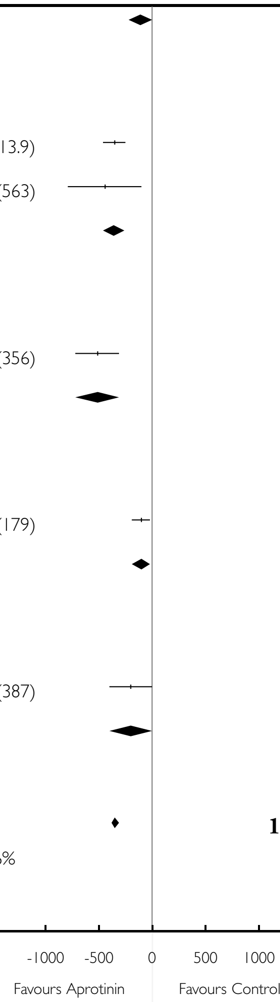
Study or subgroup	Aprotinin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Subtotal (95% CI)	**160**		**158**			**8.5 %**	**-113.58 [-223.69, -3.46]**
Heterogeneity: $Tau^2 = 13702.50$; $Chi^2 = 18.56$, df = 6 (P = 0.005); $I^2 = 68\%$							
Test for overall effect: Z = 2.02 (P = 0.043)							
3 Thoracic surgery							
Apostolakis 2008	29	412.6 (199.2)	30	764.3 (213.9)		1.5 %	-351.70 [-457.13, -246.27]
Katzel 1998	12	402 (236)	12	843 (563)		0.7 %	-441.00 [-786.40, -95.60]
Subtotal (95% CI)	**41**		**42**			**2.2 %**	**-359.31 [-460.15, -258.48]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.23$, df = 1 (P = 0.63); $I^2 = 0.0\%$							
Test for overall effect: Z = 6.98 (P < 0.00001)							
4 Orthognathic surgery							
Stewart 2001	15	473 (190)	15	986 (356)		1.1 %	-513.00 [-717.21, -308.79]
Subtotal (95% CI)	**15**		**15**			**1.1 %**	**-513.00 [-717.21, -308.79]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.92 (P < 0.00001)							
5 Liver surgery							
Marcel 1996	21	748 (120)	23	853 (179)		1.6 %	-105.00 [-194.36, -15.64]
Subtotal (95% CI)	**21**		**23**			**1.6 %**	**-105.00 [-194.36, -15.64]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.30 (P = 0.021)							
6 Vascular surgery							
Ehrlich 1998	25	717 (340)	25	920 (387)		1.1 %	-203.00 [-404.93, -1.07]
Subtotal (95% CI)	**25**		**25**			**1.1 %**	**-203.00 [-404.93, -1.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.97 (P = 0.049)							
Total (95% CI)	**4394**		**3502**			**100.0 %**	**-345.88 [-383.47, -308.29]**
Heterogeneity: $Tau^2 = 21627.05$; $Chi^2 = 620.49$, df = 86 (P<0.00001); $I^2 = 86\%$							
Test for overall effect: Z = 18.03 (P < 0.00001)							



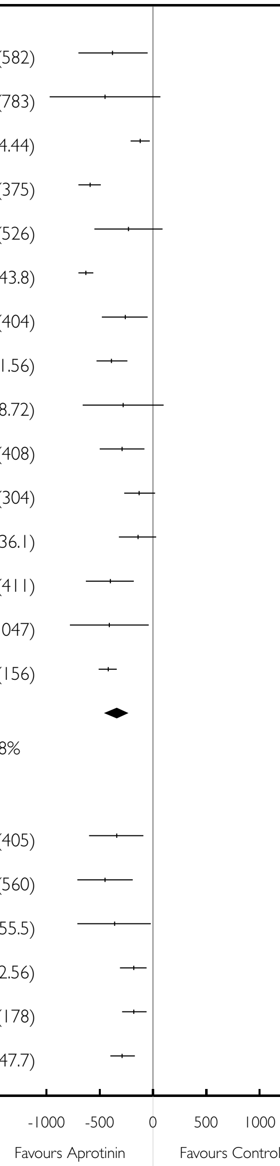
Analysis 1.11. Comparison 1 Aprotinin versus Control (Blood Transfusion & Blood Loss), Outcome 11 Blood loss - Post-operative - Dose (Cardiac Surgery).

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 1 Aprotinin versus Control (Blood Transfusion % Blood Loss)

Outcome: 11 Blood loss - Post-operative - Dose (Cardiac Surgery)

Study or subgroup	Aprotinin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Prime Dose							
Englberger 2002b	15	850 (231)	14	1227 (582)		0.7 %	-377.00 [-703.51, -50.49]
Fauli 2005	20	703 (894)	20	1157 (783)		0.4 %	-454.00 [-974.84, 66.84]
Hayashida 1997	55	415 (200.2)	57	535 (294.44)		1.5 %	-120.00 [-212.96, -27.04]
Kalangos 1994	55	784 (166)	55	1378 (375)		1.5 %	-594.00 [-702.38, -485.62]
Kipfer 2003	15	964 (355)	15	1193 (526)		0.7 %	-229.00 [-550.14, 92.14]
Kunt 2005	40	188 (51.5)	46	818 (243.8)		1.6 %	-630.00 [-702.24, -557.76]
Lavee 1993	15	487 (121)	15	752 (404)		1.1 %	-265.00 [-478.42, -51.58]
Lemmer 1996	159	899 (655.7)	157	1286 (651.56)		1.3 %	-387.00 [-531.13, -242.87]
Levy 1995	68	1420 (1088.5)	65	1700 (1128.72)		0.6 %	-280.00 [-657.13, 97.13]
Mohr 1992	17	487 (135)	16	780 (408)		1.1 %	-293.00 [-502.96, -83.04]
Rossi 1997	21	446 (155)	22	573 (304)		1.3 %	-127.00 [-270.29, 16.29]
Santamaria 2000	28	629 (338.8)	28	772 (336.1)		1.2 %	-143.00 [-319.77, 33.77]
Speekenbrink 1995	15	270 (174)	15	674 (411)		1.0 %	-404.00 [-629.86, -178.14]
Speekenbrink 1996	37	662 (467)	37	1068 (1047)		0.6 %	-406.00 [-775.40, -36.60]
Tabuchi 1994	19	416 (67)	17	841 (156)		1.6 %	-425.00 [-505.04, -344.96]
Subtotal (95% CI)	**579**		**579**			**16.1 %**	**-343.08 [-458.13, -228.04]**
Heterogeneity: $Tau^2 = 38644.59$; $Chi^2 = 112.62$, df = 14 (P<0.00001); I^2 =88%							
Test for overall effect: Z = 5.84 (P < 0.00001)							
2 Low Dose							
Alajmo 1989	22	486 (220)	11	830 (405)		0.9 %	-344.00 [-600.38, -87.62]
Alvarez 2001	26	890 (430)	29	1340 (560)		0.9 %	-450.00 [-712.41, -187.59]
Basora 1999	36	498.15 (372.58)	21	863.1 (755.5)		0.7 %	-364.95 [-710.24, -19.66]
Blauhut 1994	14	269 (142.18)	14	453 (192.56)		1.4 %	-184.00 [-309.38, -58.62]
Cicek 1996a	25	325 (237)	25	502 (178)		1.4 %	-177.00 [-293.19, -60.81]
Cicek 1996b	29	410.5 (174.8)	28	696.2 (247.7)		1.4 %	-285.70 [-397.35, -174.05]



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Study or subgroup	Aprotinin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Cicekcioglu 2006	24	547.8 (170.6)	20	660.6 (213.4)		1.4 %	-112.80 [-228.58, 2.98]
Cosgrove 1992	56	866 (1636)	56	1121 (683)		0.4 %	-255.00 [-719.33, 209.33]
Dignan 2001	99	455 (298.5)	99	689 (298.5)		1.5 %	-234.00 [-317.16, -150.84]
Gherli 1992	9	270 (150)	13	660 (185)		1.3 %	-390.00 [-530.42, -249.58]
Golanski 2000	29	660 (221)	24	1215 (587)		0.9 %	-555.00 [-803.24, -306.76]
Hardy 1993	22	565 (589)	19	631 (423)		0.7 %	-66.00 [-377.05, 245.05]
Hayashida 1997	55	368 (126.1)	57	535 (294.44)		1.5 %	-167.00 [-250.39, -83.61]
Koster 2004	100	564 (425)	100	744 (497)		1.4 %	-180.00 [-308.17, -51.83]
Kuepper 2003	60	608 (336)	59	1115 (1106)		0.8 %	-507.00 [-801.74, -212.26]
Lemmer 1996	168	811 (661.04)	157	1286 (651.56)		1.3 %	-475.00 [-617.76, -332.24]
Levy 1995	59	1040 (1098.4)	65	1700 (1128.72)		0.6 %	-660.00 [-1052.23, -267.77]
Locatelli 1990	13	399.2 (170.2)	13	524.6 (147.47)		1.4 %	-125.40 [-247.82, -2.98]
Maccario 1994	29	372 (159)	32	621 (255.87)		1.5 %	-249.00 [-354.87, -143.13]
Misfeld 1998	14	290 (110)	14	760 (320)		1.2 %	-470.00 [-647.25, -292.75]
Moran 2000	12	182 (144)	14	450 (224)		1.3 %	-268.00 [-410.85, -125.15]
Nurözler 2008	25	423 (178)	26	748 (212)		1.5 %	-325.00 [-432.28, -217.72]
Parvizi 2007	81	555 (56)	81	805 (76)		1.7 %	-250.00 [-270.56, -229.44]
Schweizer 2000	26	775 (314)	28	1185 (403)		1.1 %	-410.00 [-601.96, -218.04]
Subtotal (95% CI)	**1033**		**1005**			**28.4 %**	**-274.58 [-316.48, -232.67]**
Heterogeneity: Tau² = 4792.81; Chi² = 58.71, df = 23 (P = 0.00006); I² =61%							
Test for overall effect: Z = 12.84 (P < 0.00001)							
3 High Dose							
Asimakopoulos 2000	8	371 (62)	10	848 (126)		1.5 %	-477.00 [-566.13, -387.87]
Baele 1992	58	699 (429)	57	1198 (1124)		0.7 %	-499.00 [-810.98, -187.02]
Bidstrup 1989	40	309 (133)	37	573 (166)		1.6 %	-264.00 [-331.53, -196.47]
Bidstrup 1990	26	352 (138)	18	1393 (979)		0.5 %	-1041.00 [-1496.37, -585.63]
Bidstrup 2000	30	368.7 (164.3)	30	837.3 (404.9)		1.3 %	-468.60 [-624.96, -312.24]
Boldt 1991	10	260 (160)	10	390 (230)		1.2 %	-130.00 [-303.65, 43.65]
Boldt 1994	20	465 (195)	20	515 (155)		1.5 %	-50.00 [-159.17, 59.17]
Carrera 1994	51	431.8 (343)	51	895.2 (568)		1.2 %	-463.40 [-645.51, -281.29]
Cicek 1996a	25	295 (161)	25	502 (178)		1.5 %	-207.00 [-301.08, -112.92]
Cohen 1998	56	780 (262)	59	1497 (360)		1.4 %	-717.00 [-831.66, -602.34]

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Favours Aprotinin Favours Control

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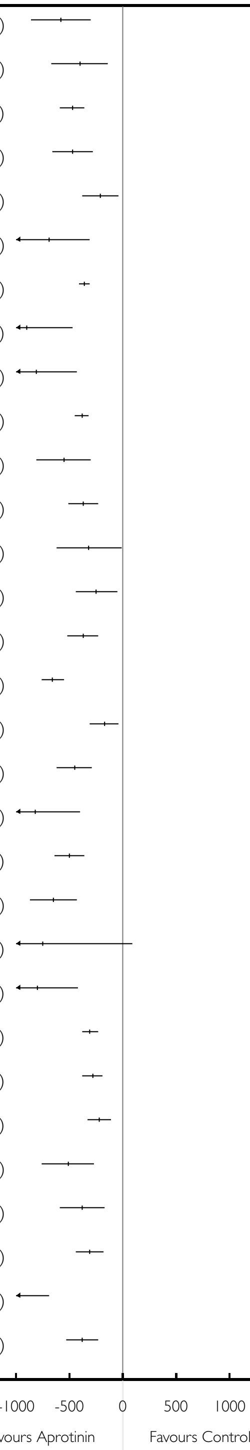
Study or subgroup	Aprotinin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Corbeau 1995	43	834 (448)	20	1416 (559)		0.8 %	-582.00 [-861.19, -302.81]
Cosgrove 1992	57	720 (753)	56	1121 (683)		0.9 %	-401.00 [-665.98, -136.02]
Defraigne 2000	100	587 (328.82)	100	1060.5 (503.84)		1.4 %	-473.50 [-591.42, -355.58]
Deleuze 1991	30	380 (125)	30	852 (522)		1.1 %	-472.00 [-664.07, -279.93]
Desai 2009	38	603 (330)	37	810 (415)		1.2 %	-207.00 [-376.97, -37.03]
Dietrich 1990	19	738 (411)	20	1431 (760)		0.6 %	-693.00 [-1073.91, -312.09]
Dietrich 1992	902	678 (419)	882	1037 (671)		1.6 %	-359.00 [-411.04, -306.96]
Dietrich 1995	15	597 (312.4)	15	1496 (785.51)		0.5 %	-899.00 [-1326.80, -471.20]
Fauli 2005	20	349 (338)	20	1157 (783)		0.6 %	-808.00 [-1181.77, -434.23]
Feindt 1994	10	279 (29)	10	664 (108)		1.6 %	-385.00 [-454.31, -315.69]
Fraedrich 1989	38	652 (382)	38	1204 (705)		0.9 %	-552.00 [-806.94, -297.06]
Gherli 1992	9	290 (140)	13	660 (185)		1.4 %	-370.00 [-505.94, -234.06]
Greilich 2009	26	685 (505)	27	1002 (627)		0.8 %	-317.00 [-622.96, -11.04]
Harmon 2004	17	520 (287)	18	769 (303)		1.1 %	-249.00 [-444.46, -53.54]
Hendrice 1995	12	328 (84)	14	699 (261)		1.3 %	-371.00 [-515.74, -226.26]
Kalangos 1994	55	720 (152)	55	1378 (375)		1.5 %	-658.00 [-764.94, -551.06]
Klein 1998	36	597 (266)	29	772 (299)		1.3 %	-175.00 [-314.26, -35.74]
Kuitunen 2005	20	540 (259.4)	20	995 (281.7)		1.2 %	-455.00 [-622.83, -287.17]
Laub 1994	16	722 (304)	16	1540 (800)		0.5 %	-818.00 [-1237.34, -398.66]
Lemmer 1996	160	786 (632.46)	157	1286 (651.56)		1.3 %	-500.00 [-641.39, -358.61]
Lemmer˙1 1994	74	855 (671)	67	1503 (671.2)		1.0 %	-648.00 [-869.82, -426.18]
Lemmer˙2 1994	23	1225 (1563.44)	32	1979 (1600.88)		0.2 %	-754.00 [-1600.11, 92.11]
Levy 1995	61	900 (1062.19)	65	1700 (1128.72)		0.6 %	-800.00 [-1182.55, -417.45]
Li 2005	40	304.3 (105.64)	30	610.67 (193.37)		1.6 %	-306.37 [-382.92, -229.82]
Locatelli 1990	12	241.6 (98.7)	13	524.6 (147.47)		1.5 %	-283.00 [-380.70, -185.30]
Maccario 1994	32	401 (178.27)	32	621 (255.87)		1.5 %	-220.00 [-328.05, -111.95]
Menichetti 1996	24	298 (140)	24	811 (600)		0.9 %	-513.00 [-759.49, -266.51]
Mohr 1992	17	397 (123)	16	780 (408)		1.1 %	-383.00 [-591.29, -174.71]
Moran 2000	12	142 (98)	14	450 (224)		1.4 %	-308.00 [-437.78, -178.22]
Murkin 1994	29	1409.7 (1251.51)	25	2765.8 (1240)		0.2 %	-1356.10 [-2022.24, -689.96]
Penta de Peppo 1995	15	344 (106)	15	724 (280)		1.3 %	-380.00 [-531.51, -228.49]



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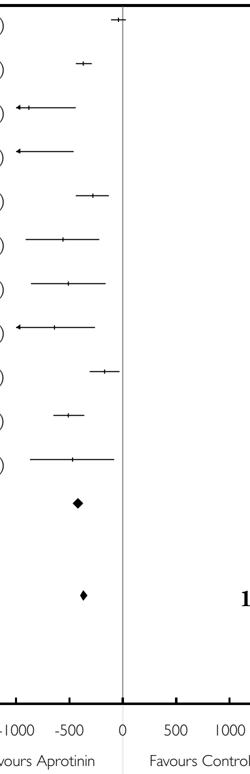
Study or subgroup	Aprotinin N	Aprotinin Mean(SD)	Control N	Control Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Prendergast 1 1996	18	510 (105)	20	550 (124)		1.6 %	-40.00 [-112.84, 32.84]
Prendergast 2 1996	16	526 (95)	16	894 (120)		1.6 %	-368.00 [-442.99, -293.01]
Rodrigus 1996	45	1051 (944)	46	1933 (1189)		0.5 %	-882.00 [-1322.60, -441.40]
Royston 1987	11	286 (159.2)	11	1509 (1286.85)		0.2 %	-1223.00 [-1989.26, -456.74]
Santamaria 2000	28	487 (259.2)	28	772 (336.1)		1.3 %	-285.00 [-442.21, -127.79]
Speekenbrink 1996	38	504 (275)	37	1068 (1047)		0.6 %	-564.00 [-912.51, -215.49]
Stammers 1997	8	435.1 (169.6)	12	944 (585.1)		0.6 %	-508.90 [-860.19, -157.61]
Tassani 2000	10	648 (202.4)	10	1284 (578.7)		0.6 %	-636.00 [-1015.98, -256.02]
Turkoz 2001	10	510 (139.14)	10	680 (183.41)		1.3 %	-170.00 [-312.69, -27.31]
Vedrinne 1992	30	328 (153.36)	30	834 (372.45)		1.3 %	-506.00 [-650.13, -361.87]
Wendel 1995	20	878.9 (438)	18	1353.6 (746.5)		0.6 %	-474.70 [-869.38, -80.02]
Subtotal (95% CI)	**2520**		**2465**			**55.5 %**	**-418.59 [-470.96, -366.22]**
Heterogeneity: Tau^2 = 24914.32; Chi^2 = 319.84, df = 51 (P<0.00001); I^2 =84%							
Test for overall effect: Z = 15.67 (P < 0.00001)							
Total (95% CI)	**4132**		**4049**			**100.0 %**	**-367.69 [-403.50, -331.87]**
Heterogeneity: Tau^2 = 19798.87; Chi^2 = 578.67, df = 90 (P<0.00001); I^2 =84%							
Test for overall effect: Z = 20.12 (P < 0.00001)							



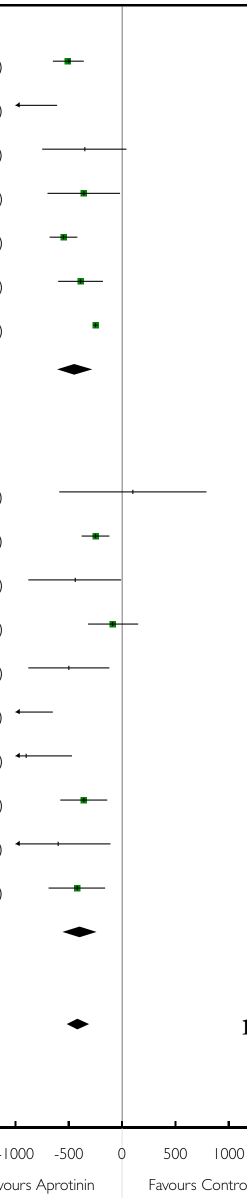
Analysis 1.12. Comparison 1 Aprotinin versus Control (Blood Transfusion & Blood Loss), Outcome 12 Blood loss - Total.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 1 Aprotinin versus Control (Blood Transfusion % Blood Loss)

Outcome: 12 Blood loss - Total

Study or subgroup	Aprotinin N	Aprotinin Mean(SD)	Control N	Control Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Cardiac surgery							
Alderman 1998	401	664 (1009)	395	1168 (1022)		9.5 %	-504.00 [-645.11, -362.89]
Bert 2008	25	901.3 (514.6)	25	2132.2 (1487.5)		2.3 %	-1230.90 [-1847.90, -613.90]
Harder 1991	40	559 (689.38)	40	911 (1075.17)		4.3 %	-352.00 [-747.80, 43.80]
Harmon 2004	17	1158 (385)	18	1520 (614)		5.2 %	-362.00 [-699.57, -24.43]
Hendrice 1995	12	553 (168)	14	1100 (168)		9.8 %	-547.00 [-676.54, -417.46]
Isetta 1993	140	608 (717.62)	70	1000 (736)		7.9 %	-392.00 [-601.42, -182.58]
Parvizi 2007	81	555 (56)	81	805 (76)		11.5 %	-250.00 [-270.56, -229.44]
Subtotal (95% CI)	**716**		**643**			**50.5 %**	**-448.86 [-612.82, -284.91]**
Heterogeneity: Tau² = 32951.29; Chi² = 42.60, df = 6 (P<0.00001); I² =86%							
Test for overall effect: Z = 5.37 (P < 0.00001)							
2 Orthopaedic surgery							
Amar 2003	23	1700 (1000)	24	1600 (1400)		1.9 %	100.00 [-593.35, 793.35]
D'Ambrosio 1999	30	715.6 (243.48)	30	965.35 (271.15)		9.8 %	-249.75 [-380.16, -119.34]
Garcia-Enguita 1998	15	1576 (452)	15	2021 (723)		3.9 %	-445.00 [-876.50, -13.50]
Hayes 1996	20	1186 (414)	20	1274 (347)		7.2 %	-88.00 [-324.74, 148.74]
Janssens 1994	20	1446 (514)	20	1943 (700)		4.6 %	-497.00 [-877.61, -116.39]
Jeserschek 2003	9	1771.3 (1153.2)	9	3604.4 (1393.4)		0.7 %	-1833.10 [-3014.77, -651.43]
Lentschener 1999	35	1935 (873)	37	2839 (993)		3.9 %	-904.00 [-1335.30, -472.70]
Llau 1998	10	817 (147)	10	1177 (325)		7.6 %	-360.00 [-581.08, -138.92]
Murkin 1995	29	1498 (592.37)	24	2096 (1092.47)		3.3 %	-598.00 [-1085.35, -110.65]
Petsatodis 2006	25	1073.2 (388.6)	25	1496.2 (545.1)		6.7 %	-423.00 [-685.41, -160.59]
Subtotal (95% CI)	**216**		**214**			**49.5 %**	**-399.09 [-562.81, -235.37]**
Heterogeneity: Tau² = 34542.41; Chi² = 22.67, df = 9 (P = 0.01); I² =60%							
Test for overall effect: Z = 4.78 (P < 0.00001)							
Total (95% CI)	**932**		**857**			**100.0 %**	**-415.95 [-520.38, -311.51]**
Heterogeneity: Tau² = 24649.74; Chi² = 66.96, df = 16 (P<0.00001); I² =76%							
Test for overall effect: Z = 7.81 (P < 0.00001)							



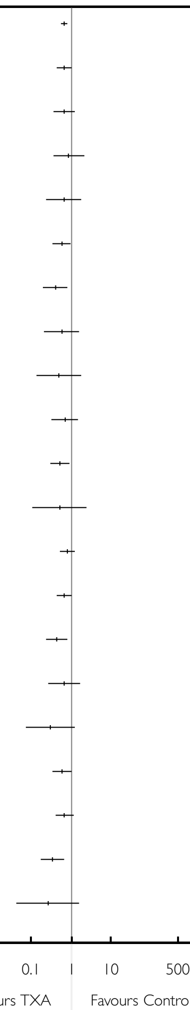
Analysis 2.1. Comparison 2 Tranexamic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 1 No. Exposed to Allogeneic Blood.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 2 Tranexamic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 1 No. Exposed to Allogeneic Blood

Study or subgroup	TXA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Tanaka 2001	47/73	26/26		0.65 [0.55, 0.78]
Karski 2005	24/147	41/165		0.66 [0.42, 1.03]
MacGillivray 2010	13/40	10/20		0.65 [0.35, 1.22]
Pleym 2003	7/40	8/39		0.85 [0.34, 2.13]
Mehr-Aein 2007	5/33	8/33		0.63 [0.23, 1.71]
Casati 2002	11/30	19/29		0.56 [0.33, 0.96]
Johansson 2005	8/47	23/53		0.39 [0.19, 0.79]
Benoni 2001	4/18	8/20		0.56 [0.20, 1.54]
Vanek 2005	3/32	6/30		0.47 [0.13, 1.71]
Casati 2004	9/52	13/50		0.67 [0.31, 1.42]
Jimenez 2007	9/24	19/26		0.51 [0.29, 0.90]
Casati 2001	2/20	4/20		0.50 [0.10, 2.43]
Wong 2008	23/73	30/74		0.78 [0.50, 1.20]
Shore-Lesserson 1996	10/17	12/13		0.64 [0.42, 0.98]
Katsaros 1996	11/104	27/106		0.42 [0.22, 0.79]
Niskanen 2005	5/19	8/20		0.66 [0.26, 1.66]
Husted 2003	2/20	7/20		0.29 [0.07, 1.21]
Benoni 2000	9/20	15/19		0.57 [0.33, 0.98]
Sadeghi 2007	12/32	20/35		0.66 [0.39, 1.12]
Benoni 1996	8/43	24/43		0.33 [0.17, 0.66]
Gill 2009	1/5	4/5		0.25 [0.04, 1.52]



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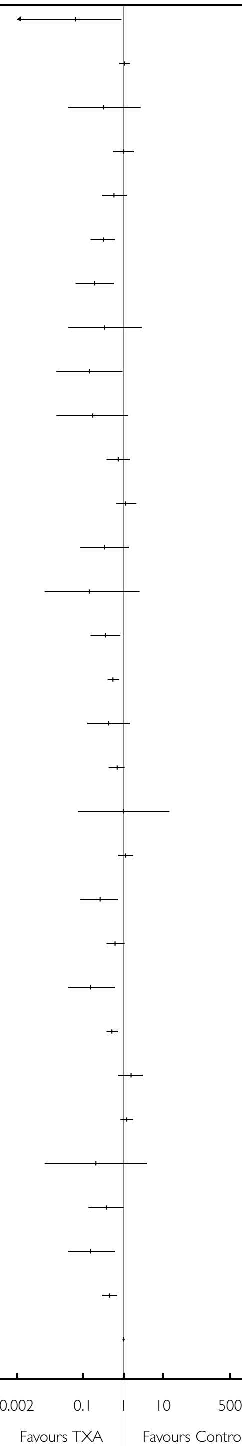
Study or subgroup	TXA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Lemay 2004	0/20	8/19		0.06 [0.00, 0.91]
Hardy 1998	28/42	27/44		1.09 [0.79, 1.49]
Orpen 2006	1/15	3/14		0.31 [0.04, 2.65]
Coffey 1995	9/16	8/14		0.98 [0.53, 1.84]
Mansour 2004	7/20	12/20		0.58 [0.29, 1.17]
Taghaddomi 2009	8/50	27/50		0.30 [0.15, 0.59]
Good 2003	3/27	14/24		0.19 [0.06, 0.58]
Penta de Peppo 1995	1/15	3/15		0.33 [0.04, 2.85]
Ellis 2001	1/10	7/10		0.14 [0.02, 0.96]
Claeys 2007	1/20	6/20		0.17 [0.02, 1.26]
Blauhut 1994	7/15	9/14		0.73 [0.37, 1.41]
Pinosky 1997	11/20	9/19		1.16 [0.63, 2.15]
Jares 2003	2/22	7/25		0.32 [0.08, 1.40]
Engel 2001	0/12	3/12		0.14 [0.01, 2.50]
Katoh 1997	7/62	10/31		0.35 [0.15, 0.83]
Armellin 2001	35/143	63/140		0.54 [0.39, 0.77]
Wei 2006	3/36	8/40		0.42 [0.12, 1.45]
Menichetti 1996	12/24	18/24		0.67 [0.42, 1.06]
Ekback 2000	1/20	1/20		1.00 [0.07, 14.90]
Garneti 2004	16/25	14/25		1.14 [0.72, 1.80]
Zohar 2004	3/20	12/20		0.25 [0.08, 0.75]
Corbeau 1995	15/41	12/20		0.61 [0.36, 1.05]
Jansen 1999	2/21	13/21		0.15 [0.04, 0.60]
Isetta 1993	24/70	46/70		0.52 [0.36, 0.75]
Caglar 2008	15/50	10/50		1.50 [0.75, 3.01]
Speekenbrink 1995	13/15	11/15		1.18 [0.82, 1.70]
Veien 2002	0/15	2/15		0.20 [0.01, 3.85]
Kazemi 2010	4/32	11/32		0.36 [0.13, 1.02]
Sorin 1999	2/21	13/21		0.15 [0.04, 0.60]
Brown 1997	18/60	20/30		0.45 [0.28, 0.71]
Pugh 1995	22/22	23/23		1.00 [0.92, 1.09]



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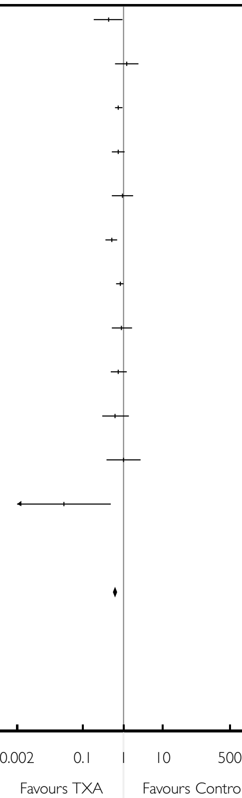
Study or subgroup	TXA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Kuitunen 2005	5/20	12/20		0.42 [0.18, 0.96]
Horrow 1995	37/121	7/27		1.18 [0.59, 2.36]
Dalmau 2000	29/42	37/40		0.75 [0.60, 0.93]
Hiipala 1995	10/15	12/13		0.72 [0.49, 1.07]
Murphy 2006	13/50	14/50		0.93 [0.49, 1.77]
Hiipala 1997	17/39	34/38		0.49 [0.34, 0.71]
Later 2009	57/99	73/103		0.81 [0.66, 1.00]
Horrow 1991	12/37	16/44		0.89 [0.49, 1.64]
Diprose 2005	20/60	27/60		0.74 [0.47, 1.17]
Santos 2006	7/29	12/31		0.62 [0.29, 1.36]
Andreasen 2004	6/20	5/17		1.02 [0.38, 2.76]
Wu 2006	0/106	17/108		0.03 [0.00, 0.48]
Yamasaki 2004	0/20	0/20		0.0 [0.0, 0.0]
Total (95% CI)	**2528**	**2314**		**0.61 [0.53, 0.70]**

Total events: 707 (TXA), 1028 (Control)

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 249.33$, df = 63 (P<0.00001); $I^2 = 75\%$

Test for overall effect: Z = 7.08 (P < 0.00001)



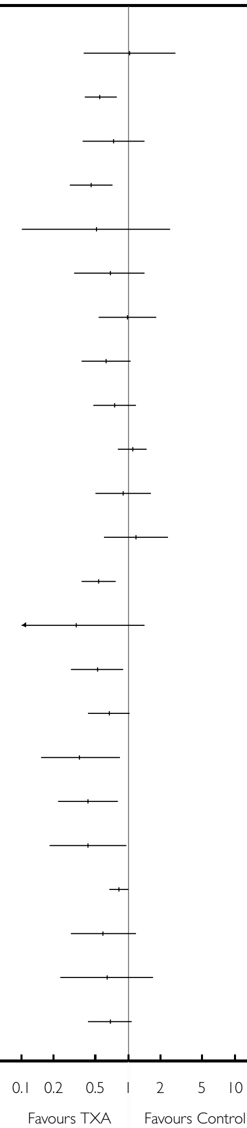
Analysis 2.2. Comparison 2 Tranexamic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 2 No. Exposed to Allogeneic Blood - Type of Surgery.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 2 Tranexamic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 2 No. Exposed to Allogeneic Blood - Type of Surgery

Study or subgroup	TXA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Cardiac surgery				
Andreasen 2004	6/20	5/17		1.02 [0.38, 2.76]
Armellin 2001	35/143	63/140		0.54 [0.39, 0.77]
Blauhut 1994	7/15	9/14		0.73 [0.37, 1.41]
Brown 1997	18/60	20/30		0.45 [0.28, 0.71]
Casati 2001	2/20	4/20		0.50 [0.10, 2.43]
Casati 2004	9/52	13/50		0.67 [0.31, 1.42]
Coffey 1995	9/16	8/14		0.98 [0.53, 1.84]
Corbeau 1995	15/41	12/20		0.61 [0.36, 1.05]
Diprose 2005	20/60	27/60		0.74 [0.47, 1.17]
Hardy 1998	28/42	27/44		1.09 [0.79, 1.49]
Horrow 1991	12/37	16/44		0.89 [0.49, 1.64]
Horrow 1995	37/121	7/27		1.18 [0.59, 2.36]
Isetta 1993	24/70	46/70		0.52 [0.36, 0.75]
Jares 2003	2/22	7/25		0.32 [0.08, 1.40]
Jimenez 2007	9/24	19/26		0.51 [0.29, 0.90]
Karski 2005	24/147	41/165		0.66 [0.42, 1.03]
Katoh 1997	7/62	10/31		0.35 [0.15, 0.83]
Katsaros 1996	11/104	27/106		0.42 [0.22, 0.79]
Kuitunen 2005	5/20	12/20		0.42 [0.18, 0.96]
Later 2009	57/99	73/103		0.81 [0.66, 1.00]
Mansour 2004	7/20	12/20		0.58 [0.29, 1.17]
Mehr-Aein 2007	5/33	8/33		0.63 [0.23, 1.71]
Menichetti 1996	12/24	18/24		0.67 [0.42, 1.06]



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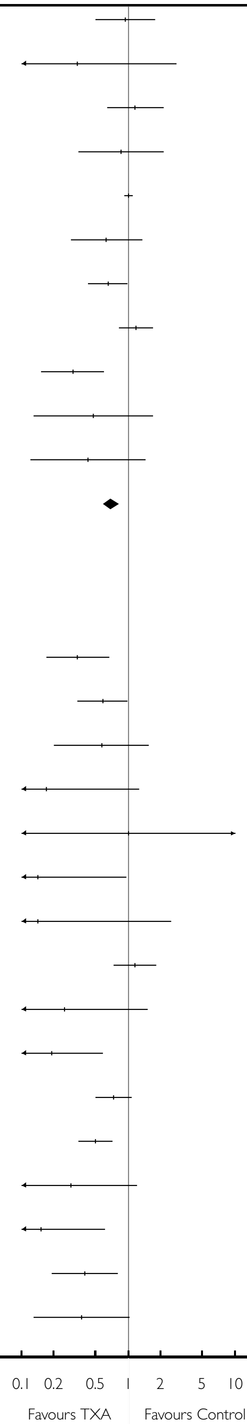
Study or subgroup	TXA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Murphy 2006	13/50	14/50		0.93 [0.49, 1.77]
Penta de Peppo 1995	1/15	3/15		0.33 [0.04, 2.85]
Pinosky 1997	11/20	9/19		1.16 [0.63, 2.15]
Pleym 2003	7/40	8/39		0.85 [0.34, 2.13]
Pugh 1995	22/22	23/23		1.00 [0.92, 1.09]
Santos 2006	7/29	12/31		0.62 [0.29, 1.36]
Shore-Lesserson 1996	10/17	12/13		0.64 [0.42, 0.98]
Speekenbrink 1995	13/15	11/15		1.18 [0.82, 1.70]
Taghaddomi 2009	8/50	27/50		0.30 [0.15, 0.59]
Vanek 2005	3/32	6/30		0.47 [0.13, 1.71]
Wei 2006	3/36	8/40		0.42 [0.12, 1.45]
Subtotal (95% CI)	**1578**	**1428**		**0.68 [0.57, 0.81]**
Total events: 459 (TXA), 617 (Control)				
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 137.35$, df = 33 ($P<0.00001$); $I^2 = 76\%$				
Test for overall effect: Z = 4.43 (P < 0.00001)				
2 Orthopaedic surgery				
Benoni 1996	8/43	24/43		0.33 [0.17, 0.66]
Benoni 2000	9/20	15/19		0.57 [0.33, 0.98]
Benoni 2001	4/18	8/20		0.56 [0.20, 1.54]
Claeys 2007	1/20	6/20		0.17 [0.02, 1.26]
Ekback 2000	1/20	1/20		1.00 [0.07, 14.90]
Ellis 2001	1/10	7/10		0.14 [0.02, 0.96]
Engel 2001	0/12	3/12		0.14 [0.01, 2.50]
Garneti 2004	16/25	14/25		1.14 [0.72, 1.80]
Gill 2009	1/5	4/5		0.25 [0.04, 1.52]
Good 2003	3/27	14/24		0.19 [0.06, 0.58]
Hiipala 1995	10/15	12/13		0.72 [0.49, 1.07]
Hiipala 1997	17/39	34/38		0.49 [0.34, 0.71]
Husted 2003	2/20	7/20		0.29 [0.07, 1.21]
Jansen 1999	2/21	13/21		0.15 [0.04, 0.60]
Johansson 2005	8/47	23/53		0.39 [0.19, 0.79]
Kazemi 2010	4/32	11/32		0.36 [0.13, 1.02]



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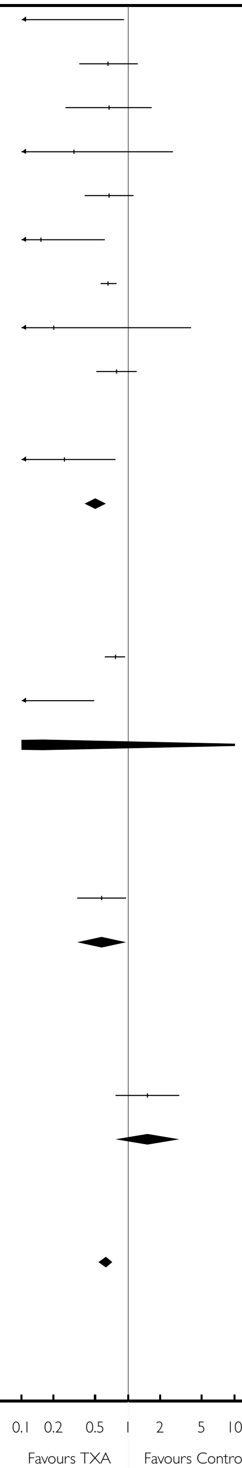
Study or subgroup	TXA n/N	Control n/N	Risk Ratio M-H,Random,95% CI
Lemay 2004	0/20	8/19	0.06 [0.00, 0.91]
MacGillivray 2010	13/40	10/20	0.65 [0.35, 1.22]
Niskanen 2005	5/19	8/20	0.66 [0.26, 1.66]
Orpen 2006	1/15	3/14	0.31 [0.04, 2.65]
Sadeghi 2007	12/32	20/35	0.66 [0.39, 1.12]
Sorin 1999	2/21	13/21	0.15 [0.04, 0.60]
Tanaka 2001	47/73	26/26	0.65 [0.55, 0.78]
Veien 2002	0/15	2/15	0.20 [0.01, 3.85]
Wong 2008	23/73	30/74	0.78 [0.50, 1.20]
Yamasaki 2004	0/20	0/20	0.0 [0.0, 0.0]
Zohar 2004	3/20	12/20	0.25 [0.08, 0.75]
Subtotal (95% CI)	**722**	**659**	**0.49 [0.39, 0.62]**
Total events: 193 (TXA), 328 (Control)			
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 53.86$, df = 25 (P = 0.00069); $I^2 = 54\%$			
Test for overall effect: Z = 6.20 (P < 0.00001)			
3 Liver surgery			
Dalmau 2000	29/42	37/40	0.75 [0.60, 0.93]
Wu 2006	0/106	17/108	0.03 [0.00, 0.48]
Subtotal (95% CI)	**148**	**148**	**0.16 [0.00, 32.47]**
Total events: 29 (TXA), 54 (Control)			
Heterogeneity: $Tau^2 = 13.57$; $Chi^2 = 14.23$, df = 1 (P = 0.00016); $I^2 = 93\%$			
Test for overall effect: Z = 0.67 (P = 0.50)			
4 Vascular surgery			
Casati 2002	11/30	19/29	0.56 [0.33, 0.96]
Subtotal (95% CI)	**30**	**29**	**0.56 [0.33, 0.96]**
Total events: 11 (TXA), 19 (Control)			
Heterogeneity: not applicable			
Test for overall effect: Z = 2.11 (P = 0.035)			
5 Gynaecological surgery			
Caglar 2008	15/50	10/50	1.50 [0.75, 3.01]
Subtotal (95% CI)	**50**	**50**	**1.50 [0.75, 3.01]**
Total events: 15 (TXA), 10 (Control)			
Heterogeneity: not applicable			
Test for overall effect: Z = 1.14 (P = 0.25)			
Total (95% CI)	**2528**	**2314**	**0.61 [0.53, 0.70]**
Total events: 707 (TXA), 1028 (Control)			
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 249.33$, df = 63 (P<0.00001); $I^2 = 75\%$			
Test for overall effect: Z = 7.08 (P < 0.00001)			



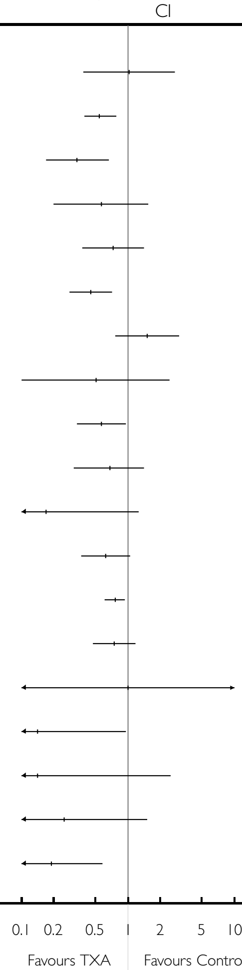
Analysis 2.3. Comparison 2 Tranexamic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 3 No. Exposed to Allogeneic Blood - Transfusion Protocol.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 2 Tranexamic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 3 No. Exposed to Allogeneic Blood - Transfusion Protocol

Study or subgroup	TXA n/N	Control n/N	Risk Ratio M-H,Random,95% CI
1 Transfusion Protocol			
Andreasen 2004	6/20	5/17	1.02 [0.38, 2.76]
Armellin 2001	35/143	63/140	0.54 [0.39, 0.77]
Benoni 1996	8/43	24/43	0.33 [0.17, 0.66]
Benoni 2001	4/18	8/20	0.56 [0.20, 1.54]
Blauhut 1994	7/15	9/14	0.73 [0.37, 1.41]
Brown 1997	18/60	20/30	0.45 [0.28, 0.71]
Caglar 2008	15/50	10/50	1.50 [0.75, 3.01]
Casati 2001	2/20	4/20	0.50 [0.10, 2.43]
Casati 2002	11/30	19/29	0.56 [0.33, 0.96]
Casati 2004	9/52	13/50	0.67 [0.31, 1.42]
Claeys 2007	1/20	6/20	0.17 [0.02, 1.26]
Corbeau 1995	15/41	12/20	0.61 [0.36, 1.05]
Dalmau 2000	29/42	37/40	0.75 [0.60, 0.93]
Diprose 2005	20/60	27/60	0.74 [0.47, 1.17]
Ekback 2000	1/20	1/20	1.00 [0.07, 14.90]
Ellis 2001	1/10	7/10	0.14 [0.02, 0.96]
Engel 2001	0/12	3/12	0.14 [0.01, 2.50]
Gill 2009	1/5	4/5	0.25 [0.04, 1.52]
Good 2003	3/27	14/24	0.19 [0.06, 0.58]



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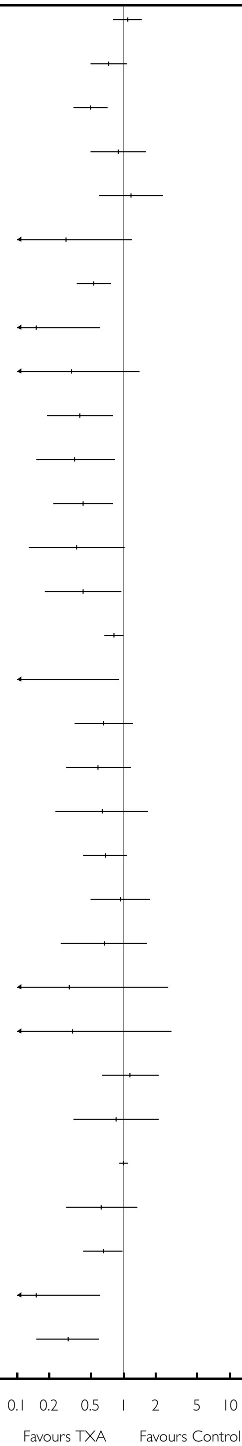
Study or subgroup	TXA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Hardy 1998	28/42	27/44		1.09 [0.79, 1.49]
Hiipala 1995	10/15	12/13		0.72 [0.49, 1.07]
Hiipala 1997	17/39	34/38		0.49 [0.34, 0.71]
Horrow 1991	12/37	16/44		0.89 [0.49, 1.64]
Horrow 1995	37/121	7/27		1.18 [0.59, 2.36]
Husted 2003	2/20	7/20		0.29 [0.07, 1.21]
Isetta 1993	24/70	46/70		0.52 [0.36, 0.75]
Jansen 1999	2/21	13/21		0.15 [0.04, 0.60]
Jares 2003	2/22	7/25		0.32 [0.08, 1.40]
Johansson 2005	8/47	23/53		0.39 [0.19, 0.79]
Katoh 1997	7/62	10/31		0.35 [0.15, 0.83]
Katsaros 1996	11/104	27/106		0.42 [0.22, 0.79]
Kazemi 2010	4/32	11/32		0.36 [0.13, 1.02]
Kuitunen 2005	5/20	12/20		0.42 [0.18, 0.96]
Later 2009	57/99	73/103		0.81 [0.66, 1.00]
Lemay 2004	0/20	8/19		0.06 [0.00, 0.91]
MacGillivray 2010	13/40	10/20		0.65 [0.35, 1.22]
Mansour 2004	7/20	12/20		0.58 [0.29, 1.17]
Mehr-Aein 2007	5/33	8/33		0.63 [0.23, 1.71]
Menichetti 1996	12/24	18/24		0.67 [0.42, 1.06]
Murphy 2006	13/50	14/50		0.93 [0.49, 1.77]
Niskanen 2005	5/19	8/20		0.66 [0.26, 1.66]
Orpen 2006	1/15	3/14		0.31 [0.04, 2.65]
Penta de Peppo 1995	1/15	3/15		0.33 [0.04, 2.85]
Pinosky 1997	11/20	9/19		1.16 [0.63, 2.15]
Pleym 2003	7/40	8/39		0.85 [0.34, 2.13]
Pugh 1995	22/22	23/23		1.00 [0.92, 1.09]
Santos 2006	7/29	12/31		0.62 [0.29, 1.36]
Shore-Lesserson 1996	10/17	12/13		0.64 [0.42, 0.98]
Sorin 1999	2/21	13/21		0.15 [0.04, 0.60]
Taghaddomi 2009	8/50	27/50		0.30 [0.15, 0.59]



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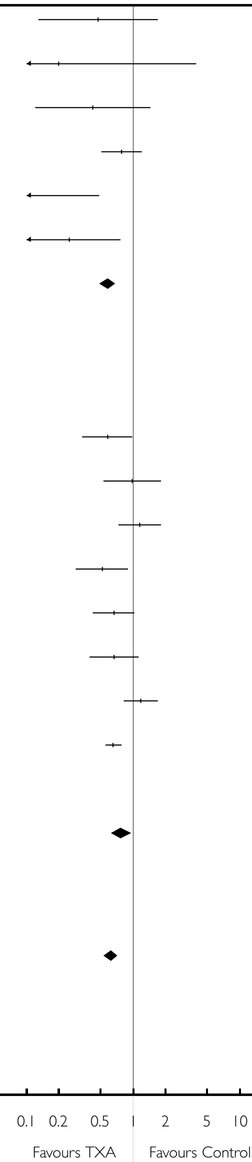
Study or subgroup	TXA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Vanek 2005	3/32	6/30		0.47 [0.13, 1.71]
Veien 2002	0/15	2/15		0.20 [0.01, 3.85]
Wei 2006	3/36	8/40		0.42 [0.12, 1.45]
Wong 2008	23/73	30/74		0.78 [0.50, 1.20]
Wu 2006	0/106	17/108		0.03 [0.00, 0.48]
Zohar 2004	3/20	12/20		0.25 [0.08, 0.75]
Subtotal (95% CI)	**2156**	**1969**		**0.57 [0.48, 0.67]**
Total events: 568 (TXA), 874 (Control)				
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 248.97$, df = 55 (P<0.00001); I^2 =78%				
Test for overall effect: Z = 6.63 (P < 0.00001)				
2 No Transfusion Protocol				
Benoni 2000	9/20	15/19		0.57 [0.33, 0.98]
Coffey 1995	9/16	8/14		0.98 [0.53, 1.84]
Garneti 2004	16/25	14/25		1.14 [0.72, 1.80]
Jimenez 2007	9/24	19/26		0.51 [0.29, 0.90]
Karski 2005	24/147	41/165		0.66 [0.42, 1.03]
Sadeghi 2007	12/32	20/35		0.66 [0.39, 1.12]
Speekenbrink 1995	13/15	11/15		1.18 [0.82, 1.70]
Tanaka 2001	47/73	26/26		0.65 [0.55, 0.78]
Yamasaki 2004	0/20	0/20		0.0 [0.0, 0.0]
Subtotal (95% CI)	**372**	**345**		**0.76 [0.61, 0.96]**
Total events: 139 (TXA), 154 (Control)				
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 15.48$, df = 7 (P = 0.03); I^2 =55%				
Test for overall effect: Z = 2.36 (P = 0.018)				
Total (95% CI)	**2528**	**2314**		**0.61 [0.53, 0.70]**
Total events: 707 (TXA), 1028 (Control)				
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 249.33$, df = 63 (P<0.00001); I^2 =75%				
Test for overall effect: Z = 7.08 (P < 0.00001)				



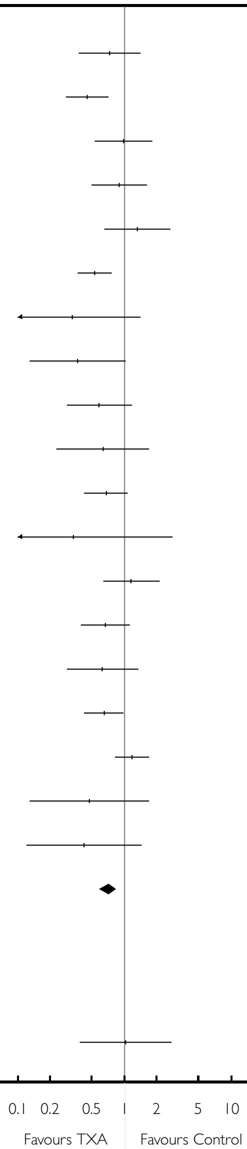
Analysis 2.4. Comparison 2 Tranexamic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 4 No. Exposed to Allogeneic Blood - Dose (Cardiac Surgery).

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 2 Tranexamic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 4 No. Exposed to Allogeneic Blood - Dose (Cardiac Surgery)

Study or subgroup	TXA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Total dose < 2.0 grams					
Blauhut 1994	7/15	9/14		2.7 %	0.73 [0.37, 1.41]
Brown 1997	18/60	20/30		3.5 %	0.45 [0.28, 0.71]
Coffey 1995	9/16	8/14		2.8 %	0.98 [0.53, 1.84]
Horrow 1991	12/37	16/44		2.9 %	0.89 [0.49, 1.64]
Horrow 1995	23/67	7/27		2.5 %	1.32 [0.65, 2.72]
Isetta 1993	24/70	46/70		3.9 %	0.52 [0.36, 0.75]
Jares 2003	2/22	7/25		1.0 %	0.32 [0.08, 1.40]
Kazemi 2010	4/32	11/32		1.6 %	0.36 [0.13, 1.02]
Mansour 2004	7/20	12/20		2.6 %	0.58 [0.29, 1.17]
Mehr-Aein 2007	5/33	8/33		1.7 %	0.63 [0.23, 1.71]
Menichetti 1996	12/24	18/24		3.5 %	0.67 [0.42, 1.06]
Penta de Peppo 1995	1/15	3/15		0.5 %	0.33 [0.04, 2.85]
Pinosky 1997	11/20	9/19		2.9 %	1.16 [0.63, 2.15]
Sadeghi 2007	12/32	20/35		3.2 %	0.66 [0.39, 1.12]
Santos 2006	7/29	12/31		2.3 %	0.62 [0.29, 1.36]
Shore-Lesserson 1996	10/17	12/13		3.6 %	0.64 [0.42, 0.98]
Speekenbrink 1995	13/15	11/15		3.9 %	1.18 [0.82, 1.70]
Vanek 2005	3/32	6/30		1.2 %	0.47 [0.13, 1.71]
Wei 2006	3/36	8/40		1.3 %	0.42 [0.12, 1.45]
Subtotal (95% CI)	**592**	**531**		**47.4 %**	**0.70 [0.58, 0.84]**
Total events: 183 (TXA), 243 (Control)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 26.93$, df = 18 (P = 0.08); $I^2 = 33\%$					
Test for overall effect: Z = 3.89 (P = 0.00010)					
2 Total dose 2.0 - 10.0 grams					
Andreasen 2004	6/20	5/17		1.7 %	1.02 [0.38, 2.76]



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Study or subgroup	TXA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Armellin 2001	35/143	63/140		4.0 %	0.54 [0.39, 0.77]
Casati 2001	2/20	4/20		0.9 %	0.50 [0.10, 2.43]
Casati 2004	9/52	13/50		2.4 %	0.67 [0.31, 1.42]
Corbeau 1995	15/41	12/20		3.2 %	0.61 [0.36, 1.05]
Diprose 2005	20/60	27/60		3.5 %	0.74 [0.47, 1.17]
Hardy 1998	28/42	27/44		4.1 %	1.09 [0.79, 1.49]
Horrow 1995	14/54	14/54		2.8 %	1.00 [0.53, 1.89]
Jimenez 2007	9/24	19/26		3.1 %	0.51 [0.29, 0.90]
Karski 2005	24/147	41/165		3.5 %	0.66 [0.42, 1.03]
Katoh 1997	7/62	10/31		2.0 %	0.35 [0.15, 0.83]
Katsaros 1996	11/104	27/106		2.7 %	0.42 [0.22, 0.79]
Kuitunen 2005	5/20	12/20		2.1 %	0.42 [0.18, 0.96]
Later 2009	57/99	73/103		4.5 %	0.81 [0.66, 1.00]
Murphy 2006	13/50	14/50		2.8 %	0.93 [0.49, 1.77]
Pleym 2003	7/40	8/39		1.9 %	0.85 [0.34, 2.13]
Pugh 1995	22/22	23/23		4.8 %	1.00 [0.92, 1.09]
Taghaddomi 2009	8/50	27/50		2.6 %	0.30 [0.15, 0.59]
Subtotal (95% CI)	**1050**	**1018**		**52.6 %**	**0.67 [0.52, 0.86]**

Total events: 292 (TXA), 419 (Control)

Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 107.97$, df = 17 (P<0.00001); I^2 =84%

Test for overall effect: Z = 3.15 (P = 0.0016)

Total (95% CI)	**1642**	**1549**		**100.0 %**	**0.68 [0.58, 0.80]**

Total events: 475 (TXA), 662 (Control)

Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 139.40$, df = 36 (P<0.00001); I^2 =74%

Test for overall effect: Z = 4.65 (P < 0.00001)

0.1 0.2 0.5 1 2 5 10

Favours TXA Favours Control

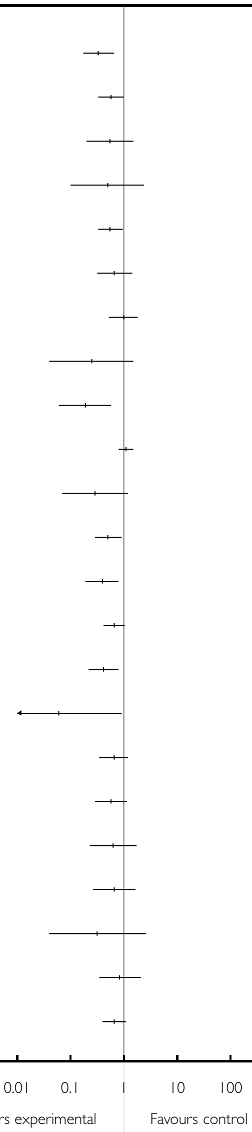
Analysis 2.5. Comparison 2 Tranexamic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 5 Trial Methodological Quality - Allocation Concealment.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 2 Tranexamic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 5 Trial Methodological Quality - Allocation Concealment

Study or subgroup	TXA n/N	Control n/N	Risk Ratio M-H,Random,95% CI
1 Allocation concealment - Yes			
Benoni 1996	8/43	24/43	0.33 [0.17, 0.66]
Benoni 2000	9/20	15/19	0.57 [0.33, 0.98]
Benoni 2001	4/18	8/20	0.56 [0.20, 1.54]
Casati 2001	2/20	4/20	0.50 [0.10, 2.43]
Casati 2002	11/30	19/29	0.56 [0.33, 0.96]
Casati 2004	9/52	13/50	0.67 [0.31, 1.42]
Coffey 1995	9/16	8/14	0.98 [0.53, 1.84]
Gill 2009	1/5	4/5	0.25 [0.04, 1.52]
Good 2003	3/27	14/24	0.19 [0.06, 0.58]
Hardy 1998	28/42	27/44	1.09 [0.79, 1.49]
Husted 2003	2/20	7/20	0.29 [0.07, 1.21]
Jimenez 2007	9/24	19/26	0.51 [0.29, 0.90]
Johansson 2005	8/47	23/53	0.39 [0.19, 0.79]
Karski 2005	24/147	41/165	0.66 [0.42, 1.03]
Katsaros 1996	11/104	27/106	0.42 [0.22, 0.79]
Lemay 2004	0/20	8/19	0.06 [0.00, 0.91]
MacGillivray 2010	13/40	10/20	0.65 [0.35, 1.22]
Mansour 2004	7/20	12/20	0.58 [0.29, 1.17]
Mehr-Aein 2007	5/33	8/33	0.63 [0.23, 1.71]
Niskanen 2005	5/19	8/20	0.66 [0.26, 1.66]
Orpen 2006	1/15	3/14	0.31 [0.04, 2.65]
Pleym 2003	7/40	8/39	0.85 [0.34, 2.13]
Sadeghi 2007	12/32	20/35	0.66 [0.39, 1.12]



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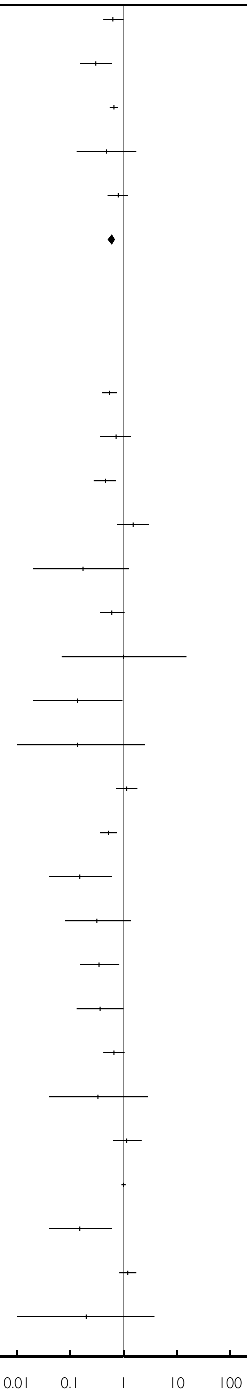
Study or subgroup	TXA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Shore-Lesserson 1996	10/17	12/13		0.64 [0.42, 0.98]
Taghaddomi 2009	8/50	27/50		0.30 [0.15, 0.59]
Tanaka 2001	47/73	26/26		0.65 [0.55, 0.78]
Vanek 2005	3/32	6/30		0.47 [0.13, 1.71]
Wong 2008	23/73	30/74		0.78 [0.50, 1.20]
Subtotal (95% CI)	**1079**	**1031**		**0.59 [0.51, 0.69]**
Total events: 279 (TXA), 431 (Control)				
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 41.35$, df = 27 (P = 0.04); I^2 =35%				
Test for overall effect: Z = 6.80 (P < 0.00001)				
2 Allocation concealment - Unclear				
Armellin 2001	35/143	63/140		0.54 [0.39, 0.77]
Blauhut 1994	7/15	9/14		0.73 [0.37, 1.41]
Brown 1997	18/60	20/30		0.45 [0.28, 0.71]
Caglar 2008	15/50	10/50		1.50 [0.75, 3.01]
Claeys 2007	1/20	6/20		0.17 [0.02, 1.26]
Corbeau 1995	15/41	12/20		0.61 [0.36, 1.05]
Ekback 2000	1/20	1/20		1.00 [0.07, 14.90]
Ellis 2001	1/10	7/10		0.14 [0.02, 0.96]
Engel 2001	0/12	3/12		0.14 [0.01, 2.50]
Garneti 2004	16/25	14/25		1.14 [0.72, 1.80]
Isetta 1993	24/70	46/70		0.52 [0.36, 0.75]
Jansen 1999	2/21	13/21		0.15 [0.04, 0.60]
Jares 2003	2/22	7/25		0.32 [0.08, 1.40]
Katoh 1997	7/62	10/31		0.35 [0.15, 0.83]
Kazemi 2010	4/32	11/32		0.36 [0.13, 1.02]
Menichetti 1996	12/24	18/24		0.67 [0.42, 1.06]
Penta de Peppo 1995	1/15	3/15		0.33 [0.04, 2.85]
Pinosky 1997	11/20	9/19		1.16 [0.63, 2.15]
Pugh 1995	22/22	23/23		1.00 [0.92, 1.09]
Sorin 1999	2/21	13/21		0.15 [0.04, 0.60]
Speekenbrink 1995	13/15	11/15		1.18 [0.82, 1.70]
Veien 2002	0/15	2/15		0.20 [0.01, 3.85]



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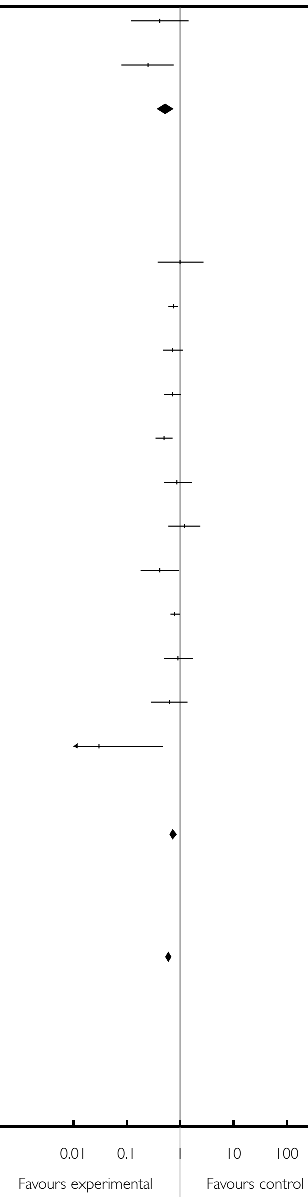
Study or subgroup	TXA n/N	Control n/N	Risk Ratio M-H,Random,95% CI
Wei 2006	3/36	8/40	0.42 [0.12, 1.45]
Zohar 2004	3/20	12/20	0.25 [0.08, 0.75]
Subtotal (95% CI)	**791**	**712**	**0.53 [0.37, 0.76]**
Total events: 215 (TXA), 331 (Control)			
Heterogeneity: $Tau^2 = 0.53$; $Chi^2 = 209.62$, df = 23 (P<0.00001); I^2 =89%			
Test for overall effect: Z = 3.44 (P = 0.00059)			
3 Allocation concealment - No			
Andreasen 2004	6/20	5/17	1.02 [0.38, 2.76]
Dalmau 2000	29/42	37/40	0.75 [0.60, 0.93]
Diprose 2005	20/60	27/60	0.74 [0.47, 1.17]
Hiipala 1995	10/15	12/13	0.72 [0.49, 1.07]
Hiipala 1997	17/39	34/38	0.49 [0.34, 0.71]
Horrow 1991	12/37	16/44	0.89 [0.49, 1.64]
Horrow 1995	37/121	7/27	1.18 [0.59, 2.36]
Kuitunen 2005	5/20	12/20	0.42 [0.18, 0.96]
Later 2009	57/99	73/103	0.81 [0.66, 1.00]
Murphy 2006	13/50	14/50	0.93 [0.49, 1.77]
Santos 2006	7/29	12/31	0.62 [0.29, 1.36]
Wu 2006	0/106	17/108	0.03 [0.00, 0.48]
Yamasaki 2004	0/20	0/20	0.0 [0.0, 0.0]
Subtotal (95% CI)	**658**	**571**	**0.73 [0.62, 0.86]**
Total events: 213 (TXA), 266 (Control)			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 16.38$, df = 11 (P = 0.13); I^2 =33%			
Test for overall effect: Z = 3.72 (P = 0.00020)			
Total (95% CI)	**2528**	**2314**	**0.61 [0.53, 0.70]**
Total events: 707 (TXA), 1028 (Control)			
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 249.33$, df = 63 (P<0.00001); I^2 =75%			
Test for overall effect: Z = 7.08 (P < 0.00001)			
Test for subgroup differences: $Chi^2 = 0.0$, df = 2 (P = 0.0), I^2 =0.0%			



Analysis 2.6. Comparison 2 Tranexamic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 6 Units Allogeneic Blood Transfused - Transfused Patients.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

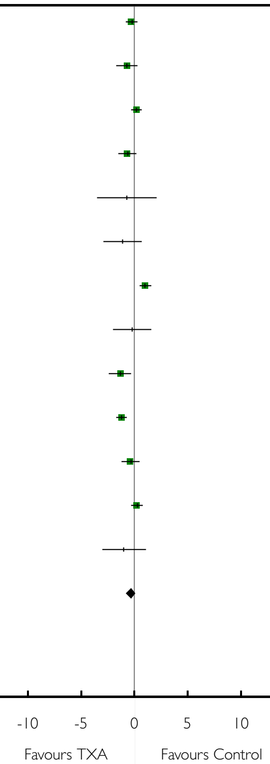
Comparison: 2 Tranexamic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 6 Units Allogeneic Blood Transfused - Transfused Patients

Study or subgroup	TXA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Armellin 2001	35	1.68 (1.2)	63	1.93 (1.3)		10.8 %	-0.25 [-0.76, 0.26]
Blauhut 1994	7	1.71 (0.95)	9	2.44 (1.13)		7.7 %	-0.73 [-1.75, 0.29]
Caglar 2008	15	1.8 (0.54)	10	1.6 (0.66)		10.9 %	0.20 [-0.29, 0.69]
Corbeau 1995	15	2.19 (0.46)	12	2.83 (1.45)		8.7 %	-0.64 [-1.49, 0.21]
Dalmau 2000	29	7.72 (5.44)	37	8.38 (6.13)		2.2 %	-0.66 [-3.46, 2.14]
Diprose 2005	20	2.61 (1.55)	27	3.73 (4.47)		4.2 %	-1.12 [-2.94, 0.70]
Garneti 2004	16	2.31 (0.87)	14	1.29 (0.73)		10.4 %	1.02 [0.45, 1.59]
Good 2003	3	2.33 (1.53)	14	2.5 (1.02)		4.2 %	-0.17 [-1.98, 1.64]
Hiipala 1995	10	2.25 (0.87)	12	3.58 (1.57)		7.6 %	-1.33 [-2.37, -0.29]
Hiipala 1997	17	2.29 (0.52)	34	3.46 (1.25)		10.9 %	-1.17 [-1.66, -0.68]
Johansson 2005	8	2.13 (0.99)	23	2.48 (1.31)		8.6 %	-0.35 [-1.22, 0.52]
Murphy 2006	13	1.46 (0.97)	14	1.21 (0.43)		10.4 %	0.25 [-0.32, 0.82]
Speekenbrink 1995	13	3.31 (1.62)	11	4.27 (3.15)		3.5 %	-0.96 [-3.02, 1.10]
Total (95% CI)	**201**		**280**			**100.0 %**	**-0.34 [-0.80, 0.11]**

Heterogeneity: $Tau^2 = 0.43$; $Chi^2 = 45.89$, df = 12 ($P<0.00001$); $I^2 = 74\%$

Test for overall effect: Z = 1.49 (P = 0.14)



Analysis 2.7. Comparison 2 Tranexamic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 7 Units of Allogeneic Blood Transfused - All Patients.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

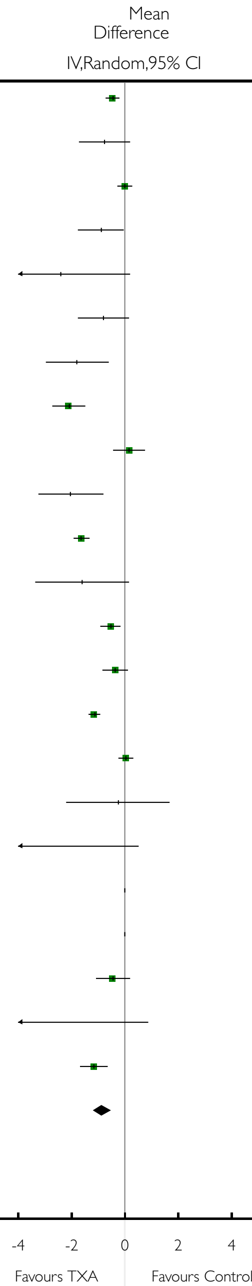
Comparison: 2 Tranexamic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 7 Units of Allogeneic Blood Transfused - All Patients

Study or subgroup	TXA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI
Armellin 2001	143	0.41 (0.93)	140	0.87 (1.3)	-0.46 [-0.72, -0.20]
Blauhut 1994	15	0.8 (1.08)	14	1.57 (1.5)	-0.77 [-1.73, 0.19]
Caglar 2008	50	0.3 (0.8)	50	0.3 (0.7)	0.0 [-0.29, 0.29]
Corbeau 1995	41	0.8 (1.1)	20	1.7 (1.8)	-0.90 [-1.76, -0.04]
Dalmau 2000	42	5.33 (5.77)	40	7.75 (6.3)	-2.42 [-5.04, 0.20]
Diprose 2005	60	0.87 (1.52)	60	1.68 (3.51)	-0.81 [-1.78, 0.16]
Hiipala 1995	15	1.5 (1.3)	13	3.3 (1.8)	-1.80 [-2.98, -0.62]
Hiipala 1997	39	1 (1.2)	38	3.1 (1.6)	-2.10 [-2.73, -1.47]
Horrow 1990	18	0.92 (0.8)	20	0.76 (1.08)	0.16 [-0.44, 0.76]
Jansen 1999	21	0.46 (1.45)	21	2.5 (2.47)	-2.04 [-3.26, -0.82]
Jimenez 2007	24	1.58 (0.49)	26	3.21 (0.55)	-1.63 [-1.92, -1.34]
Katoh 1997	62	1.42 (2.74)	31	3.03 (4.57)	-1.61 [-3.36, 0.14]
Kazemi 2010	32	0.31 (0.64)	32	0.84 (0.9)	-0.53 [-0.91, -0.15]
MacGillivray 2010	40	0.76 (0.75)	20	1.11 (0.97)	-0.35 [-0.83, 0.13]
Maddali 2007	111	2.03 (0.78)	111	3.17 (0.97)	-1.14 [-1.37, -0.91]
Murphy 2006	50	0.38 (0.81)	50	0.34 (0.59)	0.04 [-0.24, 0.32]
Speekenbrink 1995	15	2.87 (1.9)	15	3.13 (3.3)	-0.26 [-2.19, 1.67]
Uozaki 2001	6	4.1 (2.23)	6	9.16 (6.6)	-5.06 [-10.63, 0.51]
Veien 2002	15	0 (0)	15	0.27 (0.7)	0.0 [0.0, 0.0]
Wei 2006	36	1.27 (0.07)	40	1.33 (0)	0.0 [0.0, 0.0]
Wong 2008	73	0.89 (1.8)	74	1.35 (2.16)	-0.46 [-1.10, 0.18]
Yassen 1993	10	7.9 (3.3)	10	12.4 (8)	-4.50 [-9.86, 0.86]
Zabeeda 2002	25	0.52 (0.9)	25	1.68 (1)	-1.16 [-1.69, -0.63]
Total (95% CI)	**943**		**871**		**-0.87 [-1.20, -0.53]**

Heterogeneity: $Tau^2 = 0.40$; $Chi^2 = 154.24$, df = 20 ($P<0.00001$); $I^2 = 87\%$

Test for overall effect: Z = 5.04 ($P < 0.00001$)



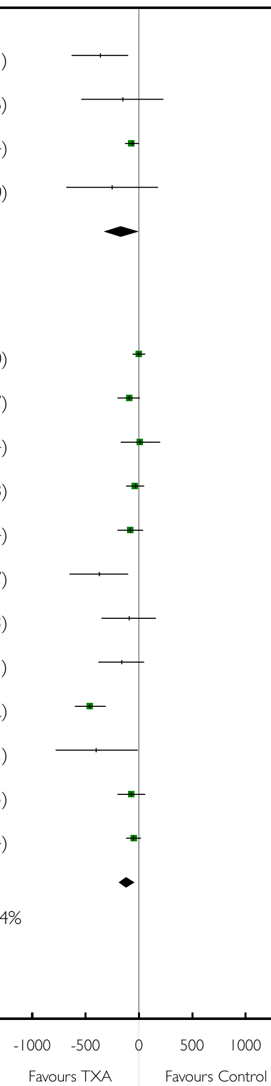
Analysis 2.8. Comparison 2 Tranexamic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 8 Blood loss - Intra-operative.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 2 Tranexamic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 8 Blood loss - Intra-operative

Study or subgroup	TXA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Cardiac surgery							
Katoh 1997	62	197 (117.8)	31	561 (746.1)		3.5 %	-364.00 [-628.27, -99.73]
Pinosky 1997	20	1318 (545.6)	19	1471 (675.6)		1.9 %	-153.00 [-539.60, 233.60]
Taghaddomi 2009	50	467 (170)	50	531 (164)		10.0 %	-64.00 [-129.47, 1.47]
Uozaki 2001	6	273 (290)	6	523 (450)		1.6 %	-250.00 [-678.36, 178.36]
Subtotal (95% CI)	**138**		**106**			**17.0 %**	**-166.76 [-331.24, -2.27]**
Heterogeneity: Tau² = 12513.66; Chi² = 5.36, df = 3 (P = 0.15); I² =44%							
Test for overall effect: Z = 1.99 (P = 0.047)							
2 Orthopaedic surgery							
Benoni 1996	43	210 (140)	43	210 (130)		10.3 %	0.0 [-57.10, 57.10]
Claeys 2007	20	423 (174)	20	516 (167)		8.4 %	-93.00 [-198.70, 12.70]
Hiipala 1995	15	428 (254)	13	415 (244)		5.4 %	13.00 [-171.70, 197.70]
Hiipala 1997	39	283 (178)	38	318 (208)		9.2 %	-35.00 [-121.57, 51.57]
Johansson 2005	47	534 (316)	53	612 (304)		7.7 %	-78.00 [-199.90, 43.90]
Kazemi 2010	32	1024 (544)	32	1399 (587)		3.2 %	-375.00 [-652.29, -97.71]
Lemay 2004	20	820.5 (447.1)	19	911 (363)		3.6 %	-90.50 [-345.52, 164.52]
Niskanen 2005	19	626 (279.05)	20	790 (408.11)		4.4 %	-164.00 [-382.48, 54.48]
Sadeghi 2007	32	652 (228)	35	1108 (372)		6.7 %	-456.00 [-602.39, -309.61]
Wong 2008	73	1203 (1060)	74	1600 (1301)		1.9 %	-397.00 [-780.40, -13.60]
Yamasaki 2004	20	570 (191)	20	640 (215)		7.5 %	-70.00 [-196.04, 56.04]
Zhang 2007	51	256 (149)	51	306 (214)		9.8 %	-50.00 [-121.57, 21.57]
Subtotal (95% CI)	**411**		**418**			**78.1 %**	**-115.52 [-187.88, -43.16]**
Heterogeneity: Tau² = 10071.83; Chi² = 42.52, df = 11 (P = 0.00001); I² =74%							
Test for overall effect: Z = 3.13 (P = 0.0018)							
3 Gynaecological surgery							



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Study or subgroup	TXA		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Caglar 2008	50	654 (460)	50	820 (558)		4.9 %	-166.00 [-366.45, 34.45]
Subtotal (95% CI)	**50**		**50**			**4.9 %**	**-166.00 [-366.45, 34.45]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.62 (P = 0.10)							
4 Head % neck surgery							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**599**		**574**			**100.0 %**	**-121.41 [-180.19, -62.63]**
Heterogeneity: $Tau^2 = 7861.99$; $Chi^2 = 49.05$, df = 16 (P = 0.00003); $I^2 = 67\%$							
Test for overall effect: Z = 4.05 (P = 0.000052)							

-1000 -500 0 500 1000

Favours TXA Favours Control

Analysis 2.9. Comparison 2 Tranexamic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 9 Blood loss - Post-operative.

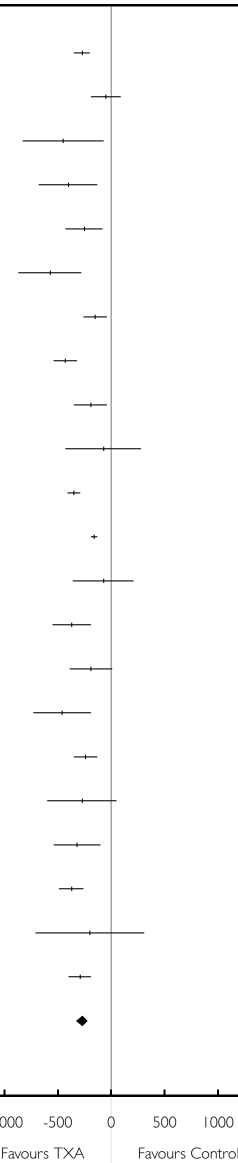
Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 2 Tranexamic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 9 Blood loss - Post-operative

Study or subgroup	TXA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Cardiac surgery							
Armellin 2001	143	447 (262)	140	720 (357)		3.9 %	-273.00 [-346.08, -199.92]
Blauhut 1994	15	403 (201.39)	14	453 (192.56)		3.1 %	-50.00 [-193.39, 93.39]
Coffey 1995	16	711 (384)	14	1160 (628.6)		1.2 %	-449.00 [-828.24, -69.76]
Corbeau 1995	41	1015 (409)	20	1416 (559)		1.8 %	-401.00 [-676.12, -125.88]
Horrow 1990	18	496 (228)	20	750 (314)		2.8 %	-254.00 [-427.30, -80.70]
Jimenez 2007	24	464 (369.2)	26	1037 (658)		1.6 %	-573.00 [-865.89, -280.11]
Katoh 1997	62	241 (79.27)	31	392 (305.67)		3.5 %	-151.00 [-260.40, -41.60]
Katsaros 1996	104	474 (244.75)	106	906 (525.1)		3.5 %	-432.00 [-542.48, -321.52]
Kuitunen 2005	20	802 (214.7)	20	995 (281.7)		3.0 %	-193.00 [-348.23, -37.77]
Kuitunen 2006	14	1008 (251)	15	1081 (654)		1.3 %	-73.00 [-429.12, 283.12]
Maddali 2007	111	633 (183.2)	111	980.9 (267.2)		4.1 %	-347.90 [-408.17, -287.63]
Mehr-Aein 2007	33	320 (38)	33	480 (75)		4.3 %	-160.00 [-188.69, -131.31]
Menichetti 1996	24	737 (400)	24	811 (600)		1.7 %	-74.00 [-362.50, 214.50]
Misfeld 1998	14	390 (120)	14	760 (320)		2.7 %	-370.00 [-549.02, -190.98]
Penta de Peppo 1995	15	534 (288)	15	724 (280)		2.4 %	-190.00 [-393.27, 13.27]
Pinosky 1997	20	600 (219.1)	19	1060 (553.5)		1.8 %	-460.00 [-726.76, -193.24]
Pleym 2003	40	475 (269)	39	713 (243)		3.5 %	-238.00 [-350.98, -125.02]
Shore-Lesserson 1996	17	649 (391)	13	923 (496)		1.4 %	-274.00 [-601.48, 53.48]
Speekenbrink 1995	15	352 (150)	15	674 (411)		2.2 %	-322.00 [-543.41, -100.59]
Taghaddomi 2009	50	471 (182)	50	844 (363)		3.5 %	-373.00 [-485.55, -260.45]
Uozaki 2001	6	646 (380)	6	846 (510)		0.7 %	-200.00 [-708.90, 308.90]
Zabeeda 2002	25	194 (135)	25	488 (238)		3.6 %	-294.00 [-401.26, -186.74]
Subtotal (95% CI)	**827**		**770**			**57.5 %**	**-272.87 [-328.85, -216.89]**

Heterogeneity: $Tau^2 = 9687.61$; $Chi^2 = 83.41$, df = 21 ($P<0.00001$); $I^2 = 75\%$



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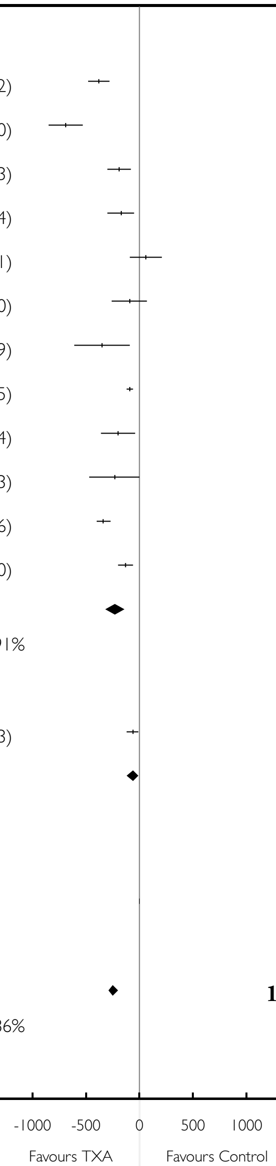
Study or subgroup	TXA N	TXA Mean(SD)	Control N	Control Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Test for overall effect: Z = 9.55 (P < 0.00001)							
2 Orthopaedic surgery							
Alvarez 2008	46	170 (109)	49	551 (352)		3.6 %	-381.00 [-484.47, -277.53]
Benoni 1996	43	520 (230)	43	1210 (480)		2.9 %	-690.00 [-849.09, -530.91]
Benoni 2001	18	199 (114.62)	20	388 (228.63)		3.5 %	-189.00 [-302.33, -75.67]
Claeys 2007	20	352 (152)	20	524 (244)		3.3 %	-172.00 [-297.99, -46.01]
Garneti 2004	25	411 (220)	25	353 (311)		3.0 %	58.00 [-91.33, 207.33]
Lemay 2004	20	487 (234)	19	580 (290)		2.8 %	-93.00 [-258.89, 72.89]
MacGillivray 2010	40	569 (294)	20	918 (549)		1.9 %	-349.00 [-606.28, -91.72]
Sadeghi 2007	32	300 (54)	35	390 (65)		4.3 %	-90.00 [-118.53, -61.47]
Wong 2008	73	536 (471)	74	737 (524)		2.9 %	-201.00 [-362.02, -39.98]
Yamasaki 2004	20	655 (418)	20	890 (353)		2.1 %	-235.00 [-474.78, 4.78]
Zhang 2007	51	478 (172)	51	814 (156)		4.0 %	-336.00 [-399.73, -272.27]
Zohar 2004	20	121 (81)	20	249 (130)		4.0 %	-128.00 [-195.13, -60.87]
Subtotal (95% CI)	**408**		**396**			**38.4 %**	**-228.52 [-321.76, -135.27]**
Heterogeneity: Tau² = 22019.78; Chi² = 125.01, df = 11 (P<0.00001); I² =91%							
Test for overall effect: Z = 4.80 (P < 0.00001)							
3 Gynaecological surgery							
Caglar 2008	50	150 (167)	50	213 (113)		4.1 %	-63.00 [-118.89, -7.11]
Subtotal (95% CI)	**50**		**50**			**4.1 %**	**-63.00 [-118.89, -7.11]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.21 (P = 0.027)							
4 Head % neck surgery							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**1285**		**1216**			**100.0 %**	**-247.17 [-294.76, -199.58]**
Heterogeneity: Tau² = 13588.50; Chi² = 248.36, df = 34 (P<0.00001); I² =86%							
Test for overall effect: Z = 10.18 (P < 0.00001)							



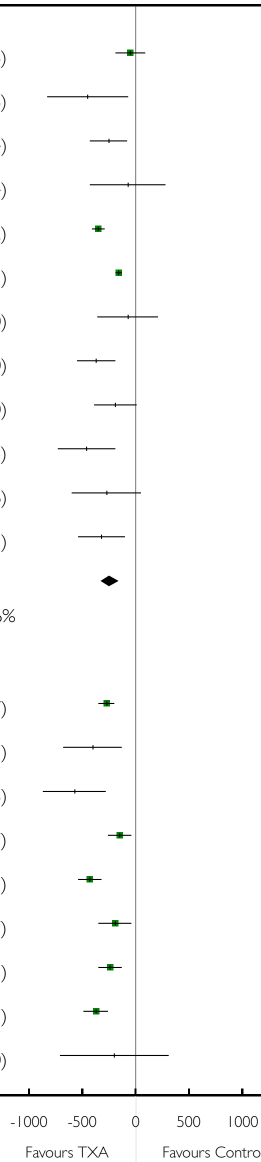
Analysis 2.10. Comparison 2 Tranexamic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 10 Blood loss - Post-operative - Dose (Cardiac Surgery).

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 2 Tranexamic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 10 Blood loss - Post-operative - Dose (Cardiac Surgery)

Study or subgroup	TXA N	TXA Mean(SD)	Control N	Control Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Total dose < 2.0 grams							
Blauhut 1994	15	403 (201.39)	14	453 (192.56)		5.4 %	-50.00 [-193.39, 93.39]
Coffey 1995	16	711 (384)	14	1160 (628.6)		1.7 %	-449.00 [-828.24, -69.76]
Horrow 1990	18	496 (228)	20	750 (314)		4.7 %	-254.00 [-427.30, -80.70]
Kuitunen 2006	14	1008 (251)	15	1081 (654)		1.9 %	-73.00 [-429.12, 283.12]
Maddali 2007	111	633 (183.2)	111	980.9 (267.2)		7.7 %	-347.90 [-408.17, -287.63]
Mehr-Aein 2007	33	320 (38)	33	480 (75)		8.2 %	-160.00 [-188.69, -131.31]
Menichetti 1996	24	737 (400)	24	811 (600)		2.6 %	-74.00 [-362.50, 214.50]
Misfeld 1998	14	390 (120)	14	760 (320)		4.5 %	-370.00 [-549.02, -190.98]
Penta de Peppo 1995	15	534 (288)	15	724 (280)		4.0 %	-190.00 [-393.27, 13.27]
Pinosky 1997	20	600 (219.1)	19	1060 (553.5)		2.9 %	-460.00 [-726.76, -193.24]
Shore-Lesserson 1996	17	649 (391)	13	923 (496)		2.2 %	-274.00 [-601.48, 53.48]
Speekenbrink 1995	15	352 (150)	15	674 (411)		3.6 %	-322.00 [-543.41, -100.59]
Subtotal (95% CI)	**312**		**307**			**49.4 %**	**-245.03 [-329.76, -160.29]**
Heterogeneity: Tau² = 11844.38; Chi² = 46.53, df = 11 (P<0.00001); I² =76%							
Test for overall effect: Z = 5.67 (P < 0.00001)							
2 Total dose 2.0 - 10.0 grams							
Armellin 2001	143	447 (262)	140	720 (357)		7.4 %	-273.00 [-346.08, -199.92]
Corbeau 1995	41	1015 (409)	20	1416 (559)		2.8 %	-401.00 [-676.12, -125.88]
Jimenez 2007	24	464 (369.2)	26	1037 (658)		2.5 %	-573.00 [-865.89, -280.11]
Katoh 1997	62	241 (79.27)	31	392 (305.67)		6.4 %	-151.00 [-260.40, -41.60]
Katsaros 1996	104	474 (244.75)	106	906 (525.1)		6.3 %	-432.00 [-542.48, -321.52]
Kuitunen 2005	20	802 (214.7)	20	995 (281.7)		5.1 %	-193.00 [-348.23, -37.77]
Pleym 2003	40	475 (269)	39	713 (243)		6.3 %	-238.00 [-350.98, -125.02]
Taghaddomi 2009	50	471 (182)	50	844 (363)		6.3 %	-373.00 [-485.55, -260.45]
Uozaki 2001	6	646 (380)	6	846 (510)		1.1 %	-200.00 [-708.90, 308.90]



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Study or subgroup	TXA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Zabeeda 2002	25	194 (135)	25	488 (238)		6.4 %	-294.00 [-401.26, -186.74]
Subtotal (95% CI)	**515**		**463**			**50.6 %**	**-297.94 [-364.49, -231.39]**
Heterogeneity: Tau^2 = 5796.93; Chi^2 = 21.50, df = 9 (P = 0.01); I^2 =58%							
Test for overall effect: Z = 8.77 (P < 0.00001)							
Total (95% CI)	**827**		**770**			**100.0 %**	**-272.87 [-328.85, -216.89]**
Heterogeneity: Tau^2 = 9687.61; Chi^2 = 83.41, df = 21 (P<0.00001); I^2 =75%							
Test for overall effect: Z = 9.55 (P < 0.00001)							

-1000 -500 0 500 1000

Favours TXA Favours Control

Analysis 2.11. Comparison 2 Tranexamic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 11 Blood loss - Total.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 2 Tranexamic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 11 Blood loss - Total

Study or subgroup	TXA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Cardiac surgery							
Isetta 1993	70	602 (562)	70	1000 (736)		4.2 %	-398.00 [-614.93, -181.07]
Jimenez 2007	24	835 (1013.57)	26	1466 (2106.95)		1.2 %	-631.00 [-1536.72, 274.72]
Katoh 1997	62	437.5 (143.76)	31	954 (846.3)		3.7 %	-516.50 [-816.56, -216.44]
Kuitunen 2006	15	1008 (251)	15	1081 (654)		3.3 %	-73.00 [-427.50, 281.50]
Mehr-Aein 2007	33	320 (38)	33	480 (75)		5.0 %	-160.00 [-188.69, -131.31]
Uozaki 2001	6	919 (365)	6	1369 (544)		2.4 %	-450.00 [-974.18, 74.18]
Subtotal (95% CI)	**210**		**181**			**19.8 %**	**-300.47 [-470.74, -130.21]**
Heterogeneity: Tau^2 = 21220.40; Chi^2 = 12.19, df = 5 (P = 0.03); I^2 =59%							
Test for overall effect: Z = 3.46 (P = 0.00054)							

-1000 -500 0 500 1000

Favours TXA Favours Control

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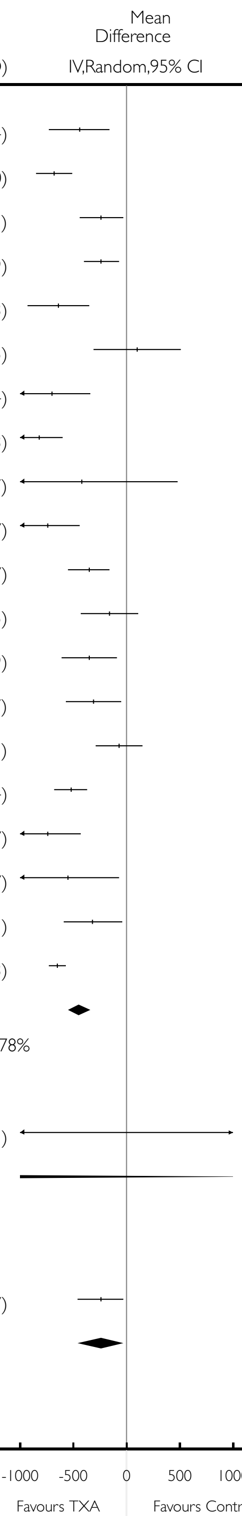
Study or subgroup	TXA N	Mean(SD)	Control N	Mean(SD)	Weight	Mean Difference IV,Random,95% CI
2 Orthopaedic surgery						
Alvarez 2008	46	1301 (621)	49	1744 (804)	3.8 %	-443.00 [-730.89, -155.11]
Benoni 1996	43	730 (280)	43	1410 (480)	4.5 %	-680.00 [-846.09, -513.91]
Benoni 2001	18	759 (260.41)	20	996 (380.33)	4.3 %	-237.00 [-442.56, -31.44]
Claeys 2007	20	801 (244)	20	1038 (289)	4.5 %	-237.00 [-402.76, -71.24]
Ekback 2000	20	1130 (400)	20	1770 (523)	3.8 %	-640.00 [-928.56, -351.44]
Garneti 2004	25	1443 (809)	25	1340 (665)	3.0 %	103.00 [-307.51, 513.51]
Hiipala 1995	15	847 (356)	13	1549 (574)	3.3 %	-702.00 [-1062.30, -341.70]
Hiipala 1997	39	689 (289)	38	1509 (643)	4.2 %	-820.00 [-1043.66, -596.34]
Husted 2003	20	814 (1264.92)	20	1231 (1617.47)	1.2 %	-417.00 [-1316.90, 482.90]
Jansen 1999	21	678 (352)	21	1419 (607)	3.7 %	-741.00 [-1041.11, -440.89]
Johansson 2005	47	969 (434)	53	1324 (577)	4.3 %	-355.00 [-553.81, -156.19]
Lemay 2004	20	1308 (462)	19	1469 (405)	3.9 %	-161.00 [-433.32, 111.32]
MacGillivray 2010	40	569 (294)	20	918 (549)	4.0 %	-349.00 [-606.28, -91.72]
Niskanen 2005	19	792 (360)	20	1102 (463.7)	3.9 %	-310.00 [-569.81, -50.19]
Orpen 2006	15	660 (296.15)	14	726 (308.29)	4.2 %	-66.00 [-286.32, 154.32]
Sadeghi 2007	32	960 (284)	35	1484 (374)	4.6 %	-524.00 [-682.22, -365.78]
Sorin 1999	21	678 (352)	21	1422 (637)	3.6 %	-744.00 [-1055.27, -432.73]
Wong 2008	73	1592 (1315)	74	2138 (1607)	2.6 %	-546.00 [-1020.40, -71.60]
Yamasaki 2004	20	1350 (477)	20	1667 (401)	3.9 %	-317.00 [-590.11, -43.89]
Zhang 2007	51	559 (159)	51	1208 (243)	4.9 %	-649.00 [-728.70, -569.30]
Subtotal (95% CI)	**605**		**596**		**76.0 %**	**-446.19 [-554.61, -337.78]**
Heterogeneity: $Tau^2 = 41720.91$; $Chi^2 = 85.30$, df = 19 (P<0.00001); I^2 =78%						
Test for overall effect: Z = 8.07 (P < 0.00001)						
3 Liver surgery						
Yassen 1993	10	6042 (3949)	10	12594 (11911)	0.0 %	-6552.00 [-14329.54, 1225.54]
Subtotal (95% CI)	**10**		**10**		**0.0 %**	**-6552.00 [-14329.54, 1225.54]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.65 (P = 0.099)						
4 Gynaecological surgery						
Caglar 2008	50	804 (482)	50	1047 (617)	4.2 %	-243.00 [-460.02, -25.98]
Subtotal (95% CI)	**50**		**50**		**4.2 %**	**-243.00 [-460.02, -25.98]**
Heterogeneity: not applicable						
Test for overall effect: Z = 2.19 (P = 0.028)						



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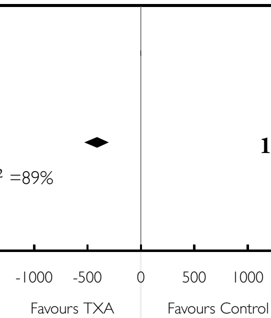
Study or subgroup	TXA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
5 Head % neck surgery							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**875**		**837**			**100.0 %**	**-414.06 [-525.19, -302.92]**
Heterogeneity: Tau^2 = 63946.73; Chi^2 = 249.58, df = 27 (P<0.00001); I^2 =89%							
Test for overall effect: Z = 7.30 (P < 0.00001)							



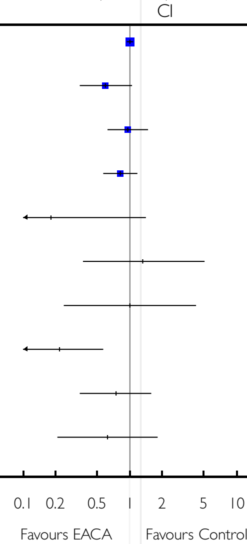
Analysis 3.1. Comparison 3 Epsilon Aminocaproic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 1 No. Exposed to Allogeneic Blood.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 3 Epsilon Aminocaproic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 1 No. Exposed to Allogeneic Blood

Study or subgroup	EACA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Berenholtz 2009	85/91	85/91		17.1 %	1.00 [0.93, 1.08]
Kluger 2003	16/58	14/30		7.3 %	0.59 [0.34, 1.04]
Greilich 2009	15/25	17/27		9.6 %	0.95 [0.62, 1.47]
Hardy 1998	23/46	27/44		10.9 %	0.81 [0.56, 1.18]
Daily 1994	1/21	5/19		0.9 %	0.18 [0.02, 1.41]
Ray 2005	4/15	3/15		2.0 %	1.33 [0.36, 4.97]
Penta de Peppo 1995	3/15	3/15		1.7 %	1.00 [0.24, 4.18]
Menichetti 1996	4/24	18/24		3.7 %	0.22 [0.09, 0.56]
Pinosky 1997	7/20	9/19		4.9 %	0.74 [0.34, 1.58]
Harley 2002	4/22	7/24		2.8 %	0.62 [0.21, 1.84]



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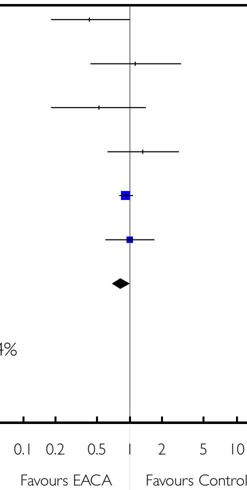
Study or subgroup	EACA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Greilich 2001	5/23	13/25		4.1 %	0.42 [0.18, 0.99]
Troianos 1999	7/34	6/33		3.3 %	1.13 [0.43, 3.02]
Kreisler 2005	4/22	9/25		3.1 %	0.51 [0.18, 1.41]
Kikura 2006	12/50	9/50		4.8 %	1.33 [0.62, 2.88]
Dalmau 2000	36/42	37/40		15.9 %	0.93 [0.80, 1.08]
Amar 2003	12/22	13/24		7.8 %	1.01 [0.59, 1.71]
Total (95% CI)	**530**	**505**		**100.0 %**	**0.81 [0.67, 0.99]**

Total events: 238 (EACA), 275 (Control)

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 41.12$, df = 15 (P = 0.00031); $I^2 = 64\%$

Test for overall effect: Z = 2.05 (P = 0.040)



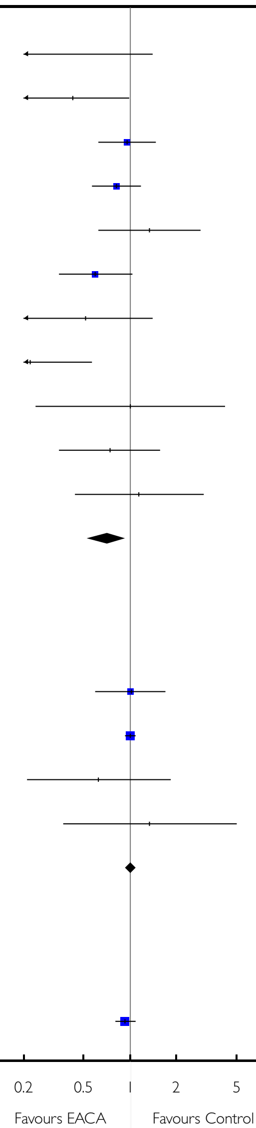
Analysis 3.2. Comparison 3 Epsilon Aminocaproic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 2 No. Exposed to Allogeneic Blood - Type of Surgery.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 3 Epsilon Aminocaproic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 2 No. Exposed to Allogeneic Blood - Type of Surgery

Study or subgroup	EACA n/N	Control n/N	Weight	Risk Ratio M-H,Random,95% CI
1 Cardiac Surgery				
Daily 1994	1/21	5/19	0.9 %	0.18 [0.02, 1.41]
Greilich 2001	5/23	13/25	4.1 %	0.42 [0.18, 0.99]
Greilich 2009	15/25	17/27	9.6 %	0.95 [0.62, 1.47]
Hardy 1998	23/46	27/44	10.9 %	0.81 [0.56, 1.18]
Kikura 2006	12/50	9/50	4.8 %	1.33 [0.62, 2.88]
Kluger 2003	16/58	14/30	7.3 %	0.59 [0.34, 1.04]
Kreisler 2005	4/22	9/25	3.1 %	0.51 [0.18, 1.41]
Menichetti 1996	4/24	18/24	3.7 %	0.22 [0.09, 0.56]
Penta de Peppo 1995	3/15	3/15	1.7 %	1.00 [0.24, 4.18]
Pinosky 1997	7/20	9/19	4.9 %	0.74 [0.34, 1.58]
Troianos 1999	7/34	6/33	3.3 %	1.13 [0.43, 3.02]
Subtotal (95% CI)	**338**	**311**	**54.4 %**	**0.70 [0.52, 0.93]**
Total events: 97 (EACA), 130 (Control)				
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 16.38$, df = 10 (P = 0.09); I^2 =39%				
Test for overall effect: Z = 2.43 (P = 0.015)				
2 Orthopaedic Surgery				
Amar 2003	12/22	13/24	7.8 %	1.01 [0.59, 1.71]
Berenholtz 2009	85/91	85/91	17.1 %	1.00 [0.93, 1.08]
Harley 2002	4/22	7/24	2.8 %	0.62 [0.21, 1.84]
Ray 2005	4/15	3/15	2.0 %	1.33 [0.36, 4.97]
Subtotal (95% CI)	**150**	**154**	**29.8 %**	**1.00 [0.93, 1.08]**
Total events: 105 (EACA), 108 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.01$, df = 3 (P = 0.80); I^2 =0.0%				
Test for overall effect: Z = 0.03 (P = 0.97)				
3 Liver Surgery				
Dalmau 2000	36/42	37/40	15.9 %	0.93 [0.80, 1.08]



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Study or subgroup	EACA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**42**	**40**		**15.9 %**	**0.93 [0.80, 1.08]**
Total events: 36 (EACA), 37 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.98 (P = 0.33)					
Total (95% CI)	**530**	**505**		**100.0 %**	**0.81 [0.67, 0.99]**
Total events: 238 (EACA), 275 (Control)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 41.12$, df = 15 (P = 0.00031); $I^2 = 64\%$					
Test for overall effect: Z = 2.05 (P = 0.040)					

0.2 0.5 1 2 5

Favours EACA Favours Control

Analysis 3.3. Comparison 3 Epsilon Aminocaproic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 3 No. Exposed to Allogeneic Blood - Transfusion Protocol.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 3 Epsilon Aminocaproic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 3 No. Exposed to Allogeneic Blood - Transfusion Protocol

Study or subgroup	EACA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Transfusion Protocol					
Amar 2003	12/22	13/24		7.8 %	1.01 [0.59, 1.71]
Berenholtz 2009	85/91	85/91		17.1 %	1.00 [0.93, 1.08]
Daily 1994	1/21	5/19		0.9 %	0.18 [0.02, 1.41]
Dalmau 2000	36/42	37/40		15.9 %	0.93 [0.80, 1.08]
Greilich 2001	5/23	13/25		4.1 %	0.42 [0.18, 0.99]
Greilich 2009	15/25	17/27		9.6 %	0.95 [0.62, 1.47]
Hardy 1998	23/46	27/44		10.9 %	0.81 [0.56, 1.18]
Harley 2002	4/22	7/24		2.8 %	0.62 [0.21, 1.84]

0.1 0.2 0.5 1 2 5 10

Favours EACA Favours Control

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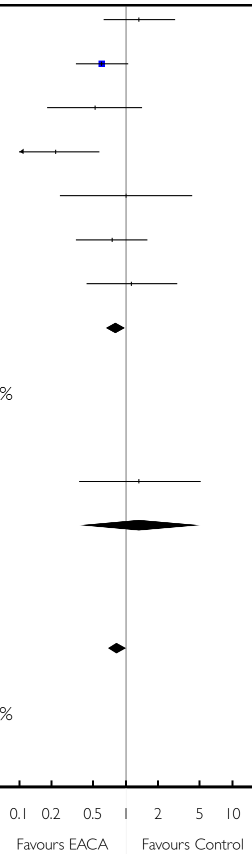
Study or subgroup	EACA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Kikura 2006	12/50	9/50		4.8 %	1.33 [0.62, 2.88]
Kluger 2003	16/58	14/30		7.3 %	0.59 [0.34, 1.04]
Kreisler 2005	4/22	9/25		3.1 %	0.51 [0.18, 1.41]
Menichetti 1996	4/24	18/24		3.7 %	0.22 [0.09, 0.56]
Penta de Peppo 1995	3/15	3/15		1.7 %	1.00 [0.24, 4.18]
Pinosky 1997	7/20	9/19		4.9 %	0.74 [0.34, 1.58]
Troianos 1999	7/34	6/33		3.3 %	1.13 [0.43, 3.02]
Subtotal (95% CI)	**515**	**490**		**98.0 %**	**0.80 [0.65, 0.98]**
Total events: 234 (EACA), 272 (Control)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 42.29$, df = 14 (P = 0.00011); I^2 =67%					
Test for overall effect: Z = 2.12 (P = 0.034)					
2 No Transfusion Protocol					
Ray 2005	4/15	3/15		2.0 %	1.33 [0.36, 4.97]
Subtotal (95% CI)	**15**	**15**		**2.0 %**	**1.33 [0.36, 4.97]**
Total events: 4 (EACA), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					
Total (95% CI)	**530**	**505**		**100.0 %**	**0.81 [0.67, 0.99]**
Total events: 238 (EACA), 275 (Control)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 41.12$, df = 15 (P = 0.00031); I^2 =64%					
Test for overall effect: Z = 2.05 (P = 0.040)					



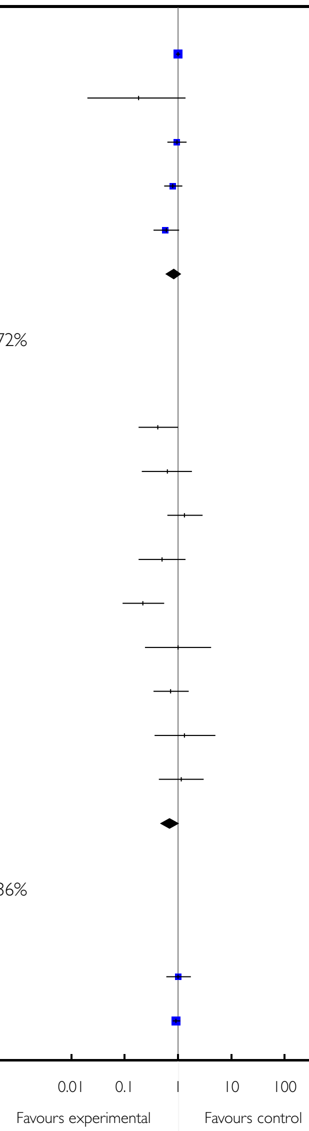
Analysis 3.4. Comparison 3 Epsilon Aminocaproic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 4 Trial Methodological Quality - Allocation Concealment.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 3 Epsilon Aminocaproic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 4 Trial Methodological Quality - Allocation Concealment

Study or subgroup	EACA n/N	Control n/N	Weight	Risk Ratio M-H,Random,95% CI
1 Allocation concealment - Yes				
Berenholtz 2009	85/91	85/91	17.1 %	1.00 [0.93, 1.08]
Daily 1994	1/21	5/19	0.9 %	0.18 [0.02, 1.41]
Greilich 2009	15/25	17/27	9.6 %	0.95 [0.62, 1.47]
Hardy 1998	23/46	27/44	10.9 %	0.81 [0.56, 1.18]
Kluger 2003	16/58	14/30	7.3 %	0.59 [0.34, 1.04]
Subtotal (95% CI)	**241**	**211**	**45.7 %**	**0.82 [0.58, 1.16]**
Total events: 140 (EACA), 148 (Control)				
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 14.35$, df = 4 (P = 0.01); $I^2 = 72\%$				
Test for overall effect: Z = 1.13 (P = 0.26)				
2 Allocation concealment - Unclear				
Greilich 2001	5/23	13/25	4.1 %	0.42 [0.18, 0.99]
Harley 2002	4/22	7/24	2.8 %	0.62 [0.21, 1.84]
Kikura 2006	12/50	9/50	4.8 %	1.33 [0.62, 2.88]
Kreisler 2005	4/22	9/25	3.1 %	0.51 [0.18, 1.41]
Menichetti 1996	4/24	18/24	3.7 %	0.22 [0.09, 0.56]
Penta de Peppo 1995	3/15	3/15	1.7 %	1.00 [0.24, 4.18]
Pinosky 1997	7/20	9/19	4.9 %	0.74 [0.34, 1.58]
Ray 2005	4/15	3/15	2.0 %	1.33 [0.36, 4.97]
Troianos 1999	7/34	6/33	3.3 %	1.13 [0.43, 3.02]
Subtotal (95% CI)	**225**	**230**	**30.6 %**	**0.68 [0.46, 1.03]**
Total events: 50 (EACA), 77 (Control)				
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 12.54$, df = 8 (P = 0.13); $I^2 = 36\%$				
Test for overall effect: Z = 1.83 (P = 0.068)				
3 Allocation concealment - No				
Amar 2003	12/22	13/24	7.8 %	1.01 [0.59, 1.71]
Dalmau 2000	36/42	37/40	15.9 %	0.93 [0.80, 1.08]



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Study or subgroup	EACA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**64**	**64**		**23.7 %**	**0.93 [0.81, 1.08]**
Total events: 48 (EACA), 50 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.13, df = 1 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 0.94 (P = 0.35)					
Total (95% CI)	**530**	**505**		**100.0 %**	**0.81 [0.67, 0.99]**
Total events: 238 (EACA), 275 (Control)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 41.12, df = 15 (P = 0.00031); I^2 =64%					
Test for overall effect: Z = 2.05 (P = 0.040)					
Test for subgroup differences: Chi^2 = 0.0, df = 2 (P = 0.0), I^2 =0.0%					

0.01 0.1 1 10 100

Favours experimental Favours control

Analysis 3.5. Comparison 3 Epsilon Aminocaproic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 5 Units of Allogeneic Blood Transfused - Transfused Patients.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 3 Epsilon Aminocaproic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 5 Units of Allogeneic Blood Transfused - Transfused Patients

Study or subgroup	EACA N	EACA Mean(SD)	Control N	Control Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Amar 2003	12	3.12 (2.67)	13	3.32 (2.55)		7.7 %	-0.20 [-2.25, 1.85]
Dalmau 2000	36	7.81 (5.67)	37	8.38 (6.13)		4.4 %	-0.57 [-3.28, 2.14]
Kikura 2006	12	2.2 (0.7)	9	1.9 (0.7)		88.0 %	0.30 [-0.30, 0.90]
Total (95% CI)	**60**		**59**			**100.0 %**	**0.22 [-0.34, 0.79]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.56, df = 2 (P = 0.76); I^2 =0.0%							
Test for overall effect: Z = 0.77 (P = 0.44)							

-10 -5 0 5 10

Favours EACA Favours Control

Analysis 3.6. Comparison 3 Epsilon Aminocaproic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 6 Units of Allogeneic Blood Transfused - All Patients.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 3 Epsilon Aminocaproic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 6 Units of Allogeneic Blood Transfused - All Patients

Study or subgroup	EACA N	EACA Mean(SD)	Control N	Control Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Amar 2003	22	1.7 (2.5)	24	1.8 (2.5)		14.5 %	-0.10 [-1.55, 1.35]
Berenholtz 2009	91	5.9 (4.7)	91	6.9 (5.4)		14.3 %	-1.00 [-2.47, 0.47]
Dalmau 2000	42	6.69 (5.92)	40	7.75 (6.3)		7.2 %	-1.06 [-3.71, 1.59]
Greilich 2009	25	1.7 (1.8)	27	1.8 (2)		18.3 %	-0.10 [-1.13, 0.93]
Liu 1998	20	6.8 (1.2)	20	9.4 (1.1)		21.4 %	-2.60 [-3.31, -1.89]
Rao 1999	15	1.2 (0.4)	15	3.2 (0.45)		24.4 %	-2.00 [-2.30, -1.70]
Total (95% CI)	**215**		**217**			**100.0 %**	**-1.30 [-2.14, -0.45]**

Heterogeneity: Tau^2 = 0.73; Chi^2 = 23.45, df = 5 (P = 0.00028); I^2 =79%

Test for overall effect: Z = 3.01 (P = 0.0026)

-10 -5 0 5 10

Favours EACA Favours Control

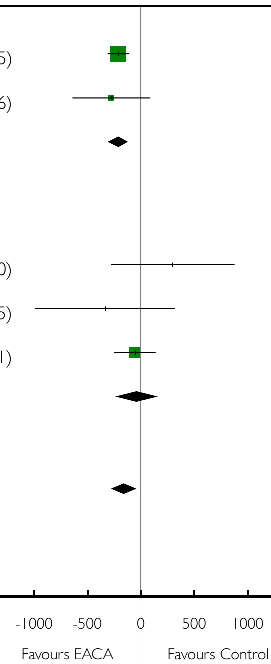
Analysis 3.7. Comparison 3 Epsilon Aminocaproic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 7 Blood loss - Intra-operative.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 3 Epsilon Aminocaproic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 7 Blood loss - Intra-operative

Study or subgroup	EACA N	EACA Mean(SD)	Control N	Control Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Cardiac surgery							
Liu 1998	20	1235 (207.6)	20	1443.9 (95)		55.5 %	-208.90 [-308.96, -108.84]
Pinosky 1997	20	1196 (451.7)	19	1471 (675.6)		9.8 %	-275.00 [-637.59, 87.59]
Subtotal (95% CI)	**40**		**39**			**65.3 %**	**-213.58 [-310.03, -117.13]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.12, df = 1 (P = 0.73); I^2 =0.0%							
Test for overall effect: Z = 4.34 (P = 0.000014)							
2 Orthopaedic surgery							
Amar 2003	22	1300 (1100)	24	1000 (900)		4.1 %	300.00 [-283.89, 883.89]
Berenholtz 2009	91	2938 (2315)	91	3273 (2195)		3.2 %	-335.00 [-990.45, 320.45]
Harley 2002	22	552 (331)	24	607 (331)		27.4 %	-55.00 [-246.49, 136.49]
Subtotal (95% CI)	**135**		**139**			**34.7 %**	**-40.66 [-236.71, 155.38]**
Heterogeneity: Tau^2 = 2904.60; Chi^2 = 2.10, df = 2 (P = 0.35); I^2 =5%							
Test for overall effect: Z = 0.41 (P = 0.68)							
Total (95% CI)	**175**		**178**			**100.0 %**	**-156.63 [-276.92, -36.33]**
Heterogeneity: Tau^2 = 4186.53; Chi^2 = 5.01, df = 4 (P = 0.29); I^2 =20%							
Test for overall effect: Z = 2.55 (P = 0.011)							



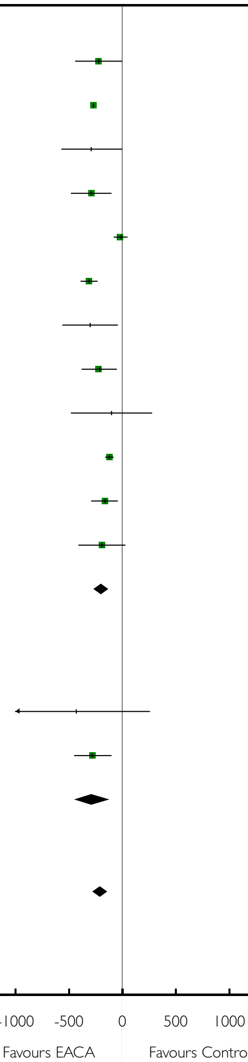
Analysis 3.8. Comparison 3 Epsilon Aminocaproic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 8 Blood loss - Post-operative.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 3 Epsilon Aminocaproic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 8 Blood loss - Post-operative

Study or subgroup	EACA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Cardiac surgery							
Daily 1994	21	623 (380)	19	845 (339)		5.5 %	-222.00 [-444.82, 0.82]
Del Rossi 1989	170	617.2 (43.9)	180	883.2 (29.3)		12.7 %	-266.00 [-273.87, -258.13]
Greilich 2009	25	715 (394)	27	1002 (627)		4.1 %	-287.00 [-569.46, -4.54]
Kikura 2006	50	650 (261)	50	940 (627)		6.5 %	-290.00 [-478.25, -101.75]
Kreisler 2005	22	269 (113)	25	284 (128)		11.2 %	-15.00 [-83.90, 53.90]
Liu 1998	20	987.2 (103.7)	20	1298.3 (143.2)		10.9 %	-311.10 [-388.59, -233.61]
Menichetti 1996	24	512 (250)	24	811 (600)		4.5 %	-299.00 [-559.05, -38.95]
Penta de Peppo 1995	15	509 (148)	15	724 (280)		7.5 %	-215.00 [-375.27, -54.73]
Pinosky 1997	20	961 (661.9)	19	1060 (553.5)		2.6 %	-99.00 [-481.22, 283.22]
Rao 1999	15	372 (55.5)	15	494 (62.4)		12.1 %	-122.00 [-164.26, -79.74]
Troianos 1999	34	529 (241)	33	691 (286)		8.9 %	-162.00 [-288.82, -35.18]
Vander-Salm 1996	51	647 (488)	52	839 (634)		5.6 %	-192.00 [-410.25, 26.25]
Subtotal (95% CI)	**467**		**479**			**92.0 %**	**-200.27 [-273.44, -127.09]**
Heterogeneity: $Tau^2 = 10265.78$; $Chi^2 = 97.18$, df = 11 (P<0.00001); I^2 =89%							
Test for overall effect: Z = 5.36 (P < 0.00001)							
2 Orthopaedic surgery							
Berenholtz 2009	91	3265 (2416)	91	3695 (2341)		0.9 %	-430.00 [-1121.19, 261.19]
Harley 2002	22	315 (207)	24	591 (374)		7.1 %	-276.00 [-448.83, -103.17]
Subtotal (95% CI)	**113**		**115**			**8.0 %**	**-285.06 [-452.73, -117.39]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.18$, df = 1 (P = 0.67); I^2 =0.0%							
Test for overall effect: Z = 3.33 (P = 0.00086)							
Total (95% CI)	**580**		**594**			**100.0 %**	**-207.49 [-276.43, -138.54]**
Heterogeneity: $Tau^2 = 9763.54$; $Chi^2 = 97.46$, df = 13 (P<0.00001); I^2 =87%							
Test for overall effect: Z = 5.90 (P < 0.00001)							



Analysis 3.9. Comparison 3 Epsilon Aminocaproic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 9 Blood loss - Total.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

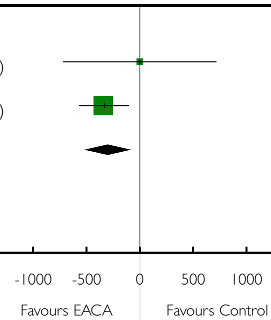
Comparison: 3 Epsilon Aminocaproic Acid versus Control (Blood Transfusion % Blood Loss)

Outcome: 9 Blood loss - Total

Study or subgroup	EACA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Orthopaedic surgery							
Amar 2003	22	1600 (1100)	24	1600 (1400)		9.5 %	0.0 [-724.57, 724.57]
Harley 2002	22	867 (207)	24	1198 (544)		90.5 %	-331.00 [-565.20, -96.80]
Total (95% CI)	**44**		**48**			**100.0 %**	**-299.69 [-522.54, -76.84]**

Heterogeneity: Tau² = 0.0; Chi² = 0.73, df = 1 (P = 0.39); I² =0.0%

Test for overall effect: Z = 2.64 (P = 0.0084)



Analysis 4.1. Comparison 4 Aprotinin versus Tranexamic Acid (Blood Transfusion & Blood Loss), Outcome 1 No. Exposed to Allogeneic Blood.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 4 Aprotinin versus Tranexamic Acid (Blood Transfusion % Blood Loss)

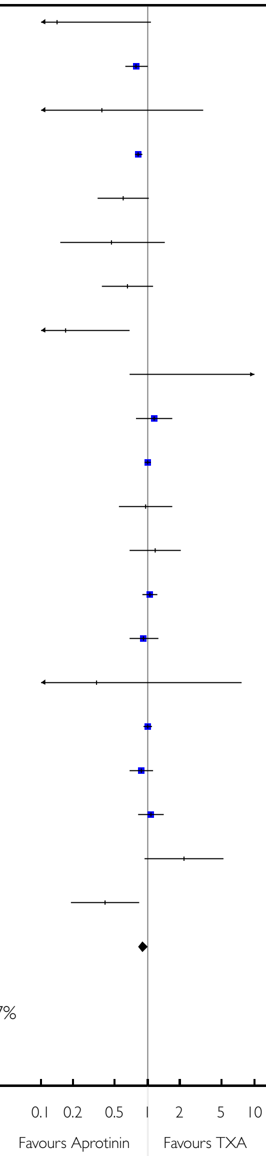
Outcome: 1 No. Exposed to Allogeneic Blood

Study or subgroup	Aprotinin n/N	TXA n/N	Weight	Risk Ratio M-H,Random,95% CI
Mansour 2004	1/20	7/20	0.3 %	0.14 [0.02, 1.06]
Dietrich 2008	52/110	67/110	8.0 %	0.78 [0.61, 0.99]
Vanek 2005	1/29	3/32	0.2 %	0.37 [0.04, 3.34]
Fergusson 2008	419/780	506/770	12.4 %	0.82 [0.75, 0.89]
Mengistu 2008	10/25	17/25	3.1 %	0.59 [0.34, 1.02]
Blauhut 1994	3/14	7/15	0.9 %	0.46 [0.15, 1.44]
Bernet 1999	11/28	17/28	3.1 %	0.65 [0.37, 1.12]
Menichetti 1996	2/24	12/24	0.6 %	0.17 [0.04, 0.67]
Engel 2001	5/12	0/12	0.2 %	11.00 [0.67, 179.29]
Isetta 1993	55/140	24/70	5.1 %	1.15 [0.78, 1.68]
Ickx 2006	24/24	27/27	12.6 %	1.00 [0.93, 1.08]
Corbeau 1995	15/43	15/41	2.9 %	0.95 [0.54, 1.69]
Casati 1999	19/67	17/70	3.0 %	1.17 [0.67, 2.05]
Casati 2000	185/518	178/522	10.3 %	1.05 [0.89, 1.24]
Speekenbrink 1995	12/15	13/15	6.3 %	0.92 [0.67, 1.27]
Penta de Peppo 1995	0/15	1/15	0.1 %	0.33 [0.01, 7.58]
Pugh 1995	21/21	22/22	12.3 %	1.00 [0.92, 1.09]
Later 2009	48/96	57/99	7.7 %	0.87 [0.67, 1.13]
Dalmau 2004	40/63	38/64	7.3 %	1.07 [0.81, 1.41]
Kuitunen 2005	11/20	5/20	1.5 %	2.20 [0.93, 5.18]
Diprose 2005	8/60	20/60	1.9 %	0.40 [0.19, 0.84]
Total (95% CI)	**2124**	**2061**	**100.0 %**	**0.90 [0.81, 1.01]**

Total events: 942 (Aprotinin), 1053 (TXA)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 60.78$, df = 20 (P<0.00001); $I^2 = 67\%$

Test for overall effect: Z = 1.79 (P = 0.074)



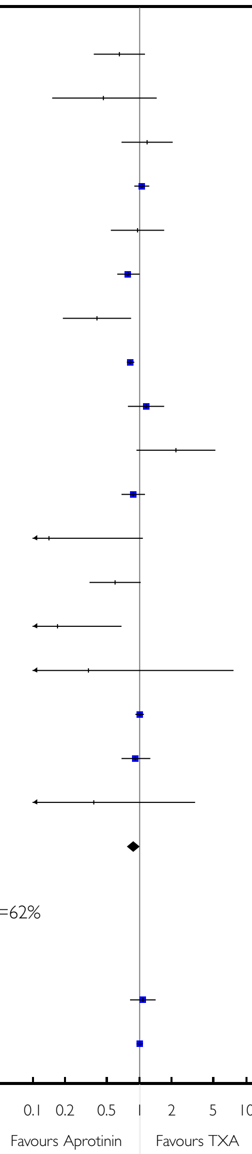
Analysis 4.2. Comparison 4 Aprotinin versus Tranexamic Acid (Blood Transfusion & Blood Loss), Outcome 2 No. Exposed to Allogeneic Blood - Type of Surgery.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 4 Aprotinin versus Tranexamic Acid (Blood Transfusion % Blood Loss)

Outcome: 2 No. Exposed to Allogeneic Blood - Type of Surgery

Study or subgroup	Aprotinin n/N	TXA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Cardiac surgery					
Bernet 1999	11/28	17/28		3.1 %	0.65 [0.37, 1.12]
Blauhut 1994	3/14	7/15		0.9 %	0.46 [0.15, 1.44]
Casati 1999	19/67	17/70		3.0 %	1.17 [0.67, 2.05]
Casati 2000	185/518	178/522		10.3 %	1.05 [0.89, 1.24]
Corbeau 1995	15/43	15/41		2.9 %	0.95 [0.54, 1.69]
Dietrich 2008	52/110	67/110		8.0 %	0.78 [0.61, 0.99]
Diprose 2005	8/60	20/60		1.9 %	0.40 [0.19, 0.84]
Fergusson 2008	419/780	506/770		12.4 %	0.82 [0.75, 0.89]
Isetta 1993	55/140	24/70		5.1 %	1.15 [0.78, 1.68]
Kuitunen 2005	11/20	5/20		1.5 %	2.20 [0.93, 5.18]
Later 2009	48/96	57/99		7.7 %	0.87 [0.67, 1.13]
Mansour 2004	1/20	7/20		0.3 %	0.14 [0.02, 1.06]
Mengistu 2008	10/25	17/25		3.1 %	0.59 [0.34, 1.02]
Menichetti 1996	2/24	12/24		0.6 %	0.17 [0.04, 0.67]
Penta de Peppo 1995	0/15	1/15		0.1 %	0.33 [0.01, 7.58]
Pugh 1995	21/21	22/22		12.3 %	1.00 [0.92, 1.09]
Speekenbrink 1995	12/15	13/15		6.3 %	0.92 [0.67, 1.27]
Vanek 2005	1/29	3/32		0.2 %	0.37 [0.04, 3.34]
Subtotal (95% CI)	**2025**	**1958**		**79.9 %**	**0.87 [0.76, 0.99]**
Total events: 873 (Aprotinin), 988 (TXA)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 45.01$, df = 17 (P = 0.00024); $I^2 = 62\%$					
Test for overall effect: Z = 2.14 (P = 0.032)					
2 Liver surgery					
Dalmau 2004	40/63	38/64		7.3 %	1.07 [0.81, 1.41]
Ickx 2006	24/24	27/27		12.6 %	1.00 [0.93, 1.08]



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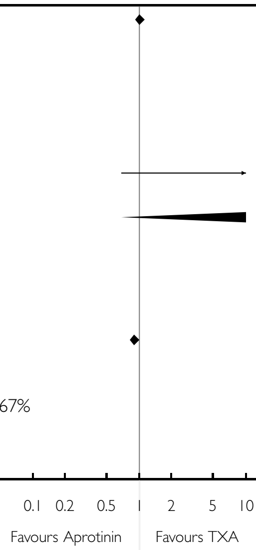
Study or subgroup	Aprotinin n/N	TXA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**87**	**91**		**19.9 %**	**1.01 [0.91, 1.11]**
Total events: 64 (Aprotinin), 65 (TXA)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.14$, df = 1 (P = 0.29); I^2 =12%					
Test for overall effect: Z = 0.16 (P = 0.87)					
3 Orthopaedic surgery					
Engel 2001	5/12	0/12		0.2 %	11.00 [0.67, 179.29]
Subtotal (95% CI)	**12**	**12**		**0.2 %**	**11.00 [0.67, 179.29]**
Total events: 5 (Aprotinin), 0 (TXA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.68 (P = 0.092)					
Total (95% CI)	**2124**	**2061**		**100.0 %**	**0.90 [0.81, 1.01]**
Total events: 942 (Aprotinin), 1053 (TXA)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 60.78$, df = 20 (P<0.00001); I^2 =67%					
Test for overall effect: Z = 1.79 (P = 0.074)					



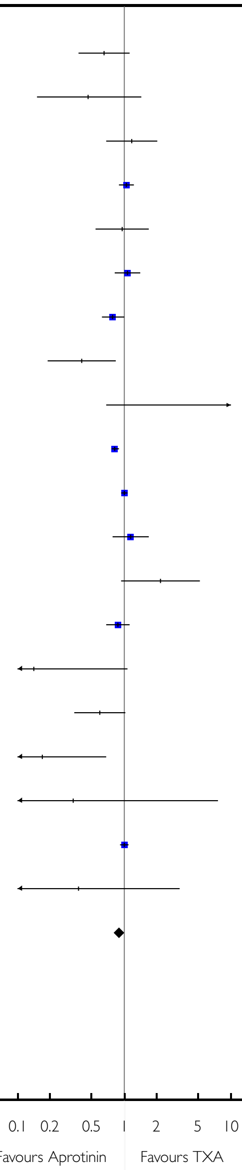
Analysis 4.3. Comparison 4 Aprotinin versus Tranexamic Acid (Blood Transfusion & Blood Loss), Outcome 3 No. Exposed to Allogeneic Blood - Transfusion Protocol.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 4 Aprotinin versus Tranexamic Acid (Blood Transfusion % Blood Loss)

Outcome: 3 No. Exposed to Allogeneic Blood - Transfusion Protocol

Study or subgroup	Aprotinin n/N	TXA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Transfusion Protocol					
Bernet 1999	11/28	17/28		3.1 %	0.65 [0.37, 1.12]
Blauhut 1994	3/14	7/15		0.9 %	0.46 [0.15, 1.44]
Casati 1999	19/67	17/70		3.0 %	1.17 [0.67, 2.05]
Casati 2000	185/518	178/522		10.3 %	1.05 [0.89, 1.24]
Corbeau 1995	15/43	15/41		2.9 %	0.95 [0.54, 1.69]
Dalmau 2004	40/63	38/64		7.3 %	1.07 [0.81, 1.41]
Dietrich 2008	52/110	67/110		8.0 %	0.78 [0.61, 0.99]
Diprose 2005	8/60	20/60		1.9 %	0.40 [0.19, 0.84]
Engel 2001	5/12	0/12		0.2 %	11.00 [0.67, 179.29]
Fergusson 2008	419/780	506/770		12.4 %	0.82 [0.75, 0.89]
Ickx 2006	24/24	27/27		12.6 %	1.00 [0.93, 1.08]
Isetta 1993	55/140	24/70		5.1 %	1.15 [0.78, 1.68]
Kuitunen 2005	11/20	5/20		1.5 %	2.20 [0.93, 5.18]
Later 2009	48/96	57/99		7.7 %	0.87 [0.67, 1.13]
Mansour 2004	1/20	7/20		0.3 %	0.14 [0.02, 1.06]
Mengistu 2008	10/25	17/25		3.1 %	0.59 [0.34, 1.02]
Menichetti 1996	2/24	12/24		0.6 %	0.17 [0.04, 0.67]
Penta de Peppo 1995	0/15	1/15		0.1 %	0.33 [0.01, 7.58]
Pugh 1995	21/21	22/22		12.3 %	1.00 [0.92, 1.09]
Vanek 2005	1/29	3/32		0.2 %	0.37 [0.04, 3.34]
Subtotal (95% CI)	**2109**	**2046**		**93.7 %**	**0.90 [0.80, 1.01]**



Total events: 930 (Aprotinin), 1040 (TXA)

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 60.87$, df = 19 (P<0.00001); I^2 =69%

Test for overall effect: Z = 1.75 (P = 0.081)

2 No Transfusion Protocol

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Study or subgroup	Aprotinin n/N	TXA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Speekenbrink 1995	12/15	13/15		6.3 %	0.92 [0.67, 1.27]
Subtotal (95% CI)	**15**	**15**		**6.3 %**	**0.92 [0.67, 1.27]**
Total events: 12 (Aprotinin), 13 (TXA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.49 (P = 0.63)					
Total (95% CI)	**2124**	**2061**		**100.0 %**	**0.90 [0.81, 1.01]**
Total events: 942 (Aprotinin), 1053 (TXA)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 60.78$, df = 20 (P<0.00001); I^2 =67%					
Test for overall effect: Z = 1.79 (P = 0.074)					

0.1 0.2 0.5 1 2 5 10

Favours Aprotinin Favours TXA

Analysis 4.4. Comparison 4 Aprotinin versus Tranexamic Acid (Blood Transfusion & Blood Loss), Outcome 4 Trial Methodological Quality - Allocation Concealment.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 4 Aprotinin versus Tranexamic Acid (Blood Transfusion % Blood Loss)

Outcome: 4 Trial Methodological Quality - Allocation Concealment

Study or subgroup	Aprotinin n/N	TXA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Allocation concealment - Yes					
Dietrich 2008	52/110	67/110		8.0 %	0.78 [0.61, 0.99]
Fergusson 2008	419/780	506/770		12.4 %	0.82 [0.75, 0.89]
Mansour 2004	1/20	7/20		0.3 %	0.14 [0.02, 1.06]
Vanek 2005	1/29	3/32		0.2 %	0.37 [0.04, 3.34]
Subtotal (95% CI)	**939**	**932**		**21.0 %**	**0.80 [0.69, 0.92]**
Total events: 473 (Aprotinin), 583 (TXA)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.60$, df = 3 (P = 0.31); I^2 =17%					
Test for overall effect: Z = 3.14 (P = 0.0017)					

0.01 0.1 1 10 100

Favours experimental Favours control

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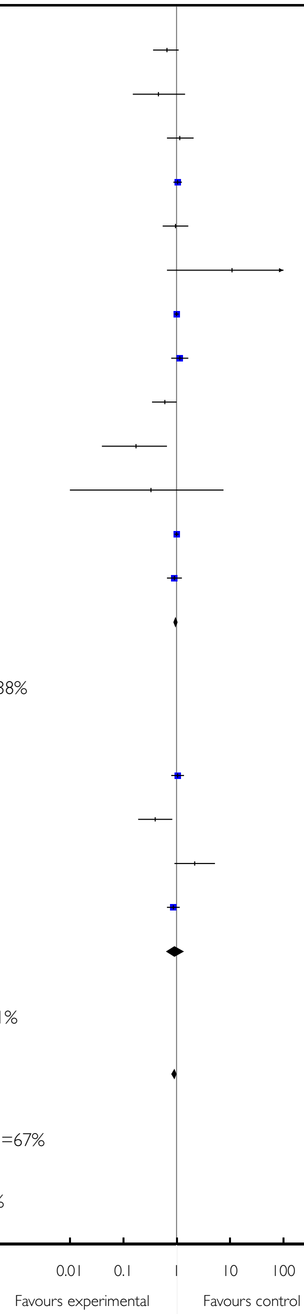
Study or subgroup	Aprotinin n/N	TXA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
2 Allocation concealment - Unclear					
Bernet 1999	11/28	17/28		3.1 %	0.65 [0.37, 1.12]
Blauhut 1994	3/14	7/15		0.9 %	0.46 [0.15, 1.44]
Casati 1999	19/67	17/70		3.0 %	1.17 [0.67, 2.05]
Casati 2000	185/518	178/522		10.3 %	1.05 [0.89, 1.24]
Corbeau 1995	15/43	15/41		2.9 %	0.95 [0.54, 1.69]
Engel 2001	5/12	0/12		0.2 %	11.00 [0.67, 179.29]
Ickx 2006	24/24	27/27		12.6 %	1.00 [0.93, 1.08]
Isetta 1993	55/140	24/70		5.1 %	1.15 [0.78, 1.68]
Mengistu 2008	10/25	17/25		3.1 %	0.59 [0.34, 1.02]
Menichetti 1996	2/24	12/24		0.6 %	0.17 [0.04, 0.67]
Penta de Peppo 1995	0/15	1/15		0.1 %	0.33 [0.01, 7.58]
Pugh 1995	21/21	22/22		12.3 %	1.00 [0.92, 1.09]
Speekenbrink 1995	12/15	13/15		6.3 %	0.92 [0.67, 1.27]
Subtotal (95% CI)	**946**	**886**		**60.6 %**	**0.97 [0.88, 1.07]**
Total events: 362 (Aprotinin), 350 (TXA)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 19.25$, df = 12 (P = 0.08); $I^2 = 38\%$					
Test for overall effect: Z = 0.58 (P = 0.56)					
3 Allocation concealment - No					
Dalmau 2004	40/63	38/64		7.3 %	1.07 [0.81, 1.41]
Diprose 2005	8/60	20/60		1.9 %	0.40 [0.19, 0.84]
Kuitunen 2005	11/20	5/20		1.5 %	2.20 [0.93, 5.18]
Later 2009	48/96	57/99		7.7 %	0.87 [0.67, 1.13]
Subtotal (95% CI)	**239**	**243**		**18.4 %**	**0.93 [0.62, 1.39]**
Total events: 107 (Aprotinin), 120 (TXA)					
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 10.29$, df = 3 (P = 0.02); $I^2 = 71\%$					
Test for overall effect: Z = 0.34 (P = 0.73)					
Total (95% CI)	**2124**	**2061**		**100.0 %**	**0.90 [0.81, 1.01]**
Total events: 942 (Aprotinin), 1053 (TXA)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 60.78$, df = 20 (P<0.00001); $I^2 = 67\%$					
Test for overall effect: Z = 1.79 (P = 0.074)					
Test for subgroup differences: $Chi^2 = 0.0$, df = 2 (P = 0.0), $I^2 = 0.0\%$					



Analysis 4.5. Comparison 4 Aprotinin versus Tranexamic Acid (Blood Transfusion & Blood Loss), Outcome 5 Units Allogeneic Blood Transfused - Transfused Patients.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 4 Aprotinin versus Tranexamic Acid (Blood Transfusion % Blood Loss)

Outcome: 5 Units Allogeneic Blood Transfused - Transfused Patients

Study or subgroup	Aprotinin		TXA		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Blauhut 1994	3	1.68 (0.48)	7	1.71 (0.95)		16.9 %	-0.03 [-0.92, 0.86]
Casati 1999	19	1.9 (1.04)	17	1.94 (0.69)		41.0 %	-0.04 [-0.61, 0.53]
Corbeau 1995	15	2.29 (1.49)	15	2.19 (0.46)		21.5 %	0.10 [-0.69, 0.89]
Dalmau 2004	40	5.2 (4.17)	38	5.09 (3.7)		4.4 %	0.11 [-1.64, 1.86]
Diprose 2005	8	2.1 (1.42)	20	2.61 (1.55)		9.4 %	-0.51 [-1.71, 0.69]
Speekenbrink 1995	12	2.91 (1.94)	13	3.31 (1.62)		6.8 %	-0.40 [-1.81, 1.01]
Total (95% CI)	**97**		**110**			**100.0 %**	**-0.07 [-0.44, 0.30]**

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.97, df = 5 (P = 0.97); I^2 =0.0%

Test for overall effect: Z = 0.37 (P = 0.71)

Analysis 4.6. Comparison 4 Aprotinin versus Tranexamic Acid (Blood Transfusion & Blood Loss), Outcome 6 Units Allogeneic Blood Transfused - All Patients.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

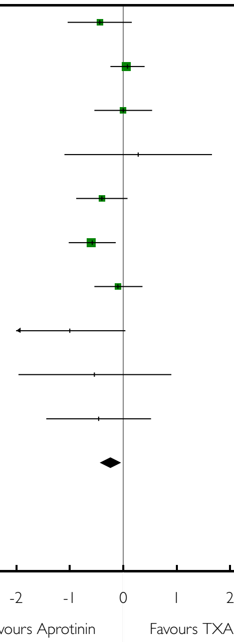
Comparison: 4 Aprotinin versus Tranexamic Acid (Blood Transfusion % Blood Loss)

Outcome: 6 Units Allogeneic Blood Transfused - All Patients

Study or subgroup	Aprotinin N	Mean(SD)	TXA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Blauhut 1994	14	0.36 (0.47)	15	0.8 (1.08)		9.5 %	-0.44 [-1.04, 0.16]
Casati 1999	67	0.54 (1.02)	70	0.47 (0.9)		23.6 %	0.07 [-0.25, 0.39]
Corbeau 1995	43	0.8 (1.4)	41	0.8 (1.1)		11.4 %	0.0 [-0.54, 0.54]
Dalmau 2004	63	3.3 (4.16)	64	3.02 (3.79)		2.0 %	0.28 [-1.10, 1.66]
Dietrich 2008	110	1.3 (1.8)	110	1.7 (1.8)		13.8 %	-0.40 [-0.88, 0.08]
Diprose 2005	60	0.28 (0.87)	60	0.87 (1.52)		15.4 %	-0.59 [-1.03, -0.15]
Hekmat 2004	60	0.7 (1.2)	58	0.8 (1.3)		14.9 %	-0.10 [-0.55, 0.35]
Mengistu 2008	25	0.8 (1.1)	25	1.8 (2.4)		3.6 %	-1.00 [-2.03, 0.03]
Speekenbrink 1995	15	2.33 (2.1)	15	2.87 (1.9)		1.9 %	-0.54 [-1.97, 0.89]
Wong 2000	39	2.03 (2.12)	38	2.49 (2.25)		4.0 %	-0.46 [-1.44, 0.52]
Total (95% CI)	**496**		**496**			**100.0 %**	**-0.24 [-0.45, -0.04]**

Heterogeneity: Tau² = 0.02; Chi² = 10.87, df = 9 (P = 0.28); I² =17%

Test for overall effect: Z = 2.38 (P = 0.017)



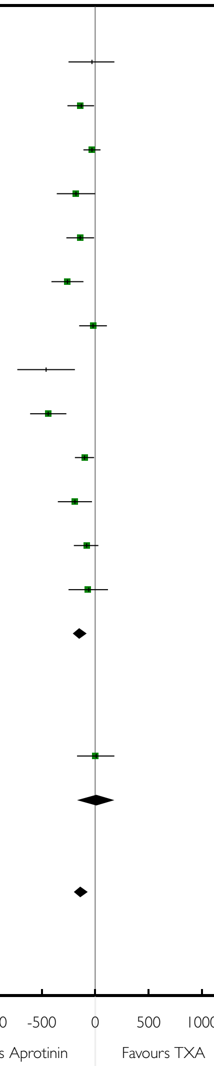
Analysis 4.7. Comparison 4 Aprotinin versus Tranexamic Acid (Blood Transfusion & Blood Loss), Outcome 7 Blood loss.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 4 Aprotinin versus Tranexamic Acid (Blood Transfusion % Blood Loss)

Outcome: 7 Blood loss

Study or subgroup	Aprotinin N	Mean(SD)	TXA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Cardiac surgery - Post-operative							
Bernet 1999	28	844 (437)	28	879 (375)		5.0 %	-35.00 [-248.29, 178.29]
Blauhut 1994	14	269 (142.18)	15	403 (201.39)		8.1 %	-134.00 [-260.23, -7.77]
Casati 1999	67	283.4 (232.7)	70	310.9 (231.1)		10.3 %	-27.50 [-105.19, 50.19]
Corbeau 1995	43	834 (448)	41	1015 (409)		5.9 %	-181.00 [-364.31, 2.31]
Hekmat 2004	60	756 (347)	58	896 (354)		8.1 %	-140.00 [-266.53, -13.47]
Kuitunen 2005	20	540 (259.4)	20	802 (214.7)		7.2 %	-262.00 [-409.57, -114.43]
Landymore 1997	48	515 (339.48)	56	535 (336.75)		7.9 %	-20.00 [-150.39, 110.39]
Mengistu 2008	25	575 (228)	25	1033 (647)		3.7 %	-458.00 [-726.91, -189.09]
Menichetti 1996	24	298 (140)	24	737 (400)		6.4 %	-439.00 [-608.55, -269.45]
Misfeld 1998	14	290 (110)	14	390 (120)		9.9 %	-100.00 [-185.27, -14.73]
Penta de Peppo 1995	15	344 (106)	15	534 (288)		6.9 %	-190.00 [-345.30, -34.70]
Speekenbrink 1995	15	270 (174)	15	352 (150)		8.5 %	-82.00 [-198.26, 34.26]
Wong 2000	39	682 (382.8)	38	746 (436.7)		5.9 %	-64.00 [-247.61, 119.61]
Subtotal (95% CI)	**412**		**419**			**93.9 %**	**-145.81 [-209.99, -81.62]**
Heterogeneity: Tau² = 8272.19; Chi² = 33.86, df = 12 (P = 0.00071); I² =65%							
Test for overall effect: Z = 4.45 (P < 0.00001)							
2 Cardiac surgery - Total							
Isetta 1993	140	608 (717.62)	70	602 (562)		6.1 %	6.00 [-171.38, 183.38]
Subtotal (95% CI)	**140**		**70**			**6.1 %**	**6.00 [-171.38, 183.38]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.07 (P = 0.95)							
Total (95% CI)	**552**		**489**			**100.0 %**	**-136.44 [-198.40, -74.47]**
Heterogeneity: Tau² = 8176.67; Chi² = 35.68, df = 13 (P = 0.00067); I² =64%							
Test for overall effect: Z = 4.32 (P = 0.000016)							



Analysis 5.1. Comparison 5 Aprotinin versus Epsilon Aminocaproic Acid (Blood Transfusion & Blood Loss), Outcome 1 No. Exposed to Allogeneic Blood.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 5 Aprotinin versus Epsilon Aminocaproic Acid (Blood Transfusion % Blood Loss)

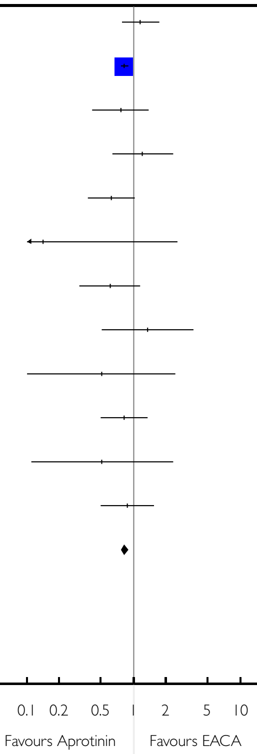
Outcome: 1 No. Exposed to Allogeneic Blood

Study or subgroup	Aprotinin n/N	EACA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Greilich 2009	18/26	15/25		3.4 %	1.15 [0.77, 1.74]
Fergusson 2008	419/780	514/780		84.9 %	0.82 [0.75, 0.89]
Eberle 1998	9/20	12/20		1.6 %	0.75 [0.41, 1.37]
Ray 2001	14/49	12/51		1.3 %	1.21 [0.63, 2.36]
Trinh-Duc 1992	12/29	18/27		2.2 %	0.62 [0.37, 1.03]
Penta de Peppo 1995	0/15	3/15		0.1 %	0.14 [0.01, 2.55]
Dorman 2008	9/30	15/30		1.4 %	0.60 [0.31, 1.15]
Greilich 2001	7/24	5/23		0.6 %	1.34 [0.50, 3.63]
Menichetti 1996	2/24	4/24		0.2 %	0.50 [0.10, 2.48]
Casati 1999	19/67	23/66		2.3 %	0.81 [0.49, 1.35]
Ray 2005	2/15	4/15		0.2 %	0.50 [0.11, 2.33]
Amar 2003	11/23	12/22		1.8 %	0.88 [0.49, 1.55]
Total (95% CI)	**1102**	**1098**		**100.0 %**	**0.82 [0.76, 0.89]**

Total events: 522 (Aprotinin), 637 (EACA)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 9.33$, df = 11 (P = 0.59); $I^2 = 0.0\%$

Test for overall effect: Z = 5.11 (P < 0.00001)



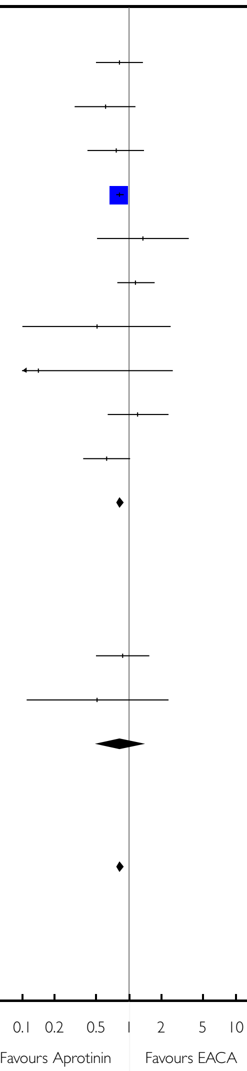
Analysis 5.2. Comparison 5 Aprotinin versus Epsilon Aminocaproic Acid (Blood Transfusion & Blood Loss), Outcome 2 No. Exposed to Allogeneic Blood - Type of Surgery.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 5 Aprotinin versus Epsilon Aminocaproic Acid (Blood Transfusion % Blood Loss)

Outcome: 2 No. Exposed to Allogeneic Blood - Type of Surgery

Study or subgroup	Aprotinin n/N	EACA n/N	Weight	Risk Ratio M-H,Random,95% CI
1 Cardiac surgery				
Casati 1999	19/67	23/66	2.3 %	0.81 [0.49, 1.35]
Dorman 2008	9/30	15/30	1.4 %	0.60 [0.31, 1.15]
Eberle 1998	9/20	12/20	1.6 %	0.75 [0.41, 1.37]
Fergusson 2008	419/780	514/780	84.9 %	0.82 [0.75, 0.89]
Greilich 2001	7/24	5/23	0.6 %	1.34 [0.50, 3.63]
Greilich 2009	18/26	15/25	3.4 %	1.15 [0.77, 1.74]
Menichetti 1996	2/24	4/24	0.2 %	0.50 [0.10, 2.48]
Penta de Peppo 1995	0/15	3/15	0.1 %	0.14 [0.01, 2.55]
Ray 2001	14/49	12/51	1.3 %	1.21 [0.63, 2.36]
Trinh-Duc 1992	12/29	18/27	2.2 %	0.62 [0.37, 1.03]
Subtotal (95% CI)	**1064**	**1061**	**98.0 %**	**0.82 [0.76, 0.89]**
Total events: 509 (Aprotinin), 621 (EACA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 8.87$, df = 9 (P = 0.45); $I^2 = 0.0\%$				
Test for overall effect: Z = 5.06 (P < 0.00001)				
2 Orthopaedic surgery				
Amar 2003	11/23	12/22	1.8 %	0.88 [0.49, 1.55]
Ray 2005	2/15	4/15	0.2 %	0.50 [0.11, 2.33]
Subtotal (95% CI)	**38**	**37**	**2.0 %**	**0.82 [0.48, 1.40]**
Total events: 13 (Aprotinin), 16 (EACA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.47$, df = 1 (P = 0.49); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.73 (P = 0.47)				
Total (95% CI)	**1102**	**1098**	**100.0 %**	**0.82 [0.76, 0.89]**
Total events: 522 (Aprotinin), 637 (EACA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 9.33$, df = 11 (P = 0.59); $I^2 = 0.0\%$				
Test for overall effect: Z = 5.11 (P < 0.00001)				



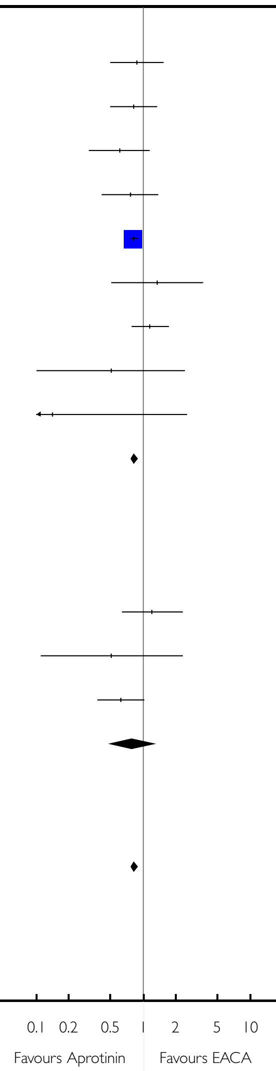
Analysis 5.3. Comparison 5 Aprotinin versus Epsilon Aminocaproic Acid (Blood Transfusion & Blood Loss), Outcome 3 No. Exposed to Allogeneic Blood - Transfusion Protocol.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 5 Aprotinin versus Epsilon Aminocaproic Acid (Blood Transfusion % Blood Loss)

Outcome: 3 No. Exposed to Allogeneic Blood - Transfusion Protocol

Study or subgroup	Aprotinin n/N	EACA n/N	Weight	Risk Ratio M-H,Random,95% CI
1 Transfusion Protocol				
Amar 2003	11/23	12/22	1.8 %	0.88 [0.49, 1.55]
Casati 1999	19/67	23/66	2.3 %	0.81 [0.49, 1.35]
Dorman 2008	9/30	15/30	1.4 %	0.60 [0.31, 1.15]
Eberle 1998	9/20	12/20	1.6 %	0.75 [0.41, 1.37]
Fergusson 2008	419/780	514/780	84.9 %	0.82 [0.75, 0.89]
Greilich 2001	7/24	5/23	0.6 %	1.34 [0.50, 3.63]
Greilich 2009	18/26	15/25	3.4 %	1.15 [0.77, 1.74]
Menichetti 1996	2/24	4/24	0.2 %	0.50 [0.10, 2.48]
Penta de Peppo 1995	0/15	3/15	0.1 %	0.14 [0.01, 2.55]
Subtotal (95% CI)	**1009**	**1005**	**96.2 %**	**0.82 [0.76, 0.89]**
Total events: 494 (Aprotinin), 603 (EACA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.45$, df = 8 (P = 0.60); I^2 =0.0%				
Test for overall effect: Z = 4.95 (P < 0.00001)				
2 No Transfusion Protocol				
Ray 2001	14/49	12/51	1.3 %	1.21 [0.63, 2.36]
Ray 2005	2/15	4/15	0.2 %	0.50 [0.11, 2.33]
Trinh-Duc 1992	12/29	18/27	2.2 %	0.62 [0.37, 1.03]
Subtotal (95% CI)	**93**	**93**	**3.8 %**	**0.78 [0.47, 1.31]**
Total events: 28 (Aprotinin), 34 (EACA)				
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 2.86$, df = 2 (P = 0.24); I^2 =30%				
Test for overall effect: Z = 0.93 (P = 0.35)				
Total (95% CI)	**1102**	**1098**	**100.0 %**	**0.82 [0.76, 0.89]**
Total events: 522 (Aprotinin), 637 (EACA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 9.33$, df = 11 (P = 0.59); I^2 =0.0%				
Test for overall effect: Z = 5.11 (P < 0.00001)				



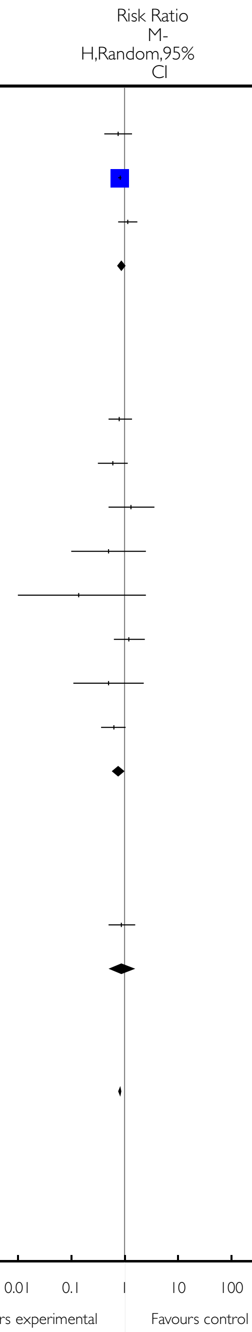
Analysis 5.4. Comparison 5 Aprotinin versus Epsilon Aminocaproic Acid (Blood Transfusion & Blood Loss), Outcome 4 Trial Methodological Quality - Allocation Concealment.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 5 Aprotinin versus Epsilon Aminocaproic Acid (Blood Transfusion % Blood Loss)

Outcome: 4 Trial Methodological Quality - Allocation Concealment

Study or subgroup	Aprotinin n/N	EACA n/N	Weight	Risk Ratio M-H,Random,95% CI
1 Allocation concealment - Yes				
Eberle 1998	9/20	12/20	1.6 %	0.75 [0.41, 1.37]
Fergusson 2008	419/780	514/780	84.9 %	0.82 [0.75, 0.89]
Greilich 2009	18/26	15/25	3.4 %	1.15 [0.77, 1.74]
Subtotal (95% CI)	**826**	**825**	**90.0 %**	**0.86 [0.71, 1.05]**
Total events: 446 (Aprotinin), 541 (EACA)				
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.75$, df = 2 (P = 0.25); I^2 =27%				
Test for overall effect: Z = 1.51 (P = 0.13)				
2 Allocation concealment - Unclear				
Casati 1999	19/67	23/66	2.3 %	0.81 [0.49, 1.35]
Dorman 2008	9/30	15/30	1.4 %	0.60 [0.31, 1.15]
Greilich 2001	7/24	5/23	0.6 %	1.34 [0.50, 3.63]
Menichetti 1996	2/24	4/24	0.2 %	0.50 [0.10, 2.48]
Penta de Peppo 1995	0/15	3/15	0.1 %	0.14 [0.01, 2.55]
Ray 2001	14/49	12/51	1.3 %	1.21 [0.63, 2.36]
Ray 2005	2/15	4/15	0.2 %	0.50 [0.11, 2.33]
Trinh-Duc 1992	12/29	18/27	2.2 %	0.62 [0.37, 1.03]
Subtotal (95% CI)	**253**	**251**	**8.3 %**	**0.76 [0.58, 0.99]**
Total events: 65 (Aprotinin), 84 (EACA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.19$, df = 7 (P = 0.52); I^2 =0.0%				
Test for overall effect: Z = 2.02 (P = 0.043)				
3 Allocation concealment - No				
Amar 2003	11/23	12/22	1.8 %	0.88 [0.49, 1.55]
Subtotal (95% CI)	**23**	**22**	**1.8 %**	**0.88 [0.49, 1.55]**
Total events: 11 (Aprotinin), 12 (EACA)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.45 (P = 0.65)				
Total (95% CI)	**1102**	**1098**	**100.0 %**	**0.82 [0.76, 0.89]**
Total events: 522 (Aprotinin), 637 (EACA)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 9.33$, df = 11 (P = 0.59); I^2 =0.0%				
Test for overall effect: Z = 5.11 (P < 0.00001)				
Test for subgroup differences: $Chi^2 = 0.0$, df = 2 (P = 0.0), I^2 =0.0%				



Analysis 5.5. Comparison 5 Aprotinin versus Epsilon Aminocaproic Acid (Blood Transfusion & Blood Loss), Outcome 5 Units of Allogeneic Blood Transfused - Transfused Patients.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

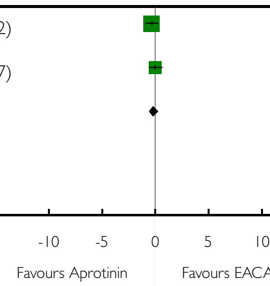
Comparison: 5 Aprotinin versus Epsilon Aminocaproic Acid (Blood Transfusion % Blood Loss)

Outcome: 5 Units of Allogeneic Blood Transfused - Transfused Patients

Study or subgroup	Aprotinin N	Aprotinin Mean(SD)	EACA N	EACA Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Casati 1999	19	1.9 (1.04)	23	2.24 (0.92)		56.8 %	-0.34 [-0.94, 0.26]
Eberle 1998	9	1.29 (0.88)	12	1.25 (0.67)		43.2 %	0.04 [-0.65, 0.73]
Total (95% CI)	**28**		**35**			**100.0 %**	**-0.18 [-0.63, 0.28]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.66$, df = 1 (P = 0.41); $I^2 = 0.0\%$

Test for overall effect: Z = 0.76 (P = 0.45)



Analysis 5.6. Comparison 5 Aprotinin versus Epsilon Aminocaproic Acid (Blood Transfusion & Blood Loss), Outcome 6 Units of Allogeneic Blood Transfused - All Patients.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

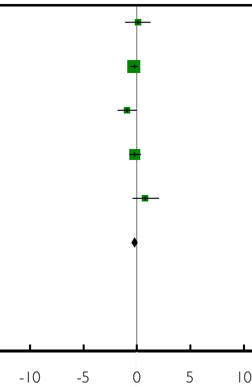
Comparison: 5 Aprotinin versus Epsilon Aminocaproic Acid (Blood Transfusion % Blood Loss)

Outcome: 6 Units of Allogeneic Blood Transfused - All Patients

Study or subgroup	Aprotinin N	Aprotinin Mean(SD)	EACA N	EACA Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Amar 2003	23	1.8 (1.5)	22	1.7 (2.5)		7.5 %	0.10 [-1.11, 1.31]
Casati 1999	67	0.54 (1.02)	66	0.78 (1.2)		42.9 %	-0.24 [-0.62, 0.14]
Dorman 2008	30	0.56 (1.1)	30	1.46 (2.2)		13.2 %	-0.90 [-1.78, -0.02]
Eberle 1998	20	0.58 (0.87)	20	0.75 (0.81)		29.4 %	-0.17 [-0.69, 0.35]
Greilich 2009	26	2.5 (2.7)	25	1.7 (1.8)		7.0 %	0.80 [-0.45, 2.05]
Total (95% CI)	**166**		**163**			**100.0 %**	**-0.21 [-0.55, 0.14]**

Heterogeneity: Tau^2 = 0.04; Chi^2 = 5.14, df = 4 (P = 0.27); I^2 =22%

Test for overall effect: Z = 1.18 (P = 0.24)



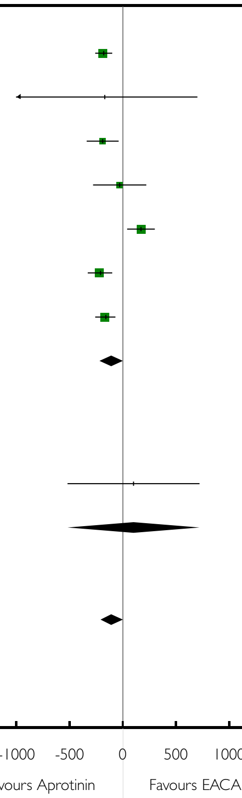
Analysis 5.7. Comparison 5 Aprotinin versus Epsilon Aminocaproic Acid (Blood Transfusion & Blood Loss), Outcome 7 Blood loss.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 5 Aprotinin versus Epsilon Aminocaproic Acid (Blood Transfusion % Blood Loss)

Outcome: 7 Blood loss

Study or subgroup	Aprotinin N	Mean(SD)	EACA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Cardiac surgery - Post-operative							
Casati 1999	67	283.4 (232.7)	66	466.9 (234.2)		19.2 %	-183.50 [-262.85, -104.15]
Dorman 2008	30	423 (1363.83)	30	596 (2026.57)		1.4 %	-173.00 [-1047.11, 701.11]
Eberle 1998	20	391 (220)	20	582 (274)		14.8 %	-191.00 [-345.00, -37.00]
Greilich 2009	26	685 (505)	25	715 (394)		9.9 %	-30.00 [-278.06, 218.06]
Landymore 1997	48	515 (339.48)	44	343 (305.13)		16.2 %	172.00 [40.27, 303.73]
Menichetti 1996	24	298 (140)	24	512 (250)		17.2 %	-214.00 [-328.63, -99.37]
Penta de Peppo 1995	15	344 (106)	15	509 (148)		18.5 %	-165.00 [-257.13, -72.87]
Subtotal (95% CI)	**230**		**224**			**97.4 %**	**-111.43 [-220.64, -2.21]**
Heterogeneity: Tau^2 = 14145.97; Chi^2 = 25.74, df = 6 (P = 0.00025); I^2 =77%							
Test for overall effect: Z = 2.00 (P = 0.046)							
2 Orthopaedic surgery - Total							
Amar 2003	23	1700 (1000)	22	1600 (1100)		2.6 %	100.00 [-515.06, 715.06]
Subtotal (95% CI)	**23**		**22**			**2.6 %**	**100.00 [-515.06, 715.06]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.32 (P = 0.75)							
Total (95% CI)	**253**		**246**			**100.0 %**	**-106.01 [-212.50, 0.47]**
Heterogeneity: Tau^2 = 13708.99; Chi^2 = 26.30, df = 7 (P = 0.00045); I^2 =73%							
Test for overall effect: Z = 1.95 (P = 0.051)							



Analysis 6.1. Comparison 6 Tranexamic Acid versus Epsilon Aminocaproic Acid (Blood Transfusion & Blood Loss), Outcome 1 No. Exposed to Allogeneic Blood.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 6 Tranexamic Acid versus Epsilon Aminocaproic Acid (Blood Transfusion % Blood Loss)

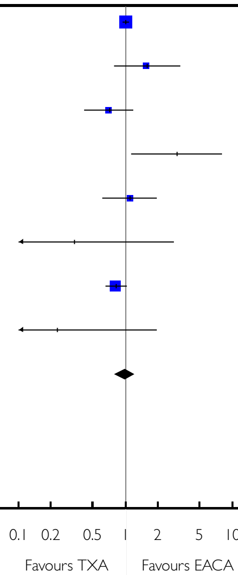
Outcome: 1 No. Exposed to Allogeneic Blood

Study or subgroup	TXA n/N	EACA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Fergusson 2008	506/770	514/780		35.8 %	1.00 [0.93, 1.07]
Pinosky 1997	11/20	7/20		7.9 %	1.57 [0.77, 3.22]
Casati 1999	17/70	23/66		12.3 %	0.70 [0.41, 1.18]
Menichetti 1996	12/24	4/24		4.7 %	3.00 [1.13, 7.99]
Maineri 2000	12/24	11/24		10.6 %	1.09 [0.60, 1.97]
Penta de Peppo 1995	1/15	3/15		1.1 %	0.33 [0.04, 2.85]
Dalmau 2000	29/42	36/42		26.5 %	0.81 [0.64, 1.02]
Camarasa 2006	1/35	4/32		1.1 %	0.23 [0.03, 1.94]
Total (95% CI)	**1000**	**1003**		**100.0 %**	**0.97 [0.77, 1.21]**

Total events: 589 (TXA), 602 (EACA)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 14.01$, df = 7 (P = 0.05); I^2 =50%

Test for overall effect: Z = 0.29 (P = 0.77)



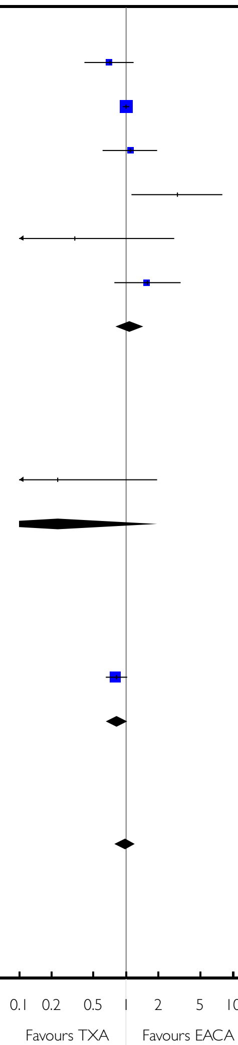
Analysis 6.2. Comparison 6 Tranexamic Acid versus Epsilon Aminocaproic Acid (Blood Transfusion & Blood Loss), Outcome 2 No. Exposed to Allogeneic Blood - Type of Surgery.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 6 Tranexamic Acid versus Epsilon Aminocaproic Acid (Blood Transfusion % Blood Loss)

Outcome: 2 No. Exposed to Allogeneic Blood - Type of Surgery

Study or subgroup	TXA n/N	EACA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Cardiac surgery					
Casati 1999	17/70	23/66		12.3 %	0.70 [0.41, 1.18]
Fergusson 2008	506/770	514/780		35.8 %	1.00 [0.93, 1.07]
Maineri 2000	12/24	11/24		10.6 %	1.09 [0.60, 1.97]
Menichetti 1996	12/24	4/24		4.7 %	3.00 [1.13, 7.99]
Penta de Peppo 1995	1/15	3/15		1.1 %	0.33 [0.04, 2.85]
Pinosky 1997	11/20	7/20		7.9 %	1.57 [0.77, 3.22]
Subtotal (95% CI)	**923**	**929**		**72.5 %**	**1.07 [0.79, 1.46]**
Total events: 559 (TXA), 562 (EACA)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 9.25$, df = 5 (P = 0.10); I^2 =46%					
Test for overall effect: Z = 0.45 (P = 0.66)					
2 Orthopaedic surgery					
Camarasa 2006	1/35	4/32		1.1 %	0.23 [0.03, 1.94]
Subtotal (95% CI)	**35**	**32**		**1.1 %**	**0.23 [0.03, 1.94]**
Total events: 1 (TXA), 4 (EACA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.35 (P = 0.18)					
3 Liver surgery					
Dalmau 2000	29/42	36/42		26.5 %	0.81 [0.64, 1.02]
Subtotal (95% CI)	**42**	**42**		**26.5 %**	**0.81 [0.64, 1.02]**
Total events: 29 (TXA), 36 (EACA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.79 (P = 0.074)					
Total (95% CI)	**1000**	**1003**		**100.0 %**	**0.97 [0.77, 1.21]**
Total events: 589 (TXA), 602 (EACA)					
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 14.01$, df = 7 (P = 0.05); I^2 =50%					
Test for overall effect: Z = 0.29 (P = 0.77)					



Analysis 6.3. Comparison 6 Tranexamic Acid versus Epsilon Aminocaproic Acid (Blood Transfusion & Blood Loss), Outcome 3 No. Exposed to Allogeneic Blood - Transfusion Protocol.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 6 Tranexamic Acid versus Epsilon Aminocaproic Acid (Blood Transfusion % Blood Loss)

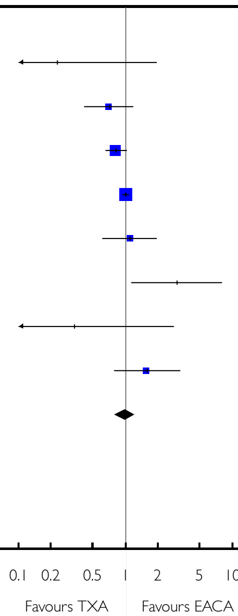
Outcome: 3 No. Exposed to Allogeneic Blood - Transfusion Protocol

Study or subgroup	TXA n/N	EACA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Transfusion Protocol					
Camarasa 2006	1/35	4/32		1.1 %	0.23 [0.03, 1.94]
Casati 1999	17/70	23/66		12.3 %	0.70 [0.41, 1.18]
Dalmau 2000	29/42	36/42		26.5 %	0.81 [0.64, 1.02]
Fergusson 2008	506/770	514/780		35.8 %	1.00 [0.93, 1.07]
Maineri 2000	12/24	11/24		10.6 %	1.09 [0.60, 1.97]
Menichetti 1996	12/24	4/24		4.7 %	3.00 [1.13, 7.99]
Penta de Peppo 1995	1/15	3/15		1.1 %	0.33 [0.04, 2.85]
Pinosky 1997	11/20	7/20		7.9 %	1.57 [0.77, 3.22]
Total (95% CI)	**1000**	**1003**		**100.0 %**	**0.97 [0.77, 1.21]**

Total events: 589 (TXA), 602 (EACA)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 14.01$, df = 7 (P = 0.05); $I^2 = 50\%$

Test for overall effect: Z = 0.29 (P = 0.77)



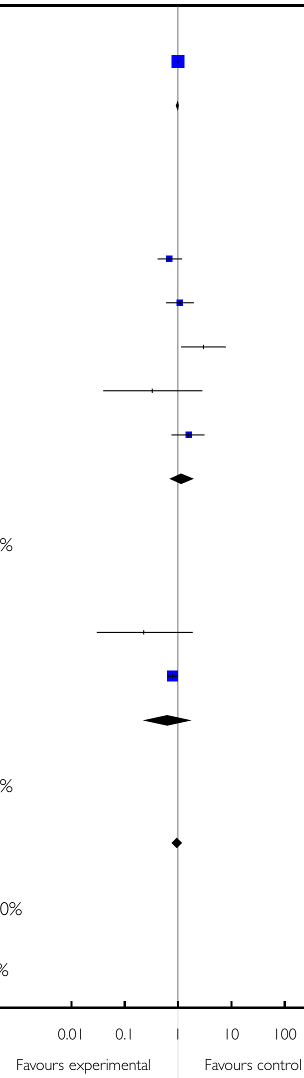
Analysis 6.4. Comparison 6 Tranexamic Acid versus Epsilon Aminocaproic Acid (Blood Transfusion & Blood Loss), Outcome 4 Trial Methodological Quality - Allocation Concealment.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 6 Tranexamic Acid versus Epsilon Aminocaproic Acid (Blood Transfusion % Blood Loss)

Outcome: 4 Trial Methodological Quality - Allocation Concealment

Study or subgroup	TXA n/N	EACA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Allocation concealment - Yes					
Fergusson 2008	506/770	514/780		35.8 %	1.00 [0.93, 1.07]
Subtotal (95% CI)	**770**	**780**		**35.8 %**	**1.00 [0.93, 1.07]**
Total events: 506 (TXA), 514 (EACA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.94)					
2 Allocation concealment - Unclear					
Casati 1999	17/70	23/66		12.3 %	0.70 [0.41, 1.18]
Maineri 2000	12/24	11/24		10.6 %	1.09 [0.60, 1.97]
Menichetti 1996	12/24	4/24		4.7 %	3.00 [1.13, 7.99]
Penta de Peppo 1995	1/15	3/15		1.1 %	0.33 [0.04, 2.85]
Pinosky 1997	11/20	7/20		7.9 %	1.57 [0.77, 3.22]
Subtotal (95% CI)	**153**	**149**		**36.6 %**	**1.16 [0.68, 1.98]**
Total events: 53 (TXA), 48 (EACA)					
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 9.01$, df = 4 (P = 0.06); $I^2 = 56\%$					
Test for overall effect: Z = 0.56 (P = 0.58)					
3 Allocation concealment - No					
Camarasa 2006	1/35	4/32		1.1 %	0.23 [0.03, 1.94]
Dalmau 2000	29/42	36/42		26.5 %	0.81 [0.64, 1.02]
Subtotal (95% CI)	**77**	**74**		**27.5 %**	**0.63 [0.22, 1.84]**
Total events: 30 (TXA), 40 (EACA)					
Heterogeneity: $Tau^2 = 0.35$; $Chi^2 = 1.58$, df = 1 (P = 0.21); $I^2 = 37\%$					
Test for overall effect: Z = 0.84 (P = 0.40)					
Total (95% CI)	**1000**	**1003**		**100.0 %**	**0.97 [0.77, 1.21]**
Total events: 589 (TXA), 602 (EACA)					
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 14.01$, df = 7 (P = 0.05); $I^2 = 50\%$					
Test for overall effect: Z = 0.29 (P = 0.77)					
Test for subgroup differences: $Chi^2 = 0.0$, df = 2 (P = 0.0), $I^2 = 0.0\%$					



Analysis 6.5. Comparison 6 Tranexamic Acid versus Epsilon Aminocaproic Acid (Blood Transfusion & Blood Loss), Outcome 5 Units of Allogeneic Blood Transfused - Transfused Patients.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

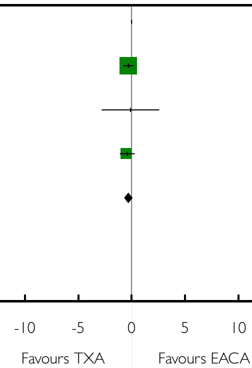
Comparison: 6 Tranexamic Acid versus Epsilon Aminocaproic Acid (Blood Transfusion % Blood Loss)

Outcome: 5 Units of Allogeneic Blood Transfused - Transfused Patients

Study or subgroup	TXA N	TXA Mean(SD)	EACA N	EACA Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Camarasa 2006	1	1 (0)	4	1.5 (0.58)		0.0 [0.0, 0.0]
Casati 1999	17	1.94 (0.69)	23	2.24 (0.92)		-0.30 [-0.80, 0.20]
Dalmau 2000	29	7.72 (5.44)	36	7.81 (5.67)		-0.09 [-2.80, 2.62]
Maineri 2000	12	1.6 (1.19)	11	2.03 (0.36)		-0.43 [-1.14, 0.28]
Total (95% CI)	**59**		**74**			**-0.34 [-0.74, 0.07]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.12$, df = 2 (P = 0.94); $I^2 = 0.0\%$

Test for overall effect: Z = 1.64 (P = 0.10)



Analysis 6.6. Comparison 6 Tranexamic Acid versus Epsilon Aminocaproic Acid (Blood Transfusion & Blood Loss), Outcome 6 Units of Allogeneic Blood Transfused - All Patients.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

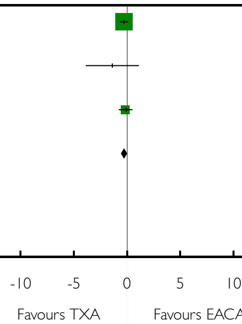
Comparison: 6 Tranexamic Acid versus Epsilon Aminocaproic Acid (Blood Transfusion % Blood Loss)

Outcome: 6 Units of Allogeneic Blood Transfused - All Patients

Study or subgroup	TXA N	TXA Mean(SD)	EACA N	EACA Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Casati 1999	70	0.47 (0.9)	66	0.78 (1.2)		74.3 %	-0.31 [-0.67, 0.05]
Dalmau 2000	42	5.33 (5.77)	42	6.69 (5.92)		1.5 %	-1.36 [-3.86, 1.14]
Maineri 2000	24	0.8 (1.16)	24	0.93 (1.06)		24.1 %	-0.13 [-0.76, 0.50]
Total (95% CI)	**136**		**132**			**100.0 %**	**-0.28 [-0.59, 0.03]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.96$, df = 2 (P = 0.62); $I^2 = 0.0\%$

Test for overall effect: Z = 1.79 (P = 0.073)



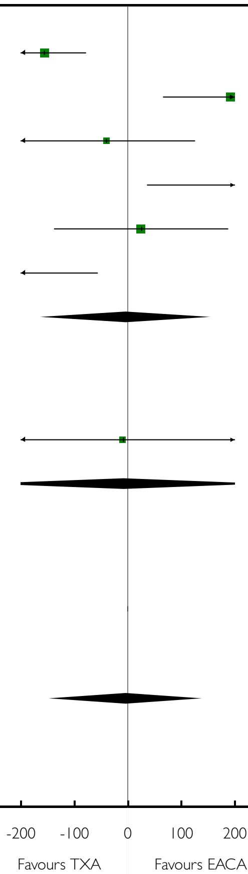
Analysis 6.7. Comparison 6 Tranexamic Acid versus Epsilon Aminocaproic Acid (Blood Transfusion & Blood Loss), Outcome 7 Blood loss.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 6 Tranexamic Acid versus Epsilon Aminocaproic Acid (Blood Transfusion % Blood Loss)

Outcome: 7 Blood loss

Study or subgroup	TXA N	TXA Mean(SD)	EACA N	EACA Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Cardiac surgery - Post-operative							
Casati 1999	70	310.9 (231.1)	66	466.9 (234.2)		17.8 %	-156.00 [-234.25, -77.75]
Landymore 1997	56	535 (336.75)	44	343 (305.13)		16.4 %	192.00 [65.87, 318.13]
Maineri 2000	24	750 (314)	24	790 (274)		15.0 %	-40.00 [-206.73, 126.73]
Menichetti 1996	24	737 (400)	24	512 (250)		14.2 %	225.00 [36.28, 413.72]
Penta de Peppo 1995	15	534 (288)	15	509 (148)		15.1 %	25.00 [-138.86, 188.86]
Pinosky 1997	20	600 (219.1)	20	961 (661.9)		10.1 %	-361.00 [-666.56, -55.44]
Subtotal (95% CI)	**209**		**193**			**88.4 %**	**-4.36 [-163.35, 154.63]**
Heterogeneity: $Tau^2 = 31640.08$; $Chi^2 = 33.81$, df = 5 (P<0.00001); I^2 =85%							
Test for overall effect: Z = 0.05 (P = 0.96)							
2 Orthopaedic surgery - Total							
Camarasa 2006	35	1095 (473)	32	1104 (603)		11.6 %	-9.00 [-270.16, 252.16]
Subtotal (95% CI)	**35**		**32**			**11.6 %**	**-9.00 [-270.16, 252.16]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.07 (P = 0.95)							
3 Gynaecological surgery - Total							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**244**		**225**			**100.0 %**	**-4.20 [-147.29, 138.89]**
Heterogeneity: $Tau^2 = 28391.91$; $Chi^2 = 33.84$, df = 6 (P<0.00001); I^2 =82%							
Test for overall effect: Z = 0.06 (P = 0.95)							



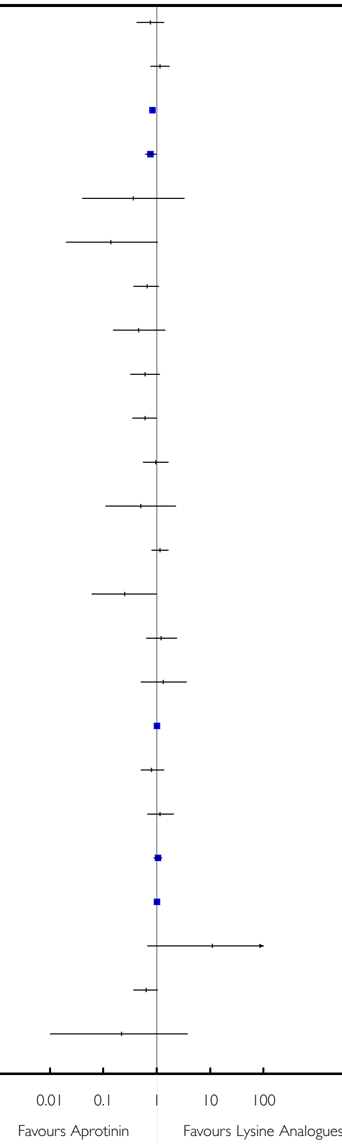
Analysis 7.1. Comparison 7 Aprotinin versus Lysine Analogues (Blood Transfusion), Outcome 1 No. Exposed to Allogeneic Blood.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 7 Aprotinin versus Lysine Analogues (Blood Transfusion)

Outcome: 1 No. Exposed to Allogeneic Blood

Study or subgroup	Aprotinin n/N	Lysine Analogues n/N	Weight	Risk Ratio M-H,Random,95% CI
Eberle 1998	9/20	12/20	2.1 %	0.75 [0.41, 1.37]
Greilich 2009	18/26	15/25	3.7 %	1.15 [0.77, 1.74]
Fergusson 2008	419/780	1020/1550	10.6 %	0.82 [0.76, 0.88]
Dietrich 2008	52/110	67/110	6.5 %	0.78 [0.61, 0.99]
Vanek 2005	1/29	3/32	0.2 %	0.37 [0.04, 3.34]
Mansour 2004	1/20	7/20	0.2 %	0.14 [0.02, 1.06]
Bernet 1999	11/28	17/28	2.4 %	0.65 [0.37, 1.12]
Blauhut 1994	3/14	7/15	0.7 %	0.46 [0.15, 1.44]
Dorman 2008	9/30	15/30	1.8 %	0.60 [0.31, 1.15]
Mengistu 2008	10/25	17/25	2.4 %	0.59 [0.34, 1.02]
Corbeau 1995	15/43	15/41	2.3 %	0.95 [0.54, 1.69]
Ray 2005	2/15	4/15	0.4 %	0.50 [0.11, 2.33]
Isetta 1993	55/140	24/70	4.1 %	1.15 [0.78, 1.68]
Menichetti 1996	2/24	16/48	0.5 %	0.25 [0.06, 1.00]
Ray 2001	14/49	12/51	1.8 %	1.21 [0.63, 2.36]
Greilich 2001	7/24	5/23	0.9 %	1.34 [0.50, 3.63]
Pugh 1995	21/21	22/22	10.3 %	1.00 [0.92, 1.09]
Casati 1999	19/67	23/66	2.8 %	0.81 [0.49, 1.35]
Casati 1999	19/67	17/70	2.3 %	1.17 [0.67, 2.05]
Casati 2000	185/518	178/522	8.5 %	1.05 [0.89, 1.24]
Ickx 2006	24/24	27/27	10.6 %	1.00 [0.93, 1.08]
Engel 2001	5/12	0/12	0.1 %	11.00 [0.67, 179.29]
Trinh-Duc 1992	12/29	18/27	2.7 %	0.62 [0.37, 1.03]
Penta de Peppo 1995	0/15	4/30	0.1 %	0.22 [0.01, 3.75]



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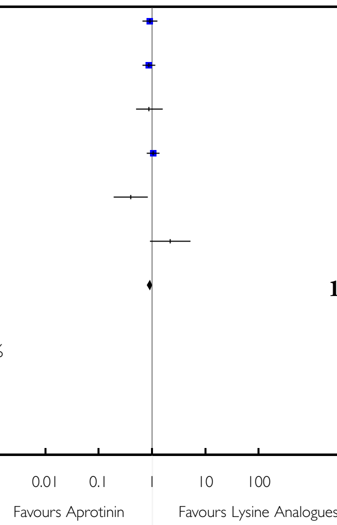
Study or subgroup	Aprotinin n/N	Lysine Analogues n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Speekenbrink 1995	12/15	13/15		5.0 %	0.92 [0.67, 1.27]
Later 2009	48/96	57/99		6.2 %	0.87 [0.67, 1.13]
Amar 2003	11/23	12/22		2.3 %	0.88 [0.49, 1.55]
Dalmau 2004	40/63	38/64		5.9 %	1.07 [0.81, 1.41]
Diprose 2005	8/60	20/60		1.5 %	0.40 [0.19, 0.84]
Kuitunen 2005	11/20	5/20		1.1 %	2.20 [0.93, 5.18]
Total (95% CI)	**2407**	**3159**		**100.0 %**	**0.90 [0.81, 0.99]**

Total events: 1043 (Aprotinin), 1690 (Lysine Analogues)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 70.06$, df = 29 (P = 0.00003); I^2 =59%

Test for overall effect: Z = 2.19 (P = 0.028)

Test for subgroup differences: Not applicable



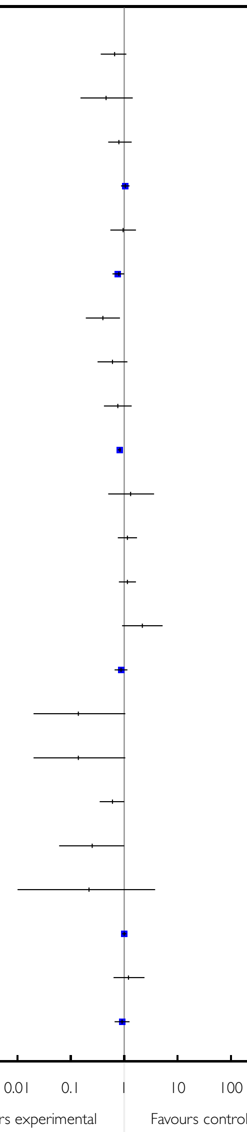
Analysis 7.2. Comparison 7 Aprotinin versus Lysine Analogues (Blood Transfusion), Outcome 2 No. Exposed to Allogeneic Blood - Type of Surgery.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 7 Aprotinin versus Lysine Analogues (Blood Transfusion)

Outcome: 2 No. Exposed to Allogeneic Blood - Type of Surgery

Study or subgroup	Aprotinin n/N	Lysine Analogues n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Cardiac surgery					
Bernet 1999	11/28	17/28		2.6 %	0.65 [0.37, 1.12]
Blauhut 1994	3/14	7/15		0.7 %	0.46 [0.15, 1.44]
Casati 1999	19/67	23/66		3.0 %	0.81 [0.49, 1.35]
Casati 2000	185/518	178/522		8.5 %	1.05 [0.89, 1.24]
Corbeau 1995	15/43	15/41		2.4 %	0.95 [0.54, 1.69]
Dietrich 2008	52/110	67/110		6.6 %	0.78 [0.61, 0.99]
Diprose 2005	8/60	20/60		1.6 %	0.40 [0.19, 0.84]
Dorman 2008	9/30	15/30		2.0 %	0.60 [0.31, 1.15]
Eberle 1998	9/20	12/20		2.2 %	0.75 [0.41, 1.37]
Fergusson 2008	419/780	1020/1550		10.3 %	0.82 [0.76, 0.88]
Greilich 2001	7/24	5/23		0.9 %	1.34 [0.50, 3.63]
Greilich 2009	18/26	15/25		3.9 %	1.15 [0.77, 1.74]
Isetta 1993	55/140	24/70		4.2 %	1.15 [0.78, 1.68]
Kuitunen 2005	11/20	5/20		1.2 %	2.20 [0.93, 5.18]
Later 2009	48/96	57/99		6.3 %	0.87 [0.67, 1.13]
Mansour 2004	1/20	7/20		0.2 %	0.14 [0.02, 1.06]
Mansour 2004	1/20	7/20		0.2 %	0.14 [0.02, 1.06]
Mengistu 2008	10/25	17/25		2.6 %	0.59 [0.34, 1.02]
Menichetti 1996	2/24	16/48		0.5 %	0.25 [0.06, 1.00]
Penta de Peppo 1995	0/15	4/30		0.1 %	0.22 [0.01, 3.75]
Pugh 1995	21/21	22/22		10.1 %	1.00 [0.92, 1.09]
Ray 2001	14/49	12/51		1.9 %	1.21 [0.63, 2.36]
Speekenbrink 1995	12/15	13/15		5.2 %	0.92 [0.67, 1.27]



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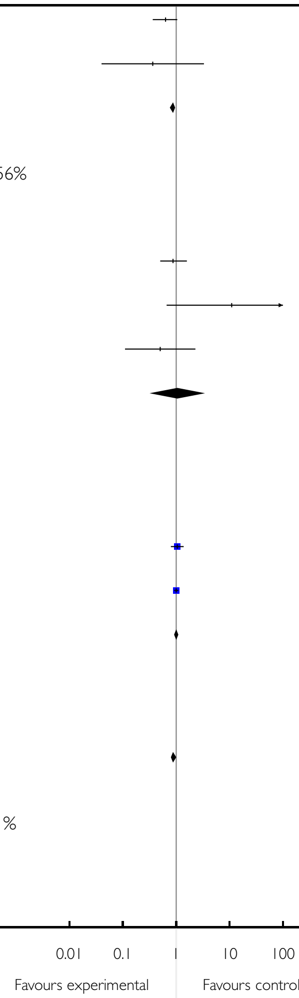
Study or subgroup	Aprotinin n/N	Lysine Analogues n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Trinh-Duc 1992	12/29	18/27		2.9 %	0.62 [0.37, 1.03]
Vanek 2005	1/29	3/32		0.2 %	0.37 [0.04, 3.34]
Subtotal (95% CI)	**2223**	**2969**		**80.7 %**	**0.86 [0.76, 0.96]**
Total events: 943 (Aprotinin), 1599 (Lysine Analogues)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 54.55$, df = 24 (P = 0.00036); I^2 =56%					
Test for overall effect: Z = 2.64 (P = 0.0083)					
2 Orthopaedic surgery					
Amar 2003	11/23	12/22		2.4 %	0.88 [0.49, 1.55]
Engel 2001	5/12	0/12		0.1 %	11.00 [0.67, 179.29]
Ray 2005	2/15	4/15		0.4 %	0.50 [0.11, 2.33]
Subtotal (95% CI)	**50**	**49**		**3.0 %**	**1.06 [0.32, 3.48]**
Total events: 18 (Aprotinin), 16 (Lysine Analogues)					
Heterogeneity: $Tau^2 = 0.59$; $Chi^2 = 4.17$, df = 2 (P = 0.12); I^2 =52%					
Test for overall effect: Z = 0.09 (P = 0.93)					
3 Liver surgery					
Dalmau 2004	40/63	38/64		6.0 %	1.07 [0.81, 1.41]
Ickx 2006	24/24	27/27		10.3 %	1.00 [0.93, 1.08]
Subtotal (95% CI)	**87**	**91**		**16.4 %**	**1.01 [0.91, 1.11]**
Total events: 64 (Aprotinin), 65 (Lysine Analogues)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.14$, df = 1 (P = 0.29); I^2 =12%					
Test for overall effect: Z = 0.16 (P = 0.87)					
Total (95% CI)	**2360**	**3109**		**100.0 %**	**0.89 [0.80, 0.98]**
Total events: 1025 (Aprotinin), 1680 (Lysine Analogues)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 75.01$, df = 29 (P<0.00001); I^2 =61%					
Test for overall effect: Z = 2.36 (P = 0.018)					
Test for subgroup differences: $Chi^2 = 0.0$, df = 2 (P = 0.0), I^2 =0.0%					



Analysis 7.3. Comparison 7 Aprotinin versus Lysine Analogues (Blood Transfusion), Outcome 3 No. Exposed to Allogeneic Blood - Transfusion Protocol.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 7 Aprotinin versus Lysine Analogues (Blood Transfusion)

Outcome: 3 No. Exposed to Allogeneic Blood - Transfusion Protocol

Study or subgroup	Aprotinin n/N	Lysine Analogues n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Transfusion Protocol					
Amar 2003	11/23	12/22		2.4 %	0.88 [0.49, 1.55]
Bernet 1999	11/28	17/28		2.5 %	0.65 [0.37, 1.12]
Blauhut 1994	3/14	7/15		0.7 %	0.46 [0.15, 1.44]
Casati 1999	19/67	23/66		2.9 %	0.81 [0.49, 1.35]
Casati 2000	185/518	178/522		8.6 %	1.05 [0.89, 1.24]
Corbeau 1995	15/43	15/41		2.4 %	0.95 [0.54, 1.69]
Dalmau 2004	40/63	38/64		6.0 %	1.07 [0.81, 1.41]
Dietrich 2008	52/110	67/110		6.6 %	0.78 [0.61, 0.99]
Diprose 2005	8/60	20/60		1.6 %	0.40 [0.19, 0.84]
Dorman 2008	9/30	15/30		1.9 %	0.60 [0.31, 1.15]
Eberle 1998	9/20	12/20		2.2 %	0.75 [0.41, 1.37]
Engel 2001	5/12	0/12		0.1 %	11.00 [0.67, 179.29]
Fergusson 2008	419/780	1020/1550		10.7 %	0.82 [0.76, 0.88]
Greilich 2001	7/24	5/23		0.9 %	1.34 [0.50, 3.63]
Greilich 2009	18/26	15/25		3.9 %	1.15 [0.77, 1.74]
Ickx 2006	24/24	27/27		10.7 %	1.00 [0.93, 1.08]
Isetta 1993	55/140	24/70		4.2 %	1.15 [0.78, 1.68]
Kuitunen 2005	11/20	5/20		1.2 %	2.20 [0.93, 5.18]
Later 2009	48/96	57/99		6.3 %	0.87 [0.67, 1.13]
Mansour 2004	1/20	7/20		0.2 %	0.14 [0.02, 1.06]
Mengistu 2008	10/25	17/25		2.5 %	0.59 [0.34, 1.02]
Menichetti 1996	2/24	16/48		0.5 %	0.25 [0.06, 1.00]
Penta de Peppo 1995	0/15	4/30		0.1 %	0.22 [0.01, 3.75]

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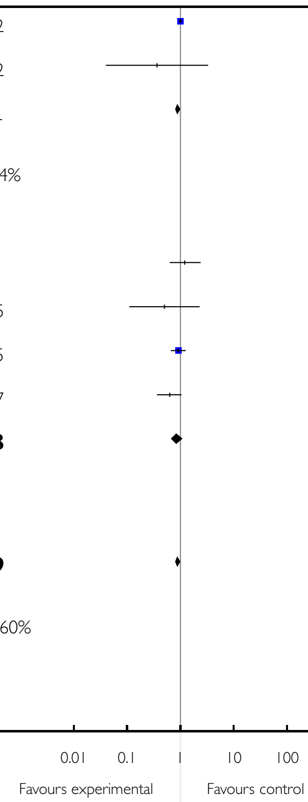
Study or subgroup	Aprotinin n/N	Lysine Analogues n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Pugh 1995	21/21	22/22		10.4 %	1.00 [0.92, 1.09]
Vanek 2005	1/29	3/32		0.2 %	0.37 [0.04, 3.34]
Subtotal (95% CI)	**2232**	**2981**		**89.7 %**	**0.89 [0.80, 0.99]**
Total events: 984 (Aprotinin), 1626 (Lysine Analogues)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 66.84$, df = 24 (P<0.00001); I^2 =64%					
Test for overall effect: Z = 2.05 (P = 0.040)					
2 No Transfusion Protocol					
Ray 2001	14/49	12/51		1.9 %	1.21 [0.63, 2.36]
Ray 2005	2/15	4/15		0.4 %	0.50 [0.11, 2.33]
Speekenbrink 1995	12/15	13/15		5.2 %	0.92 [0.67, 1.27]
Trinh-Duc 1992	12/29	18/27		2.8 %	0.62 [0.37, 1.03]
Subtotal (95% CI)	**108**	**108**		**10.3 %**	**0.85 [0.65, 1.12]**
Total events: 40 (Aprotinin), 47 (Lysine Analogues)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.31$, df = 3 (P = 0.35); I^2 =9%					
Test for overall effect: Z = 1.13 (P = 0.26)					
Total (95% CI)	**2340**	**3089**		**100.0 %**	**0.89 [0.81, 0.98]**
Total events: 1024 (Aprotinin), 1673 (Lysine Analogues)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 70.40$, df = 28 (P = 0.00002); I^2 =60%					
Test for overall effect: Z = 2.29 (P = 0.022)					
Test for subgroup differences: $Chi^2 = 0.0$, df = 1 (P = 0.0), I^2 =0.0%					



Analysis 7.4. Comparison 7 Aprotinin versus Lysine Analogues (Blood Transfusion), Outcome 4 Units of Allogeneic Blood Transfused - Transfused Patients.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 7 Aprotinin versus Lysine Analogues (Blood Transfusion)

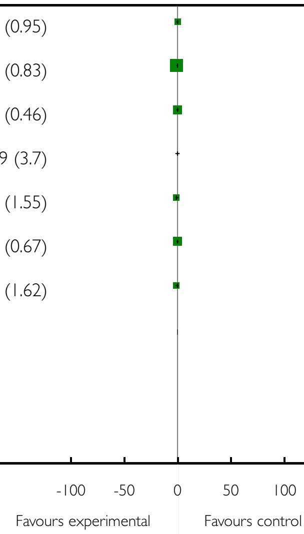
Outcome: 4 Units of Allogeneic Blood Transfused - Transfused Patients

Study or subgroup	Aprotinin N	Aprotinin Mean(SD)	Lysine Analogues N	Lysine Analogues Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Blauhut 1994	3	1.68 (0.48)	7	1.71 (0.95)		12.6 %	-0.03 [-0.92, 0.86]
Casati 1999	19	1.9 (1.04)	40	2.11 (0.83)		35.0 %	-0.21 [-0.74, 0.32]
Corbeau 1995	15	2.29 (1.49)	15	2.19 (0.46)		16.0 %	0.10 [-0.69, 0.89]
Dalmau 2004	40	5.2 (4.17)	38	5.09 (3.7)		3.3 %	0.11 [-1.64, 1.86]
Diprose 2005	8	2.1 (1.42)	20	2.61 (1.55)		7.0 %	-0.51 [-1.71, 0.69]
Eberle 1998	9	1.29 (0.88)	12	1.25 (0.67)		21.0 %	0.04 [-0.65, 0.73]
Speekenbrink 1995	12	2.91 (1.94)	13	3.31 (1.62)		5.0 %	-0.40 [-1.81, 1.01]
Total (95% CI)	**106**		**145**			**100.0 %**	**-0.11 [-0.42, 0.21]**

Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.27, df = 6 (P = 0.97); I^2 =0.0%

Test for overall effect: Z = 0.65 (P = 0.51)

Test for subgroup differences: Not applicable



Analysis 7.5. Comparison 7 Aprotinin versus Lysine Analogues (Blood Transfusion), Outcome 5 Units of Allogeneic Blood Transfused - All Patients.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 7 Aprotinin versus Lysine Analogues (Blood Transfusion)

Outcome: 5 Units of Allogeneic Blood Transfused - All Patients

Study or subgroup	Aprotinin N	Aprotinin Mean(SD)	Lysine Analogues N	Lysine Analogues Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Amar 2003	23	1.8 (1.5)	22	1.7 (2.5)		1.8 %	0.10 [-1.11, 1.31]
Blauhut 1994	14	0.36 (0.47)	15	0.8 (1.08)		7.1 %	-0.44 [-1.04, 0.16]
Casati 1999	67	0.54 (1.02)	136	0.62 (1.06)		24.6 %	-0.08 [-0.38, 0.22]
Corbeau 1995	43	0.8 (1.4)	41	0.8 (1.1)		8.7 %	0.0 [-0.54, 0.54]
Dalmau 2004	63	3.3 (4.16)	64	3.02 (3.79)		1.4 %	0.28 [-1.10, 1.66]
Dietrich 2008	110	1.3 (1.8)	110	1.7 (1.8)		11.0 %	-0.40 [-0.88, 0.08]
Diprose 2005	60	0.28 (0.87)	60	0.87 (1.52)		12.5 %	-0.59 [-1.03, -0.15]
Dorman 2008	30	0.56 (1.1)	30	1.46 (2.2)		3.4 %	-0.90 [-1.78, -0.02]
Eberle 1998	20	0.58 (0.87)	20	0.75 (0.81)		9.3 %	-0.17 [-0.69, 0.35]
Greilich 2009	26	2.5 (2.7)	25	1.7 (1.8)		1.7 %	0.80 [-0.45, 2.05]
Hekmat 2004	60	0.7 (1.2)	58	0.8 (1.3)		12.1 %	-0.10 [-0.55, 0.35]
Mengistu 2008	25	0.8 (1.1)	25	1.8 (2.4)		2.5 %	-1.00 [-2.03, 0.03]
Speekenbrink 1995	15	2.33 (2.1)	15	2.87 (1.9)		1.3 %	-0.54 [-1.97, 0.89]
Wong 2000	39	2.03 (2.12)	38	2.49 (2.25)		2.8 %	-0.46 [-1.44, 0.52]
Total (95% CI)	**595**		**659**			**100.0 %**	**-0.25 [-0.42, -0.09]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 13.61$, df = 13 (P = 0.40); $I^2 = 4\%$

Test for overall effect: Z = 3.02 (P = 0.0025)

Test for subgroup differences: Not applicable

-100 -50 0 50 100

Favours experimental Favours control

Analysis 7.6. Comparison 7 Aprotinin versus Lysine Analogues (Blood Transfusion), Outcome 6 Trial Methodological Quality - Allocation Concealment.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 7 Aprotinin versus Lysine Analogues (Blood Transfusion)

Outcome: 6 Trial Methodological Quality - Allocation Concealment

Study or subgroup	Aprotinin n/N	Lysine Analogues n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Allocation concealment - Yes					
Dietrich 2008	52/110	67/110		6.5 %	0.78 [0.61, 0.99]
Eberle 1998	9/20	12/20		2.1 %	0.75 [0.41, 1.37]
Fergusson 2008	419/780	1020/1550		10.6 %	0.82 [0.76, 0.88]
Greilich 2009	18/26	15/25		3.7 %	1.15 [0.77, 1.74]
Mansour 2004	1/20	7/20		0.2 %	0.14 [0.02, 1.06]
Vanek 2005	1/29	3/32		0.2 %	0.37 [0.04, 3.34]
Subtotal (95% CI)	**985**	**1757**		**23.3 %**	**0.82 [0.71, 0.95]**
Total events: 500 (Aprotinin), 1124 (Lysine Analogues)					
Heterogeneity: Tau² = 0.01; Chi² = 6.44, df = 5 (P = 0.27); I² =22%					
Test for overall effect: Z = 2.59 (P = 0.0096)					
2 Allocation concealment - Unclear					
Bernet 1999	11/28	17/28		2.4 %	0.65 [0.37, 1.12]
Blauhut 1994	3/14	7/15		0.7 %	0.46 [0.15, 1.44]
Casati 1999	19/67	23/66		2.8 %	0.81 [0.49, 1.35]
Casati 1999	19/67	17/70		2.3 %	1.17 [0.67, 2.05]
Casati 2000	185/518	178/522		8.5 %	1.05 [0.89, 1.24]
Corbeau 1995	15/43	15/41		2.3 %	0.95 [0.54, 1.69]
Dorman 2008	9/30	15/30		1.8 %	0.60 [0.31, 1.15]
Engel 2001	5/12	0/12		0.1 %	11.00 [0.67, 179.29]
Greilich 2001	7/24	5/23		0.9 %	1.34 [0.50, 3.63]
Ickx 2006	24/24	27/27		10.6 %	1.00 [0.93, 1.08]
Isetta 1993	55/140	24/70		4.1 %	1.15 [0.78, 1.68]
Mengistu 2008	10/25	17/25		2.4 %	0.59 [0.34, 1.02]
Menichetti 1996	2/24	16/48		0.5 %	0.25 [0.06, 1.00]
Penta de Peppo 1995	0/15	4/30		0.1 %	0.22 [0.01, 3.75]

0.01 0.1 1 10 100

Favours experimental Favours control

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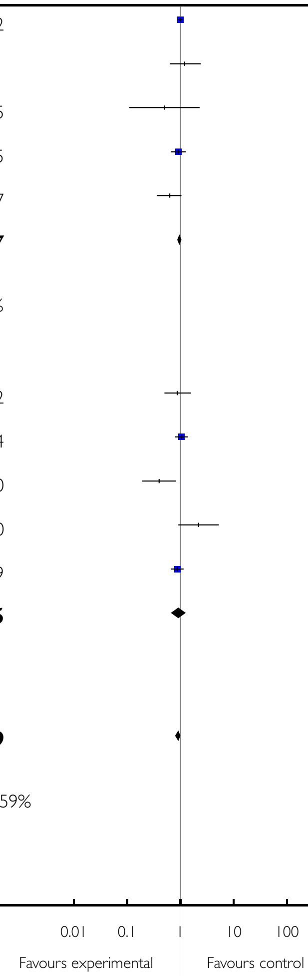
Study or subgroup	Aprotinin n/N	Lysine Analogues n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Pugh 1995	21/21	22/22		10.3 %	1.00 [0.92, 1.09]
Ray 2001	14/49	12/51		1.8 %	1.21 [0.63, 2.36]
Ray 2005	2/15	4/15		0.4 %	0.50 [0.11, 2.33]
Speekenbrink 1995	12/15	13/15		5.0 %	0.92 [0.67, 1.27]
Trinh-Duc 1992	12/29	18/27		2.7 %	0.62 [0.37, 1.03]
Subtotal (95% CI)	**1160**	**1137**		**59.7 %**	**0.95 [0.86, 1.04]**
Total events: 425 (Aprotinin), 434 (Lysine Analogues)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 26.77$, df = 18 (P = 0.08); I^2 =33%					
Test for overall effect: Z = 1.13 (P = 0.26)					
3 Allocation concealment - No					
Amar 2003	11/23	12/22		2.3 %	0.88 [0.49, 1.55]
Dalmau 2004	40/63	38/64		5.9 %	1.07 [0.81, 1.41]
Diprose 2005	8/60	20/60		1.5 %	0.40 [0.19, 0.84]
Kuitunen 2005	11/20	5/20		1.1 %	2.20 [0.93, 5.18]
Later 2009	48/96	57/99		6.2 %	0.87 [0.67, 1.13]
Subtotal (95% CI)	**262**	**265**		**17.0 %**	**0.92 [0.67, 1.28]**
Total events: 118 (Aprotinin), 132 (Lysine Analogues)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 10.34$, df = 4 (P = 0.04); I^2 =61%					
Test for overall effect: Z = 0.48 (P = 0.63)					
Total (95% CI)	**2407**	**3159**		**100.0 %**	**0.90 [0.81, 0.99]**
Total events: 1043 (Aprotinin), 1690 (Lysine Analogues)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 70.06$, df = 29 (P = 0.00003); I^2 =59%					
Test for overall effect: Z = 2.19 (P = 0.028)					
Test for subgroup differences: $Chi^2 = 0.0$, df = 2 (P = 0.0), I^2 =0.0%					



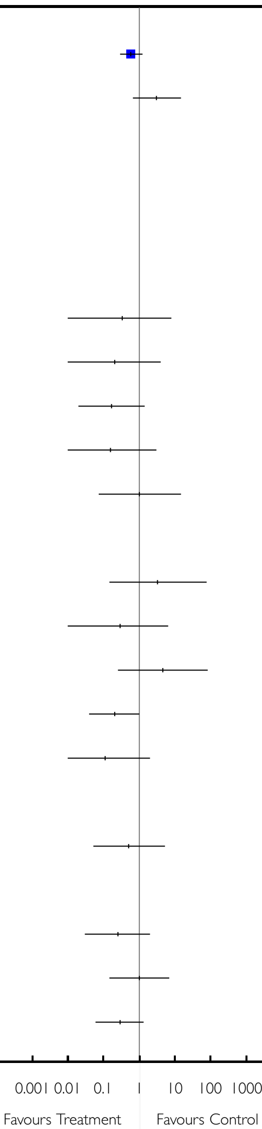
Analysis 8.1. Comparison 8 Adverse Events and Other Outcomes (Active versus Control), Outcome 1 Re-operation for bleeding.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 8 Adverse Events and Other Outcomes (Active versus Control)

Outcome: 1 Re-operation for bleeding

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI
1 Aprotinin versus Control			
Alderman 1998	11/436	19/434	0.58 [0.28, 1.20]
Alvarez 1995	6/49	2/51	3.12 [0.66, 14.73]
Alvarez 2001	0/26	0/29	0.0 [0.0, 0.0]
Apostolakis 2008	0/29	0/30	0.0 [0.0, 0.0]
Ashraf 1997	0/19	0/19	0.0 [0.0, 0.0]
Asimakopoulos 2000	0/8	0/10	0.0 [0.0, 0.0]
Bert 2008	0/25	1/25	0.33 [0.01, 7.81]
Bidstrup 1989	0/40	2/40	0.20 [0.01, 4.04]
Bidstrup 1990	1/26	4/18	0.17 [0.02, 1.42]
Bidstrup 1993	0/43	3/47	0.16 [0.01, 2.93]
Bidstrup 2000	1/30	1/30	1.00 [0.07, 15.26]
Boldt 1994	0/20	0/20	0.0 [0.0, 0.0]
Casas 1995	1/47	0/51	3.25 [0.14, 77.88]
Cicekcioglu 2006	0/24	1/20	0.28 [0.01, 6.52]
Cosgrove 1992	4/113	0/56	4.50 [0.25, 82.14]
D'Ambra 1996	2/141	5/71	0.20 [0.04, 1.01]
Deleuze 1991	0/30	4/30	0.11 [0.01, 1.98]
Demeyere 2006	0/20	0/20	0.0 [0.0, 0.0]
Desai 2009	1/38	2/37	0.49 [0.05, 5.14]
Dietrich 1990	0/19	0/20	0.0 [0.0, 0.0]
Dietrich 1995	1/15	4/15	0.25 [0.03, 1.98]
Dignan 2001	2/101	2/99	0.98 [0.14, 6.82]
Diprose 2005	2/60	7/60	0.29 [0.06, 1.32]



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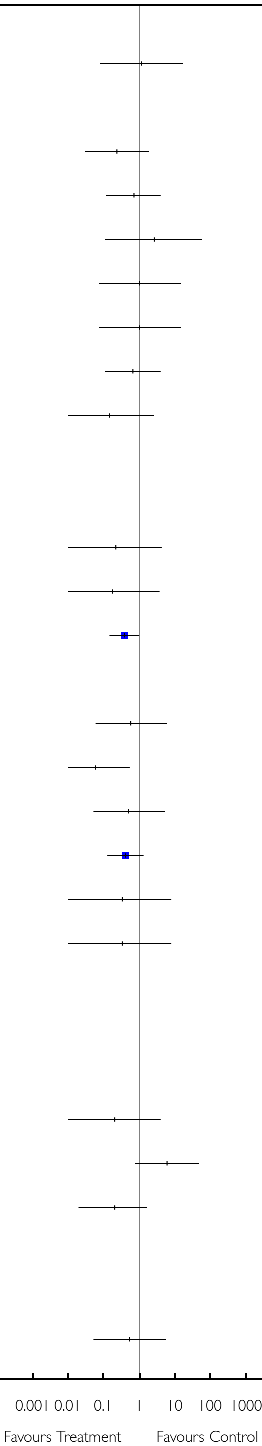
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Ehrlich 1998	0/25	0/25		0.0 [0.0, 0.0]
Englberger 2002a	1/22	1/25		1.14 [0.08, 17.11]
Englberger 2002b	0/15	0/14		0.0 [0.0, 0.0]
Findlay 2001	1/33	4/30		0.23 [0.03, 1.92]
Garcia-Huete 1997	2/39	3/41		0.70 [0.12, 3.97]
Hardy 1993	1/22	0/19		2.61 [0.11, 60.51]
Hardy 1997	1/26	1/26		1.00 [0.07, 15.15]
Kipfer 2003	1/15	1/15		1.00 [0.07, 14.55]
Koster 2004	2/100	3/100		0.67 [0.11, 3.90]
Kuepper 2003	0/60	3/59		0.14 [0.01, 2.66]
Kuitunen 2005	0/20	0/20		0.0 [0.0, 0.0]
Kunt 2005	0/40	0/46		0.0 [0.0, 0.0]
Kyriss 2001	0/18	2/20		0.22 [0.01, 4.32]
Lass 1995	0/51	2/47		0.18 [0.01, 3.75]
Later 2009	5/96	14/103		0.38 [0.14, 1.02]
Laub 1994	0/16	0/16		0.0 [0.0, 0.0]
Leijdekkers 2006	1/16	2/19		0.59 [0.06, 5.96]
Lemmer 1996	1/487	5/157		0.06 [0.01, 0.55]
Lemmer I 1994	1/108	2/108		0.50 [0.05, 5.43]
Levy 1995	6/215	5/72		0.40 [0.13, 1.28]
Liu 1993	0/20	1/20		0.33 [0.01, 7.72]
Mansour 2004	0/20	1/20		0.33 [0.01, 7.72]
Menichetti 1996	0/24	0/24		0.0 [0.0, 0.0]
Mohr 1992	0/34	0/16		0.0 [0.0, 0.0]
Moran 2000	0/28	0/14		0.0 [0.0, 0.0]
Nurözler 2008	0/25	2/26		0.21 [0.01, 4.12]
Nuttall 2000	6/45	1/45		6.00 [0.75, 47.85]
Parvizi 2007	1/81	5/81		0.20 [0.02, 1.67]
Penta de Peppo 1995	0/15	0/15		0.0 [0.0, 0.0]
Pugh 1995	0/15	0/15		0.0 [0.0, 0.0]
Ray 1997	1/21	2/23		0.55 [0.05, 5.61]



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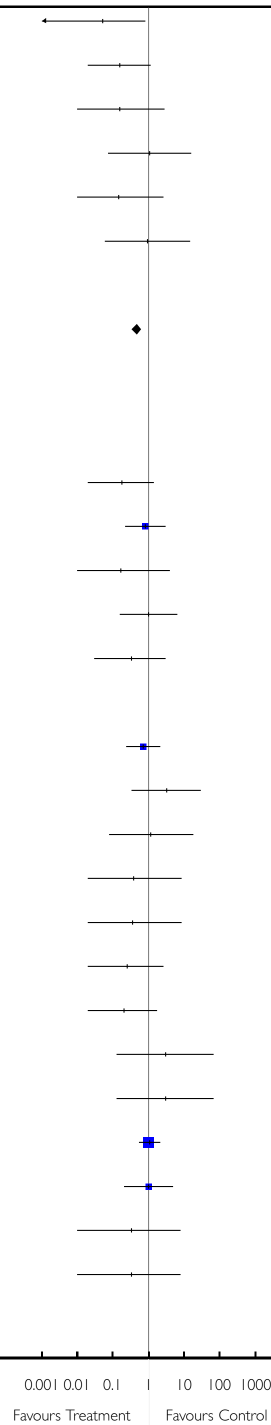
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Ray 1999	0/100	5/50		0.05 [0.00, 0.81]
Rodrigus 1996	1/46	7/47		0.15 [0.02, 1.14]
Rossi 1997	0/21	3/22		0.15 [0.01, 2.73]
Schweizer 2000	1/28	1/29		1.04 [0.07, 15.77]
Tabuchi 1994	0/20	3/20		0.14 [0.01, 2.60]
Taggart 2003	1/36	1/34		0.94 [0.06, 14.51]
Vedrinne 1992	0/30	0/30		0.0 [0.0, 0.0]
Subtotal (95% CI)	**3392**	**2725**		**0.46 [0.34, 0.62]**
Total events: 66 (Treatment), 137 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 35.44, df = 42 (P = 0.75); I^2 =0.0%				
Test for overall effect: Z = 5.03 (P < 0.00001)				
2 Tranexamic Acid versus Control				
Andreasen 2004	1/21	6/23		0.18 [0.02, 1.39]
Armellin 2001	4/150	5/150		0.80 [0.22, 2.92]
Brown 1997	0/60	1/30		0.17 [0.01, 4.04]
Casati 2002	2/29	2/29		1.00 [0.15, 6.63]
Casati 2004	1/52	3/50		0.32 [0.03, 2.98]
Demeyere 2006	0/20	0/20		0.0 [0.0, 0.0]
Diprose 2005	5/60	7/60		0.71 [0.24, 2.13]
Hardy 1998	3/43	1/45		3.14 [0.34, 29.03]
Horrow 1991	1/38	1/45		1.18 [0.08, 18.30]
Jares 2003	0/22	1/25		0.38 [0.02, 8.80]
Jimenez 2007	0/24	1/26		0.36 [0.02, 8.43]
Karski 1995	1/100	2/50		0.25 [0.02, 2.69]
Katsaros 1996	1/104	5/106		0.20 [0.02, 1.72]
Kuitunen 2005	1/20	0/20		3.00 [0.13, 69.52]
Kuitunen 2006	1/15	0/15		3.00 [0.13, 68.26]
Later 2009	14/99	14/103		1.04 [0.52, 2.07]
Maddali 2007	3/111	3/111		1.00 [0.21, 4.85]
Mansour 2004	0/20	1/20		0.33 [0.01, 7.72]
Mehr-Aein 2007	0/33	1/33		0.33 [0.01, 7.90]
Menichetti 1996	0/24	0/24		0.0 [0.0, 0.0]



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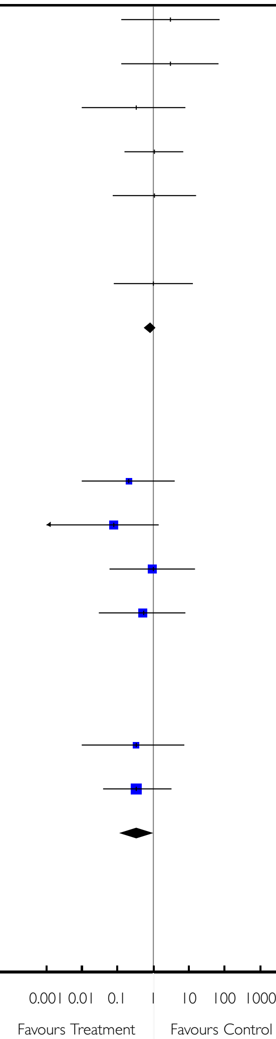
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Murphy 2006	1/50	0/50		3.00 [0.13, 71.92]
Penta de Peppo 1995	1/15	0/15		3.00 [0.13, 68.26]
Pleym 2003	0/40	1/39		0.33 [0.01, 7.75]
Pugh 1995	2/22	2/23		1.05 [0.16, 6.79]
Santos 2006	1/29	1/31		1.07 [0.07, 16.31]
Shore-Lesserson 1996	0/17	0/13		0.0 [0.0, 0.0]
Uozaki 2001	1/6	1/6		1.00 [0.08, 12.56]
Subtotal (95% CI)	**1224**	**1162**		**0.80 [0.55, 1.17]**
Total events: 44 (Treatment), 59 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 12.66$, df = 23 (P = 0.96); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.16 (P = 0.25)				
3 Epsilon Aminocaproic Acid versus Control				
Berenholtz 2009	0/91	2/91		0.20 [0.01, 4.11]
Del Rossi 1989	0/170	6/180		0.08 [0.00, 1.43]
Hardy 1998	1/46	1/45		0.98 [0.06, 15.17]
Kluger 2003	1/58	1/30		0.52 [0.03, 7.98]
Menichetti 1996	0/24	0/24		0.0 [0.0, 0.0]
Penta de Peppo 1995	0/15	0/15		0.0 [0.0, 0.0]
Rao 1999	0/15	1/15		0.33 [0.01, 7.58]
Vander-Salm 1996	1/51	3/52		0.34 [0.04, 3.16]
Subtotal (95% CI)	**470**	**452**		**0.32 [0.11, 0.99]**
Total events: 3 (Treatment), 14 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.84$, df = 5 (P = 0.87); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.97 (P = 0.048)				



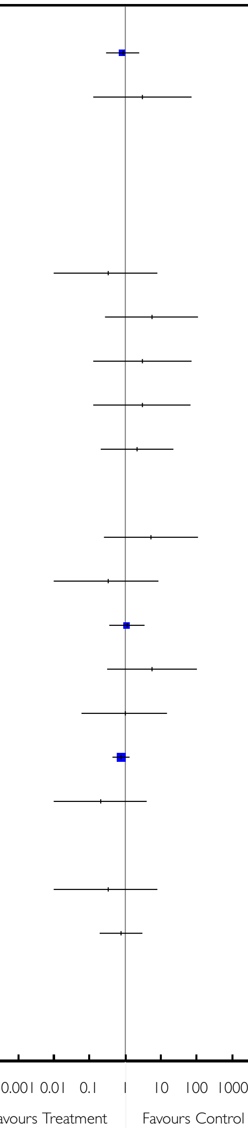
Analysis 8.2. Comparison 8 Adverse Events and Other Outcomes (Active versus Control), Outcome 2 Mortality.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 8 Adverse Events and Other Outcomes (Active versus Control)

Outcome: 2 Mortality

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI
1 Aprotinin versus Control			
Alderman 1998	6/436	7/434	0.85 [0.29, 2.52]
Alvarez 1995	1/49	0/51	3.12 [0.13, 74.80]
Alvarez 2001	0/26	0/29	0.0 [0.0, 0.0]
Apostolakis 2008	0/29	0/30	0.0 [0.0, 0.0]
Ashraf 1997	0/19	0/19	0.0 [0.0, 0.0]
Bidstrup 1989	0/40	1/40	0.33 [0.01, 7.95]
Bidstrup 1993	2/43	0/47	5.45 [0.27, 110.51]
Bidstrup 2000	1/30	0/30	3.00 [0.13, 70.83]
Blauhut 1994	1/14	0/14	3.00 [0.13, 67.91]
Casas 1995	2/47	1/51	2.17 [0.20, 23.16]
Cicekcioglu 2006	0/24	0/20	0.0 [0.0, 0.0]
Cohen 1998	2/56	0/59	5.26 [0.26, 107.27]
Colwell 2007	0/175	1/178	0.34 [0.01, 8.27]
Cosgrove 1992	9/113	4/56	1.12 [0.36, 3.46]
D'Ambra 1996	5/141	0/71	5.58 [0.31, 99.47]
Desai 2009	1/38	1/37	0.97 [0.06, 15.00]
Dietrich 1992	24/902	31/882	0.76 [0.45, 1.28]
Dietrich 1995	0/15	2/15	0.20 [0.01, 3.85]
Dignan 2001	0/101	0/99	0.0 [0.0, 0.0]
Diprose 2005	0/60	1/60	0.33 [0.01, 8.02]
Ehrlich 1998	3/25	4/25	0.75 [0.19, 3.01]
Englberger 2002a	0/22	0/25	0.0 [0.0, 0.0]
Englberger 2002b	0/15	0/14	0.0 [0.0, 0.0]



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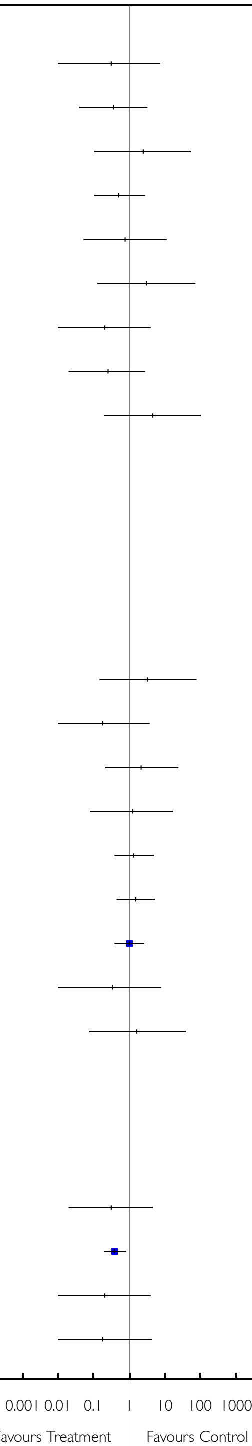
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Feindt 1994	0/10	0/10		0.0 [0.0, 0.0]
Findlay 2001	0/33	1/30		0.30 [0.01, 7.19]
Garcia-Huete 1997	1/39	3/41		0.35 [0.04, 3.23]
Golanski 2000	1/30	0/24		2.42 [0.10, 56.85]
Gott 1998	2/109	4/112		0.51 [0.10, 2.75]
Green 1995	1/48	1/36		0.75 [0.05, 11.59]
Greilich 2009	1/26	0/27		3.11 [0.13, 73.09]
Hardy 1993	0/22	2/22		0.20 [0.01, 3.94]
Hayashida 1997	1/110	2/57		0.26 [0.02, 2.80]
Jamieson 1997	1/24	0/36		4.44 [0.19, 104.67]
Kipfer 2003	0/15	0/15		0.0 [0.0, 0.0]
Koster 2004	0/100	0/100		0.0 [0.0, 0.0]
Kuepper 2003	0/60	0/59		0.0 [0.0, 0.0]
Kuitunen 2005	0/20	0/20		0.0 [0.0, 0.0]
Kunt 2005	0/40	0/46		0.0 [0.0, 0.0]
Kyriss 2001	1/18	0/20		3.32 [0.14, 76.60]
Lass 1995	0/51	2/47		0.18 [0.01, 3.75]
Later 2009	2/96	1/103		2.15 [0.20, 23.29]
Leijdekkers 2006	1/16	1/19		1.19 [0.08, 17.51]
Lemmer 1996	12/526	3/178		1.35 [0.39, 4.74]
Lemmer˙1 1994	6/108	4/108		1.50 [0.44, 5.17]
Levy 1995	15/215	5/72		1.00 [0.38, 2.67]
Liu 1993	0/20	1/20		0.33 [0.01, 7.72]
Maccario 1994	1/61	0/32		1.60 [0.07, 38.11]
Misfeld 1998	0/14	0/14		0.0 [0.0, 0.0]
Mohr 1992	0/34	0/16		0.0 [0.0, 0.0]
Moran 2000	0/28	0/14		0.0 [0.0, 0.0]
Murkin 2000	1/228	1/68		0.30 [0.02, 4.71]
Norman 2009	4/11	9/9		0.39 [0.19, 0.83]
Nuttall 2000	0/45	2/45		0.20 [0.01, 4.05]
Okita 1996	0/39	1/21		0.18 [0.01, 4.31]



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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Palmer 2003	0/30	0/26		0.0 [0.0, 0.0]
Rocha 1994	0/28	0/28		0.0 [0.0, 0.0]
Rodrigus 1996	1/46	2/47		0.51 [0.05, 5.44]
Royston 1987	0/11	1/11		0.33 [0.02, 7.39]
Schweizer 2000	1/28	0/29		3.10 [0.13, 73.12]
Stammers 1997	1/8	0/12		4.33 [0.20, 94.83]
Swart 1994	2/49	4/49		0.50 [0.10, 2.60]
Van der Linden 2005	3/37	1/38		3.08 [0.34, 28.30]
Wei 2006	0/36	0/40		0.0 [0.0, 0.0]
Subtotal (95% CI)	**4889**	**3987**		**0.81 [0.63, 1.06]**
Total events: 116 (Treatment), 104 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 29.54, df = 43 (P = 0.94); I^2 =0.0%				
Test for overall effect: Z = 1.55 (P = 0.12)				
2 Tranexamic Acid versus Control				
Andreasen 2004	1/21	0/23		3.27 [0.14, 76.21]
Armellin 2001	1/150	3/150		0.33 [0.04, 3.17]
Blauhut 1994	0/15	0/14		0.0 [0.0, 0.0]
Boylan 1996	0/25	3/20		0.12 [0.01, 2.11]
Brown 1997	1/60	0/30		1.52 [0.06, 36.34]
Casati 2002	2/29	2/29		1.00 [0.15, 6.63]
Coffey 1995	0/16	1/14		0.29 [0.01, 6.69]
Dalmau 2000	3/42	4/40		0.71 [0.17, 2.99]
Diprose 2005	0/60	1/60		0.33 [0.01, 8.02]
Dryden 1997	1/22	4/19		0.22 [0.03, 1.77]
Hardy 1998	0/43	0/45		0.0 [0.0, 0.0]
Hiipala 1997	0/39	1/38		0.33 [0.01, 7.74]
Jares 2003	0/22	0/25		0.0 [0.0, 0.0]
Jimenez 2007	0/24	0/26		0.0 [0.0, 0.0]
Karski 2005	3/147	1/165		3.37 [0.35, 32.02]
Kaspar 1997	1/16	0/16		3.00 [0.13, 68.57]
Katoh 1997	1/62	0/31		1.52 [0.06, 36.36]
Katsaros 1996	0/104	2/106		0.20 [0.01, 4.19]

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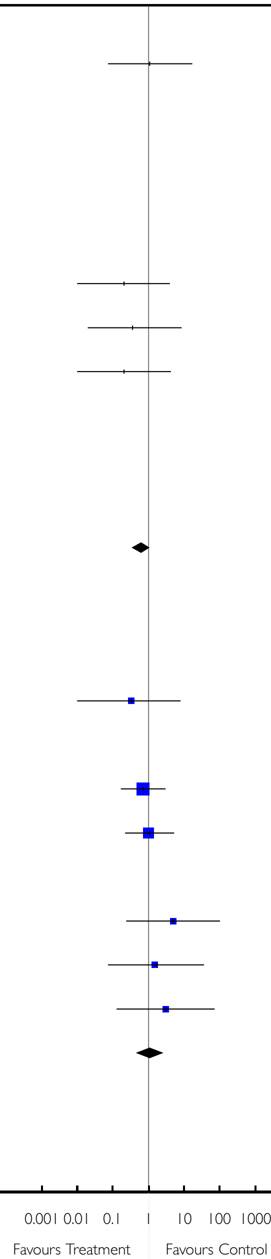
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Kuitunen 2005	0/20	0/20		0.0 [0.0, 0.0]
Later 2009	1/99	1/103		1.04 [0.07, 16.41]
Maddali 2007	0/111	0/111		0.0 [0.0, 0.0]
Mehr-Aein 2007	0/33	0/33		0.0 [0.0, 0.0]
Misfeld 1998	0/14	0/14		0.0 [0.0, 0.0]
Murphy 2006	0/50	0/50		0.0 [0.0, 0.0]
Nuttall 2000	0/45	2/45		0.20 [0.01, 4.05]
Sadeghi 2007	0/32	1/35		0.36 [0.02, 8.62]
Santos 2006	0/29	2/31		0.21 [0.01, 4.26]
Shore-Lesserson 1996	0/17	0/13		0.0 [0.0, 0.0]
Wu 2006	0/106	0/108		0.0 [0.0, 0.0]
Zabeeda 2002	0/25	0/25		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1478**	**1439**		**0.60 [0.33, 1.10]**
Total events: 15 (Treatment), 28 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 10.00, df = 17 (P = 0.90); I^2 =0.0%				
Test for overall effect: Z = 1.64 (P = 0.10)				
3 Epsilon Aminocaproic Acid versus Control				
Berenholtz 2009	0/91	1/91		0.33 [0.01, 8.08]
Daily 1994	0/21	0/19		0.0 [0.0, 0.0]
Dalmau 2000	3/42	4/40		0.71 [0.17, 2.99]
Del Rossi 1989	3/170	3/180		1.06 [0.22, 5.17]
Greilich 2009	0/25	0/27		0.0 [0.0, 0.0]
Hardy 1998	2/46	0/45		4.89 [0.24, 99.18]
Kluger 2003	1/58	0/30		1.58 [0.07, 37.56]
Vander-Salm 1996	1/51	0/52		3.06 [0.13, 73.36]
Subtotal (95% CI)	**504**	**484**		**1.07 [0.44, 2.57]**
Total events: 10 (Treatment), 8 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.30, df = 5 (P = 0.81); I^2 =0.0%				
Test for overall effect: Z = 0.14 (P = 0.89)				



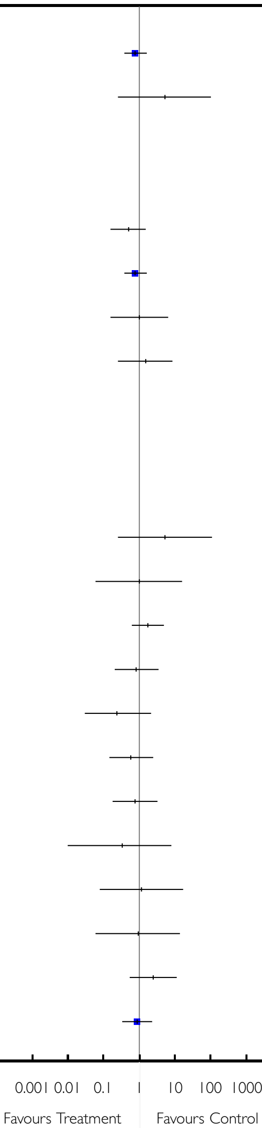
Analysis 8.3. Comparison 8 Adverse Events and Other Outcomes (Active versus Control), Outcome 3 Myocardial Infarction (MI).

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 8 Adverse Events and Other Outcomes (Active versus Control)

Outcome: 3 Myocardial Infarction (MI)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Aprotinin versus Control				
Alderman 1998	12/410	16/421		0.77 [0.37, 1.61]
Alvarez 1995	2/49	0/51		5.20 [0.26, 105.65]
Alvarez 2001	0/26	0/29		0.0 [0.0, 0.0]
Asimakopoulos 2000	0/8	0/10		0.0 [0.0, 0.0]
Baele 1992	4/58	8/57		0.49 [0.16, 1.54]
Bidstrup 1993	12/410	16/421		0.77 [0.37, 1.61]
Bidstrup 2000	2/30	2/30		1.00 [0.15, 6.64]
Carrera 1994	3/51	2/51		1.50 [0.26, 8.60]
Cicek 1996a	0/50	0/25		0.0 [0.0, 0.0]
Cicek 1996b	0/29	0/28		0.0 [0.0, 0.0]
Cicekcioglu 2006	0/24	0/20		0.0 [0.0, 0.0]
Cohen 1998	2/56	0/59		5.26 [0.26, 107.27]
Colwell 2007	1/175	1/177		1.01 [0.06, 16.04]
Cosgrove 1992	14/113	4/56		1.73 [0.60, 5.03]
D'Ambra 1996	5/141	3/71		0.84 [0.21, 3.41]
Desai 2009	1/38	4/37		0.24 [0.03, 2.08]
Dignan 2001	3/101	5/99		0.59 [0.14, 2.40]
Diprose 2005	3/60	4/60		0.75 [0.18, 3.21]
Ehrlich 1998	0/25	1/25		0.33 [0.01, 7.81]
Englberger 2002a	1/22	1/25		1.14 [0.08, 17.11]
Englberger 2002b	1/15	1/14		0.93 [0.06, 13.54]
Golanski 2000	6/30	2/24		2.40 [0.53, 10.84]
Greilich 2009	6/26	7/27		0.89 [0.34, 2.30]



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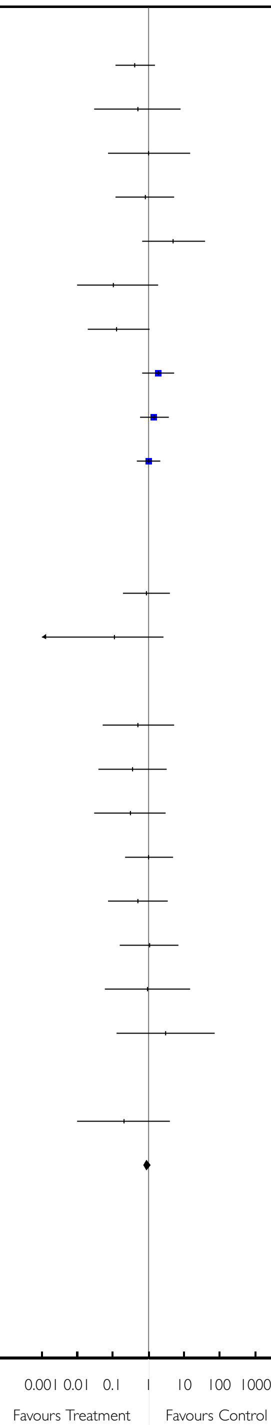
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Harder 1991	0/40	0/40		0.0 [0.0, 0.0]
Hayashida 1997	4/110	5/57		0.41 [0.12, 1.48]
Kalangos 1994	1/110	1/55		0.50 [0.03, 7.84]
Kipfer 2003	1/15	1/15		1.00 [0.07, 14.55]
Klein 1998	2/38	2/30		0.79 [0.12, 5.28]
Kuitunen 2005	5/20	1/20		5.00 [0.64, 39.06]
Lass 1995	0/51	4/47		0.10 [0.01, 1.86]
Later 2009	1/96	8/103		0.13 [0.02, 1.05]
Lemmer 1996	22/526	4/178		1.86 [0.65, 5.33]
Lemmer˙1 1994	10/108	7/108		1.43 [0.56, 3.61]
Levy 1995	24/206	8/67		0.98 [0.46, 2.07]
Mansour 2004	0/20	0/20		0.0 [0.0, 0.0]
Moran 2000	0/28	0/14		0.0 [0.0, 0.0]
Murkin 1994	3/29	3/25		0.86 [0.19, 3.90]
Murkin 2000	0/228	1/73		0.11 [0.00, 2.62]
Nurözler 2008	0/25	0/26		0.0 [0.0, 0.0]
Parvizi 2007	1/81	2/81		0.50 [0.05, 5.41]
Poston 2006	1/29	3/31		0.36 [0.04, 3.23]
Ranaboldo 1997	1/66	3/62		0.31 [0.03, 2.93]
Rodrigus 1996	3/46	3/47		1.02 [0.22, 4.80]
Santamaria 2000	2/56	2/28		0.50 [0.07, 3.37]
Schweizer 2000	2/28	2/29		1.04 [0.16, 6.86]
Taggart 2003	1/36	1/34		0.94 [0.06, 14.51]
Van der Linden 2005	1/37	0/38		3.08 [0.13, 73.25]
Wei 2006	0/36	0/40		0.0 [0.0, 0.0]
Wendel 1995	0/20	2/20		0.20 [0.01, 3.92]
Subtotal (95% CI)	**4032**	**3105**		**0.87 [0.69, 1.11]**
Total events: 163 (Treatment), 140 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 27.71$, df = 38 (P = 0.89); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.11 (P = 0.27)				
2 Tranexamic Acid versus Control				
Andreasen 2004	0/21	0/23		0.0 [0.0, 0.0]



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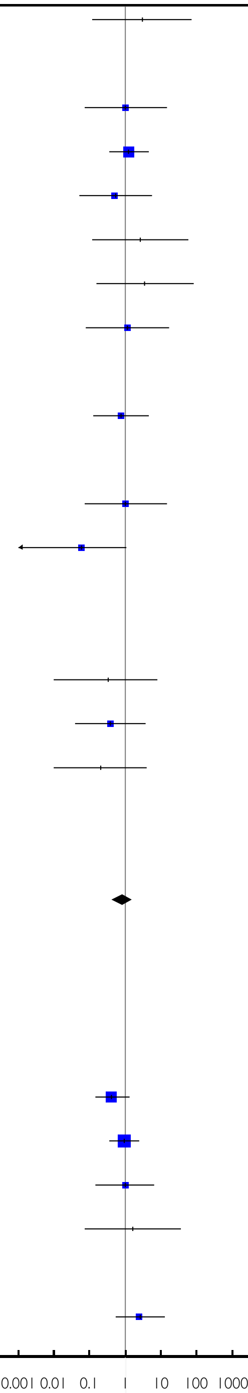
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Armellin 2001	1/150	0/150		3.00 [0.12, 73.06]
Brown 1997	0/60	0/30		0.0 [0.0, 0.0]
Casati 2002	1/29	1/29		1.00 [0.07, 15.24]
Diprose 2005	5/60	4/60		1.25 [0.35, 4.43]
Hardy 1998	1/43	2/45		0.52 [0.05, 5.56]
Hiipala 1995	1/15	0/13		2.63 [0.12, 59.40]
Horrow 1991	1/37	0/44		3.55 [0.15, 84.69]
Jares 2003	1/22	1/25		1.14 [0.08, 17.11]
Karski 1995	0/100	0/50		0.0 [0.0, 0.0]
Karski 2005	2/147	3/165		0.75 [0.13, 4.42]
Katsaros 1996	0/104	0/106		0.0 [0.0, 0.0]
Kuitunen 2005	1/20	1/20		1.00 [0.07, 14.90]
Later 2009	0/99	8/103		0.06 [0.00, 1.05]
Mansour 2004	0/20	0/20		0.0 [0.0, 0.0]
Mehr-Aein 2007	0/33	0/33		0.0 [0.0, 0.0]
Murphy 2006	0/50	1/50		0.33 [0.01, 7.99]
Shore-Lesserson 1996	1/17	2/13		0.38 [0.04, 3.77]
Speekenbrink 1995	0/15	2/15		0.20 [0.01, 3.85]
Taghaddomi 2009	0/50	0/50		0.0 [0.0, 0.0]
Zabeeda 2002	0/25	0/25		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1117**	**1069**		**0.79 [0.41, 1.52]**
Total events: 15 (Treatment), 25 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 7.84$, df = 12 (P = 0.80); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.69 (P = 0.49)				
3 Epsilon aminocaproic Acid versus Control				
Berenholtz 2009	0/91	0/91		0.0 [0.0, 0.0]
Del Rossi 1989	4/170	10/180		0.42 [0.14, 1.32]
Greilich 2009	6/25	7/27		0.93 [0.36, 2.38]
Hardy 1998	2/46	2/45		0.98 [0.14, 6.65]
Kluger 2003	1/58	0/30		1.58 [0.07, 37.56]
Rao 1999	0/15	0/15		0.0 [0.0, 0.0]
Vander-Salm 1996	5/51	2/52		2.55 [0.52, 12.55]



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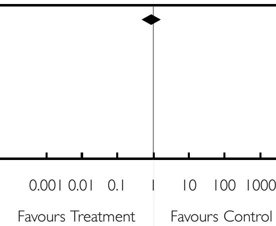
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**456**	**440**		**0.88 [0.48, 1.63]**
Total events: 18 (Treatment), 21 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.44, df = 4 (P = 0.49); I^2 =0.0%				
Test for overall effect: Z = 0.41 (P = 0.68)				



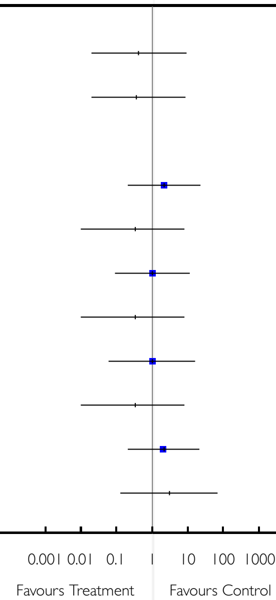
Analysis 8.4. Comparison 8 Adverse Events and Other Outcomes (Active versus Control), Outcome 4 Stroke (CVA).

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 8 Adverse Events and Other Outcomes (Active versus Control)

Outcome: 4 Stroke (CVA)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Aprotinin versus Control				
Asimakopoulos 2000	0/8	1/10		0.41 [0.02, 8.84]
Bidstrup 1993	0/43	1/47		0.36 [0.02, 8.70]
Casas 1995	0/47	0/51		0.0 [0.0, 0.0]
Cohen 1998	2/56	1/59		2.11 [0.20, 22.60]
Colwell 2007	0/175	1/177		0.34 [0.01, 8.22]
D'Ambra 1996	2/141	1/71		1.01 [0.09, 10.92]
Desai 2009	0/38	1/37		0.32 [0.01, 7.73]
Dignan 2001	1/101	1/99		0.98 [0.06, 15.45]
Ehrlich 1998	0/25	1/25		0.33 [0.01, 7.81]
Greilich 2009	2/26	1/27		2.08 [0.20, 21.55]
Kuitunen 2005	1/20	0/20		3.00 [0.13, 69.52]



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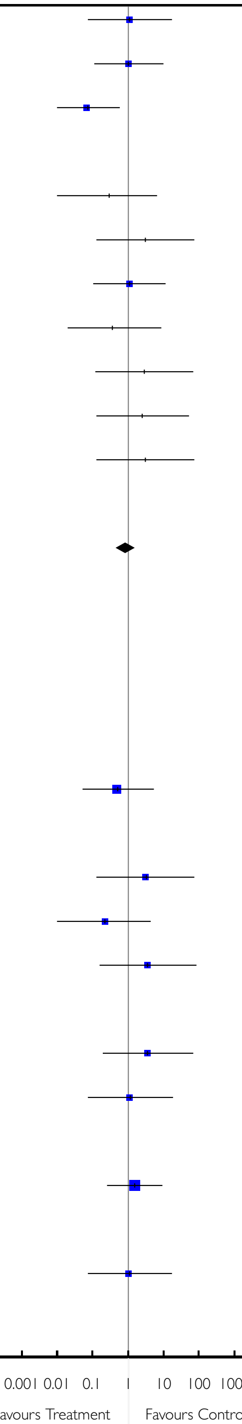
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Later 2009	1/96	1/103		1.07 [0.07, 16.92]
Lemmer 1996	3/526	1/178		1.02 [0.11, 9.70]
Levy 1995	1/215	5/72		0.07 [0.01, 0.56]
Moran 2000	0/28	0/14		0.0 [0.0, 0.0]
Murkin 1995	0/29	1/24		0.28 [0.01, 6.52]
Nurözler 2008	1/25	0/26		3.12 [0.13, 73.06]
Okita 1996	2/39	1/21		1.08 [0.10, 11.19]
Poston 2006	0/29	1/31		0.36 [0.02, 8.39]
Ranaboldo 1997	1/66	0/62		2.82 [0.12, 67.97]
Santamaria 2000	2/56	0/28		2.54 [0.13, 51.26]
Van der Linden 2005	1/37	0/38		3.08 [0.13, 73.25]
Wei 2006	0/36	0/40		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1862**	**1260**		**0.82 [0.44, 1.52]**
Total events: 20 (Treatment), 19 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 11.97, df = 19 (P = 0.89); I^2 =0.0%				
Test for overall effect: Z = 0.63 (P = 0.53)				
2 Tranexamic Acid versus Control				
Andreasen 2004	0/21	0/23		0.0 [0.0, 0.0]
Brown 1997	0/60	0/30		0.0 [0.0, 0.0]
Casati 2002	1/29	2/29		0.50 [0.05, 5.21]
Casati 2004	0/52	0/50		0.0 [0.0, 0.0]
Hardy 1998	1/43	0/45		3.14 [0.13, 74.95]
Horrow 1990	0/18	2/20		0.22 [0.01, 4.32]
Horrow 1991	1/37	0/44		3.55 [0.15, 84.69]
Jares 2003	0/22	0/25		0.0 [0.0, 0.0]
Karski 1995	3/100	0/50		3.53 [0.19, 67.13]
Karski 2005	1/147	1/165		1.12 [0.07, 17.79]
Katoh 1997	0/62	0/31		0.0 [0.0, 0.0]
Katsaros 1996	3/104	2/106		1.53 [0.26, 8.96]
Kuitunen 2005	0/20	0/20		0.0 [0.0, 0.0]
Later 2009	1/99	1/103		1.04 [0.07, 16.41]
Maddali 2007	0/111	0/111		0.0 [0.0, 0.0]



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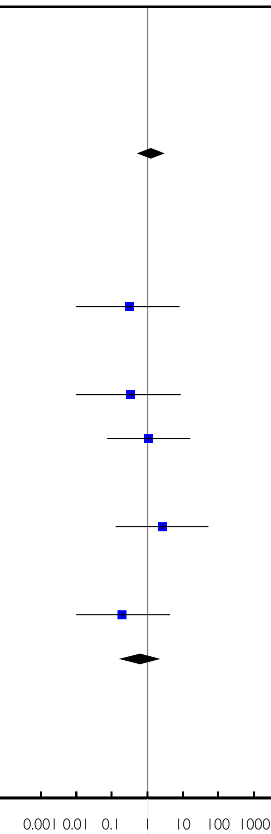
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Murphy 2006	0/50	0/50		0.0 [0.0, 0.0]
Taghaddomi 2009	0/50	0/50		0.0 [0.0, 0.0]
Zabeeda 2002	0/25	0/25		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1050**	**977**		**1.23 [0.49, 3.07]**
Total events: 11 (Treatment), 8 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.18, df = 7 (P = 0.87); I^2 =0.0%				
Test for overall effect: Z = 0.44 (P = 0.66)				
3 Epsilon Aminocaproic Acid versus Control				
Berenholtz 2009	0/91	1/91		0.33 [0.01, 8.08]
Daily 1994	0/21	0/19		0.0 [0.0, 0.0]
Del Rossi 1989	0/170	1/180		0.35 [0.01, 8.60]
Greilich 2009	1/25	1/27		1.08 [0.07, 16.36]
Hardy 1998	0/46	0/45		0.0 [0.0, 0.0]
Kluger 2003	2/58	0/30		2.63 [0.13, 53.04]
Rao 1999	0/15	0/15		0.0 [0.0, 0.0]
Vander-Salm 1996	0/51	2/52		0.20 [0.01, 4.14]
Subtotal (95% CI)	**477**	**459**		**0.62 [0.16, 2.36]**
Total events: 3 (Treatment), 5 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.84, df = 4 (P = 0.77); I^2 =0.0%				
Test for overall effect: Z = 0.71 (P = 0.48)				



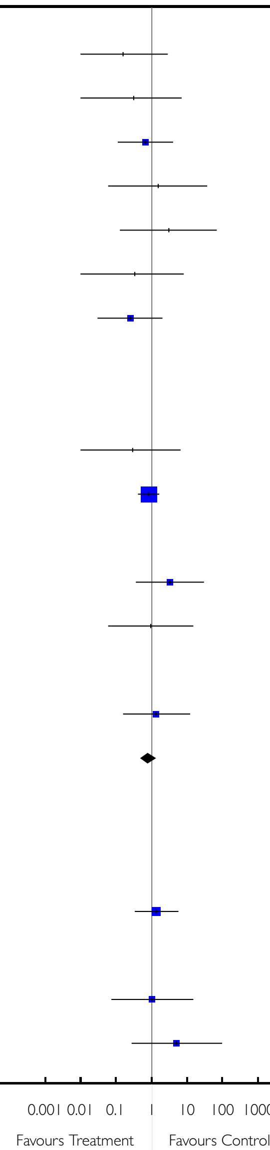
Analysis 8.5. Comparison 8 Adverse Events and Other Outcomes (Active versus Control), Outcome 5 Deep Vein Thrombosis (DVT).

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 8 Adverse Events and Other Outcomes (Active versus Control)

Outcome: 5 Deep Vein Thrombosis (DVT)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI
1 Aprotinin versus Control			
Amar 2003	0/23	3/24	0.15 [0.01, 2.73]
Capdevila 1998	0/12	1/11	0.31 [0.01, 6.85]
Colwell 2007	2/175	3/177	0.67 [0.11, 3.99]
D'Ambra 1996	1/141	0/71	1.52 [0.06, 36.87]
Engel 2001	1/12	0/12	3.00 [0.13, 67.06]
Hayes 1996	0/20	1/20	0.33 [0.01, 7.72]
Janssens 1994	1/20	4/20	0.25 [0.03, 2.05]
Jeserschek 2003	0/9	0/9	0.0 [0.0, 0.0]
Llau 1998	0/10	0/10	0.0 [0.0, 0.0]
Murkin 1995	0/29	1/24	0.28 [0.01, 6.52]
Murkin 2000	26/228	10/73	0.83 [0.42, 1.64]
Petsatodis 2006	0/25	0/25	0.0 [0.0, 0.0]
Poston 2006	3/29	1/31	3.21 [0.35, 29.11]
Ranaboldo 1997	1/66	1/62	0.94 [0.06, 14.70]
Ray 2005	0/15	0/15	0.0 [0.0, 0.0]
Samama 2002	3/40	1/18	1.35 [0.15, 12.11]
Subtotal (95% CI)	**854**	**602**	**0.78 [0.47, 1.29]**
Total events: 38 (Treatment), 26 (Control)			
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.22$, df = 11 (P = 0.86); $I^2 = 0.0\%$			
Test for overall effect: Z = 0.97 (P = 0.33)			
2 Tranexamic Acid versus Control			
Benoni 1996	4/43	3/43	1.33 [0.32, 5.61]
Claeys 2007	0/20	0/20	0.0 [0.0, 0.0]
Ekback 2000	1/20	1/20	1.00 [0.07, 14.90]
Engel 2001	2/12	0/12	5.00 [0.27, 94.34]



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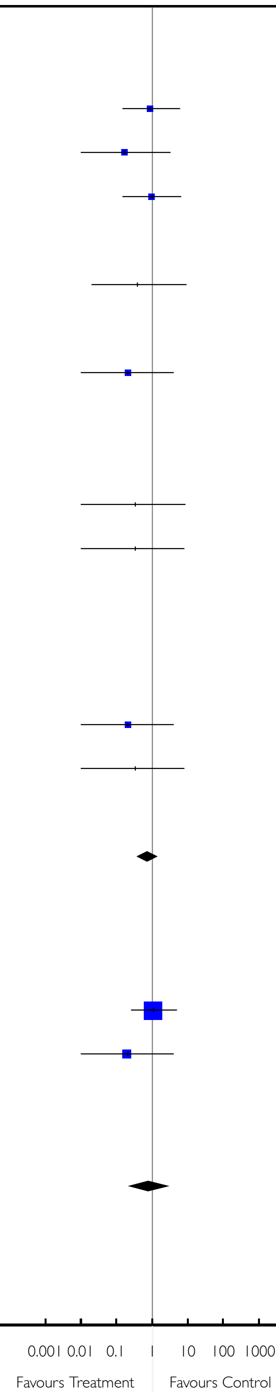
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Garneti 2004	0/25	0/25		0.0 [0.0, 0.0]
Gill 2009	0/5	0/5		0.0 [0.0, 0.0]
Good 2003	2/27	2/24		0.89 [0.14, 5.83]
Hiipala 1995	0/15	2/13		0.18 [0.01, 3.34]
Hiipala 1997	2/39	2/38		0.97 [0.14, 6.57]
Horrow 1990	0/18	0/20		0.0 [0.0, 0.0]
Horrow 1991	0/37	1/44		0.39 [0.02, 9.41]
Husted 2003	0/20	0/20		0.0 [0.0, 0.0]
Jansen 1999	0/21	2/21		0.20 [0.01, 3.93]
Johansson 2005	0/47	0/53		0.0 [0.0, 0.0]
Katoh 1997	0/62	0/31		0.0 [0.0, 0.0]
Katsaros 1996	0/104	1/106		0.34 [0.01, 8.24]
Kazemi 2010	0/32	1/32		0.33 [0.01, 7.89]
Lemay 2004	0/20	0/19		0.0 [0.0, 0.0]
Niskanen 2005	0/19	0/20		0.0 [0.0, 0.0]
Orpen 2006	0/15	0/14		0.0 [0.0, 0.0]
Sorin 1999	0/21	2/21		0.20 [0.01, 3.93]
Wong 2008	0/73	1/74		0.34 [0.01, 8.16]
Zhang 2007	0/51	0/51		0.0 [0.0, 0.0]
Subtotal (95% CI)	**746**	**726**		**0.71 [0.35, 1.43]**
Total events: 11 (Treatment), 18 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 5.71, df = 11 (P = 0.89); I^2 =0.0%				
Test for overall effect: Z = 0.95 (P = 0.34)				
3 Epsilon Aminocaproic Acid versus Control				
Amar 2003	3/22	3/24		1.09 [0.25, 4.85]
Berenholtz 2009	0/91	2/91		0.20 [0.01, 4.11]
Harley 2002	0/22	0/24		0.0 [0.0, 0.0]
Ray 2005	0/15	0/15		0.0 [0.0, 0.0]
Subtotal (95% CI)	**150**	**154**		**0.78 [0.20, 3.03]**
Total events: 3 (Treatment), 5 (Control)				
Heterogeneity: Tau^2 = 0.03; Chi^2 = 1.02, df = 1 (P = 0.31); I^2 =2%				
Test for overall effect: Z = 0.37 (P = 0.71)				



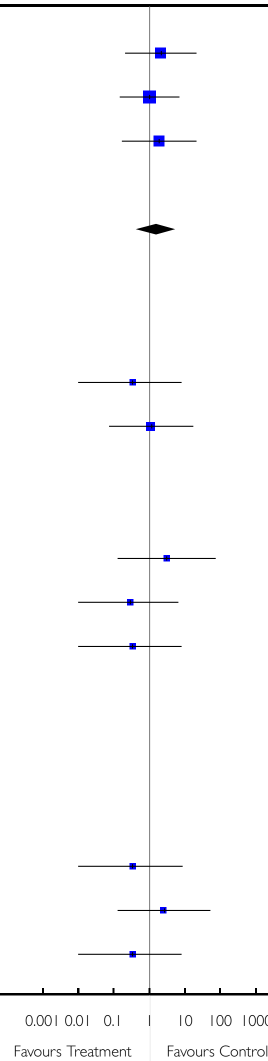
Analysis 8.6. Comparison 8 Adverse Events and Other Outcomes (Active versus Control), Outcome 6 Pulmonary Embolism (PE).

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 8 Adverse Events and Other Outcomes (Active versus Control)

Outcome: 6 Pulmonary Embolism (PE)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Aprotinin versus Control				
Amar 2003	2/23	1/24		2.09 [0.20, 21.48]
Colwell 2007	2/175	2/177		1.01 [0.14, 7.10]
Ranaboldo 1997	2/66	1/62		1.88 [0.17, 20.20]
Samama 2002	0/40	0/18		0.0 [0.0, 0.0]
Subtotal (95% CI)	**304**	**281**		**1.49 [0.42, 5.29]**
Total events: 6 (Treatment), 4 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.27, df = 2 (P = 0.87); I^2 =0.0%				
Test for overall effect: Z = 0.62 (P = 0.54)				
2 Tranexamic Acid versus Control				
Benoni 1996	0/43	1/43		0.33 [0.01, 7.96]
Benoni 2001	1/18	1/20		1.11 [0.07, 16.49]
Casati 2002	0/29	0/29		0.0 [0.0, 0.0]
Casati 2004	0/52	0/50		0.0 [0.0, 0.0]
Garneti 2004	1/25	0/25		3.00 [0.13, 70.30]
Hiipala 1995	0/15	1/13		0.29 [0.01, 6.60]
Hiipala 1997	0/39	1/38		0.33 [0.01, 7.74]
Horrow 1990	0/18	0/20		0.0 [0.0, 0.0]
Husted 2003	0/20	0/20		0.0 [0.0, 0.0]
Jares 2003	0/22	0/25		0.0 [0.0, 0.0]
Katoh 1997	0/62	0/31		0.0 [0.0, 0.0]
Katsaros 1996	0/104	1/106		0.34 [0.01, 8.24]
MacGillivray 2010	2/40	0/20		2.56 [0.13, 50.95]
Pleym 2003	0/40	1/39		0.33 [0.01, 7.75]



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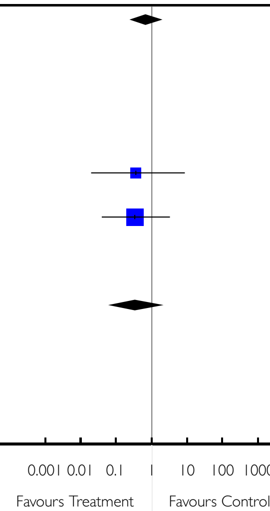
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**527**	**479**		**0.67 [0.23, 1.99]**
Total events: 4 (Treatment), 6 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.81$, df = 7 (P = 0.90); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.71 (P = 0.48)				
3 Epsilon Aminocaproic Acid versus Control				
Amar 2003	0/22	1/24		0.36 [0.02, 8.46]
Berenholtz 2009	1/91	3/91		0.33 [0.04, 3.15]
Harley 2002	0/22	0/24		0.0 [0.0, 0.0]
Subtotal (95% CI)	**135**	**139**		**0.34 [0.06, 2.13]**
Total events: 1 (Treatment), 4 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.97); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.15 (P = 0.25)				



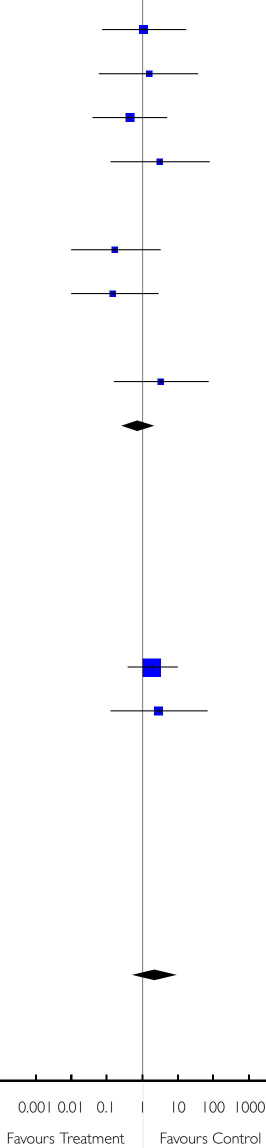
Analysis 8.7. Comparison 8 Adverse Events and Other Outcomes (Active versus Control), Outcome 7 Other Thrombosis.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 8 Adverse Events and Other Outcomes (Active versus Control)

Outcome: 7 Other Thrombosis

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI
1 Aprotinin versus Control			
Casas 1995	1/47	1/51	1.09 [0.07, 16.86]
D'Ambra 1996	1/141	0/71	1.52 [0.06, 36.87]
Findlay 2001	1/33	2/30	0.45 [0.04, 4.76]
Garcia-Huete 1997	1/39	0/41	3.15 [0.13, 75.08]
Lentschener 1997	0/48	0/49	0.0 [0.0, 0.0]
Murkin 1995	0/29	2/24	0.17 [0.01, 3.31]
Poston 2006	0/29	3/31	0.15 [0.01, 2.83]
Rocha 1994	0/28	0/28	0.0 [0.0, 0.0]
Thorpe 1994	1/8	0/9	3.33 [0.15, 71.90]
Subtotal (95% CI)	**402**	**334**	**0.73 [0.25, 2.15]**
Total events: 5 (Treatment), 8 (Control)			
Heterogeneity: Tau^2 = 0.0; Chi^2 = 4.27, df = 6 (P = 0.64); I^2 =0.0%			
Test for overall effect: Z = 0.58 (P = 0.57)			
2 Tranexamic Acid versus Control			
Alvarez 2008	0/46	0/49	0.0 [0.0, 0.0]
Boylan 1996	0/25	0/20	0.0 [0.0, 0.0]
Dalmau 2000	4/42	2/40	1.90 [0.37, 9.83]
Kaspar 1997	1/16	0/16	3.00 [0.13, 68.57]
Taghaddomi 2009	0/50	0/50	0.0 [0.0, 0.0]
Veien 2002	0/15	0/15	0.0 [0.0, 0.0]
Yamasaki 2004	0/20	0/20	0.0 [0.0, 0.0]
Yassen 1993	0/10	0/10	0.0 [0.0, 0.0]
Zohar 2004	0/20	0/20	0.0 [0.0, 0.0]
Subtotal (95% CI)	**244**	**240**	**2.10 [0.49, 8.99]**
Total events: 5 (Treatment), 2 (Control)			
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.06, df = 1 (P = 0.80); I^2 =0.0%			



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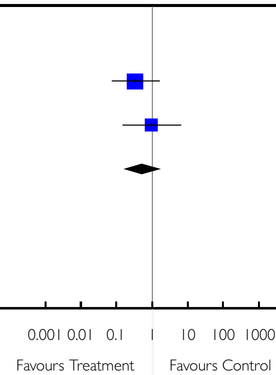
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 1.00 (P = 0.32)				
3 Epsilon Aminocaproic Acid versus Control				
Berenholtz 2009	2/91	6/91		0.33 [0.07, 1.61]
Dalmau 2000	2/42	2/40		0.95 [0.14, 6.44]
Subtotal (95% CI)	**133**	**131**		**0.51 [0.15, 1.72]**
Total events: 4 (Treatment), 8 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.69$, df = 1 (P = 0.40); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.09 (P = 0.28)				



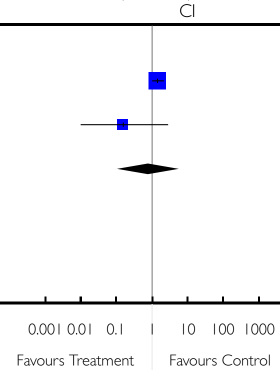
Analysis 8.8. Comparison 8 Adverse Events and Other Outcomes (Active versus Control), Outcome 8 Coronary artery graft occlusion.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 8 Adverse Events and Other Outcomes (Active versus Control)

Outcome: 8 Coronary artery graft occlusion

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Aprotinin versus Control					
Alderman 1998	54/340	36/328		71.2 %	1.45 [0.98, 2.14]
Poston 2006	0/29	3/31		28.8 %	0.15 [0.01, 2.83]
Total (95% CI)	**369**	**359**		**100.0 %**	**0.76 [0.10, 5.67]**
Total events: 54 (Treatment), 39 (Control)					
Heterogeneity: $Tau^2 = 1.45$; $Chi^2 = 2.28$, df = 1 (P = 0.13); $I^2 = 56\%$					
Test for overall effect: Z = 0.27 (P = 0.79)					



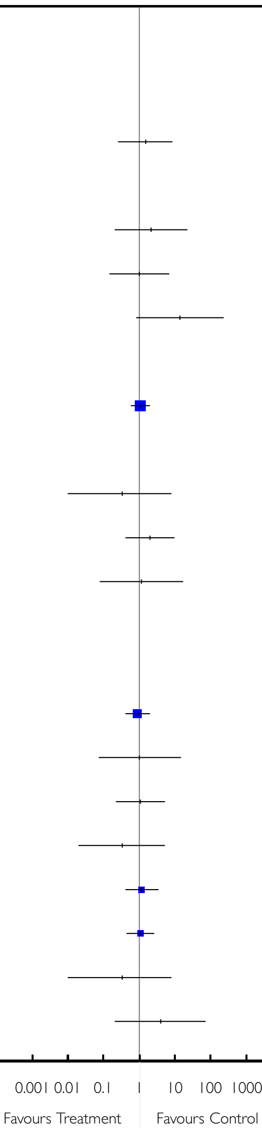
Analysis 8.9. Comparison 8 Adverse Events and Other Outcomes (Active versus Control), Outcome 9 Renal Failure / Dysfunction.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 8 Adverse Events and Other Outcomes (Active versus Control)

Outcome: 9 Renal Failure / Dysfunction

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI
1 Aprotinin versus Control			
Alvarez 2001	0/26	0/29	0.0 [0.0, 0.0]
Asimakopoulos 2000	0/8	0/10	0.0 [0.0, 0.0]
Baele 1992	3/58	2/57	1.47 [0.26, 8.50]
Cicek 1996b	0/29	0/28	0.0 [0.0, 0.0]
Cohen 1998	2/56	1/59	2.11 [0.20, 22.60]
Colwell 2007	2/175	2/177	1.01 [0.14, 7.10]
D'Ambra 1996	13/141	0/71	13.69 [0.83, 227.03]
Desai 2009	0/38	0/37	0.0 [0.0, 0.0]
Dietrich 1992	21/902	19/882	1.08 [0.59, 2.00]
Dignan 2001	0/101	0/99	0.0 [0.0, 0.0]
Diprose 2005	0/60	1/60	0.33 [0.01, 8.02]
Ehrlich 1998	4/25	2/25	2.00 [0.40, 9.95]
Englberger 2002a	1/22	1/25	1.14 [0.08, 17.11]
Englberger 2002b	0/15	0/14	0.0 [0.0, 0.0]
Gherli 1992	0/18	0/13	0.0 [0.0, 0.0]
Greilich 2009	8/26	9/27	0.92 [0.42, 2.02]
Kipfer 2003	1/15	1/15	1.00 [0.07, 14.55]
Later 2009	3/96	3/103	1.07 [0.22, 5.19]
Lemmer 1996	1/526	1/178	0.34 [0.02, 5.38]
Lemmer'1 1994	7/108	6/108	1.17 [0.41, 3.36]
Levy 1995	19/215	6/72	1.06 [0.44, 2.55]
Mansour 2004	0/20	1/20	0.33 [0.01, 7.72]
Okita 1996	3/39	0/21	3.85 [0.21, 71.18]



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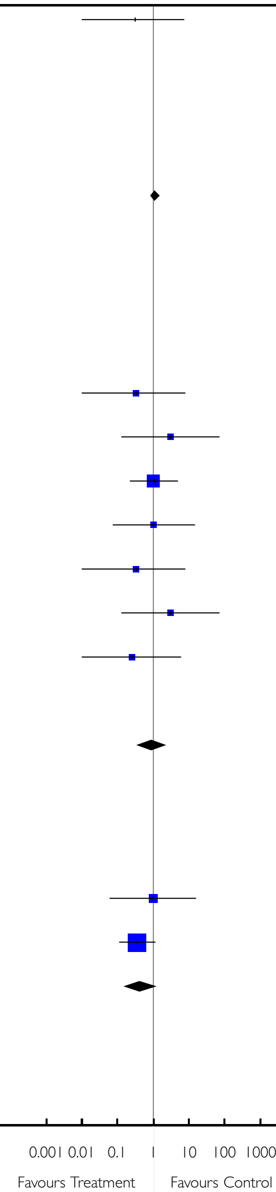
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Ranaboldo 1997	0/66	1/62		0.31 [0.01, 7.55]
Speekenbrink 1996	0/75	0/37		0.0 [0.0, 0.0]
Stammers 1997	0/8	0/12		0.0 [0.0, 0.0]
Wei 2006	0/36	0/40		0.0 [0.0, 0.0]
Subtotal (95% CI)	**2904**	**2281**		**1.10 [0.79, 1.54]**
Total events: 88 (Treatment), 56 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 7.64$, df = 16 (P = 0.96); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.58 (P = 0.56)				
2 Tranexamic Acid versus Control				
Andreasen 2004	0/21	0/23		0.0 [0.0, 0.0]
Diprose 2005	0/60	1/60		0.33 [0.01, 8.02]
Katsaros 1996	1/104	0/106		3.06 [0.13, 74.20]
Later 2009	3/99	3/103		1.04 [0.22, 5.03]
Mansour 2004	1/20	1/20		1.00 [0.07, 14.90]
Mehr-Aein 2007	0/33	1/33		0.33 [0.01, 7.90]
Murphy 2006	1/50	0/50		3.00 [0.13, 71.92]
Shore-Lesserson 1996	0/17	1/13		0.26 [0.01, 5.89]
Taghaddomi 2009	0/50	0/50		0.0 [0.0, 0.0]
Subtotal (95% CI)	**454**	**458**		**0.89 [0.33, 2.37]**
Total events: 6 (Treatment), 7 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.52$, df = 6 (P = 0.87); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.23 (P = 0.81)				
3 Epsilon Aminocaproic Acid versus control				
Berenholtz 2009	1/91	1/91		1.00 [0.06, 15.75]
Greilich 2009	3/26	9/27		0.35 [0.11, 1.14]
Subtotal (95% CI)	**117**	**118**		**0.41 [0.14, 1.22]**
Total events: 4 (Treatment), 10 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.48$, df = 1 (P = 0.49); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.60 (P = 0.11)				



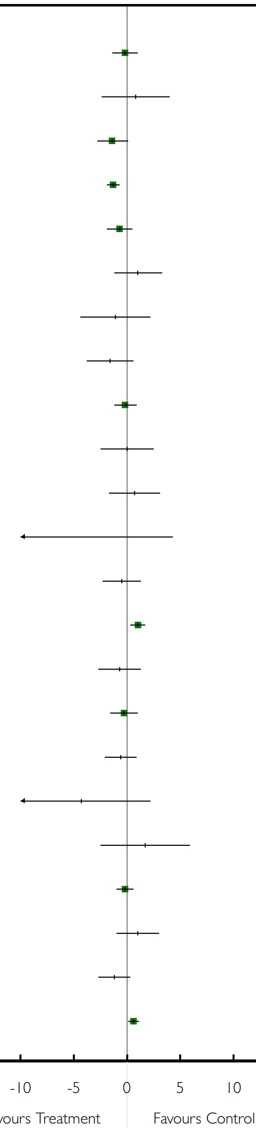
Analysis 8.10. Comparison 8 Adverse Events and Other Outcomes (Active versus Control), Outcome 10 Hospital Length of Stay.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 8 Adverse Events and Other Outcomes (Active versus Control)

Outcome: 10 Hospital Length of Stay

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Aprotinin versus Control							
Alderman 1998	401	7.6 (8.5)	395	7.8 (8.6)		6.1 %	-0.20 [-1.39, 0.99]
Amar 2003	23	9.8 (5.3)	24	9 (5.9)		1.7 %	0.80 [-2.40, 4.00]
Apostolakis 2008	29	5.83 (1.65)	30	7.2 (3.61)		5.1 %	-1.37 [-2.79, 0.05]
Asimakopoulos 2000	8	6.3 (0.2)	10	7.6 (0.9)		8.9 %	-1.30 [-1.87, -0.73]
Cicekcioglu 2006	24	6.2 (1.8)	20	6.9 (2.1)		6.2 %	-0.70 [-1.87, 0.47]
Cohen 1998	56	10.9 (7.2)	59	9.9 (4.8)		2.9 %	1.00 [-1.25, 3.25]
Englberger 2002a	22	8 (2.2)	25	9.1 (8)		1.6 %	-1.10 [-4.37, 2.17]
Englberger 2002b	15	9.7 (2.4)	14	11.3 (3.6)		2.9 %	-1.60 [-3.84, 0.64]
Fauli 2005	40	6.65 (1.81)	20	6.8 (2.1)		6.6 %	-0.15 [-1.23, 0.93]
Harmon 2004	17	11.8 (3.1)	18	11.8 (4.3)		2.5 %	0.0 [-2.47, 2.47]
Janssens 1994	20	13.9 (5)	20	13.2 (2.3)		2.6 %	0.70 [-1.71, 3.11]
Jeserschek 2003	9	17.6 (7.73)	9	27.8 (20.74)		0.1 %	-10.20 [-24.66, 4.26]
Kipfer 2003	15	9.7 (2.4)	15	10.2 (2.7)		3.9 %	-0.50 [-2.33, 1.33]
Kunt 2005	40	8 (1)	46	7 (2)		8.6 %	1.00 [0.34, 1.66]
Later 2009	96	7.8 (6.7)	103	8.5 (7.4)		3.5 %	-0.70 [-2.66, 1.26]
Liu 1993	20	7.3 (2.68)	20	7.6 (1.34)		5.6 %	-0.30 [-1.61, 1.01]
Mansour 2004	20	5.8 (1.8)	20	6.4 (3)		4.7 %	-0.60 [-2.13, 0.93]
Murkin 1994	29	11.1 (4.85)	25	15.4 (16)		0.5 %	-4.30 [-10.82, 2.22]
Murkin 1995	29	13.1 (9.15)	24	11.4 (6.37)		1.0 %	1.70 [-2.49, 5.89]
Nurözler 2008	25	5.3 (1.6)	26	5.5 (1.4)		7.7 %	-0.20 [-1.03, 0.63]
Poston 2006	29	8 (4.1)	31	7 (3.8)		3.4 %	1.00 [-1.00, 3.00]
Stammers 1997	8	6.1 (0.8)	12	7.3 (2.5)		4.8 %	-1.20 [-2.72, 0.32]
Wei 2006	36	7.9 (1.2)	40	7.3 (1.2)		9.1 %	0.60 [0.06, 1.14]



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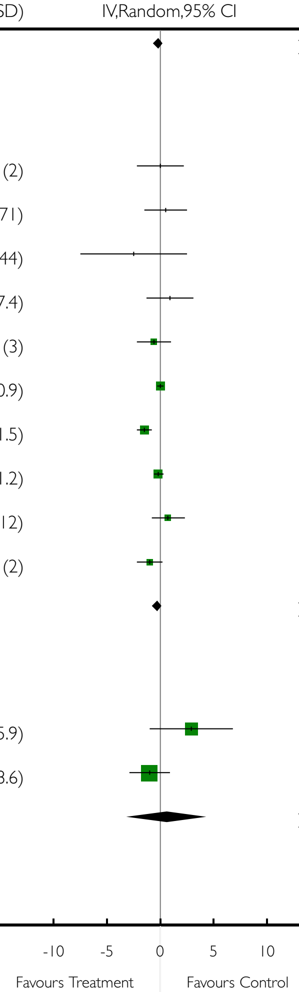
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Subtotal (95% CI)	**1011**		**1006**			**100.0 %**	**-0.25 [-0.71, 0.20]**
Heterogeneity: Tau² = 0.51; Chi² = 50.13, df = 22 (P = 0.00056); I² =56%							
Test for overall effect: Z = 1.10 (P = 0.27)							
2 Tranexamic Acid versus Control							
Ellis 2001	10	10 (3)	10	10 (2)		3.9 %	0.0 [-2.23, 2.23]
Jimenez 2007	24	4.5 (3.55)	26	4 (3.71)		4.7 %	0.50 [-1.51, 2.51]
Kazemi 2010	32	13 (12.4)	32	15.5 (7.44)		0.9 %	-2.50 [-7.51, 2.51]
Later 2009	99	9.4 (8.6)	103	8.5 (7.4)		4.0 %	0.90 [-1.32, 3.12]
Mansour 2004	20	5.8 (2.2)	20	6.4 (3)		6.5 %	-0.60 [-2.23, 1.03]
Mehr-Aein 2007	33	4.8 (0.4)	33	4.8 (0.9)		24.6 %	0.0 [-0.34, 0.34]
Sadeghi 2007	32	4.3 (1.6)	35	5.8 (1.5)		16.6 %	-1.50 [-2.24, -0.76]
Wei 2006	36	7.1 (0.8)	40	7.3 (1.2)		22.3 %	-0.20 [-0.65, 0.25]
Wong 2008	73	9.19 (5.48)	74	8.47 (4.12)		6.9 %	0.72 [-0.85, 2.29]
Zohar 2004	20	8 (2)	20	9 (2)		9.7 %	-1.00 [-2.24, 0.24]
Subtotal (95% CI)	**379**		**393**			**100.0 %**	**-0.34 [-0.82, 0.13]**
Heterogeneity: Tau² = 0.21; Chi² = 18.42, df = 9 (P = 0.03); I² =51%							
Test for overall effect: Z = 1.41 (P = 0.16)							
3 Epsilon Aminocaproic Acid versus Control							
Amar 2003	22	11.9 (7.3)	24	9 (5.9)		40.5 %	2.90 [-0.96, 6.76]
Berenholtz 2009	91	8.5 (3.9)	91	9.5 (8.6)		59.5 %	-1.00 [-2.94, 0.94]
Subtotal (95% CI)	**113**		**115**			**100.0 %**	**0.58 [-3.17, 4.33]**
Heterogeneity: Tau² = 5.18; Chi² = 3.13, df = 1 (P = 0.08); I² =68%							
Test for overall effect: Z = 0.30 (P = 0.76)							



Analysis 9.1. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 1 Re-operation for bleeding - Aprotinin versus Tranexamic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

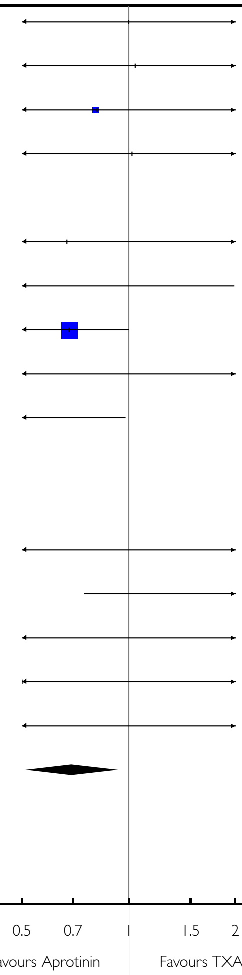
Outcome: 1 Re-operation for bleeding - Aprotinin versus Tranexamic Acid

Study or subgroup	Aprotinin n/N	Tranexamic Acid n/N	Risk Ratio M-H,Random,95% CI
Bernet 1999	2/28	2/28	1.00 [0.15, 6.61]
Casati 1999	2/67	2/70	1.04 [0.15, 7.21]
Casati 2000	8/518	10/522	0.81 [0.32, 2.03]
Dalmau 2004	2/63	2/64	1.02 [0.15, 6.99]
Demeyere 2006	0/20	0/20	0.0 [0.0, 0.0]
Dietrich 2008	2/110	3/110	0.67 [0.11, 3.91]
Diprose 2005	2/60	5/60	0.40 [0.08, 1.98]
Fergusson 2008	43/780	62/770	0.68 [0.47, 1.00]
Kuitunen 2005	0/20	1/20	0.33 [0.01, 7.72]
Later 2009	5/96	14/99	0.37 [0.14, 0.98]
Mansour 2004	0/20	0/20	0.0 [0.0, 0.0]
Menichetti 1996	0/24	0/24	0.0 [0.0, 0.0]
Mongan 1998	1/75	0/75	3.00 [0.12, 72.49]
Nuttall 2000	6/45	0/45	13.00 [0.75, 224.13]
Penta de Peppo 1995	0/15	1/15	0.33 [0.01, 7.58]
Pugh 1995	1/25	2/25	0.50 [0.05, 5.17]
Wong 2000	1/39	0/38	2.93 [0.12, 69.64]
Total (95% CI)	**2005**	**2005**	**0.69 [0.51, 0.93]**

Total events: 75 (Aprotinin), 104 (Tranexamic Acid)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 8.90$, df = 13 (P = 0.78); $I^2 = 0.0\%$

Test for overall effect: Z = 2.46 (P = 0.014)



Analysis 9.2. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 2 Re-operation for bleeding - Aprotinin versus Epsilon Aminocaproic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

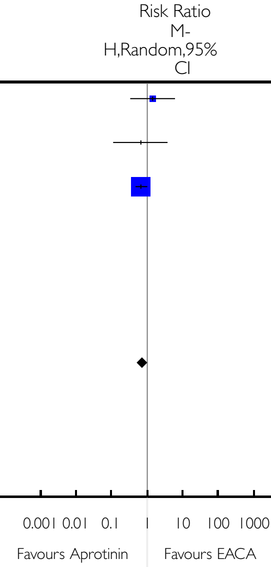
Outcome: 2 Re-operation for bleeding - Aprotinin versus Epsilon Aminocaproic Acid

Study or subgroup	Aprotinin n/N	EACA n/N	Risk Ratio M-H,Random,95% CI
Bennett-Guerrero 1997	4/99	3/105	1.41 [0.32, 6.16]
Casati 1999	2/67	3/66	0.66 [0.11, 3.80]
Fergusson 2008	43/780	64/780	0.67 [0.46, 0.98]
Menichetti 1996	0/24	0/24	0.0 [0.0, 0.0]
Penta de Peppo 1995	0/15	0/15	0.0 [0.0, 0.0]
Ray 2001	0/49	0/51	0.0 [0.0, 0.0]
Total (95% CI)	**1034**	**1041**	**0.70 [0.49, 1.00]**

Total events: 49 (Aprotinin), 70 (EACA)

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.93, df = 2 (P = 0.63); I^2 =0.0%

Test for overall effect: Z = 1.96 (P = 0.049)



Analysis 9.3. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 3 Re-operation for bleeding - Tranexamic Acid versus Epsilon Aminocaproic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

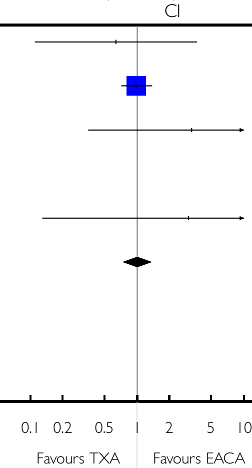
Outcome: 3 Re-operation for bleeding - Tranexamic Acid versus Epsilon Aminocaproic Acid

Study or subgroup	Tranexamic Acid n/N	EACA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Casati 1999	2/70	3/66		0.63 [0.11, 3.64]
Fergusson 2008	62/770	64/780		0.98 [0.70, 1.37]
Hardy 1998	3/43	1/46		3.21 [0.35, 29.69]
Menichetti 1996	0/24	0/24		0.0 [0.0, 0.0]
Penta de Peppo 1995	1/15	0/15		3.00 [0.13, 68.26]
Total (95% CI)	**922**	**931**		**1.00 [0.73, 1.39]**

Total events: 68 (Tranexamic Acid), 68 (EACA)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.81$, df = 3 (P = 0.61); $I^2 = 0.0\%$

Test for overall effect: Z = 0.02 (P = 0.99)



Analysis 9.4. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 4 Mortality - Aprotinin versus Tranexamic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

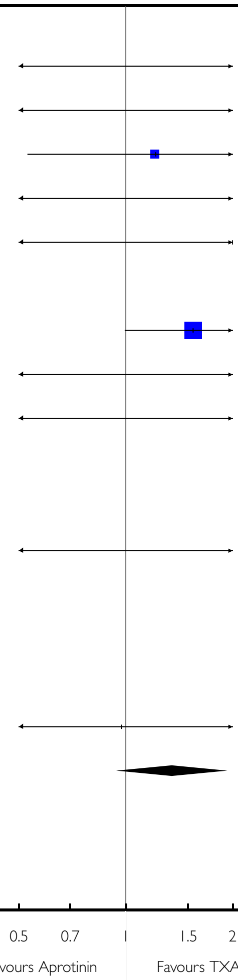
Outcome: 4 Mortality - Aprotinin versus Tranexamic Acid

Study or subgroup	Aprotinin n/N	Tranexamic Acid n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Bernet 1999	0/28	0/28		0.0 [0.0, 0.0]
Blauhut 1994	1/14	0/15		3.20 [0.14, 72.62]
Casati 1999	1/67	0/70		3.13 [0.13, 75.57]
Casati 2000	12/518	10/522		1.21 [0.53, 2.77]
Dalmau 2004	1/63	4/64		0.25 [0.03, 2.21]
Dietrich 2008	2/110	1/110		2.00 [0.18, 21.74]
Diprose 2005	0/60	0/60		0.0 [0.0, 0.0]
Fergusson 2008	47/779	30/769		1.55 [0.99, 2.42]
Hekmat 2004	0/60	2/58		0.19 [0.01, 3.94]
Ickx 2006	0/24	2/27		0.22 [0.01, 4.45]
Kuitunen 2005	0/20	0/20		0.0 [0.0, 0.0]
Landymore 1997	0/48	0/56		0.0 [0.0, 0.0]
Later 2009	1/96	0/99		3.09 [0.13, 75.00]
Misfeld 1998	0/14	0/14		0.0 [0.0, 0.0]
Mongan 1998	0/75	0/75		0.0 [0.0, 0.0]
Nuttall 2000	0/45	0/45		0.0 [0.0, 0.0]
Wong 2000	2/39	2/38		0.97 [0.14, 6.57]
Total (95% CI)	**2060**	**2070**		**1.35 [0.94, 1.93]**

Total events: 67 (Aprotinin), 51 (Tranexamic Acid)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.78$, df = 9 (P = 0.66); $I^2 = 0.0\%$

Test for overall effect: Z = 1.61 (P = 0.11)



Analysis 9.5. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 5 Mortality - Aprotinin versus Epsilon Aminocaproic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

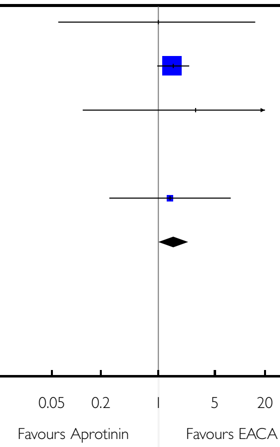
Outcome: 5 Mortality - Aprotinin versus Epsilon Aminocaproic Acid

Study or subgroup	Aprotinin n/N	EACA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Casati 1999	1/67	1/66		0.99 [0.06, 15.42]
Fergusson 2008	47/779	31/780		1.52 [0.98, 2.36]
Greilich 2009	1/26	0/25		2.89 [0.12, 67.75]
Landymore 1997	0/48	0/44		0.0 [0.0, 0.0]
Trinh-Duc 1992	3/29	2/27		1.40 [0.25, 7.73]
Total (95% CI)	**949**	**942**		**1.51 [0.99, 2.30]**

Total events: 52 (Aprotinin), 34 (EACA)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.26$, df = 3 (P = 0.97); I^2 =0.0%

Test for overall effect: Z = 1.93 (P = 0.053)



Analysis 9.6. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 6 Mortality - Tranexamic Acid versus Epsilon Aminocaproic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

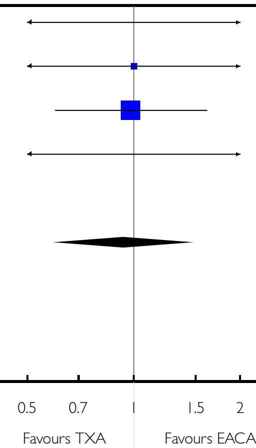
Outcome: 6 Mortality - Tranexamic Acid versus Epsilon Aminocaproic Acid

Study or subgroup	Tranexamic Acid n/N	EACA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Casati 1999	0/70	1/66		0.31 [0.01, 7.59]
Dalmau 2000	3/42	3/42		1.00 [0.21, 4.67]
Fergusson 2008	30/769	31/780		0.98 [0.60, 1.61]
Hardy 1998	0/43	2/46		0.21 [0.01, 4.33]
Landymore 1997	0/56	0/44		0.0 [0.0, 0.0]
Total (95% CI)	**980**	**978**		**0.93 [0.59, 1.47]**

Total events: 33 (Tranexamic Acid), 37 (EACA)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.43$, df = 3 (P = 0.70); $I^2 = 0.0\%$

Test for overall effect: Z = 0.32 (P = 0.75)



Analysis 9.7. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 7 Mortality - Aprotinin versus Lysine Analogues.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

Outcome: 7 Mortality - Aprotinin versus Lysine Analogues

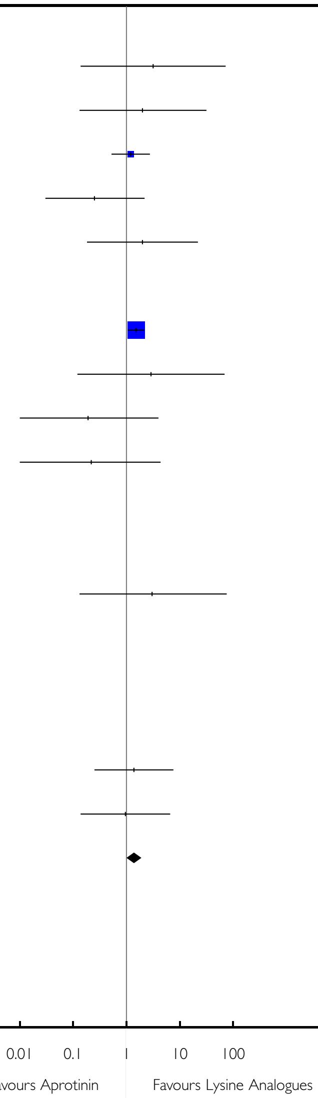
Study or subgroup	Aprotinin n/N	Lysine Analogues n/N	Risk Ratio M-H,Random,95% CI
Bernet 1999	0/28	0/28	0.0 [0.0, 0.0]
Blauhut 1994	1/14	0/15	3.20 [0.14, 72.62]
Casati 1999	1/67	1/136	2.03 [0.13, 31.95]
Casati 2000	12/518	10/522	1.21 [0.53, 2.77]
Dalmau 2004	1/63	4/64	0.25 [0.03, 2.21]
Dietrich 2008	2/110	1/110	2.00 [0.18, 21.74]
Diprose 2005	0/60	0/60	0.0 [0.0, 0.0]
Fergusson 2008	47/779	61/1549	1.53 [1.06, 2.22]
Greilich 2009	1/26	0/25	2.89 [0.12, 67.75]
Hekmat 2004	0/60	2/58	0.19 [0.01, 3.94]
Ickx 2006	0/24	2/27	0.22 [0.01, 4.45]
Kuitunen 2005	0/20	0/20	0.0 [0.0, 0.0]
Landymore 1997	0/48	0/100	0.0 [0.0, 0.0]
Later 2009	1/96	0/99	3.09 [0.13, 75.00]
Misfeld 1998	0/14	0/14	0.0 [0.0, 0.0]
Mongan 1998	0/75	0/75	0.0 [0.0, 0.0]
Nuttall 2000	0/45	0/45	0.0 [0.0, 0.0]
Trinh-Duc 1992	3/29	2/27	1.40 [0.25, 7.73]
Wong 2000	2/39	2/38	0.97 [0.14, 6.57]
Total (95% CI)	**2115**	**3012**	**1.39 [1.02, 1.89]**

Total events: 71 (Aprotinin), 85 (Lysine Analogues)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.89$, df = 11 (P = 0.81); $I^2 = 0.0\%$

Test for overall effect: Z = 2.07 (P = 0.039)

Test for subgroup differences: Not applicable



Analysis 9.8. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 8 Myocardial Infarction - Aprotinin versus Tranexamic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

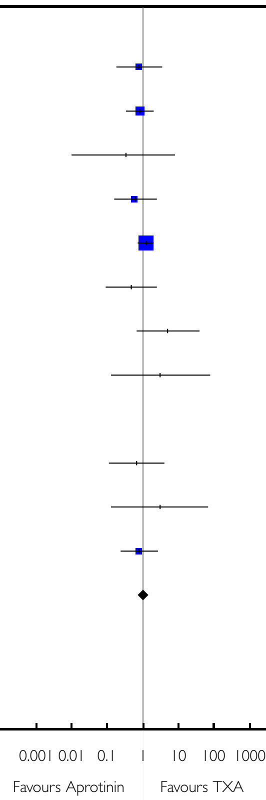
Outcome: 8 Myocardial Infarction - Aprotinin versus Tranexamic Acid

Study or subgroup	Aprotinin n/N	Tranexamic Acid n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Bernet 1999	0/28	0/28		0.0 [0.0, 0.0]
Casati 1999	3/67	4/70		0.78 [0.18, 3.37]
Casati 2000	9/518	11/522		0.82 [0.34, 1.97]
Dalmau 2004	0/63	1/64		0.34 [0.01, 8.16]
Diprose 2005	3/60	5/60		0.60 [0.15, 2.40]
Fergusson 2008	33/717	28/727		1.20 [0.73, 1.96]
Hekmat 2004	2/60	4/58		0.48 [0.09, 2.54]
Kuitunen 2005	5/20	1/20		5.00 [0.64, 39.06]
Later 2009	1/96	0/99		3.09 [0.13, 75.00]
Mansour 2004	0/20	0/20		0.0 [0.0, 0.0]
Mongan 1998	2/75	3/75		0.67 [0.11, 3.88]
Speekenbrink 1995	1/15	0/15		3.00 [0.13, 68.26]
Wong 2000	4/39	5/38		0.78 [0.23, 2.68]
Total (95% CI)	**1778**	**1796**		**1.00 [0.71, 1.42]**

Total events: 63 (Aprotinin), 62 (Tranexamic Acid)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.18$, df = 10 (P = 0.80); $I^2 = 0.0\%$

Test for overall effect: Z = 0.03 (P = 0.98)



Analysis 9.9. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 9 Myocardial Infarction - Aprotinin versus Epsilon Aminocaproic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

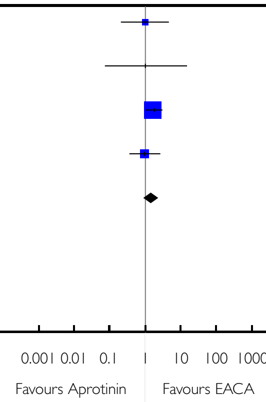
Outcome: 9 Myocardial Infarction - Aprotinin versus Epsilon Aminocaproic Acid

Study or subgroup	Aprotinin n/N	EACA n/N	Weight	Risk Ratio M-H,Random,95% CI
Casati 1999	3/67	3/66	8.3 %	0.99 [0.21, 4.71]
Eberle 1998	1/20	1/20	2.8 %	1.00 [0.07, 14.90]
Fergusson 2008	33/717	20/735	68.2 %	1.69 [0.98, 2.92]
Greilich 2009	6/26	6/25	20.7 %	0.96 [0.36, 2.59]
Total (95% CI)	**830**	**846**	**100.0 %**	**1.42 [0.90, 2.22]**

Total events: 43 (Aprotinin), 30 (EACA)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.27$, df = 3 (P = 0.74); $I^2 = 0.0\%$

Test for overall effect: Z = 1.52 (P = 0.13)



Analysis 9.10. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 10 Myocardial Infarction - Tranexamic Acid versus Epsilon Aminocaproic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

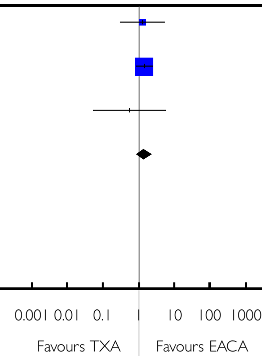
Outcome: 10 Myocardial Infarction - Tranexamic Acid versus Epsilon Aminocaproic Acid

Study or subgroup	Tranexamic Acid n/N	EACA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Casati 1999	4/70	3/66		12.4 %	1.26 [0.29, 5.41]
Fergusson 2008	28/727	20/735		82.9 %	1.42 [0.80, 2.49]
Hardy 1998	1/43	2/46		4.7 %	0.53 [0.05, 5.69]
Total (95% CI)	**840**	**847**		**100.0 %**	**1.33 [0.80, 2.23]**

Total events: 33 (Tranexamic Acid), 25 (EACA)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.62$, df = 2 (P = 0.73); $I^2 = 0.0\%$

Test for overall effect: Z = 1.09 (P = 0.27)



Analysis 9.11. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 11 Myocardial infarction - Aprotinin versus Lysine Analogues.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

Outcome: 11 Myocardial infarction - Aprotinin versus Lysine Analogues

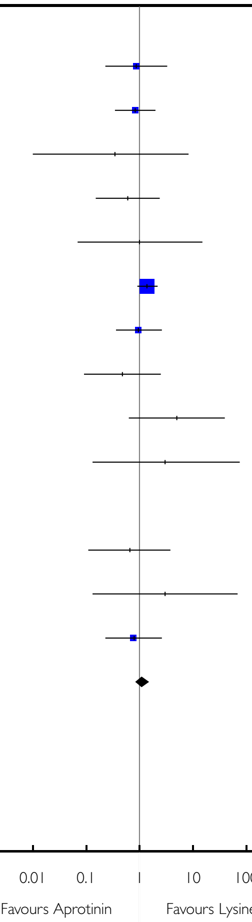
Study or subgroup	Aprotinin n/N	Lysine Analogues n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Bernet 1999	0/28	0/28		0.0 [0.0, 0.0]
Casati 1999	3/67	7/136		0.87 [0.23, 3.26]
Casati 2000	9/518	11/522		0.82 [0.34, 1.97]
Dalmau 2004	0/63	1/64		0.34 [0.01, 8.16]
Diprose 2005	3/60	5/60		0.60 [0.15, 2.40]
Eberle 1998	1/20	1/20		1.00 [0.07, 14.90]
Fergusson 2008	33/717	48/1462		1.40 [0.91, 2.16]
Greilich 2009	6/26	6/25		0.96 [0.36, 2.59]
Hekmat 2004	2/60	4/58		0.48 [0.09, 2.54]
Kuitunen 2005	5/20	1/20		5.00 [0.64, 39.06]
Later 2009	1/96	0/99		3.09 [0.13, 75.00]
Mansour 2004	0/20	0/20		0.0 [0.0, 0.0]
Mongan 1998	2/75	3/75		0.67 [0.11, 3.88]
Speekenbrink 1995	1/15	0/15		3.00 [0.13, 68.26]
Wong 2000	4/39	5/38		0.78 [0.23, 2.68]
Total (95% CI)	**1824**	**2642**		**1.11 [0.82, 1.50]**

Total events: 70 (Aprotinin), 92 (Lysine Analogues)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 7.52$, df = 12 (P = 0.82); $I^2 = 0.0\%$

Test for overall effect: Z = 0.65 (P = 0.51)

Test for subgroup differences: Not applicable



Analysis 9.12. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 12 Stroke (CVA) - Aprotinin versus Tranexamic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

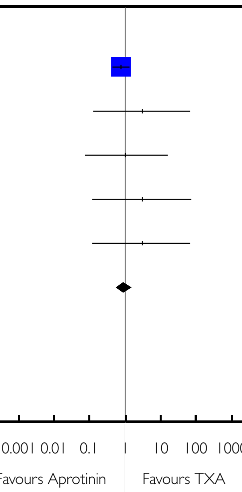
Outcome: 12 Stroke (CVA) - Aprotinin versus Tranexamic Acid

Study or subgroup	Aprotinin n/N	Tranexamic Acid n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Bernet 1999	0/28	0/28		0.0 [0.0, 0.0]
Fergusson 2008	22/759	28/753		0.78 [0.45, 1.35]
Kuitunen 2005	1/20	0/20		3.00 [0.13, 69.52]
Later 2009	1/96	1/99		1.03 [0.07, 16.25]
Mongan 1998	1/75	0/75		3.00 [0.12, 72.49]
Wong 2000	1/39	0/38		2.93 [0.12, 69.64]
Total (95% CI)	**1017**	**1013**		**0.88 [0.52, 1.47]**

Total events: 26 (Aprotinin), 29 (Tranexamic Acid)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.91$, df = 4 (P = 0.75); $I^2 = 0.0\%$

Test for overall effect: Z = 0.50 (P = 0.62)



Analysis 9.13. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 13 Stroke (CVA) - Aprotinin versus Epsilon Aminocaproic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

Outcome: 13 Stroke (CVA) - Aprotinin versus Epsilon Aminocaproic Acid

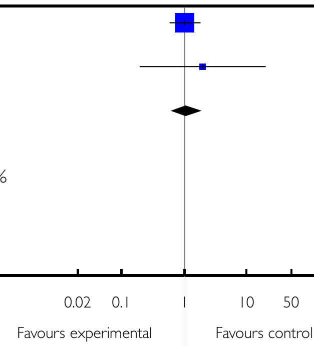
Study or subgroup	Aprotinin n/N	Epsilon Aminocaproic Acid n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Fergusson 2008	22/759	22/768		94.2 %	1.01 [0.57, 1.81]
Greilich 2009	2/26	1/25		5.8 %	1.92 [0.19, 19.90]
Total (95% CI)	**785**	**793**		**100.0 %**	**1.05 [0.60, 1.85]**

Total events: 24 (Aprotinin), 23 (Epsilon Aminocaproic Acid)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.27$, df = 1 (P = 0.60); $I^2 = 0.0\%$

Test for overall effect: Z = 0.17 (P = 0.86)

Test for subgroup differences: Not applicable



Analysis 9.14. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 14 Stroke (CVA) - Tranexamic Acid versus Epsilon Aminocaproic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

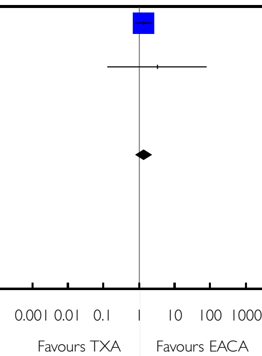
Outcome: 14 Stroke (CVA) - Tranexamic Acid versus Epsilon Aminocaproic Acid

Study or subgroup	Tranexamic Acid n/N	EACA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Fergusson 2008	28/753	22/768		1.30 [0.75, 2.25]
Hardy 1998	1/43	0/46		3.20 [0.13, 76.60]
Maineri 2000	0/24	0/24		0.0 [0.0, 0.0]
Total (95% CI)	**820**	**838**		**1.33 [0.78, 2.29]**

Total events: 29 (Tranexamic Acid), 22 (EACA)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.30$, df = 1 (P = 0.58); $I^2 = 0.0\%$

Test for overall effect: Z = 1.04 (P = 0.30)



Analysis 9.15. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 15 Deep Vein Thrombosis (DVT) - Aprotinin versus Tranexamic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

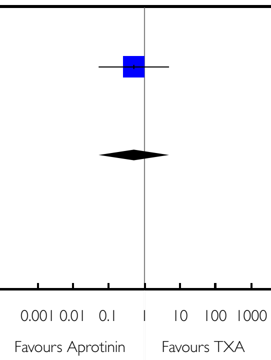
Outcome: 15 Deep Vein Thrombosis (DVT) - Aprotinin versus Tranexamic Acid

Study or subgroup	Aprotinin n/N	Tranexamic Acid n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Casati 1999	0/67	0/70		0.0 [0.0, 0.0]
Engel 2001	1/12	2/12		0.50 [0.05, 4.81]
Landymore 1997	0/48	0/56		0.0 [0.0, 0.0]
Total (95% CI)	**127**	**138**		**0.50 [0.05, 4.81]**

Total events: 1 (Aprotinin), 2 (Tranexamic Acid)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.60 (P = 0.55)



Analysis 9.16. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 16 Deep Vein Thrombosis (DVT) - Aprotinin versus Epsilon Aminocaproic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

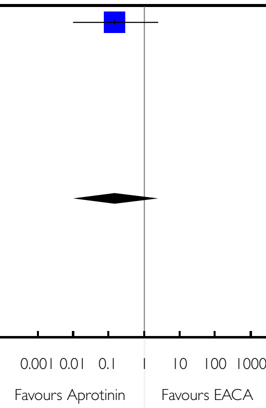
Outcome: 16 Deep Vein Thrombosis (DVT) - Aprotinin versus Epsilon Aminocaproic Acid

Study or subgroup	Aprotinin n/N	EACA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Amar 2003	0/23	3/22		0.14 [0.01, 2.51]
Casati 1999	0/67	0/66		0.0 [0.0, 0.0]
Landymore 1997	0/48	0/44		0.0 [0.0, 0.0]
Ray 2005	0/15	0/15		0.0 [0.0, 0.0]
Total (95% CI)	**153**	**147**		**0.14 [0.01, 2.51]**

Total events: 0 (Aprotinin), 3 (EACA)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 1.34 (P = 0.18)



Analysis 9.17. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 17 Deep Vein Thrombosis (DVT) - Tranexamic Acid versus Epsilon Aminocaproic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

Outcome: 17 Deep Vein Thrombosis (DVT) - Tranexamic Acid versus Epsilon Aminocaproic Acid

Study or subgroup	Tranexamic Acid n/N	EACA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Camarasa 2006	0/35	0/32		0.0 [0.0, 0.0]
Casati 1999	0/70	0/66		0.0 [0.0, 0.0]
Landymore 1997	0/56	0/44		0.0 [0.0, 0.0]
Total (95% CI)	**161**	**142**		**0.0 [0.0, 0.0]**

Total events: 0 (Tranexamic Acid), 0 (EACA)

Heterogeneity: Tau^2 = ; Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%

Test for overall effect: Z = 0.0 (P < 0.00001)

0.001 0.01 0.1 1 10 100 1000

Favours TXA Favours EACA

Analysis 9.18. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 18 Pulmonary Embolism (PE) - Aprotinin versus Tranexamic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

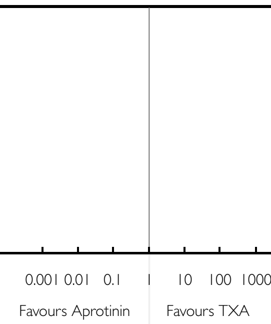
Outcome: 18 Pulmonary Embolism (PE) - Aprotinin versus Tranexamic Acid

Study or subgroup	Aprotinin n/N	Tranexamic Acid n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Casati 1999	0/67	0/70		0.0 [0.0, 0.0]
Landymore 1997	0/48	0/56		0.0 [0.0, 0.0]
Total (95% CI)	**115**	**126**		**0.0 [0.0, 0.0]**

Total events: 0 (Aprotinin), 0 (Tranexamic Acid)

Heterogeneity: Tau^2 = ; Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%

Test for overall effect: Z = 0.0 (P < 0.00001)



Analysis 9.19. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 19 Pulmonary Embolism (PE) - Aprotinin versus Epsilon Aminocaproic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

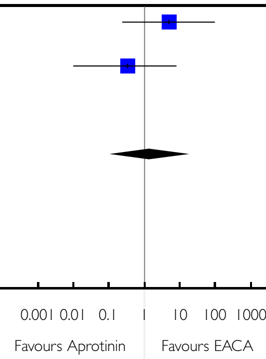
Outcome: 19 Pulmonary Embolism (PE) - Aprotinin versus Epsilon Aminocaproic Acid

Study or subgroup	Aprotinin n/N	EACA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Amar 2003	2/23	0/22		4.79 [0.24, 94.53]
Casati 1999	0/67	1/66		0.33 [0.01, 7.92]
Landymore 1997	0/48	0/44		0.0 [0.0, 0.0]
Total (95% CI)	**138**	**132**		**1.33 [0.10, 18.42]**

Total events: 2 (Aprotinin), 1 (EACA)

Heterogeneity: $Tau^2 = 1.12$; $Chi^2 = 1.45$, df = 1 (P = 0.23); $I^2 = 31\%$

Test for overall effect: Z = 0.21 (P = 0.83)



Analysis 9.20. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 20 Pulmonary Embolism (PE) - Tranexamic Acid versus Epsilon Aminocaproic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

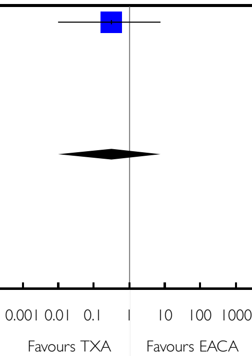
Outcome: 20 Pulmonary Embolism (PE) - Tranexamic Acid versus Epsilon Aminocaproic Acid

Study or subgroup	Tranexamic Acid n/N	EACA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Casati 1999	0/70	1/66		0.31 [0.01, 7.59]
Landymore 1997	0/56	0/44		0.0 [0.0, 0.0]
Maineri 2000	0/24	0/24		0.0 [0.0, 0.0]
Total (95% CI)	**150**	**134**		**0.31 [0.01, 7.59]**

Total events: 0 (Tranexamic Acid), 1 (EACA)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.71 (P = 0.48)



Analysis 9.21. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 21 Other Thrombosis - Aprotinin versus Tranexamic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

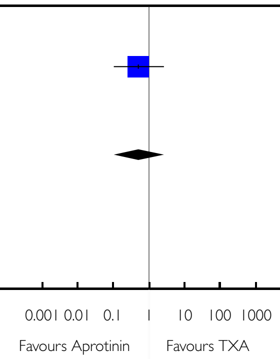
Outcome: 21 Other Thrombosis - Aprotinin versus Tranexamic Acid

Study or subgroup	Aprotinin n/N	Tranexamic Acid n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Bernet 1999	0/28	0/28		0.0 [0.0, 0.0]
Dalmau 2004	2/63	4/64		0.51 [0.10, 2.68]
Landymore 1997	0/48	0/56		0.0 [0.0, 0.0]
Total (95% CI)	**139**	**148**		**0.51 [0.10, 2.68]**

Total events: 2 (Aprotinin), 4 (Tranexamic Acid)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.80 (P = 0.42)



Analysis 9.22. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 22 Other Thrombosis - Aprotinin versus Epsilon Aminocaproic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

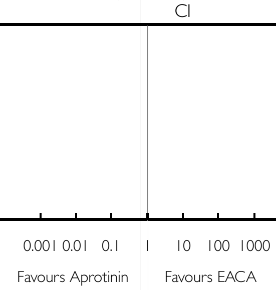
Outcome: 22 Other Thrombosis - Aprotinin versus Epsilon Aminocaproic Acid

Study or subgroup	Aproinin n/N	EACA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Landymore 1997	0/48	0/44		0.0 [0.0, 0.0]
Total (95% CI)	**48**	**44**		**0.0 [0.0, 0.0]**

Total events: 0 (Aproinin), 0 (EACA)

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)



Analysis 9.23. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 23 Other Thrombosis - Tranexamic Acid versus Epsilon Aminocaproic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

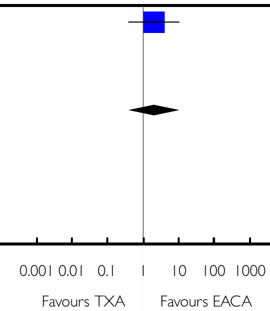
Outcome: 23 Other Thrombosis - Tranexamic Acid versus Epsilon Aminocaproic Acid

Study or subgroup	Tranexamic Acid n/N	EACA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Dalmau 2000	4/42	2/42		2.00 [0.39, 10.34]
Landymore 1997	0/56	0/44		0.0 [0.0, 0.0]
Total (95% CI)	**98**	**86**		**2.00 [0.39, 10.34]**

Total events: 4 (Tranexamic Acid), 2 (EACA)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.83 (P = 0.41)



Analysis 9.24. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 24 Renal Failure / Dysfunction - Aprotinin versus Tranexamic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

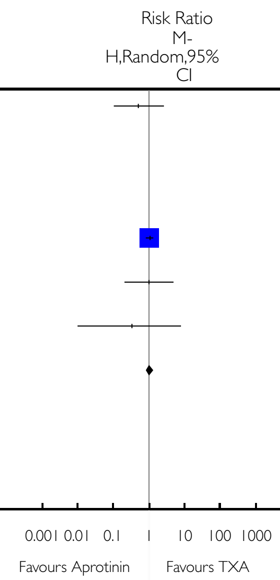
Outcome: 24 Renal Failure / Dysfunction - Aprotinin versus Tranexamic Acid

Study or subgroup	Aprotinin n/N	Tranexamic Acid n/N	Risk Ratio M-H,Random,95% CI
Dalmau 2004	2/63	4/64	0.51 [0.10, 2.68]
Dietrich 2008	0/110	0/110	0.0 [0.0, 0.0]
Diprose 2005	0/60	0/60	0.0 [0.0, 0.0]
Fergusson 2008	102/770	97/766	1.05 [0.81, 1.36]
Later 2009	3/96	3/99	1.03 [0.21, 4.98]
Mansour 2004	0/20	1/20	0.33 [0.01, 7.72]
Total (95% CI)	**1119**	**1119**	**1.02 [0.79, 1.31]**

Total events: 107 (Aprotinin), 105 (Tranexamic Acid)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.20$, df = 3 (P = 0.75); $I^2 = 0.0\%$

Test for overall effect: Z = 0.16 (P = 0.87)



Analysis 9.25. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 25 Renal Failure / Dysfunction - Aprotinin versus Epsilon Aminocaproic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

Outcome: 25 Renal Failure / Dysfunction - Aprotinin versus Epsilon Aminocaproic Acid

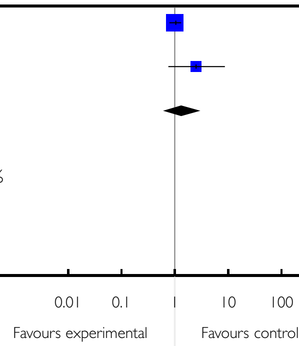
Study or subgroup	Aprotinin n/N	Epsilon Aminocaproic Acid n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Fergusson 2008	102/770	100/774		71.6 %	1.03 [0.79, 1.33]
Greilich 2009	8/26	3/25		28.4 %	2.56 [0.77, 8.58]
Total (95% CI)	**796**	**799**		**100.0 %**	**1.33 [0.59, 2.99]**

Total events: 110 (Aprotinin), 103 (Epsilon Aminocaproic Acid)

Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 2.12$, df = 1 (P = 0.15); $I^2 = 53\%$

Test for overall effect: Z = 0.69 (P = 0.49)

Test for subgroup differences: Not applicable



Analysis 9.26. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 26 Renal Failure / Dysfunction - Tranexamic Acid versus Epsilon Aminocaproic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

Outcome: 26 Renal Failure / Dysfunction - Tranexamic Acid versus Epsilon Aminocaproic Acid

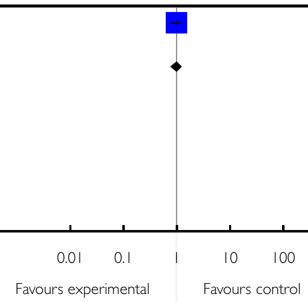
Study or subgroup	Tranexamic Acid n/N	Epsilon Aminocaproic Acid n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Fergusson 2008	97/766	100/774		100.0 %	0.98 [0.76, 1.27]
Total (95% CI)	**766**	**774**		**100.0 %**	**0.98 [0.76, 1.27]**

Total events: 97 (Tranexamic Acid), 100 (Epsilon Aminocaproic Acid)

Heterogeneity: not applicable

Test for overall effect: Z = 0.15 (P = 0.88)

Test for subgroup differences: Not applicable



Analysis 9.27. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 27 Hospital Length of Stay - Aprotinin versus Tranexamic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

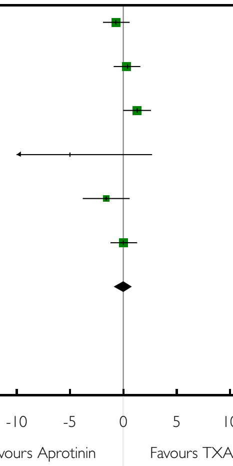
Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

Outcome: 27 Hospital Length of Stay - Aprotinin versus Tranexamic Acid

Study or subgroup	Aprotinin N	Aprotinin Mean(SD)	Tranexamic Acid N	Tranexamic Acid Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Dietrich 2008	110	10.4 (4.3)	110	11.1 (5.1)		22.0 %	-0.70 [-1.95, 0.55]
Fergusson 2008	780	11.92 (14.02)	770	11.56 (10.86)		21.9 %	0.36 [-0.89, 1.61]
Hekmat 2004	60	10.3 (4)	58	9 (3.1)		21.3 %	1.30 [0.01, 2.59]
Ickx 2006	24	26 (7)	27	31 (19)		1.2 %	-5.00 [-12.69, 2.69]
Later 2009	96	7.8 (6.7)	99	9.4 (8.6)		11.6 %	-1.60 [-3.76, 0.56]
Mansour 2004	20	5.8 (1.8)	20	5.8 (2.2)		22.0 %	0.0 [-1.25, 1.25]
Total (95% CI)	**1090**		**1084**			**100.0 %**	**-0.05 [-0.92, 0.83]**

Heterogeneity: $Tau^2 = 0.50$; $Chi^2 = 9.14$, df = 5 (P = 0.10); $I^2 = 45\%$

Test for overall effect: Z = 0.10 (P = 0.92)



Analysis 9.28. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 28 Hospital Length of Stay - Aprotinin versus Epsilon Aminocaproic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

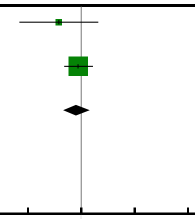
Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

Outcome: 28 Hospital Length of Stay - Aprotinin versus Epsilon Aminocaproic Acid

Study or subgroup	Aprotinin N	Aprotinin Mean(SD)	EACA N	EACA Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Amar 2003	23	9.8 (5.3)	22	11.9 (7.3)		11.3 %	-2.10 [-5.84, 1.64]
Fergusson 2008	780	11.92 (14.02)	780	12.2 (12.86)		88.7 %	-0.28 [-1.62, 1.06]
Total (95% CI)	**803**		**802**			**100.0 %**	**-0.49 [-1.74, 0.77]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.81$, df = 1 (P = 0.37); $I^2 = 0.0\%$

Test for overall effect: Z = 0.76 (P = 0.45)



Analysis 9.29. Comparison 9 Adverse Events and Other Outcomes (Active versus Active), Outcome 29 Hospital Length of Stay - Tranexamic Acid versus Epsilon Aminocaproic Acid.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 9 Adverse Events and Other Outcomes (Active versus Active)

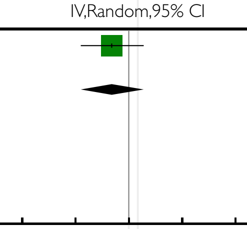
Outcome: 29 Hospital Length of Stay - Tranexamic Acid versus Epsilon Aminocaproic Acid

Study or subgroup	TXA N	TXA Mean(SD)	EACA N	EACA Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Fergusson 2008	770	11.56 (10.86)	780	12.2 (12.86)		100.0 %	-0.64 [-1.82, 0.54]
Total (95% CI)	**770**		**780**			**100.0 %**	**-0.64 [-1.82, 0.54]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.06 (P = 0.29)

Test for subgroup differences: Not applicable



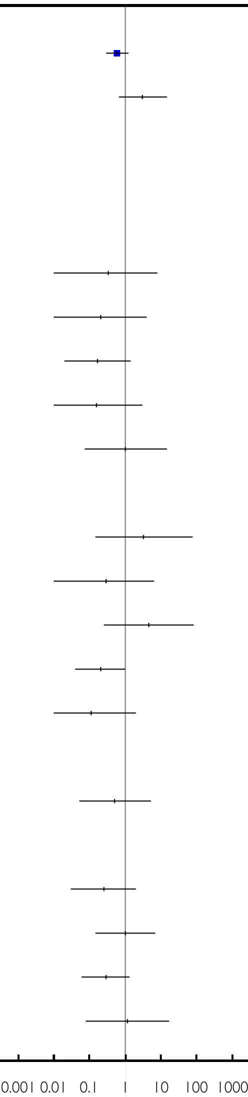
Analysis 10.1. Comparison 10 Adverse Events and Other Outcomes (Active versus Control) - Cardiac Surgery, Outcome 1 Re-operation for bleeding.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 10 Adverse Events and Other Outcomes (Active versus Control) - Cardiac Surgery

Outcome: 1 Re-operation for bleeding

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Aprotinin versus Control				
Alderman 1998	11/436	19/434		0.58 [0.28, 1.20]
Alvarez 1995	6/49	2/51		3.12 [0.66, 14.73]
Alvarez 2001	0/26	0/29		0.0 [0.0, 0.0]
Ashraf 1997	0/19	0/19		0.0 [0.0, 0.0]
Asimakopoulos 2000	0/8	0/10		0.0 [0.0, 0.0]
Bert 2008	0/25	1/25		0.33 [0.01, 7.81]
Bidstrup 1989	0/40	2/40		0.20 [0.01, 4.04]
Bidstrup 1990	1/26	4/18		0.17 [0.02, 1.42]
Bidstrup 1993	0/43	3/47		0.16 [0.01, 2.93]
Bidstrup 2000	1/30	1/30		1.00 [0.07, 15.26]
Boldt 1994	0/20	0/20		0.0 [0.0, 0.0]
Casas 1995	1/47	0/51		3.25 [0.14, 77.88]
Cicekcioglu 2006	0/24	1/20		0.28 [0.01, 6.52]
Cosgrove 1992	4/113	0/56		4.50 [0.25, 82.14]
D'Ambra 1996	2/141	5/71		0.20 [0.04, 1.01]
Deleuze 1991	0/30	4/30		0.11 [0.01, 1.98]
Demeyere 2006	0/20	0/20		0.0 [0.0, 0.0]
Desai 2009	1/38	2/37		0.49 [0.05, 5.14]
Dietrich 1990	0/19	0/20		0.0 [0.0, 0.0]
Dietrich 1995	1/15	4/15		0.25 [0.03, 1.98]
Dignan 2001	2/101	2/99		0.98 [0.14, 6.82]
Diprose 2005	2/60	7/60		0.29 [0.06, 1.32]
Englberger 2002a	1/22	1/25		1.14 [0.08, 17.11]



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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Englberger 2002b	0/15	0/14		0.0 [0.0, 0.0]
Hardy 1993	1/22	0/19		2.61 [0.11, 60.51]
Hardy 1997	1/26	1/26		1.00 [0.07, 15.15]
Kipfer 2003	1/15	1/15		1.00 [0.07, 14.55]
Koster 2004	2/100	3/100		0.67 [0.11, 3.90]
Kuepper 2003	0/60	3/59		0.14 [0.01, 2.66]
Kuitunen 2005	0/20	0/20		0.0 [0.0, 0.0]
Kunt 2005	0/40	0/46		0.0 [0.0, 0.0]
Lass 1995	0/51	2/47		0.18 [0.01, 3.75]
Later 2009	5/96	14/103		0.38 [0.14, 1.02]
Laub 1994	0/16	0/16		0.0 [0.0, 0.0]
Leijdekkers 2006	1/16	2/19		0.59 [0.06, 5.96]
Lemmer 1996	1/487	5/157		0.06 [0.01, 0.55]
Lemmer˙1 1994	1/108	2/108		0.50 [0.05, 5.43]
Levy 1995	6/215	5/72		0.40 [0.13, 1.28]
Liu 1993	0/20	1/20		0.33 [0.01, 7.72]
Mansour 2004	0/20	1/20		0.33 [0.01, 7.72]
Menichetti 1996	0/24	0/24		0.0 [0.0, 0.0]
Mohr 1992	0/34	0/16		0.0 [0.0, 0.0]
Moran 2000	0/28	0/14		0.0 [0.0, 0.0]
Nurözler 2008	0/25	2/26		0.21 [0.01, 4.12]
Nuttall 2000	6/45	1/45		6.00 [0.75, 47.85]
Parvizi 2007	1/81	5/81		0.20 [0.02, 1.67]
Penta de Peppo 1995	0/15	0/15		0.0 [0.0, 0.0]
Pugh 1995	0/15	0/15		0.0 [0.0, 0.0]
Ray 1997	1/21	2/23		0.55 [0.05, 5.61]
Ray 1999	0/100	5/50		0.05 [0.00, 0.81]
Rodrigus 1996	1/46	7/47		0.15 [0.02, 1.14]
Rossi 1997	0/21	3/22		0.15 [0.01, 2.73]
Schweizer 2000	1/28	1/29		1.04 [0.07, 15.77]
Tabuchi 1994	0/20	3/20		0.14 [0.01, 2.60]

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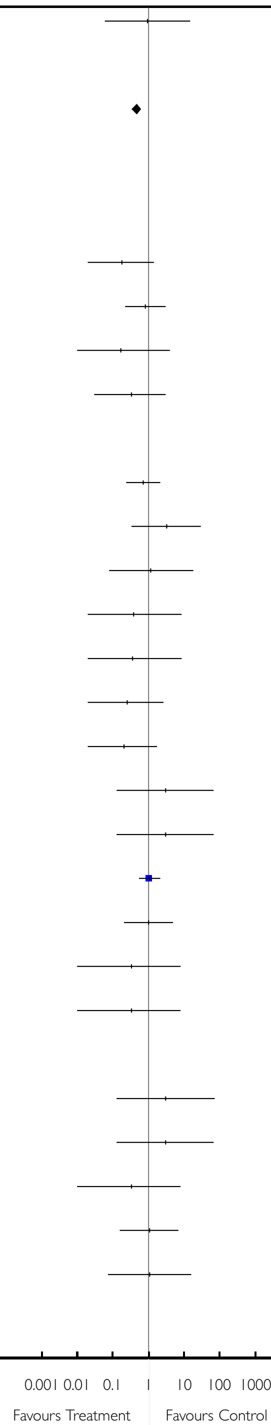
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Taggart 2003	1/36	1/34		0.94 [0.06, 14.51]
Vedrinne 1992	0/30	0/30		0.0 [0.0, 0.0]
Subtotal (95% CI)	**3248**	**2579**		**0.46 [0.34, 0.63]**
Total events: 63 (Treatment), 128 (Control)				
Heterogeneity: Tau² = 0.0; Chi² = 34.56, df = 39 (P = 0.67); I² =0.0%				
Test for overall effect: Z = 4.82 (P < 0.00001)				
2 Tranexamic Acid versus Control				
Andreasen 2004	1/21	6/23		0.18 [0.02, 1.39]
Armellin 2001	4/150	5/150		0.80 [0.22, 2.92]
Brown 1997	0/60	1/30		0.17 [0.01, 4.04]
Casati 2004	1/52	3/50		0.32 [0.03, 2.98]
Demeyere 2006	0/20	0/20		0.0 [0.0, 0.0]
Diprose 2005	5/60	7/60		0.71 [0.24, 2.13]
Hardy 1998	3/43	1/45		3.14 [0.34, 29.03]
Horrow 1991	1/38	1/45		1.18 [0.08, 18.30]
Jares 2003	0/22	1/25		0.38 [0.02, 8.80]
Jimenez 2007	0/24	1/26		0.36 [0.02, 8.43]
Karski 1995	1/100	2/50		0.25 [0.02, 2.69]
Katsaros 1996	1/104	5/106		0.20 [0.02, 1.72]
Kuitunen 2005	1/20	0/20		3.00 [0.13, 69.52]
Kuitunen 2006	1/15	0/15		3.00 [0.13, 68.26]
Later 2009	14/99	14/103		1.04 [0.52, 2.07]
Maddali 2007	3/111	3/111		1.00 [0.21, 4.85]
Mansour 2004	0/20	1/20		0.33 [0.01, 7.72]
Mehr-Aein 2007	0/33	1/33		0.33 [0.01, 7.90]
Menichetti 1996	0/24	0/24		0.0 [0.0, 0.0]
Murphy 2006	1/50	0/50		3.00 [0.13, 71.92]
Penta de Peppo 1995	1/15	0/15		3.00 [0.13, 68.26]
Pleym 2003	0/40	1/39		0.33 [0.01, 7.75]
Pugh 1995	2/22	2/23		1.05 [0.16, 6.79]
Santos 2006	1/29	1/31		1.07 [0.07, 16.31]
Shore-Lesserson 1996	0/17	0/13		0.0 [0.0, 0.0]



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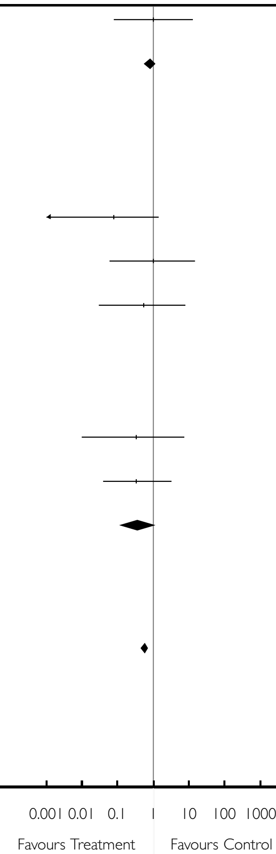
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Uozaki 2001	1/6	1/6		1.00 [0.08, 12.56]
Subtotal (95% CI)	**1195**	**1133**		**0.79 [0.54, 1.17]**
Total events: 42 (Treatment), 57 (Control)				
Heterogeneity: Tau² = 0.0; Chi² = 12.60, df = 22 (P = 0.94); I² =0.0%				
Test for overall effect: Z = 1.18 (P = 0.24)				
3 Epsilon Aminocaproic Acid versus Control				
Del Rossi 1989	0/170	6/180		0.08 [0.00, 1.43]
Hardy 1998	1/46	1/45		0.98 [0.06, 15.17]
Kluger 2003	1/58	1/30		0.52 [0.03, 7.98]
Menichetti 1996	0/24	0/24		0.0 [0.0, 0.0]
Penta de Peppo 1995	0/15	0/15		0.0 [0.0, 0.0]
Rao 1999	0/15	1/15		0.33 [0.01, 7.58]
Vander-Salm 1996	1/51	3/52		0.34 [0.04, 3.16]
Subtotal (95% CI)	**379**	**361**		**0.35 [0.11, 1.17]**
Total events: 3 (Treatment), 12 (Control)				
Heterogeneity: Tau² = 0.0; Chi² = 1.74, df = 4 (P = 0.78); I² =0.0%				
Test for overall effect: Z = 1.71 (P = 0.087)				
Total (95% CI)	**4822**	**4073**		**0.56 [0.44, 0.71]**
Total events: 108 (Treatment), 197 (Control)				
Heterogeneity: Tau² = 0.0; Chi² = 54.09, df = 67 (P = 0.87); I² =0.0%				
Test for overall effect: Z = 4.73 (P < 0.00001)				



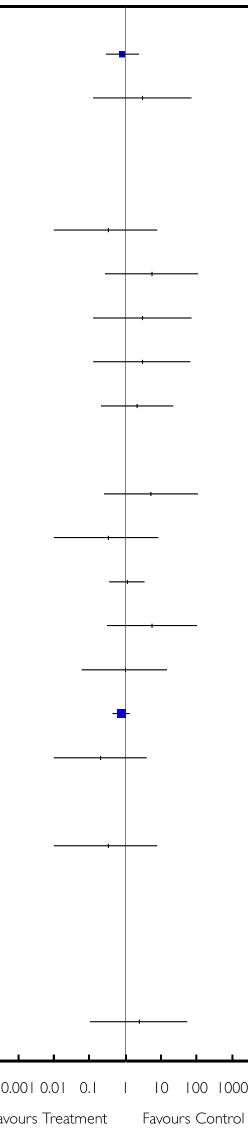
Analysis 10.2. Comparison 10 Adverse Events and Other Outcomes (Active versus Control) - Cardiac Surgery, Outcome 2 Mortality.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 10 Adverse Events and Other Outcomes (Active versus Control) - Cardiac Surgery

Outcome: 2 Mortality

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI
1 Aprotinin versus Control			
Alderman 1998	6/436	7/434	0.85 [0.29, 2.52]
Alvarez 1995	1/49	0/51	3.12 [0.13, 74.80]
Alvarez 2001	0/26	0/29	0.0 [0.0, 0.0]
Ashraf 1997	0/19	0/19	0.0 [0.0, 0.0]
Bidstrup 1989	0/40	1/40	0.33 [0.01, 7.95]
Bidstrup 1993	2/43	0/47	5.45 [0.27, 110.51]
Bidstrup 2000	1/30	0/30	3.00 [0.13, 70.83]
Blauhut 1994	1/14	0/14	3.00 [0.13, 67.91]
Casas 1995	2/47	1/51	2.17 [0.20, 23.16]
Cicekcioglu 2006	0/20	0/24	0.0 [0.0, 0.0]
Cohen 1998	2/56	0/59	5.26 [0.26, 107.27]
Colwell 2007	0/175	1/178	0.34 [0.01, 8.27]
Cosgrove 1992	9/113	4/56	1.12 [0.36, 3.46]
D'Ambra 1996	5/141	0/71	5.58 [0.31, 99.47]
Desai 2009	1/38	1/37	0.97 [0.06, 15.00]
Dietrich 1992	24/902	31/882	0.76 [0.45, 1.28]
Dietrich 1995	0/15	2/15	0.20 [0.01, 3.85]
Dignan 2001	0/101	0/99	0.0 [0.0, 0.0]
Diprose 2005	0/60	1/60	0.33 [0.01, 8.02]
Englberger 2002a	0/22	0/25	0.0 [0.0, 0.0]
Englberger 2002b	0/15	0/14	0.0 [0.0, 0.0]
Feindt 1994	0/10	0/10	0.0 [0.0, 0.0]
Golanski 2000	1/30	0/24	2.42 [0.10, 56.85]



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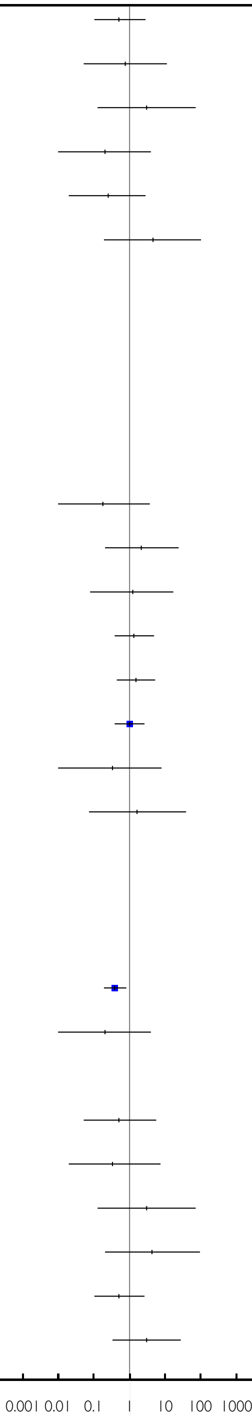
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Gott 1998	2/109	4/112		0.51 [0.10, 2.75]
Green 1995	1/48	1/36		0.75 [0.05, 11.59]
Greilich 2009	1/26	0/27		3.11 [0.13, 73.09]
Hardy 1993	0/22	2/22		0.20 [0.01, 3.94]
Hayashida 1997	1/110	2/57		0.26 [0.02, 2.80]
Jamieson 1997	1/24	0/36		4.44 [0.19, 104.67]
Kipfer 2003	0/15	0/15		0.0 [0.0, 0.0]
Koster 2004	0/100	0/100		0.0 [0.0, 0.0]
Kuepper 2003	0/60	0/59		0.0 [0.0, 0.0]
Kuitunen 2005	0/20	0/20		0.0 [0.0, 0.0]
Kunt 2005	0/40	0/46		0.0 [0.0, 0.0]
Lass 1995	0/51	2/47		0.18 [0.01, 3.75]
Later 2009	2/96	1/103		2.15 [0.20, 23.29]
Leijdekkers 2006	1/16	1/19		1.19 [0.08, 17.51]
Lemmer 1996	12/526	3/178		1.35 [0.39, 4.74]
Lemmer I 1994	6/108	4/108		1.50 [0.44, 5.17]
Levy 1995	15/215	5/72		1.00 [0.38, 2.67]
Liu 1993	0/20	1/20		0.33 [0.01, 7.72]
Maccario 1994	1/61	0/32		1.60 [0.07, 38.11]
Misfeld 1998	0/14	0/14		0.0 [0.0, 0.0]
Mohr 1992	0/34	0/16		0.0 [0.0, 0.0]
Moran 2000	0/28	0/14		0.0 [0.0, 0.0]
Norman 2009	4/11	9/9		0.39 [0.19, 0.83]
Nuttall 2000	0/45	2/45		0.20 [0.01, 4.05]
Rocha 1994	0/28	0/28		0.0 [0.0, 0.0]
Rodrigus 1996	1/46	2/47		0.51 [0.05, 5.44]
Royston 1987	0/11	1/11		0.33 [0.02, 7.39]
Schweizer 2000	1/28	0/29		3.10 [0.13, 73.12]
Stammers 1997	1/8	0/12		4.33 [0.20, 94.83]
Swart 1994	2/49	4/49		0.50 [0.10, 2.60]
Van der Linden 2005	3/37	1/38		3.08 [0.34, 28.30]



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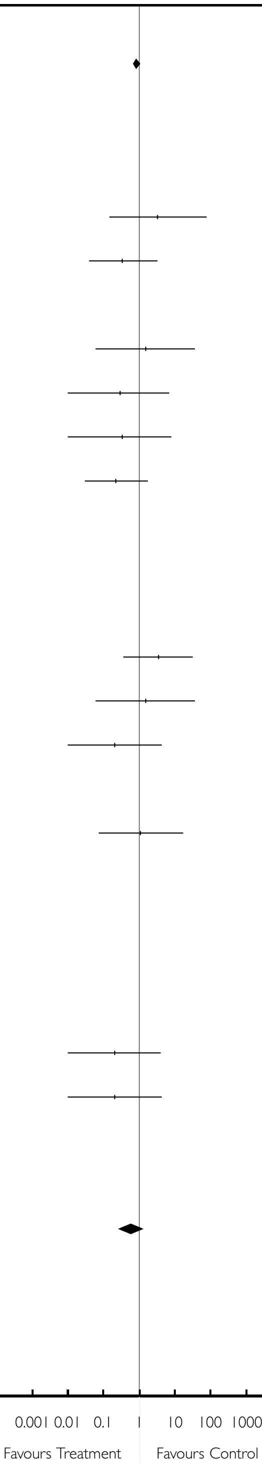
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Wei 2006	0/36	0/40		0.0 [0.0, 0.0]
Subtotal (95% CI)	**4444**	**3730**		**0.84 [0.64, 1.10]**
Total events: 110 (Treatment), 94 (Control)				
Heterogeneity: Tau² = 0.0; Chi² = 26.44, df = 37 (P = 0.90); I² =0.0%				
Test for overall effect: Z = 1.24 (P = 0.21)				
2 Tranexamic Acid versus Control				
Andreasen 2004	1/21	0/23		3.27 [0.14, 76.21]
Armellin 2001	1/150	3/150		0.33 [0.04, 3.17]
Blauhut 1994	0/15	0/14		0.0 [0.0, 0.0]
Brown 1997	1/60	0/30		1.52 [0.06, 36.34]
Coffey 1995	0/16	1/14		0.29 [0.01, 6.69]
Diprose 2005	0/60	1/60		0.33 [0.01, 8.02]
Dryden 1997	1/22	4/19		0.22 [0.03, 1.77]
Hardy 1998	0/43	0/45		0.0 [0.0, 0.0]
Jares 2003	0/22	0/25		0.0 [0.0, 0.0]
Jimenez 2007	0/24	0/26		0.0 [0.0, 0.0]
Karski 2005	3/147	1/165		3.37 [0.35, 32.02]
Katoh 1997	1/62	0/31		1.52 [0.06, 36.36]
Katsaros 1996	0/104	2/106		0.20 [0.01, 4.19]
Kuitunen 2005	0/20	0/20		0.0 [0.0, 0.0]
Later 2009	1/99	1/103		1.04 [0.07, 16.41]
Maddali 2007	0/111	0/111		0.0 [0.0, 0.0]
Mehr-Aein 2007	0/33	0/33		0.0 [0.0, 0.0]
Misfeld 1998	0/14	0/14		0.0 [0.0, 0.0]
Murphy 2006	0/50	0/50		0.0 [0.0, 0.0]
Nuttall 2000	0/45	2/45		0.20 [0.01, 4.05]
Santos 2006	0/29	2/31		0.21 [0.01, 4.26]
Shore-Lesserson 1996	0/17	0/13		0.0 [0.0, 0.0]
Zabeeda 2002	0/25	0/25		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1189**	**1153**		**0.58 [0.26, 1.28]**
Total events: 9 (Treatment), 17 (Control)				
Heterogeneity: Tau² = 0.0; Chi² = 7.14, df = 11 (P = 0.79); I² =0.0%				
Test for overall effect: Z = 1.36 (P = 0.17)				
3 Epsilon Aminocaproic Acid versus Control				



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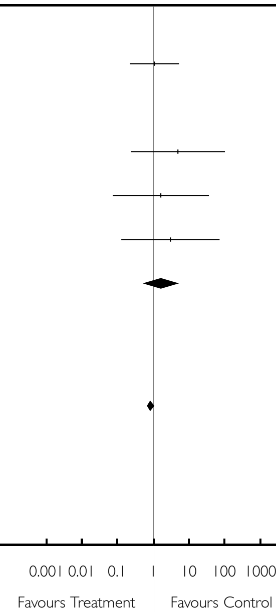
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Daily 1994	0/21	0/19		0.0 [0.0, 0.0]
Del Rossi 1989	3/170	3/180		1.06 [0.22, 5.17]
Greilich 2009	0/25	0/27		0.0 [0.0, 0.0]
Hardy 1998	2/46	0/45		4.89 [0.24, 99.18]
Kluger 2003	1/58	0/30		1.58 [0.07, 37.56]
Vander-Salm 1996	1/51	0/52		3.06 [0.13, 73.36]
Subtotal (95% CI)	**371**	**353**		**1.65 [0.50, 5.43]**
Total events: 7 (Treatment), 3 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.96$, df = 3 (P = 0.81); I^2 =0.0%				
Test for overall effect: Z = 0.83 (P = 0.41)				
Total (95% CI)	**6004**	**5236**		**0.84 [0.65, 1.07]**
Total events: 126 (Treatment), 114 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 36.51$, df = 53 (P = 0.96); I^2 =0.0%				
Test for overall effect: Z = 1.41 (P = 0.16)				



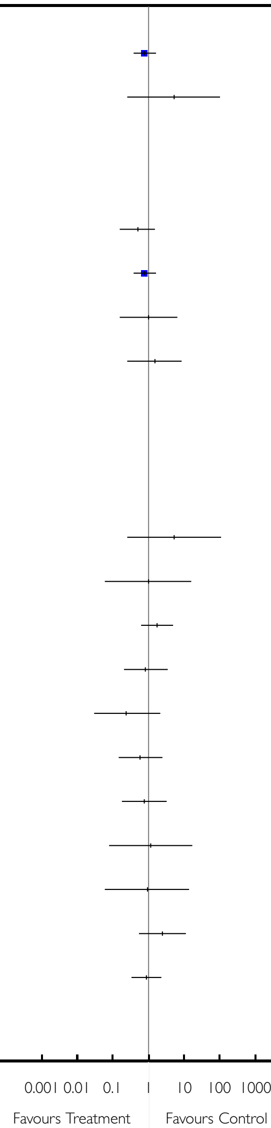
Analysis 10.3. Comparison 10 Adverse Events and Other Outcomes (Active versus Control) - Cardiac Surgery, Outcome 3 Myocardial Infarction.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 10 Adverse Events and Other Outcomes (Active versus Control) - Cardiac Surgery

Outcome: 3 Myocardial Infarction

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Aprotinin versus Control				
Alderman 1998	12/410	16/421		0.77 [0.37, 1.61]
Alvarez 1995	2/49	0/51		5.20 [0.26, 105.65]
Alvarez 2001	0/26	0/29		0.0 [0.0, 0.0]
Asimakopoulos 2000	0/8	0/10		0.0 [0.0, 0.0]
Baele 1992	4/58	8/57		0.49 [0.16, 1.54]
Bidstrup 1993	12/410	16/421		0.77 [0.37, 1.61]
Bidstrup 2000	2/30	2/30		1.00 [0.15, 6.64]
Carrera 1994	3/51	2/51		1.50 [0.26, 8.60]
Cicek 1996a	0/50	0/25		0.0 [0.0, 0.0]
Cicek 1996b	0/29	0/28		0.0 [0.0, 0.0]
Cicekcioglu 2006	0/24	0/20		0.0 [0.0, 0.0]
Cohen 1998	2/56	0/59		5.26 [0.26, 107.27]
Colwell 2007	1/175	1/177		1.01 [0.06, 16.04]
Cosgrove 1992	14/113	4/56		1.73 [0.60, 5.03]
D'Ambra 1996	5/141	3/71		0.84 [0.21, 3.41]
Desai 2009	1/38	4/37		0.24 [0.03, 2.08]
Dignan 2001	3/101	5/99		0.59 [0.14, 2.40]
Diprose 2005	3/60	4/60		0.75 [0.18, 3.21]
Englberger 2002a	1/22	1/25		1.14 [0.08, 17.11]
Englberger 2002b	1/15	1/14		0.93 [0.06, 13.54]
Golanski 2000	6/30	2/24		2.40 [0.53, 10.84]
Greilich 2009	6/26	7/27		0.89 [0.34, 2.30]
Harder 1991	0/40	0/40		0.0 [0.0, 0.0]



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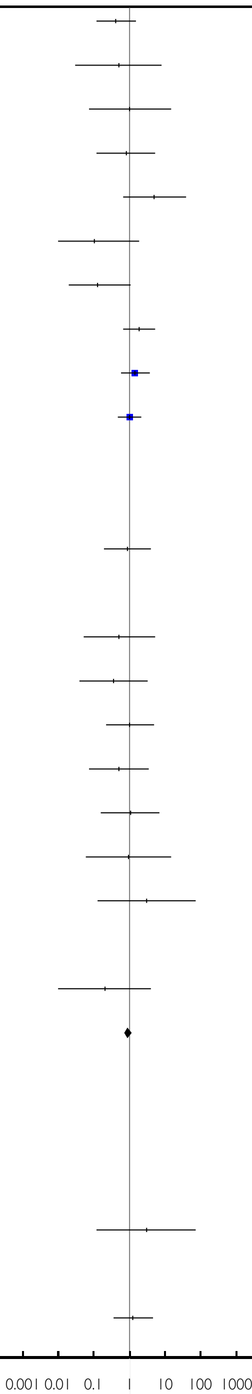
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Hayashida 1997	4/110	5/57		0.41 [0.12, 1.48]
Kalangos 1994	1/110	1/55		0.50 [0.03, 7.84]
Kipfer 2003	1/15	1/15		1.00 [0.07, 14.55]
Klein 1998	2/38	2/30		0.79 [0.12, 5.28]
Kuitunen 2005	5/20	1/20		5.00 [0.64, 39.06]
Lass 1995	0/51	4/47		0.10 [0.01, 1.86]
Later 2009	1/96	8/103		0.13 [0.02, 1.05]
Lemmer 1996	22/526	4/178		1.86 [0.65, 5.33]
Lemmer`1 1994	10/108	7/108		1.43 [0.56, 3.61]
Levy 1995	24/206	8/67		0.98 [0.46, 2.07]
Mansour 2004	0/20	0/20		0.0 [0.0, 0.0]
Moran 2000	0/28	0/14		0.0 [0.0, 0.0]
Murkin 1994	3/29	3/25		0.86 [0.19, 3.90]
Nurözler 2008	0/25	0/26		0.0 [0.0, 0.0]
Parvizi 2007	1/81	2/81		0.50 [0.05, 5.41]
Poston 2006	1/29	3/31		0.36 [0.04, 3.23]
Rodrigus 1996	3/46	3/47		1.02 [0.22, 4.80]
Santamaria 2000	2/56	2/28		0.50 [0.07, 3.37]
Schweizer 2000	2/28	2/29		1.04 [0.16, 6.86]
Taggart 2003	1/36	1/34		0.94 [0.06, 14.51]
Van der Linden 2005	1/37	0/38		3.08 [0.13, 73.25]
Wei 2006	0/36	0/40		0.0 [0.0, 0.0]
Wendel 1995	0/20	2/20		0.20 [0.01, 3.92]
Subtotal (95% CI)	**3713**	**2945**		**0.90 [0.71, 1.14]**
Total events: 162 (Treatment), 135 (Control)				
Heterogeneity: Tau² = 0.0; Chi² = 24.82, df = 35 (P = 0.90); I² =0.0%				
Test for overall effect: Z = 0.86 (P = 0.39)				
2 Tranexamic Acid versus Control				
Andreasen 2004	0/21	0/23		0.0 [0.0, 0.0]
Armellin 2001	1/150	0/150		3.00 [0.12, 73.06]
Brown 1997	0/60	0/30		0.0 [0.0, 0.0]
Diprose 2005	5/60	4/60		1.25 [0.35, 4.43]



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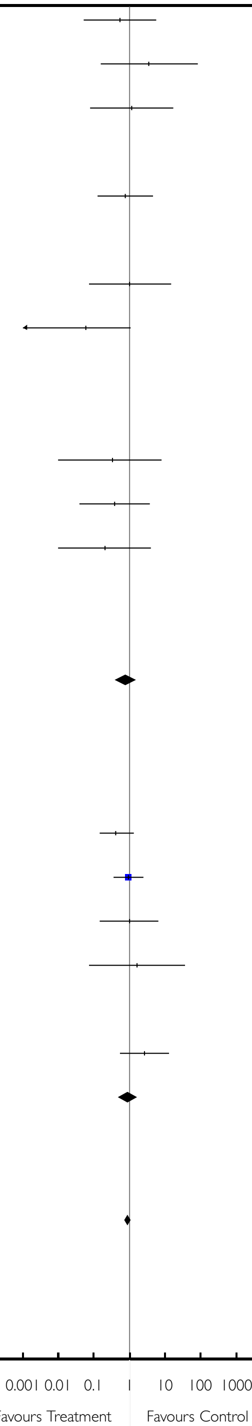
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Hardy 1998	1/43	2/45		0.52 [0.05, 5.56]
Horrow 1991	1/37	0/44		3.55 [0.15, 84.69]
Jares 2003	1/22	1/25		1.14 [0.08, 17.11]
Karski 1995	0/100	0/50		0.0 [0.0, 0.0]
Karski 2005	2/147	3/165		0.75 [0.13, 4.42]
Katsaros 1996	0/104	0/106		0.0 [0.0, 0.0]
Kuitunen 2005	1/20	1/20		1.00 [0.07, 14.90]
Later 2009	0/99	8/103		0.06 [0.00, 1.05]
Mansour 2004	0/20	0/20		0.0 [0.0, 0.0]
Mehr-Aein 2007	0/33	0/33		0.0 [0.0, 0.0]
Murphy 2006	0/50	1/50		0.33 [0.01, 7.99]
Shore-Lesserson 1996	1/17	2/13		0.38 [0.04, 3.77]
Speekenbrink 1995	0/15	2/15		0.20 [0.01, 3.85]
Taghaddomi 2009	0/50	0/50		0.0 [0.0, 0.0]
Zabeeda 2002	0/25	0/25		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1073**	**1027**		**0.74 [0.37, 1.47]**
Total events: 13 (Treatment), 24 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 7.21$, df = 10 (P = 0.71); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.86 (P = 0.39)				
3 Epsilon Aminocaproic Acid versus Control				
Del Rossi 1989	4/170	10/180		0.42 [0.14, 1.32]
Greilich 2009	6/25	7/27		0.93 [0.36, 2.38]
Hardy 1998	2/46	2/45		0.98 [0.14, 6.65]
Kluger 2003	1/58	0/30		1.58 [0.07, 37.56]
Rao 1999	0/15	0/15		0.0 [0.0, 0.0]
Vander-Salm 1996	5/51	2/52		2.55 [0.52, 12.55]
Subtotal (95% CI)	**365**	**349**		**0.88 [0.48, 1.63]**
Total events: 18 (Treatment), 21 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.44$, df = 4 (P = 0.49); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.41 (P = 0.68)				
Total (95% CI)	**5151**	**4321**		**0.88 [0.71, 1.09]**
Total events: 193 (Treatment), 180 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 35.49$, df = 51 (P = 0.95); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.17 (P = 0.24)				



Analysis 10.4. Comparison 10 Adverse Events and Other Outcomes (Active versus Control) - Cardiac Surgery, Outcome 4 Stroke.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 10 Adverse Events and Other Outcomes (Active versus Control) - Cardiac Surgery

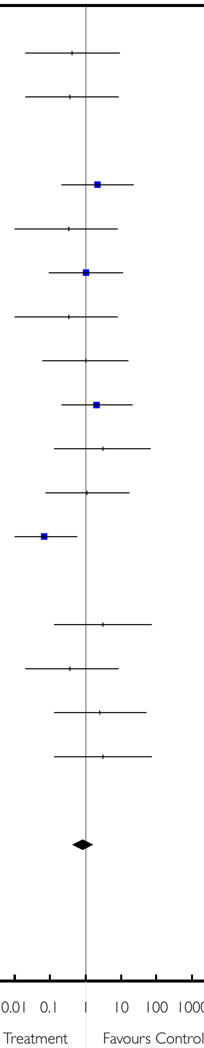
Outcome: 4 Stroke

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI
1 Aprotinin versus Control			
Asimakopoulos 2000	0/8	1/10	0.41 [0.02, 8.84]
Bidstrup 1993	0/43	1/47	0.36 [0.02, 8.70]
Casas 1995	0/47	0/51	0.0 [0.0, 0.0]
Cohen 1998	2/56	1/59	2.11 [0.20, 22.60]
Colwell 2007	0/175	1/177	0.34 [0.01, 8.22]
D'Ambra 1996	2/141	1/71	1.01 [0.09, 10.92]
Desai 2009	0/38	1/37	0.32 [0.01, 7.73]
Dignan 2001	1/101	1/99	0.98 [0.06, 15.45]
Greilich 2009	2/26	1/27	2.08 [0.20, 21.55]
Kuitunen 2005	1/20	0/20	3.00 [0.13, 69.52]
Later 2009	1/96	1/103	1.07 [0.07, 16.92]
Levy 1995	1/215	5/72	0.07 [0.01, 0.56]
Moran 2000	0/28	0/14	0.0 [0.0, 0.0]
Nurözler 2008	1/25	0/26	3.12 [0.13, 73.06]
Poston 2006	0/29	1/31	0.36 [0.02, 8.39]
Santamaria 2000	2/56	0/28	2.54 [0.13, 51.26]
Van der Linden 2005	1/37	0/38	3.08 [0.13, 73.25]
Wei 2006	0/36	0/40	0.0 [0.0, 0.0]
Subtotal (95% CI)	**1177**	**950**	**0.81 [0.40, 1.67]**

Total events: 14 (Treatment), 15 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 10.55$, df = 14 (P = 0.72); $I^2 = 0.0\%$

Test for overall effect: Z = 0.56 (P = 0.57)



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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
2 Tranexamic Acid versus Control				
Andreasen 2004	0/21	0/23		0.0 [0.0, 0.0]
Brown 1997	0/60	0/30		0.0 [0.0, 0.0]
Casati 2004	0/52	0/50		0.0 [0.0, 0.0]
Hardy 1998	1/43	0/45		3.14 [0.13, 74.95]
Horrow 1990	0/18	2/20		0.22 [0.01, 4.32]
Horrow 1991	1/37	0/44		3.55 [0.15, 84.69]
Jares 2003	0/22	0/25		0.0 [0.0, 0.0]
Karski 1995	3/100	0/50		3.53 [0.19, 67.13]
Karski 2005	1/147	1/165		1.12 [0.07, 17.79]
Katoh 1997	0/62	0/31		0.0 [0.0, 0.0]
Katsaros 1996	3/104	2/106		1.53 [0.26, 8.96]
Kuitunen 2005	0/20	0/20		0.0 [0.0, 0.0]
Later 2009	1/99	1/103		1.04 [0.07, 16.41]
Maddali 2007	0/111	0/111		0.0 [0.0, 0.0]
Murphy 2006	0/50	0/50		0.0 [0.0, 0.0]
Taghaddomi 2009	0/50	0/50		0.0 [0.0, 0.0]
Zabeeda 2002	0/25	0/25		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1021**	**948**		**1.44 [0.53, 3.91]**
Total events: 10 (Treatment), 6 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.52$, df = 6 (P = 0.87); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.72 (P = 0.47)				
3 Epsilon Aminocaproic Acid versus Control				
Daily 1994	0/21	0/19		0.0 [0.0, 0.0]
Del Rossi 1989	0/170	1/180		0.35 [0.01, 8.60]
Greilich 2009	1/25	1/27		1.08 [0.07, 16.36]
Hardy 1998	0/46	0/45		0.0 [0.0, 0.0]
Kluger 2003	2/58	0/30		2.63 [0.13, 53.04]
Rao 1999	0/15	0/15		0.0 [0.0, 0.0]
Vander-Salm 1996	0/51	2/52		0.20 [0.01, 4.14]
Subtotal (95% CI)	**386**	**368**		**0.70 [0.16, 3.10]**
Total events: 3 (Treatment), 4 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.66$, df = 3 (P = 0.64); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.47 (P = 0.64)				

0.001 0.01 0.1 1 10 100 1000

Favours Treatment Favours Control

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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Total (95% CI)	**2584**	**2266**		**0.95 [0.55, 1.63]**
Total events: 27 (Treatment), 25 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 15.75, df = 25 (P = 0.92); I^2 =0.0%				
Test for overall effect: Z = 0.20 (P = 0.84)				

0.001 0.01 0.1 1 10 100 1000

Favours Treatment Favours Control

Analysis 10.5. Comparison 10 Adverse Events and Other Outcomes (Active versus Control) - Cardiac Surgery, Outcome 5 Deep Vein Thrombosis (DVT).

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 10 Adverse Events and Other Outcomes (Active versus Control) - Cardiac Surgery

Outcome: 5 Deep Vein Thrombosis (DVT)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Aprotinin versus Control				
Colwell 2007	2/175	3/177		0.67 [0.11, 3.99]
D'Ambra 1996	1/141	0/71		1.52 [0.06, 36.87]
Poston 2006	3/29	1/31		3.21 [0.35, 29.11]
Subtotal (95% CI)	**345**	**279**		**1.29 [0.36, 4.58]**
Total events: 6 (Treatment), 4 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.18, df = 2 (P = 0.55); I^2 =0.0%				
Test for overall effect: Z = 0.39 (P = 0.70)				
2 Tranexamic Acid versus Control				
Horrow 1990	0/18	0/20		0.0 [0.0, 0.0]
Horrow 1991	0/37	1/44		0.39 [0.02, 9.41]
Katoh 1997	0/62	0/31		0.0 [0.0, 0.0]
Katsaros 1996	0/104	1/106		0.34 [0.01, 8.24]

0.001 0.01 0.1 1 10 100 1000

Favours Treatment Favours Control

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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**221**	**201**		**0.37 [0.04, 3.47]**
Total events: 0 (Treatment), 2 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%				
Test for overall effect: Z = 0.88 (P = 0.38)				
Total (95% CI)	**566**	**480**		**0.95 [0.31, 2.87]**
Total events: 6 (Treatment), 6 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.09, df = 4 (P = 0.72); I^2 =0.0%				
Test for overall effect: Z = 0.09 (P = 0.93)				

0.001 0.01 0.1 1 10 100 1000

Favours Treatment Favours Control

Analysis 10.6. Comparison 10 Adverse Events and Other Outcomes (Active versus Control) - Cardiac Surgery, Outcome 6 Pulmonary Embolism.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 10 Adverse Events and Other Outcomes (Active versus Control) - Cardiac Surgery

Outcome: 6 Pulmonary Embolism

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Tranexamic Acid versus Control				
Casati 2004	0/52	0/50		0.0 [0.0, 0.0]
Horrow 1990	0/18	0/20		0.0 [0.0, 0.0]
Jares 2003	0/22	0/25		0.0 [0.0, 0.0]
Katoh 1997	0/62	0/31		0.0 [0.0, 0.0]
Katsaros 1996	0/104	1/106		0.34 [0.01, 8.24]
Pleym 2003	0/40	1/39		0.33 [0.01, 7.75]
Subtotal (95% CI)	**298**	**271**		**0.33 [0.04, 3.15]**
Total events: 0 (Treatment), 2 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 0.98); I^2 =0.0%				

0.001 0.01 0.1 1 10 100 1000

Favours Treatment Favours Control

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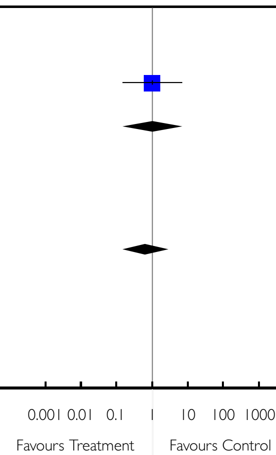
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 0.96 (P = 0.34)				
2 Aprotinin versus Control				
Colwell 2007	2/175	2/177		1.01 [0.14, 7.10]
Subtotal (95% CI)	**175**	**177**		**1.01 [0.14, 7.10]**
Total events: 2 (Treatment), 2 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.01 (P = 0.99)				
Total (95% CI)	**473**	**448**		**0.63 [0.14, 2.74]**
Total events: 2 (Treatment), 4 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.54$, df = 2 (P = 0.76); I^2 =0.0%				
Test for overall effect: Z = 0.62 (P = 0.54)				



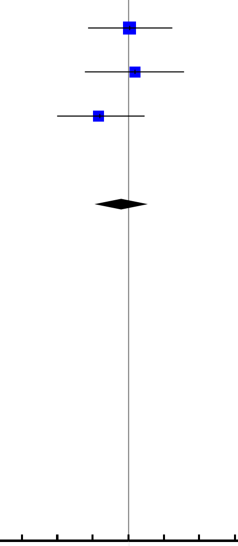
Analysis 10.7. Comparison 10 Adverse Events and Other Outcomes (Active versus Control) - Cardiac Surgery, Outcome 7 Other Thrombosis.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 10 Adverse Events and Other Outcomes (Active versus Control) - Cardiac Surgery

Outcome: 7 Other Thrombosis

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI
1 Aprotinin versus Control			
Casas 1995	1/47	1/51	1.09 [0.07, 16.86]
D'Ambra 1996	1/141	0/71	1.52 [0.06, 36.87]
Poston 2006	0/29	3/31	0.15 [0.01, 2.83]
Rocha 1994	0/28	0/28	0.0 [0.0, 0.0]
Subtotal (95% CI)	**245**	**181**	**0.62 [0.11, 3.36]**
Total events: 2 (Treatment), 4 (Control)			
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.40, df = 2 (P = 0.50); I^2 =0.0%			
Test for overall effect: Z = 0.56 (P = 0.58)			
2 Tranexamic Acid versus Control			
Taghaddomi 2009	0/50	0/50	0.0 [0.0, 0.0]
Subtotal (95% CI)	**50**	**50**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)			
Heterogeneity: not applicable			
Test for overall effect: Z = 0.0 (P < 0.00001)			



0.001 0.01 0.1 1 10 100 1000

Favours Treatment Favours Control

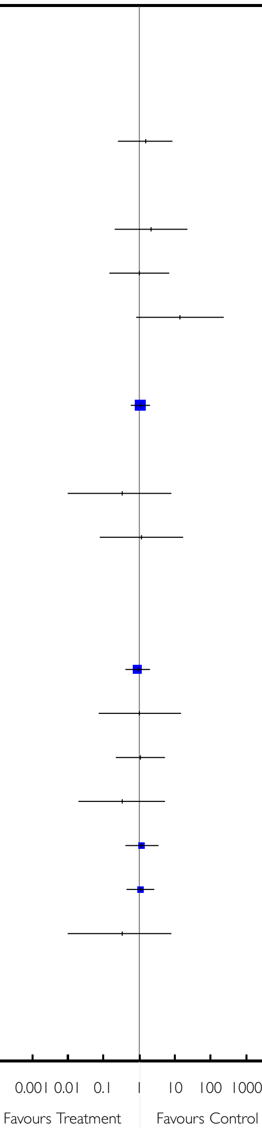
Analysis 10.8. Comparison 10 Adverse Events and Other Outcomes (Active versus Control) - Cardiac Surgery, Outcome 8 Renal Failure / Dysfunction.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 10 Adverse Events and Other Outcomes (Active versus Control) - Cardiac Surgery

Outcome: 8 Renal Failure / Dysfunction

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI
1 Aprotinin versus Control			
Alvarez 2001	0/26	0/29	0.0 [0.0, 0.0]
Asimakopoulos 2000	0/8	0/10	0.0 [0.0, 0.0]
Baele 1992	3/58	2/57	1.47 [0.26, 8.50]
Cicek 1996b	0/29	0/28	0.0 [0.0, 0.0]
Cohen 1998	2/56	1/59	2.11 [0.20, 22.60]
Colwell 2007	2/175	2/177	1.01 [0.14, 7.10]
D'Ambra 1996	13/141	0/71	13.69 [0.83, 227.03]
Desai 2009	0/38	0/37	0.0 [0.0, 0.0]
Dietrich 1992	21/902	19/882	1.08 [0.59, 2.00]
Dignan 2001	0/101	0/99	0.0 [0.0, 0.0]
Diprose 2005	0/60	1/60	0.33 [0.01, 8.02]
Englberger 2002a	1/22	1/25	1.14 [0.08, 17.11]
Englberger 2002b	0/15	0/14	0.0 [0.0, 0.0]
Gherli 1992	0/18	0/13	0.0 [0.0, 0.0]
Greilich 2009	8/26	9/27	0.92 [0.42, 2.02]
Kipfer 2003	1/15	1/15	1.00 [0.07, 14.55]
Later 2009	3/96	3/103	1.07 [0.22, 5.19]
Lemmer 1996	1/526	1/178	0.34 [0.02, 5.38]
Lemmer`1 1994	7/108	6/108	1.17 [0.41, 3.36]
Levy 1995	19/215	6/72	1.06 [0.44, 2.55]
Mansour 2004	0/20	1/20	0.33 [0.01, 7.72]
Speekenbrink 1996	0/75	0/37	0.0 [0.0, 0.0]
Stammers 1997	0/8	0/12	0.0 [0.0, 0.0]



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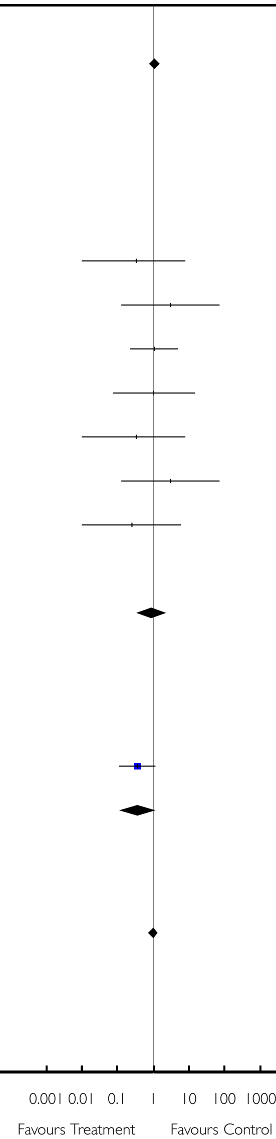
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Wei 2006	0/36	0/40		0.0 [0.0, 0.0]
Subtotal (95% CI)	**2774**	**2173**		**1.07 [0.76, 1.51]**
Total events: 81 (Treatment), 53 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 5.78, df = 13 (P = 0.95); I^2 =0.0%				
Test for overall effect: Z = 0.39 (P = 0.70)				
2 Tranexamic Acid versus Control				
Andreasen 2004	0/21	0/23		0.0 [0.0, 0.0]
Diprose 2005	0/60	1/60		0.33 [0.01, 8.02]
Katsaros 1996	1/104	0/106		3.06 [0.13, 74.20]
Later 2009	3/99	3/103		1.04 [0.22, 5.03]
Mansour 2004	1/20	1/20		1.00 [0.07, 14.90]
Mehr-Aein 2007	0/33	1/33		0.33 [0.01, 7.90]
Murphy 2006	1/50	0/50		3.00 [0.13, 71.92]
Shore-Lesserson 1996	0/17	1/13		0.26 [0.01, 5.89]
Taghaddomi 2009	0/50	0/50		0.0 [0.0, 0.0]
Subtotal (95% CI)	**454**	**458**		**0.89 [0.33, 2.37]**
Total events: 6 (Treatment), 7 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.52, df = 6 (P = 0.87); I^2 =0.0%				
Test for overall effect: Z = 0.23 (P = 0.81)				
3 Epsilon Aminocaproic Acid versus control				
Greilich 2009	3/26	9/27		0.35 [0.11, 1.14]
Subtotal (95% CI)	**26**	**27**		**0.35 [0.11, 1.14]**
Total events: 3 (Treatment), 9 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.75 (P = 0.081)				
Total (95% CI)	**3254**	**2658**		**0.97 [0.71, 1.33]**
Total events: 90 (Treatment), 69 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 11.43, df = 21 (P = 0.95); I^2 =0.0%				
Test for overall effect: Z = 0.19 (P = 0.85)				



Analysis 10.9. Comparison 10 Adverse Events and Other Outcomes (Active versus Control) - Cardiac Surgery, Outcome 9 Hospital Length of Stay.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 10 Adverse Events and Other Outcomes (Active versus Control) - Cardiac Surgery

Outcome: 9 Hospital Length of Stay

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Aprotinin versus Control							
Alderman 1998	401	7.6 (8.5)	395	7.8 (8.6)		7.3 %	-0.20 [-1.39, 0.99]
Asimakopoulos 2000	8	6.3 (0.2)	10	7.6 (0.9)		10.5 %	-1.30 [-1.87, -0.73]
Cohen 1998	56	10.9 (7.2)	59	9.9 (4.8)		3.6 %	1.00 [-1.25, 3.25]
Englberger 2002a	22	8 (2.2)	25	9.1 (8)		2.0 %	-1.10 [-4.37, 2.17]
Englberger 2002b	15	9.7 (2.4)	14	11.3 (3.6)		3.6 %	-1.60 [-3.84, 0.64]
Fauli 2005	40	6.65 (1.81)	20	6.8 (2.1)		7.8 %	-0.15 [-1.23, 0.93]
Harmon 2004	17	11.8 (3.1)	18	11.8 (4.3)		3.1 %	0.0 [-2.47, 2.47]
Kipfer 2003	15	9.7 (2.4)	15	10.2 (2.7)		4.7 %	-0.50 [-2.33, 1.33]
Kunt 2005	40	8 (1)	46	7 (2)		10.1 %	1.00 [0.34, 1.66]
Later 2009	96	7.8 (6.7)	103	8.5 (7.4)		4.3 %	-0.70 [-2.66, 1.26]
Liu 1993	20	7.3 (2.68)	20	7.6 (1.34)		6.7 %	-0.30 [-1.61, 1.01]
Mansour 2004	20	5.8 (1.8)	20	6.4 (3)		5.8 %	-0.60 [-2.13, 0.93]
Murkin 1994	29	11.1 (4.85)	25	15.4 (16)		0.6 %	-4.30 [-10.82, 2.22]
Nurözler 2008	25	5.3 (1.6)	26	5.5 (1.4)		9.2 %	-0.20 [-1.03, 0.63]
Poston 2006	29	8 (4.1)	31	7 (3.8)		4.2 %	1.00 [-1.00, 3.00]
Stammers 1997	8	6.1 (0.8)	12	7.3 (2.5)		5.8 %	-1.20 [-2.72, 0.32]
Wei 2006	36	7.9 (1.2)	40	7.3 (1.2)		10.7 %	0.60 [0.06, 1.14]
Subtotal (95% CI)	**877**		**879**			**100.0 %**	**-0.22 [-0.73, 0.29]**
Heterogeneity: $Tau^2 = 0.55$; $Chi^2 = 42.90$, df = 16 (P = 0.00029); $I^2 = 63\%$							
Test for overall effect: Z = 0.85 (P = 0.39)							
2 Tranexamic Acid versus Control							
Jimenez 2007	24	4.5 (3.55)	26	5 (3.71)		1.7 %	-0.50 [-2.51, 1.51]
Later 2009	99	9.4 (8.9)	103	8.5 (7.4)		1.3 %	0.90 [-1.36, 3.16]
Mansour 2004	20	5.8 (2.2)	20	6.4 (3)		2.6 %	-0.60 [-2.23, 1.03]
Mehr-Aein 2007	33	4.8 (0.4)	33	4.8 (0.9)		61.0 %	0.0 [-0.34, 0.34]

-4 -2 0 2 4

Favours Treatment Favours Control

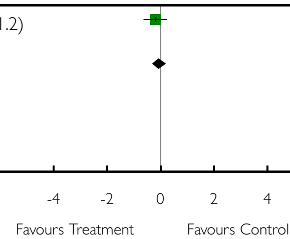
(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Wei 2006	36	7.1 (0.8)	40	7.3 (1.2)		33.3 %	-0.20 [-0.65, 0.25]
Subtotal (95% CI)	**212**		**222**			**100.0 %**	**-0.08 [-0.34, 0.18]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.76$, df = 4 (P = 0.78); $I^2 = 0.0\%$

Test for overall effect: Z = 0.59 (P = 0.56)



APPENDICES

Appendix 1. Search strategy

The original search strategy at the outset of the review included the following terms;
Exploded MeSH terms: 'aprotinin' 'tranexamic acid' 'Aminocaproic acids' 'Blood transfusion' 'Hemorrhage' 'Anesthesia'.
Text-word terms:aprotinin, antilysin, contrical, kallikrein-trypsin, bovine pancreatic trypsin, tranexamic, cyklokapron, pharmacia, t-amcha, amcha, ugurol, transamin, kabi, epsilon-aminocaproic acid, aminocaproic, lederle, amicar, transfusion$, bleed$, blood loss$, hemorrhag$.

Appendix 2. Search strategy: 2010 update

Cochrane Injuries Group Specialised Register (searched July 2010)

(Aprotinin* or kallikrein-trypsin inactivator* or bovine kunitz pancreatic trypsin inhibitor* or bovine pancreatic trypsin inhibitor* or basic pancreatic trypsin inhibitor* or BPTI or contrykal or kontrykal or kontrikal or contrical or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or epsikapron or antilysin or iniprol or kontrikal or kontrykal or pulmin* or Trasylol or Antilysin Spofa or rp?9921 or antagosan or antilysin or antilysine or apronitin* or apronitrine or bayer a?128 or bovine pancreatic secretory trypsin inhibitor* or contrycal or frey inhibitor* or gordox or kallikrein trypsin inhibitor* or kazal type trypsin inhibitor* or (Kunitz adj3 inhibitor*) or midran or (pancrea* adj2 antitrypsin) or (pancrea* adj2 trypsin inhibitor*) or riker?52g or rp?9921or tracylol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren) or (tranexamic or Cyclohexanecarboxylic Acid* or Methylamine* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA) or (aminocaproic or amino?caproic or aminohexanoic or amino?hexanoic or epsilon-aminocaproic or E-aminocaproic) adj2 acid*) or epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or lederle or Aminocaproic or aminohexanoic or amino caproic or amino n hexanoic or acikaprin or afibrin or capracid or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or cl 10304 or EACA or eaca roche or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or tachostyptan)

MEDLINE(Ovid) 1950 to July Week 2 2010

1. exp Antifibrinolytic Agents/
2. (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or ((plasmin or fibrinolysis) adj3 inhibitor*)).ab,ti.
3. exp Aprotinin/
4. (Aprotinin* or kallikrein-trypsin inactivator* or bovine kunitz pancreatic trypsin inhibitor* or bovine pancreatic trypsin inhibitor* or basic pancreatic trypsin inhibitor* or BPTI or contrykal or kontrykal or kontrikal or contrical or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or epsikapron or antilysin or iniprol or kontrikal or kontrykal or pulmin* or Trasylol or Antilysin Spofa or rp?9921 or antagosan or antilysin or antilysine or apronitin* or apronitrine or bayer a?128 or bovine pancreatic secretory trypsin inhibitor* or contrycal or frey inhibitor* or gordox or kallikrein trypsin inhibitor* or kazal type trypsin inhibitor* or (Kunitz adj3 inhibitor*) or midran or (pancrea* adj2 antitrypsin) or (pancrea* adj2 trypsin inhibitor*) or riker?52g or rp?9921or tracylol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren).ab,ti.
5. exp Tranexamic Acid/
6. (tranexamic or Cyclohexanecarboxylic Acid* or Methylamine* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA).ab,ti.
7. exp Aminocaproic Acids/ or exp 6-Aminocaproic Acid/
8. (((aminocaproic or amino?caproic or aminohexanoic or amino?hexanoic or epsilon-aminocaproic or E-aminocaproic) adj2 acid*) or epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or lederle or Aminocaproic or aminohexanoic or amino caproic or amino n hexanoic or acikaprin or afibrin or capracid or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or cl 10304 or EACA or eaca roche or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or tachostyptan).ab,ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. randomi?ed.ab,ti.
11. randomized controlled trial.pt.
12. controlled clinical trial.pt.
13. placebo.ab.
14. clinical trials as topic.sh.
15. randomly.ab.
16. trial.ti.
17. 10 or 11 or 12 or 13 or 14 or 15 or 16
18. (animals not (humans and animals)).sh.
19.17 not 18
20. 9 and 19

EMBASE (Ovid) 1980 to 2010 Week 28

1. exp Antifibrinolytic Agent/
2. (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or ((plasmin or fibrinolysis) adj3 inhibitor*)).ab,ti.
3. exp Aprotinin/
4. (Aprotinin* or kallikrein-trypsin inactivator* or bovine kunitz pancreatic trypsin inhibitor* or bovine pancreatic trypsin inhibitor* or basic pancreatic trypsin inhibitor* or BPTI or contrykal or kontrykal or kontrikal or contrical or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or epsikapron or antilysin or iniprol or kontrikal or kontrykal or pulmin* or Trasylol or Antilysin Spofa or rp?9921 or antagosan or antilysin or antilysine or apronitin* or apronitrine or bayer a?128 or bovine pancreatic secretory trypsin inhibitor* or contrycal or frey inhibitor* or gordox or kallikrein trypsin inhibitor* or kazal type trypsin inhibitor* or (Kunitz adj3 inhibitor*) or midran or (pancrea* adj2 antitrypsin) or (pancrea* adj2 trypsin inhibitor*) or riker?52g or rp?9921or tracylol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren).ab,ti.
5. exp Tranexamic Acid/

6. (tranexamic or Cyclohexanecarboxylic Acid* or Methylamine* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA).ab,ti.
7. exp Aminocaproic Acid/
8. (((aminocaproic or amino?caproic or aminohexanoic or amino?hexanoic or epsilon-aminocaproic or E-aminocaproic) adj2 acid*) or epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or lederle or Aminocaproic or aminohexanoic or amino caproic or amino n hexanoic or acikaprin or afibrin or capracid or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or cl 10304 or EACA or eaca roche or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or tachostyptan).ab,ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp Randomized Controlled Trial/
11. exp controlled clinical trial/
12. randomi?ed.ab,ti.
13. placebo.ab.
14. *Clinical Trial/
15. randomly.ab.
16. trial.ti.
17. 10 or 11 or 12 or 13 or 14 or 15 or 16
18. exp animal/ not (exp human/ and exp animal/)
19. 17 not 18
20. 9 and 19

Cochrane Central Register of Controlled Trials (The Cochrane Library 2010, Issue 3)
#1 MeSH descriptor Antifibrinolytic Agents explode all trees
#2 (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin*):ab,ti or ((plasmin or fibrinolysis) near3 inhibitor*):ab,ti
#3 MeSH descriptor Aprotinin explode all trees
#4 (Aprotinin* or kallikrein-trypsin inactivator* or bovine kunitz pancreatic trypsin inhibitor* or bovine pancreatic trypsin inhibitor* or basic pancreatic trypsin inhibitor* or BPTI or contrykal or kontrykal or kontrikal or contrical or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or epsikapron or antilysin or iniprol or kontrikal or kontrykal or pulmin* or Trasylol or Antilysin Spofa or rp?9921 or antagosan or antilysin or antilysine or apronitin* or apronitrine or bayer a?128 or bovine pancreatic secretory trypsin inhibitor* or contrycal or frey inhibitor* or gordox or kallikrein trypsin inhibitor* or kazal type trypsin inhibitor or riker?52g or rp?9921or tracylol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren or midran):ab,ti or ((Kunitz near3 inhibitor*) or (pancrea* near3 antitrypsin) or (pancrea* near3 trypsin next inhibitor*)):ab,ti
#5 MeSH descriptor Tranexamic Acid explode all trees
#6 (tranexamic or Cyclohexanecarboxylic Acid* or Methylamine* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA):ab,ti
#7 MeSH descriptor Aminocaproic Acids explode all trees
#8 MeSH descriptor 6-Aminocaproic Acid explode all trees
#9 (epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or lederle or Aminocaproic or aminohexanoic or amino caproic or amino n hexanoic or acikaprin or afibrin or capracid or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or cl 10304 or EACA or eaca roche or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or

epsilon aminocaproate or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or tachostyptan):ab,ti
#10 (aminocaproic or amino?caproic or aminohexanoic or amino?hexanoic or epsilon-aminocaproic or E-aminocaproic):ab,ti
#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)

WHAT'S NEW

Last assessed as up-to-date: 31 January 2010.

Date	Event	Description
10 February 2011	New citation required but conclusions have not changed	The editorial group is aware that a clinical trial by Prof. Joachim Boldt has been found to have been fabricated (Boldt 2009). As the editors who revealed this fabrication point out (Reinhart 2011; Shafer 2011), this casts some doubt on the veracity of other studies by the same author. All Cochrane Injuries Group reviews which include studies by this author have therefore been edited to show the results with this author's trials included and excluded. Readers can now judge the potential impact of trials by this author (Boldt 1991, Boldt 1994, Mengistu 2008) on the conclusions of the review.

HISTORY

Protocol first published: Issue 1, 1999

Review first published: Issue 1, 1999

Date	Event	Description
31 May 2010	New citation required and conclusions have changed	The searches were updated to February 2010. An additional 40 trials have been included. The updated data show a lower rate of death with the lysine analogues than aprotinin, which has been withdrawn from world markets
10 September 2008	Amended	The text of 'Type of surgery' under 'Aprotinin' in the 'Effects of interventions' section was amended
8 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Contributors (names are listed alphabetically)

Paul Carless (University of Newcastle) obtained relevant papers, applied inclusion/ exclusion criteria to retrieved papers, quality assessed trials, extracted data from the trials, entered data into RevMan Analyses, entered study details into Review Manager 4.2.8, and co-wrote review; Dean Fergusson (ISPOT Coordinator*) co-conceived the review, performed the original literature searches, data extraction, and analyses; David Henry (University of Newcastle) obtained funding for the study, was involved in study design, screened abstracts and titles for relevant articles, and co-wrote review; Katharine Ker (London School of Hygiene & Tropical Medicine) performed updated literature searches extracted data and co-wrote the updated review; Annette Moxey (University of Newcastle) obtained relevant papers, applied inclusion/ exclusion criteria to retrieved papers, quality assessed trials, extracted data from the trials and entered data into MetaView 3.1; Dianne O'Connell (University of Newcastle) provided statistical consultancy for the review, checked data for consistency, analysed and interpreted the results, provided methodological content, and co-wrote review, Barrie Stokes (University of Newcastle) provided statistical consultancy for the review and performed Bayesian analyses.

* ISPOT - International Study of Peri-Operative Transfusion

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Special purpose grant, Hunter Area Pathology Service, Australia.

External sources

- Australian Health Ministers' Advisory Committee. National Health and Medical Research Council of Australia, Australia.

NOTES

The editorial group is aware that a clinical trial by Prof. Joachim Boldt has been found to have been fabricated (Boldt 2009). As the editors who revealed this fabrication point out (Reinhart 2011; Shafer 2011), this casts some doubt on the veracity of other studies by the same author. All Cochrane Injuries Group reviews which include studies by this author have therefore been edited to show the results with this author's trials included and excluded. Readers can now judge the potential impact of trials by this author (Boldt 1991, Boldt 1994, Mengistu 2008) on the conclusions of the review.

INDEX TERMS

Medical Subject Headings (MeSH)

6-Aminocaproic Acid [*therapeutic use]; Antifibrinolytic Agents [*therapeutic use]; Aprotinin [*therapeutic use]; Blood Loss, Surgical [*prevention & control]; Erythrocyte Transfusion [*utilization]; Randomized Controlled Trials as Topic; Tranexamic Acid [*therapeutic use]; Transplantation, Homologous

MeSH check words

Adult; Humans