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Antifibrinolytics in cardiac surgical patients receiving aspirin: a systematic review and meta-analysis

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While conventional practice is to discontinue aspirin prior to elective cardiac surgery there is evidence that its continuation may be associated with improved perioperative outcomes. However, uncertainty exists regarding the efficacy of antifibrinolytic agents in the presence of aspirin. We performed a systematic review and meta-analysis of the literature to address the question of the effects of antifibrinolytic agents in cardiac surgery patients maintained on aspirin in terms of both efficacy and adverse events. We conducted an extensive search for randomized controlled trials of antifibrinolytic use in adult patients undergoing coronary artery bypass grafting ± valve surgery, where aspirin therapy was maintained or initiated through the preoperative period. Data from 17 trials (n=1620) confirmed the efficacy of antifibrinolytic therapy to reduce both chest-tube drainage (weighted mean difference 374 ml, 95% CI 275–473 ml; $P<0.00001$) and blood transfusion requirements (odds ratio 0.37, 95% CI 0.27–0.49; $P<0.00001$) in cardiac surgical patients receiving aspirin. We found no difference in the rates of adverse events between groups but observed a trend towards a reduced risk for the composite outcome of thrombotic complications (odds ratio 0.49, 95% CI 0.21–1.13; P=0.09). Antifibrinolytic agents are effective for reducing both chest-tube drainage and transfusion requirements in cardiac surgical patients receiving aspirin. We found no difference between antifibrinolytic and placebo in terms of adverse events but the population was predominantly low-risk. Further studies are required to determine the optimal balance between antiplatelet and antifibrinolytic effects in cardiac surgery.

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Intraoperative and postoperative bleeding remains a major cause of morbidity, mortality and economic cost in cardiac surgery. Typically 50–60% of cardiac surgical patients receive some form of allogeneic blood transfusion in the perioperative period[14 44] and this population use approximately 20% of all blood-bank products. Pharmacological strategies to reduce bleeding in cardiac surgery include aprotinin and the lysine analogues (tranexamic acid and ε-aminocaproic acid). Meta-analyses of randomized-controlled trials consistently demonstrate a reduction in bleeding and transfusion requirements with these agents.[8 21 27 29 35 42] However, the safety of antifibrinolytics remain uncertain with concern regarding their potential to promote thrombotic events and increase mortality in cardiac surgery. While much of this concern has focused on aprotinin,[18 31] there are theoretical reasons along with several case reports to raise similar potential concerns with the lysine analogues.[11 15 25 37]

The majority of cardiac surgery patients receive aspirin for secondary prevention of coronary events and yet, because of the association between aspirin and increased perioperative bleeding,[2 16 46] it is typically stopped 5–7 days prior to elective cardiac surgery. However, a retrospective case–control study by Dacey and colleagues[13] found a 45% reduction in perioperative mortality among coronary artery bypass graft (CABG) surgery patients receiving aspirin prior to surgery, and Mangano[30] reported a 65% reduction in mortality and 40% reduction in non-fatal ischaemic complications in a large observational study of patients undergoing CABG surgery who were administered aspirin within 48 h after operation. Despite potential limitations of these studies by unrecognized confounding variables, they raise the question of whether routine aspirin should be maintained up until the time of cardiac surgery. In recently published guidelines, the Society of Thoracic Surgeons and the Society of

Cardiovascular Anesthesiologists[19] recommend that aspirin be discontinued for no more than 2–3 days prior to elective cardiac surgery. However, the net effect of continued aspirin in combination with intraoperative antifibrinolytic therapy, with their opposing effects on a complex haemostatic system, has not been adequately defined. The efficacy of various antifibrinolytic agents to reduce bleeding and transfusion requirements in the presence of aspirin has been addressed by a number of small randomized controlled trials but uncertainty remains particularly with regard to other outcomes. Of the current meta-analyses in the published literature, only two have addressed the subgroup of patients receiving aspirin.[27 42] However, both of these studies assessed the effect of aspirin exposure as an inclusion–exclusion design feature of component studies rather than at an individual patient level. A further question regarding the adverse event profile of antifibrinolytics in the presence of aspirin also remains unanswered. We therefore sought to perform a systematic review and meta-analysis of the literature to address the question of the effects of antifibrinolytic agents in cardiac surgery patients maintained on aspirin in terms of both efficacy and adverse events.

Methods

Search strategy

We conducted an extensive search for randomized controlled trials of antifibrinolytic use in adult patients undergoing CABG ± valve surgery, where aspirin therapy had been maintained or initiated through the preoperative period. Medline and EMBASE databases and the Cochrane Central Register of Controlled Trials were searched using the terms aspirin, aprotinin, antifibrinolytic agents, aminocaproic acids, tranexamic acid, thoracic surgery and coronary artery bypass as exploded MeSH (Medical Subject Headings) terms. We also used aspirin, aprotinin, trasylol, antifibrinolytic, lysine analog(ue), aminocaproic acid, tranexamic acid, cardiac surgery and coronary artery (bypass) graft as specific text words. We restricted these searches using the filters of human and randomized controlled trial and searched for all papers published between January 1, 1960 and July 31, 2008. We placed no language restrictions on our search.

We followed appropriate methods for conducting a systematic review and meta-analysis as set out in The QUORUM statement.[32] Three reviewers independently performed the searches, with disagreement on trial inclusion resolved by consensus. The initial search yielded 45 papers. We included all dosing regimens of i.v. aprotinin, tranexamic acid or aminocaproic acid used in placebo-controlled trials or head-to-head comparison. We restricted our search to studies using an antifibrinolytic as prophylaxis rather than rescue therapy and where participants had been exposed to aspirin within 7 days prior to surgery. Studies which included patients taking anti-platelet medication other than aspirin or using any other form of anti-coagulation were excluded. Thirty-one studies were excluded at this stage (see Supplementary material, Appendix E1 for detailed description of excluded studies). We scrutinized the reference lists of included and excluded studies and identified three additional studies that met the inclusion criteria for our review.[7 28 41] This left 17 studies for inclusion in the meta-analysis[3–7 10 12 17 26 28 33 36 38–41 45] (Fig. 1). Detailed reading of manuscripts revealed one study used a process of pseudo-randomization[5] and four studies were open-label in design.[5 7 40 41] However, these studies were included in our review with a planned sensitivity analysis to assess their effect on summary results. Table 1 gives a description of the 17 included studies.

Data abstraction

Data were abstracted from the 17 included studies on seven efficacy outcomes including chest-tube drainage, mean number of packed cells and mean number of all blood products transfused per patient, proportion of patients receiving packed cells and proportion receiving any allogeneic blood products, proportion of patients requiring surgical re-exploration and mortality. Data were also abstracted on the adverse events of myocardial infarction (MI), stroke, and the composite outcome of any thrombotic complication. Reports of MI, stroke, and deep venous thrombosis or pulmonary embolus were considered together as thrombotic complications. None of the studies reported adverse renal outcomes. All data were independently abstracted by two reviewers (D.R.M., L.E.P.), with disagreement resolved by consensus.

Seven studies[3–5 33 39–41] reported volume of chest-tube drainage at 24 h postoperatively, six studies[6 7 10 12 26 36] reported volume of drainage at removal of drains, two studies[17 45] at 12 h postoperatively, one study[28] at 6 h postoperatively, and one study[38] at 16 h postoperatively. Ten studies[3 4 7 17 26 28 33 38 39 45] used a transfusion algorithm although only seven studies[4 6 28 33 36 38 45] specified the duration of time after surgery for which transfusion was assessed. No study defined the time criteria for assessment of surgical re-exploration or mortality. Five studies[3 28 33 36 39] explicitly described the criteria to be met for the diagnosis of postoperative MI. Only one study[39] explicitly defined the criteria for classification of either stroke or prothrombotic complications. Reports of 'no major complications' were not taken to represent zero events for each complication in a study. Explicit description of the absence of each specific adverse event was required in order to be included in the analysis as a count of zero. Requests for additional data or clarification of trial design were made via the corresponding author of 13 included studies[4 6 7 10 12 17 26 28 33 36 38–40] and three excluded studies.[1 18 23] Further information was obtained for four studies.[6 7 36 39]

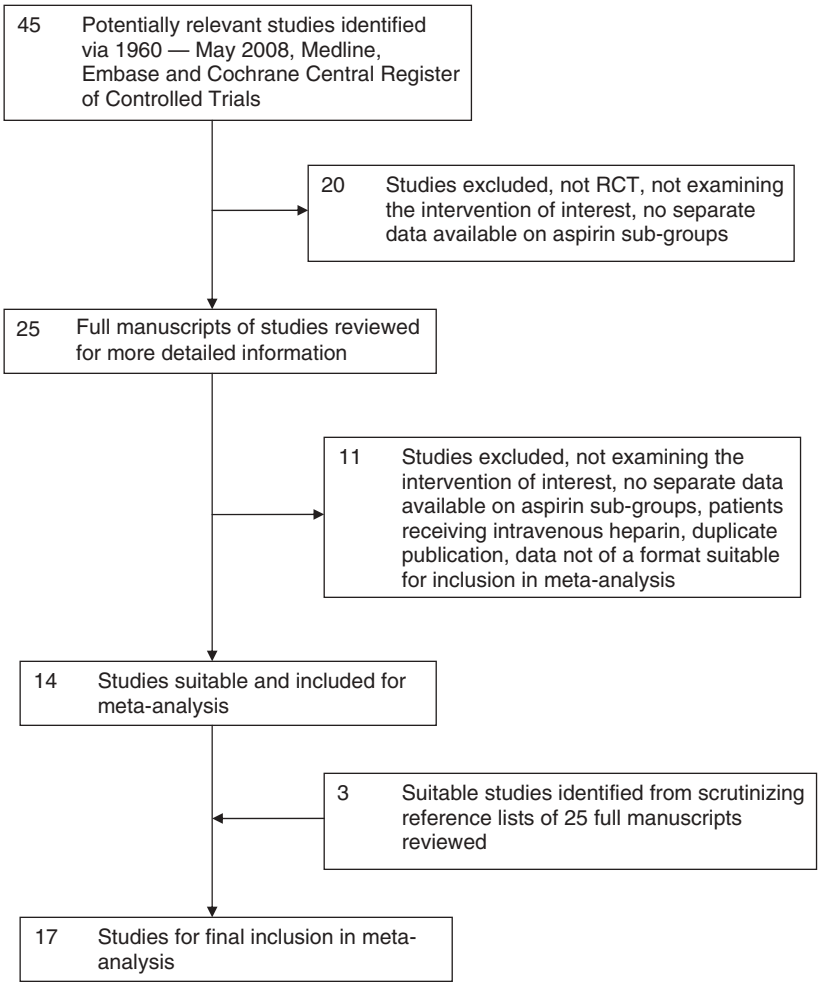

Fig 1 Flow chart of search and selection process for identification of studies for inclusion in meta-analysis.

Quality assessment of included studies

Quality of included studies was independently assessed by two reviewers (D.R.M., L.E.P.), with disagreement resolved by consensus. For each study, quality was determined according to an assessment of susceptibility to bias across the domains of allocation concealment, selection bias, performance bias, attrition bias, and detection bias (Table 2).

Statistical analysis

All analyses were conducted with the Cochrane Collaborative software, RevMan 5.0, beta-version, using a random-effects model. Continuous variables were assessed using the inverse variance method to generate point estimates with 95% confidence interval for each study and a weighted mean difference with 95% confidence interval for the summary estimate. A P-value <0.05 was considered statistically significant. Statistical heterogeneity was assessed using the I^2 statistic. Dichotomous variables were assessed using a Mantel–Haenszel random-effects model to generate an odds ratio with 95% confidence interval for both individual studies and the pooled estimate. If a single cell had zero events, the software automatically added 0.5 to that cell to maintain its contribution to the analysis. If a study reported no events in either treatment or control arms it was not included in calculation of the summary statistic. Statistical heterogeneity was assessed in the same way as for continuous variables. Funnel plots were used to assess for evidence of publication or small-study bias.

Pre-planned sub-group analyses included aprotinin *vs* placebo, lysine analogue *vs* placebo, and aprotinin *vs* the lysine analogues. Sensitivity analyses were planned to determine if exclusion of studies on the basis of quality, aprotinin dosage regimen, type of surgery, use of transfusion algorithm or time of recording chest-tube drainage significantly affected the summary result.

Results

Characteristics of included studies

A total of 17 studies involving 1620 patients, published between 1989 and 2006 were included in this meta-analysis. Twelve studies compared aprotinin with

Table 1 Description of included studies. *n, number of participants in study; †Last ASA, time between last aspirin ingestion and surgery; ‡CABG, coronary artery bypass graft; ¶OPCABG, off-pump CABG; §TXA, tranexamic acid; ||Amikar, ϵ-aminocaproic acid; #KIU, kilo International Units; **full-dose aprotinin, 2×10^6 KIU i.v. load+2×10^6 KIU in CPB circuit prime+i.v. infusion at 5×10^5 KIU h^{-1}; $CPB, cardio-pulmonary bypass; [3–7 10 12 17 26 28 33 36 38–41 45] Full bibliographic citation in References

Study	*n**	Surgery	Last ASA†	Comparison	Dosing regimen
Alvarez 2001[3]	55	Primary CABG‡	<24/24	Aprotinin *vs* placebo	Aprotinin 2×10^6 KIU#, single dose at skin closure
Bernet 1999[4]	70	Elective primary CABG	<24/24	Aprotinin *vs* TXA§	Aprotinin full-dose** *vs* TXA 10 g pre-incision
Bertrand 1993[5]	60	Elective primary CABG	<24/24	Aprotinin *vs* nil	Aprotinin 2×10^6 KIU load+2×10^6 KIU in CPB$ prime, no infusion
Bidstrup 2000[6]	60	Elective primary CABG	<24/24	Aprotinin *vs* placebo	Aprotinin full-dose
Bidstrup 1990[7]	44	CABG	<24/24	Aprotinin *vs* nil	Aprotinin full-dose
Casati 1996[10]	298	Elective CABG	5 days	Aprotinin *vs* TXA	Aprotinin full-dose *vs* TXA 1 g load pre-sternotomy+500 mg in CPB prime+400 mg h^{-1} infusion
Cosgrove 1992[12]	36	Re-operative CABG	?	Full-dose aprotinin *vs* half-dose aprotinin *vs* placebo	Aprotinin full-dose *vs* aprotinin half-dose *vs* placebo
Dignan 2001[17]	102	Primary CABG	<7 days	Aprotinin *vs* placebo	Aprotinin 5×10^5 KIU pre-incision+5×10^5 KIU at commencement of CPB
Landymore 1997[26]	198	Primary CABG	<48/24	Aprotinin *vs* TXA *vs* Amikar|| *vs* placebo	Aprotinin 2×10^5 KIU load+2×10^5 infusion till end of CPB *vs* Amikar 5 g load+1 g hr^{-1} *vs* TXA 10 mg kg^{-1} load+1 mg kg^{-1} h^{-1}
Lemmer 1996[28]	371	Primary CABG	<5 days	Full-dose aprotinn *vs* placebo; half-dose aprotinin *vs* placebo	Aprotinin full-dose *vs* placebo; aprotinin half-dose *vs* placebo
Moran 2000[33]	42	Elective primary CABG	<72/24	Aprotinin *vs* placebo	Aprotinin 2×10^6 KIU load+2×10^6 KIU in CPB prime $\pm2\times10^6$ KIU bolus at end of CPB *vs* placebo
Murkin 1994[36]	57	Elective primary CABG or valve	<48/24	Aprotinin *vs* placebo	Aprotinin full-dose *vs* placebo
Pleym 2003[38]	80	Elective primary CABG	<24/24	TXA *vs* placebo	TXA 30 mg kg^{-1} load pre-CPB *vs* placebo
Poston 2006[39]	60	OPCABG¶	<24/24	Aprotinin *vs* placebo	Aprotinin 2×10^6 KIU load+5×10^5 KIU h^{-1} *vs* placebo
Rao 1999[40]	30	Elective primary CABG	<24/24	Amikar *vs* nil	Amikar 100 mg kg^{-1} load pre-sternotomy+1 g h^{-1} infusion for 6 h
Royston 1989[41]	17	Elective primary CABG	?	Aprotinin *vs* nil	Aprotinin full-dose
Tabuchi 1994[45]	40	Elective primary CABG	<24/24	Aprotinin *vs* placebo	Aprotinin 2×10^6 KIU, single dose into CPB pump prime

Table 2 Appraisal of the internal validity of included studies. *R, randomized; †DB, double-blind; ‡PC, placebo-controlled; ¶OL, open-label; §Allocation concealment: X–adequate, Y–unclear, Z–inadequate; ||Risk of bias: A–low risk, B–moderate risk, C–high risk, D–unable to judge. [3–7 10 12 17 26 28 33 36 38–41 45] Full bibliographic citation in References

Study	Design	Allocation concealment§	Risk of selection bias||	Risk of performance bias||	Risk of attrition bias||	Risk of detection bias||	Risk of reporting bias||
Alvarez 2001[3]	R*, DB†, PC‡	X	A	A	B	A	A
Bernet 1999[4]	R, DB, PC	Y	D	A	B	D	A
Bertrand 1993[5]	Pseudo-R, OL¶	Z	C	C	A	C	A
Bidstrup 2000[6]	R, DB, PC	Y	D	A	A	D	A
Bidstrup 1990[7]	R, OL	Y	D	C	A	C	A
Casati 1996[10]	R	Y	D	D	D	D	D
Cosgrove 1992[12]	R, DB, PC	Y	D	A	A	A	A
Dignan 2001[17]	R, DB, PC	Y	D	A	A	A	A
Landymore 1997[26]	R, DB, PC	X	D	A	D	D	D
Lemmer 1996[28]	R, DB, PC	Y	D	A	D	A	A
Moran 2000[33]	R, DB, PC	Y	D	A	B	D	A
Murkin 1994[36]	R, DB, PC	X	D	A	A	A	A
Pleym 2003[38]	R, DB, PC	X	D	A	A	D	A
Poston 2006[39]	R, DB, PC	Y	D	A	A	D	A
Rao 1999[40]	R, OL	Y	D	C	D	C	D
Royston 1989[41]	R, OL	Y	D	C	D	C	D
Tabuchi 1994[45]	R, DB, PC	X	D	A	B	A	A

placebo,[3 5–7 12 17 28 33 36 39 41 45] two studies compared lysine analogue with placebo,[38 40] two studies compared aprotinin with lysine analogues,[4 10] and one study was a 4-arm parallel group study comparing aprotinin, tranexamic acid, aminocaproic acid, and placebo.[26] Twelve studies were double-blinded,[3 4 6 12 17 26 28 33 36 38 39 45] five

were either open-label or had no description of blinding. Study size ranged from n=17 to n=371. Gender was reported in 11 studies and involved a predominantly male population (range 70–100%). Mean age of participants was reported in 11 studies and ranged from 54 to 63.8 yr. Fourteen studies enrolled only patients undergoing on-pump CABG surgery, predominantly elective. Only one study enrolled patients undergoing re-operative CABG surgery,[12] one study patients undergoing CABG ± valve surgery,[36] and one study exclusively enrolled patients undergoing off-pump CABG surgery.[39] In nine studies patients received aspirin in the 24 h prior to surgery.[3–7 38–40 45] A full description of antifibrinolytic dosage regimens is given in Table 1. All but one of the studies was published in English, the remaining study being published in French.

Methodologic quality of included studies

Internal validity of included trials was assessed according to methods described by the Cochrane Collaboration (risk of selection, performance, attrition, and detection bias).[22] Additionally, we have explicitly categorized allocation concealment as adequate (X), unclear (Y), or not used (Z).

Allocation concealment was generally unclear. Risk of selection bias was generally not addressed with only one study describing enrolment of patients as 'consecutive'.[3] No study addressed non-enrolment of eligible patients. Several studies described exclusion of patients requiring re-exploration for surgical bleeding. Where the group to which these patients were randomized was made clear in the manuscript, we have included their re-exploration in the pooled analysis of this outcome.

Chest-tube drainage

Chest-tube drainage was reported in 12 studies (n=992) comparing aprotinin with placebo and in three studies (n=259) comparing lysine analogues with placebo. Both types of antifibrinolytic were effective at reducing chest-tube drainage which was on average 374 ml (95% CI 275–473; P<0.00001) less than in those who received placebo (Fig. 2). There was statistical heterogeneity with a calculated I^2 of 85%, in keeping with the varied time of reporting for this outcome. Chest-tube drainage was reported in three studies (n=502) comparing aprotinin head-to-head with lysine analogues. There was no difference between groups, with patients receiving aprotinin draining on average 24 ml (95% CI −12 to 60; P=0.18) less than patients receiving lysine analogues (Supplementary material, Fig. E1). There was no measurable statistical heterogeneity between studies with a calculated I^2 of 0%.

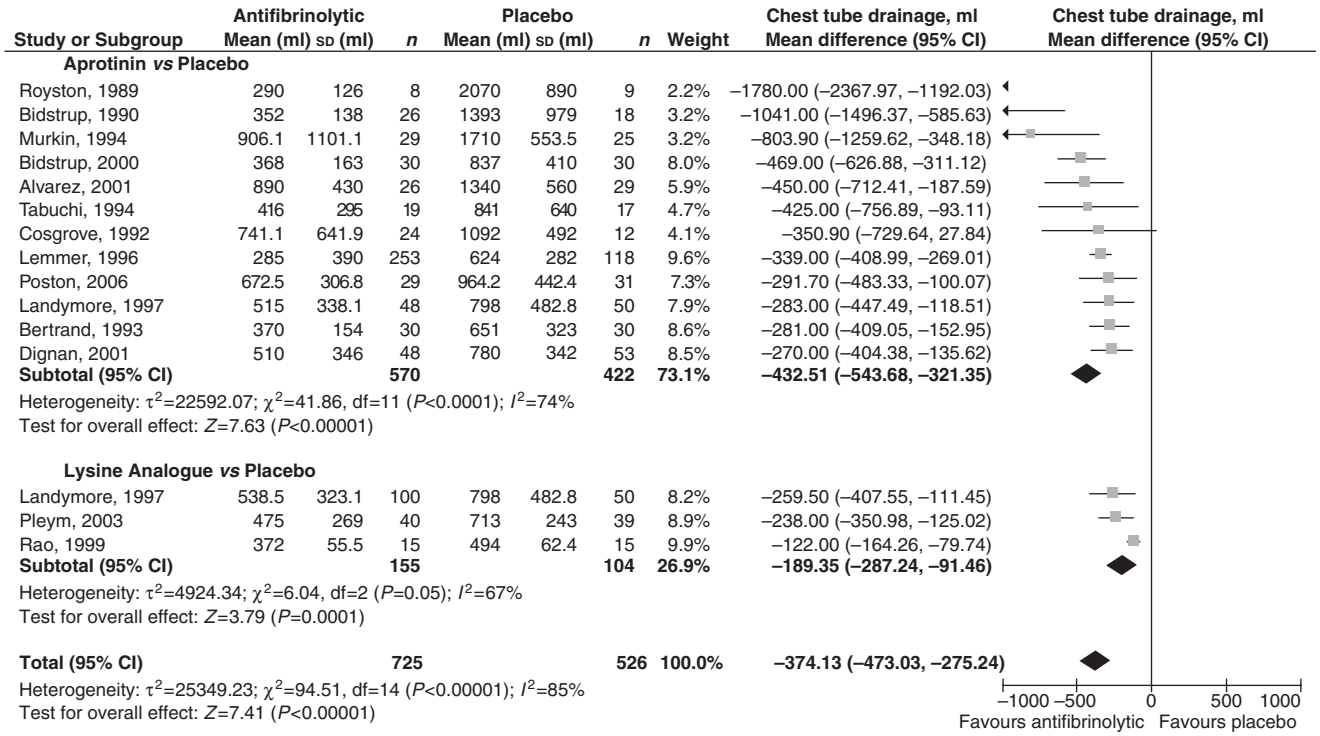

Fig 2 Pooled estimates of mean postoperative chest-tube drainage (ml): antifibrinolytic *vs* placebo. Results are presented as mean difference with 95% confidence interval represented by horizontal line. Sub-group analysis is presented for both aprotinin *vs* placebo and lysine analogue *vs* placebo. A random effects model has been used. The size of the square represents the relative weighting of a study and is positioned at the point estimate of mean difference. Diamond markings represent 95% confidence interval for pooled summary effect estimate within each subgroup and as a total measure of effect (lower diamond).

Transfusion

Mean number of units of packed red blood cells (PRBCs) transfused per patient was reported in nine studies (n=788), eight comparing aprotinin with placebo and one comparing ϵ-aminocaproic acid with placebo. Patients receiving an antifibrinolytic received on average 1.30 less units of PRBCs (95% CI 0.76–1.83; P<0.0001) than the placebo group (Supplementary material, Fig. E2). There was a calculated I^2 of 71%, the heterogeneity largely attributable to one open-label study.[40] The mean number of units transfused for all blood products was reported in five studies (n=836), five comparing aprotinin with placebo and four comparing ϵ-aminocaproic acid with placebo. Patients receiving an antifibrinolytic received on average 1.72 less units of allogeneic blood product (95% CI 1.08–2.36; P<0.0001) than the placebo group (Supplementary material, Fig. E3). There was a calculated I^2 of 24% indicating minimal heterogeneity between studies.

The proportion of patients receiving at least 1 unit of PRBCs was reported in three studies (n=216), each comparing aprotinin with placebo. Patients receiving antifibrinolytic were less likely to receive any PRBCs (odds ratio 0.36, 95% CI 0.20–0.65; P=0.0006) compared with placebo (Supplementary material, Fig. E4). There was no measurable statistical heterogeneity between studies with a calculated I^2 of 0%. The proportion of patients exposed to any blood product was reported in 11 studies (n=935), 10 comparing aprotinin with placebo and one comparing tranexamic acid with placebo. Patients receiving antifibrinolytic were less likely to receive any blood products (odds ratio 0.37, 95% CI 0.27–0.49; P<0.00001) compared with placebo (Fig. 3). There was no measurable statistical heterogeneity between studies with a calculated I^2 of 0%.

Surgical re-exploration

Nine studies (n=461) reported the need for surgical re-exploration, seven comparing aprotinin with placebo and two comparing lysine analogues with placebo. Only 17 events were reported in six studies. Despite a trend towards a reduced rate of re-exploration in both subgroups as well as the overall summary estimate, there was no significant difference in the rate for re-exploration between patients receiving antifibrinolytic and placebo (odds ratio 0.40, 95% CI 0.14–1.13; P=0.08) (Fig. 4). There was no measurable statistical heterogeneity between studies with a calculated I^2 of 0%.

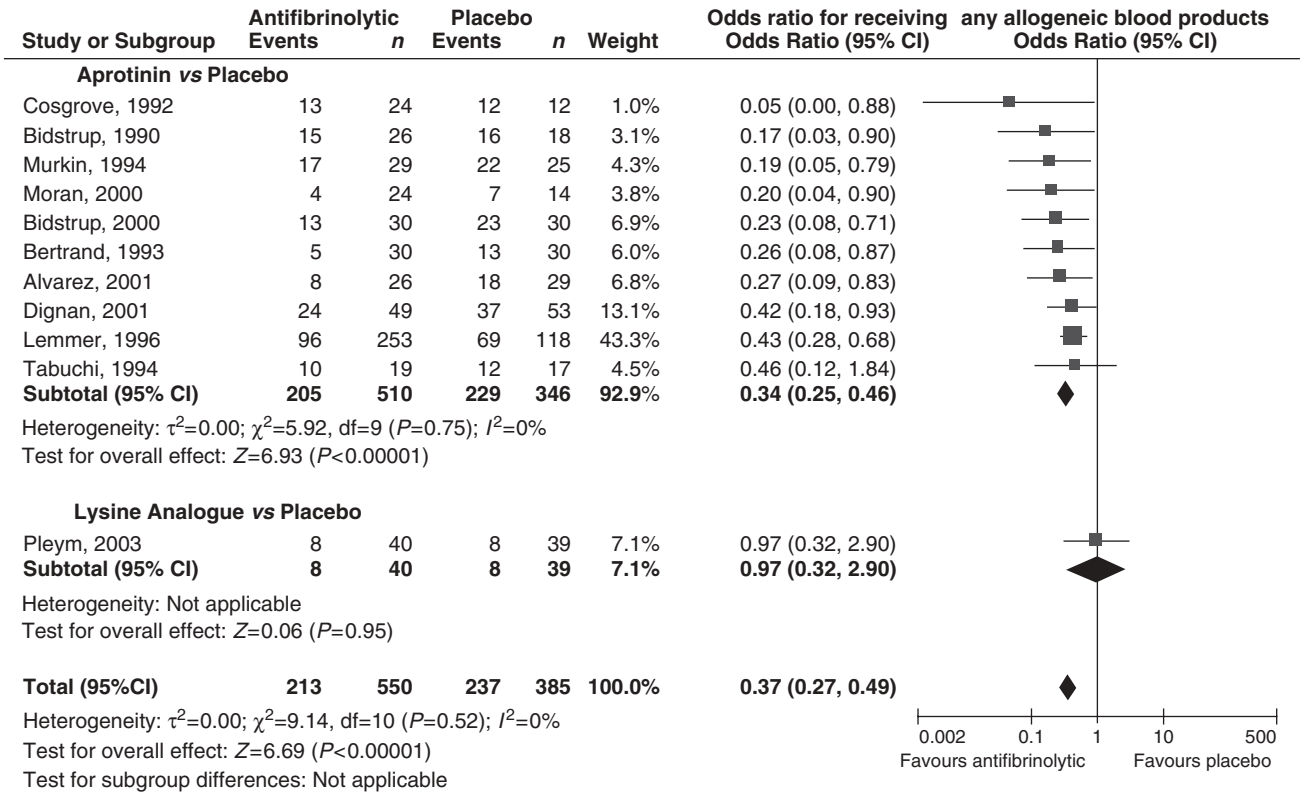

Fig 3 Pooled estimates of proportion of patients receiving any allogeneic blood products: antifibrinolytic *vs* placebo. Results are presented as odds ratio with 95% confidence interval represented by horizontal line. Sub-group analysis is presented for both aprotinin *vs* placebo and lysine analogue *vs* placebo. A random effects model has been used. The size of the square represents the relative weighting of a study and is positioned at the point estimate of the odds ratio. Diamond markings represent 95% confidence interval for pooled summary effect estimate within each subgroup and as a total measure of effect (lower diamond).

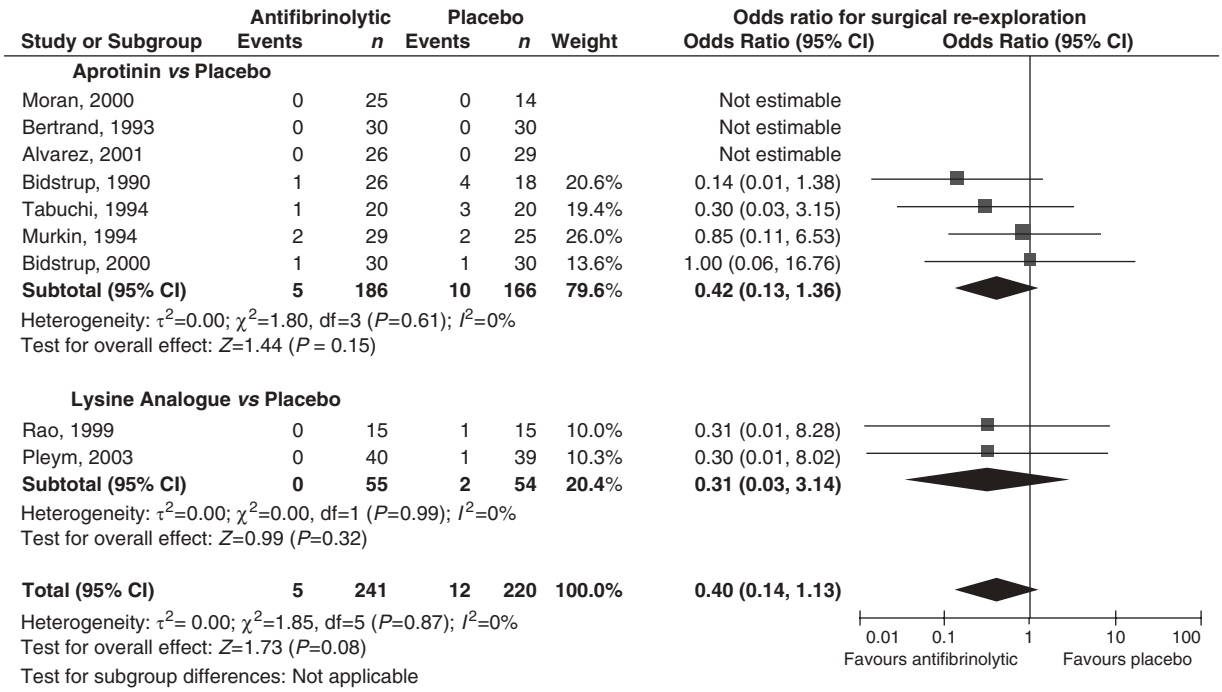

Fig 4 Pooled estimates of proportion of patients undergoing surgical re-exploration: antifibrinolytic *vs* placebo. Results are presented as odds ratio with 95% confidence interval represented by horizontal line. Sub-group analysis is presented for both aprotinin *vs* placebo and lysine analogue *vs* placebo. A random effects model has been used. The size of the square represents the relative weighting of a study and is positioned at the point estimate of the odds ratio. Diamond markings represent 95% confidence interval for pooled summary effect estimate within each subgroup and as a total measure of effect (lower diamond).

Mortality

Seven studies (n=646) reported mortality, six comparing aprotinin with placebo and two comparing lysine analogues with placebo. There were only five deaths reported across all studies. There was no difference in mortality between patients receiving antifibrinolytic and patients receiving placebo (odds ratio 1.80, 95% CI 0.29–11.31; P=0.53). There was no measurable statistical heterogeneity between studies with a calculated I^2 of 0% (Supplementary material, Fig. E5).

Adverse events (MI, stroke, prothrombotic events)

Seven studies (n=361) reported MI, six comparing aprotinin with placebo and one comparing ϵ-aminocaproic acid with placebo. There were 14 MIs reported across all studies with no significant difference in the rate of MI between patients receiving antifibrinolytic and placebo (odds ratio 0.71, 95% CI 0.23–2.22; P=0.56). There was no measurable statistical heterogeneity between studies with a calculated I^2 of 0% (Supplementary material, Fig. E6).

Although five studies (n=241) reported stroke as an adverse event, only six events occurred in two studies. The pooled odds ratio for stroke in patients receiving antifibrinolytic was 0.23 (95% CI 0.04–1.46; P=0.12) compared with placebo. There was no measurable statistical heterogeneity between studies with a calculated I^2 of 0%.

Ten studies (n=786) reported events classified as thrombotic complications, eight comparing aprotinin with placebo and three comparing lysine analogues with placebo. There was no difference in the thrombotic event rate between patients receiving antifibrinolytic and placebo (odds ratio 0.49, 95% CI 0.21–1.13; P=0.09). There was no measurable statistical heterogeneity between studies with a calculated I^2 of 0% (Fig. 5).

Sensitivity analysis

No single study appeared to individually impact the pooled summary estimates of effect. The analysis was redone excluding each study in turn with none of the results for either efficacy or adverse events being significantly altered. Simultaneous exclusion of three studies with the greatest magnitude of effect on chest-tube drainage[7 36 41] made no significant difference to the pooled estimate of reduction in drainage. Simultaneous exclusion of studies involving valve surgery or revision CABG surgery[12 36] did not alter results for chest-tube drainage, transfusion, or other outcomes. To assess for evidence of a dose effect, studies in which the total administered dose of aprotinin was $\leq 2\times10^6$ KIU were excluded from analysis. None of the outcomes were significantly altered. Exclusion of studies in which the last exposure to aspirin was more than 48 h prior to surgery had no impact on summary results, nor did analysis on the basis of whether

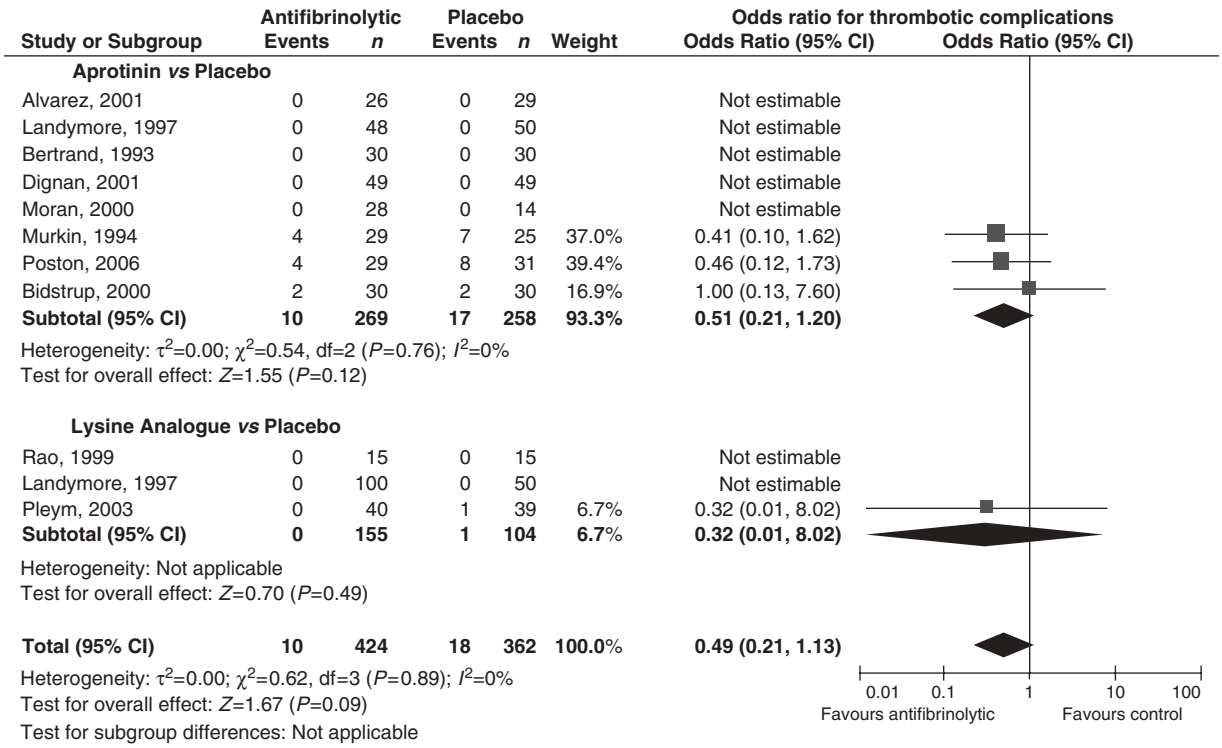

Fig 5 Pooled estimates of proportion of patients with a thrombotic complication: antifibrinolytic *vs* placebo. Results are presented as odds ratio with 95% confidence interval represented by horizontal line. Sub-group analysis is presented for both aprotinin *vs* placebo and lysine analogue *vs* placebo. A random effects model has been used. The size of the square represents the relative weighting of a study and is positioned at the point estimate of the odds ratio. Diamond markings represent 95% confidence interval for pooled summary effect estimate within each subgroup and as a total measure of effect (lower diamond).

or not a transfusion algorithm was used or time of recording chest-tube drainage.

We assessed the impact of study quality on outcomes by repeating the analysis following sequential exclusion of studies with less than adequate allocation concealment or inadequate blinding with no significant change in summary outcome results. Funnel plots were constructed to look for evidence of publication or small-study bias (Supplementary material, Figs E7 and E8). There was no evidence to support such bias.

Discussion

In this systematic review and meta-analysis of randomized controlled trials of antifibrinolytic use in adult cardiac surgery patients with recent exposure to aspirin, we found a reduction in both chest-tube drainage and transfusion requirements. We found no evidence of increased adverse events due to antifibrinolytics in this group of patients.

Patients receiving antifibrinolytic therapy had on average 374 ml less chest-tube drainage and were 63% less likely to receive any allogeneic blood products compared with placebo. This effect size is comparable, if not greater, than recent meta-analyses of aspirin naïve or unselected patients.[8 42] A recently published Australasian survey of anaesthesia practice in cardiac surgery indicated more than 40% of patients were operated on for non-elective surgery and therefore unable to stop aspirin prior to surgery.[14] Our review confirms antifibrinolytic therapy is effective at reducing allogeneic transfusion in this context with little evidence for heterogeneity of effect between agents. However, all but one of the studies in our analysis involved patients who would be otherwise considered a low-risk bleeding group and it remains unclear if this efficacy translates into a higher-risk population. The lack of observed heterogeneity of effect between agents is consistent with multiple previous studies reporting no difference in transfusion requirements between aprotinin and lysine analogues.[8 24 35]

The observed 60% reduction in need for surgical re-exploration in the antifibrinolytic group failed to achieve significance but the estimate lacks precision with only 17 events among 461 patients for analysis. The 3.7% event rate is typical of a low-risk population, making any difference between groups more difficult to demonstrate. However, the point estimate of risk reduction is consistent with previous reports[8 29 35] supporting the potential efficacy of these agents for reducing re-exploration in the presence of aspirin.

Two previous studies reported improved outcomes in cardiac surgical patients receiving aspirin either prior to

surgery[13] or within the first 48 h after surgery.[30] However, it remains unclear if the presence of aspirin in combination with an antifibrinolytic at the time of surgery may favourably alter the net balance of procoagulatory and anticoagulatory systems. While this analysis is unable to specifically answer that question, we found no evidence for an increased risk of perioperative thrombotic events in the group exposed to antifibrinolytic therapy in addition to aspirin, but rather a non-significant trend towards risk reduction (RR 0.49, 95% CI 0.21–1.13, P=0.09). Although the upper limit of our 95% confidence interval is consistent with a possible 13% increase in relative risk for antifibrinolytic compared with placebo in aspirin exposed patients, this remains markedly lower than the 30–50% increase in similar events with aprotinin use reported by Mangano and colleagues[31] and further raises the question of a possible protective effect of aspirin at the time of cardiac surgery. However, the small number of these complications make it impossible to draw conclusions from this analysis regarding prothrombotic effects of antifibrinolytics in the presence of aspirin and further large, appropriately designed studies are required to adequately define the effect of this combination therapy on clinically relevant endpoints. We found no difference in the risk of individual adverse events. However, the pooled analysis for MI analysed data from just 361 patients and the event rate was low (<4%) confirming the population was predominantly low-risk. Consequently, small but clinically significant differences in risk may be difficult to detect, making conclusions difficult to draw. Furthermore, none of the included studies reported renal outcomes. While a number of recent studies have reported a significant increase in adverse renal outcomes in patients exposed to aprotinin[8 24 31 43] other large observational studies have disputed this[20] or suggest a more complex relationship than exposure to aprotinin alone.[34] This serves to highlight the importance of including clinically relevant renal endpoints in future studies involving combinations of aspirin and antifibrinolytic agents in cardiac surgery. A pooled analysis of randomized studies in which all patients receive antifibrinolytic therapy, with aspirin exposure as the independent variable, would be required to adequately address the question of a potential protective effect of aspirin. However, few such studies are currently available to support such an undertaking.

The BART study, a large randomized controlled trial of aprotinin and lysine analogues in high-risk cardiac surgery, has recently been published following early termination due to an increased mortality in the aprotinin treatment group.[18] While this has resulted in the cessation of aprotinin marketing it does not lessen the relevance of the current analysis. In fact, the BART study finding of an increased mortality in the aprotinin group, despite an observed reduction in the primary outcome of major haemorrhage, highlights the continued uncertainty surrounding the optimal balance of procoagulatory and anticoagulatory effects in cardiac surgery. Furthermore, although absolute figures are not presented for subgroups, the excess observed mortality risk with aprotinin in the BART study appears to be negated in the group of patients receiving aspirin up until the time of surgery. While it is hoped that the results of a more detailed analysis on this particular subgroup will be published by the investigators, the high-risk nature of the BART population may limit generalizability to the predominantly low-risk population represented in our pooled analysis. However, data from the BART study further support that any difference in efficacy between aprotinin and lysine analogues is modest, even in a high-risk population where any difference in efficacy may be expected to appear most marked. In fact, the observed 18–21% difference in both their primary outcome and the use of any PRBCs is at the margins of equivalence described by Carless and colleagues[9] in a recent meta-analysis to assess comparative efficacy of aprotinin and lysine analogues in cardiac surgery.

The current systematic review may be criticized for pooling clinically heterogeneous studies to arrive at summary effect estimates. However, we believe there is sufficient similarity between trials to allow sensible interpretation of the pooled result. A pooled result of this nature allows an estimate of the average effect of the intervention across each of the various trial designs included and potentially increases applicability of our results. While several of the included studies had methodological flaws, our detailed sensitivity analysis confirmed robust results that were not materially altered with exclusion of such studies. Another criticism may be lack of precision, the result of relatively small numbers of patients included in trials that met our inclusion criteria. Between-study differences for some methods of endpoint detection will add noise and so also limit the precision of our analysis. However, it should not create bias or invalidate the pooled results and this is further supported by the results of our detailed sensitivity analysis. The low adverse event rate is consistent with the predominantly low-risk nature of the participants and also with previous large studies addressing adverse outcome in cardiac surgery patients receiving aspirin which reported a similarly low incidence of both MI and perioperative mortality.[13 30] However this does limit the power of our analysis to detect subtle differences that may exist, particularly in a higher-risk population.

In conclusion, we have observed a reduction in both chest-tube drainage and allogeneic transfusion requirements with antifibrinolytic use in predominantly low-risk cardiac surgical patients receiving aspirin, confirming efficacy of these agents in this setting. Our analysis is consistent with a lack of difference between agents for clinically relevant efficacy outcomes such as transfusion. We found no significant difference between antifibrinolytic and placebo groups in terms of mortality, surgical re-exploration, or other adverse events. However, our study remained underpowered to draw conclusions on these endpoints. While this

study represents a synthesis of the currently available evidence on antifibrinolytics in cardiac surgery patients receiving aspirin, larger studies including higher-risk patients are required to more precisely determine the adverse-event profile associated with antifibrinolytic agents in these patients and to determine the optimal balance of antiplatelet and antifibrinolytic effects in cardiac surgery.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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