

The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a meta-analysis

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ABSTRACT

Background: Because of recent concerns about the safety of aprotinin, we updated our 2007 Cochrane review that compared the relative benefits and risks of aprotinin and the lysine analogues tranexamic acid and epsilon aminocaproic acid.

Methods: We searched electronic databases, including CENTRAL, MEDLINE, EMBASE, Google and Google Scholar for trials of antifibrinolytic drugs used in adults scheduled for cardiac surgery. Searches were updated to January 2008. By comparing aprotinin and the 2 lysine analogues to control, we derived indirect head-to-head comparisons of aprotinin to the other drugs. We derived direct estimates of risks and benefits by pooling estimates from head-to-head trials of aprotinin and tranexamic acid or epsilon aminocaproic acid.

Results: For indirect estimates, we identified 49 trials involving 182 deaths among 7439 participants. The summary relative risk (RR) for death with aprotinin versus placebo was 0.93 (95% confidence interval [CI] 0.69–1.25). In the 19 trials that included tranexamic acid, there were 24 deaths among 1802 participants. The summary RR was 0.55 (95% CI 0.24–1.25). From the risk estimates derived for individual drugs, we calculated an indirect summary RR of death with use of aprotinin versus tranexamic acid of 1.69 (95% CI 0.70–4.10). To calculate direct estimates of death for aprotinin versus tranexamic acid, we identified 13 trials with 107 deaths among 3537 participants. The summary RR was 1.43 (95% CI 0.98–2.08). Among the 1840 participants, the calculated estimates of death for aprotinin compared directly to epsilon aminocaproic acid was 1.49 (95% CI 0.98–2.28). We found no evidence of an increased risk of myocardial infarction with use of aprotinin compared with the lysine analogues in either direct or indirect analyses. Compared with placebo or no treatment, all 3 drugs were effective in reducing the need for red blood cell transfusion. The RR of transfusion with use of aprotinin was 0.66 (95% CI 0.61–0.72). The RR of transfusion was 0.70 (95% CI 0.61–0.80) for tranexamic acid, and it was 0.75 (95% CI 0.58–0.96) for use of epsilon aminocaproic acid. Aprotinin was also effective in reducing the need for reoperation because of bleeding (RR 0.48, 95% CI 0.34–0.67).

Interpretation: The risk of death tended to be consistently higher with use of aprotinin than with use of lysine analogues. Aprotinin had no clear advantages to offset these harms. Either tranexamic acid or epsilon aminocaproic acid should be recommended to prevent bleeding after cardiac surgery.

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Antifibrinolytic drugs, such as the bovine-derived polypeptide aprotinin, have been used to minimize blood loss during cardiac surgery for many years.¹ Meta-analyses of randomized controlled trials have shown convincing and consistent evidence that the use of aprotinin reduces the need for blood transfusion. Some studies have shown that use of aprotinin reduces the need for reoperation because of continued or recurrent bleeding.²⁻⁵ The synthetic lysine derivatives tranexamic acid and epsilon aminocaproic acid have become more popular in recent years because of randomized controlled trials reporting a decrease in blood loss compared with placebo and because they are considerably less costly than aprotinin. However, there is uncertainty about whether lysine analogues are as effective as aprotinin in controlling perioperative blood loss and reducing the need for allogeneic red blood cell transfusion.^{2,6}

Published meta-analyses of placebo controlled trials of aprotinin have found no increase in mortality or vascular thrombosis (a theoretical adverse effect of antifibrinolytic drugs).^{2,3,5} There have also been no increases in mortality or vascular thrombosis in placebo controlled trials of lysine analogues.² The head-to-head randomized controlled trial comparing aprotinin and lysine analogues had few participants; however, there was no difference in the risk of adverse events between aprotinin and lysine analogues.^{2,6} These findings have been criticized because the trials were small, of poor quality, and neither death nor thrombosis was specified as a trial outcome.⁷ As a consequence, there may have been underreporting of these events leading to false negative results.⁷

Several observational studies have suggested that the risk of death, vascular events and renal failure may be greater with the use of aprotinin than with the use of lysine analogues.⁸⁻¹⁰ These initial studies were criticized for inadequate adjustment for known confounding factors, including the type of surgery and patient acuity.^{2,11,12} However, a recent large observational study with careful propensity score matching found a 32% relative increase in hospital mortality with the use of aprotinin compared with the use of epsilon aminocaproic acid.⁹

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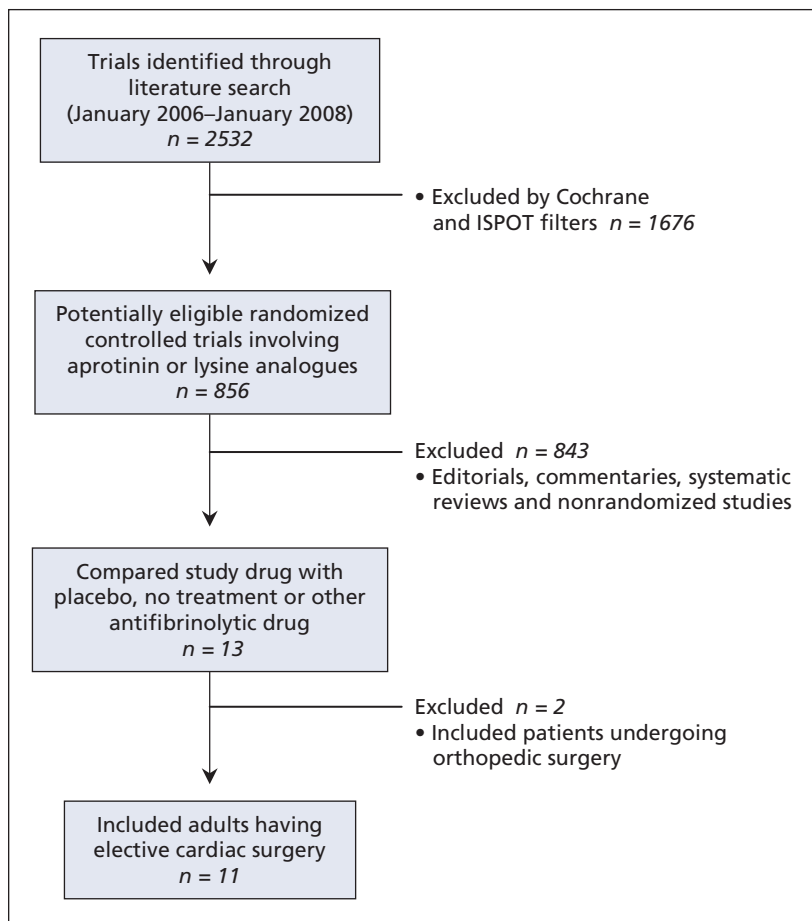


Figure 1: Selection of studies for inclusion in the meta-analysis of the use of aprotinin and lysine analogues in cardiac surgery. Note: ISPO = International Study of Perioperative Transfusion.

New information has been provided by the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) study,¹³ which compared the efficacy and safety of aprotinin and lysine analogues in cardiac surgery patients at high risk of perioperative mortality. This large trial was designed to compare the impact of these drugs with respect to clinically important bleeding outcomes. The trial was stopped prematurely (after recruitment of over 80% of the target sample size) because of an increased number of deaths among the group that received aprotinin. This trial reported a greater than 53% relative increase in the risk of all-cause mortality and a doubling of the risk of death from cardiac causes among patients who received aprotinin compared to those who received a lysine analogue.¹³

In view of this new information and the apparently conflicting results, we have updated our 2007 Cochrane review² of randomized controlled trials of antifibrinolytic drugs. We have concentrated on trials that examined the use of antifibrinolytic drugs in cardiac surgery, which is a subset of the trials included in the 2007 update of our Cochrane review.² Although the primary outcomes were the need for perioperative allogeneic transfusion and reoperation because of bleeding, we have focused on the safety of antifibrinolytic drugs. We

compared the rates of death and vascular occlusion by conducting and updating meta-analyses of direct (head to head) and indirect (common comparator) trials of aprotinin and lysine analogues.^{2,3}

Methods

Search strategy

The methods used in this review have been described elsewhere and followed the approach recommended by the Cochrane Collaboration.^{2,14} This search was an update of the search performed as part of our 2007 Cochrane review² and covered the period from Jan. 1, 2006, to Jan. 31, 2008. We searched CENTRAL, MEDLINE and EMBASE. We searched the Internet using Google and Google Scholar. The search strategy included the following exploded MEDLINE subject heading terms: aprotinin, tranexamic acid, aminocaproic acids, blood transfusion, hemorrhage, and anesthesia. The text-word terms included in the search strategy included: 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\$.

The initial electronic searches of MEDLINE were unrestricted to maximize sensitivity. In subsequent MEDLINE searches, 2 filters were used to restrict the searches and improve the specificity. First, we used the International Study of Perioperative Transfusion (ISPO) filter, which identifies blood transfusion trials. Second, we used a modified version of the Cochrane Collaboration filter, which primarily identifies randomized controlled trials.² These search filters were coupled with the specified medical subject headings and the relevant text-word terms. We also checked the reference lists of relevant reviews, published trials and editorials for potentially relevant trials.

Study selection

We designed the literature search for the Cochrane review to retrieve trials that examined the use of antifibrinolytic drugs in all types of surgery.² In this review, we included only randomized controlled trials that used antifibrinolytic drugs in adults scheduled for nonurgent cardiac surgery. We considered trials eligible for inclusion if they compared antifibrinolytic drugs with placebo, no treatment or each other.

Statistical analyses

Two authors (P.C. and D.F.) independently assessed trial quality and extracted data about deaths and vascular events. Differences between authors were resolved by consensus. We assessed trial quality by grading allocation concealment by the method recommended by the Cochrane Collaboration.¹⁴

We used 2 approaches to pool the data. For head-to-head randomized controlled trials that compared aprotinin with either lysine analogue, data were pooled using a random-effects model. The summary relative risk (RR) and 95% confidence interval (CI) for aprotinin versus the comparator drug was the principal measure of effect. A similar method was used to derive the summary RR from trials that compared aprotinin and either of the lysine analogues (tranexamic acid or epsilon aminocaproic acid) with a placebo or inactive control. We derived indirect estimates of the summary RR for aprotinin compared with each lysine analogue by dividing the summary values in pairwise comparisons of active treatment versus placebo or no treatment. We used the method of Bucher and colleagues,¹⁵ which evaluates the differences between treatment and placebo in 2 sets of clinical trials and preserves the randomization of the originally assigned patient groups.¹⁵ We felt that these additional analyses were justified because the total number of deaths in the placebo or inactive controlled trials was about double the number seen in the direct comparison trials.

There have been concerns that small controlled trials of aprotinin, which are of uncertain quality, may have failed to report uncommon events, such as renal failure, vascular

thrombosis and death, which were not specified outcomes.⁷ Consequently, we carried out sensitivity analyses that included only trials that recruited more than 100 patients in the active treatment arm. We also examined the effect of allocation concealment on the size of the effect of treatment in the larger trials.

Results

Study characteristics

We identified 11 randomized controlled trials^{13,16-25} of the use of antifibrinolytic drugs in cardiac surgery that had not been included in our 2007 Cochrane review.² The retrieval of these trials and aspects of the literature search are described in Figure 1. There was a total of 3054 participants in these 11 trials (Table 1). The details of all other trials included in our analyses are provided in our 2007 Cochrane review.²

This updated review summarizes data from 81 placebo or inactive controlled trials of the use of aprotinin in cardiac surgery, including blood transfusions, with a total of 9139 participants. Of these, 49 (60%) trials with 7439 (81%) participants reported mortality, and 42 (52%) trials with 5884 (64%) participants reported myocardial infarct-

Table 1: Characteristics of the randomized controlled trials of the use of aprotinin and lysine analogues identified by the updated literature search

Study	Year	Country	Type of cardiac surgery	Interventions
Rhydderch et al. ²³	1993	Saudi Arabia	Primary coronary artery bypass graft, valve, atrial septal defect	Pump prime* aprotinin (n = 25) v. placebo (n = 25)
Feindt et al. ¹⁹	1994	Germany	Primary coronary artery bypass graft	High-dose aprotinin† (n = 10) v. placebo (n = 10)
Gott et al. ²⁰	1998	United States	Primary coronary artery bypass graft, valve, re-operation, ascending aorta	Low-dose aprotinin‡ (n = 109) v. leukocyte filtration (n = 112) v. heparin-bonded circuit (n = 67) v. control (n = 112)
Luo et al. ²²	1998	China	Valve replacement	Low-dose aprotinin (n = 10) v. control (n = 10)
Asimakopoulou et al. ¹⁶	2000	United Kingdom	Primary coronary artery bypass graft	High-dose aprotinin (n = 8) v. placebo (n = 10)
Cicekcioglu et al. ¹⁷	2006	Turkey	Primary coronary artery bypass graft	Low-dose aprotinin (n = 24) v. placebo (n = 20)
Kuitunen et al. ²¹	2006	Finland	Primary coronary artery bypass graft and valve	Tranexamic acid§ (n = 15) v. placebo (n = 15)
Murphy et al. ²⁴	2006	Italy	Primary off-pump coronary artery bypass graft	Tranexamic acid§ (n = 50) v. placebo (n = 50)
Wei et al. ¹⁸	2006	China	Primary off-pump coronary artery bypass graft	Low-dose aprotinin (n = 36) v. placebo (n = 40)
Parvizi et al. ²⁵	2007	Iran	Primary coronary artery bypass graft, valve	Low-dose aprotinin (n = 81) v. placebo (n = 81)
Fergusson et al. ¹³	2008	Canada	Repeat coronary artery bypass graft, isolated mitral valve replacement, combined valve, multiple valve replacement and repair, ascending aorta or aortic arch	High-dose aprotinin (n = 781) v. tranexamic acid¶ (n = 770) v. epsilon aminocaproic acid** (n = 780)

*Pump prime = 2×10^5 Kallikrein inhibitor units (KIU) added to the pump prime.

†High dose = 2×10^6 KIU at induction, 2×10^6 KIU added to the pump prime, 2×10^6 KIU or 500 000 KIU/hr continuous infusion during operation.

‡Low dose = less than 3×10^5 KIU total dose.

§Total dose of tranexamic acid 1–4 g.

¶Tranexamic acid regimen: 30 mg/kg loading dose, 16 mg/kg maintenance dose, 2 mg/kg added to the pump prime.

**Epsilon aminocaproic acid regimen: 10 g loading dose, 2 g maintenance infusion.

tions. Mortality was reported in 19 (61%) trials of tranexamic acid, which included a total of 1802 (69%) participants. Thirteen trials, with a total of 3537 participants, compared aprotinin directly with tranexamic acid and re-

ported the number of deaths. Eleven trials, with a total of 3252 participants, recorded myocardial infarctions. In comparison, 15 trials that compared aprotinin and tranexamic acid, with a total of 3528 participants, reported the number

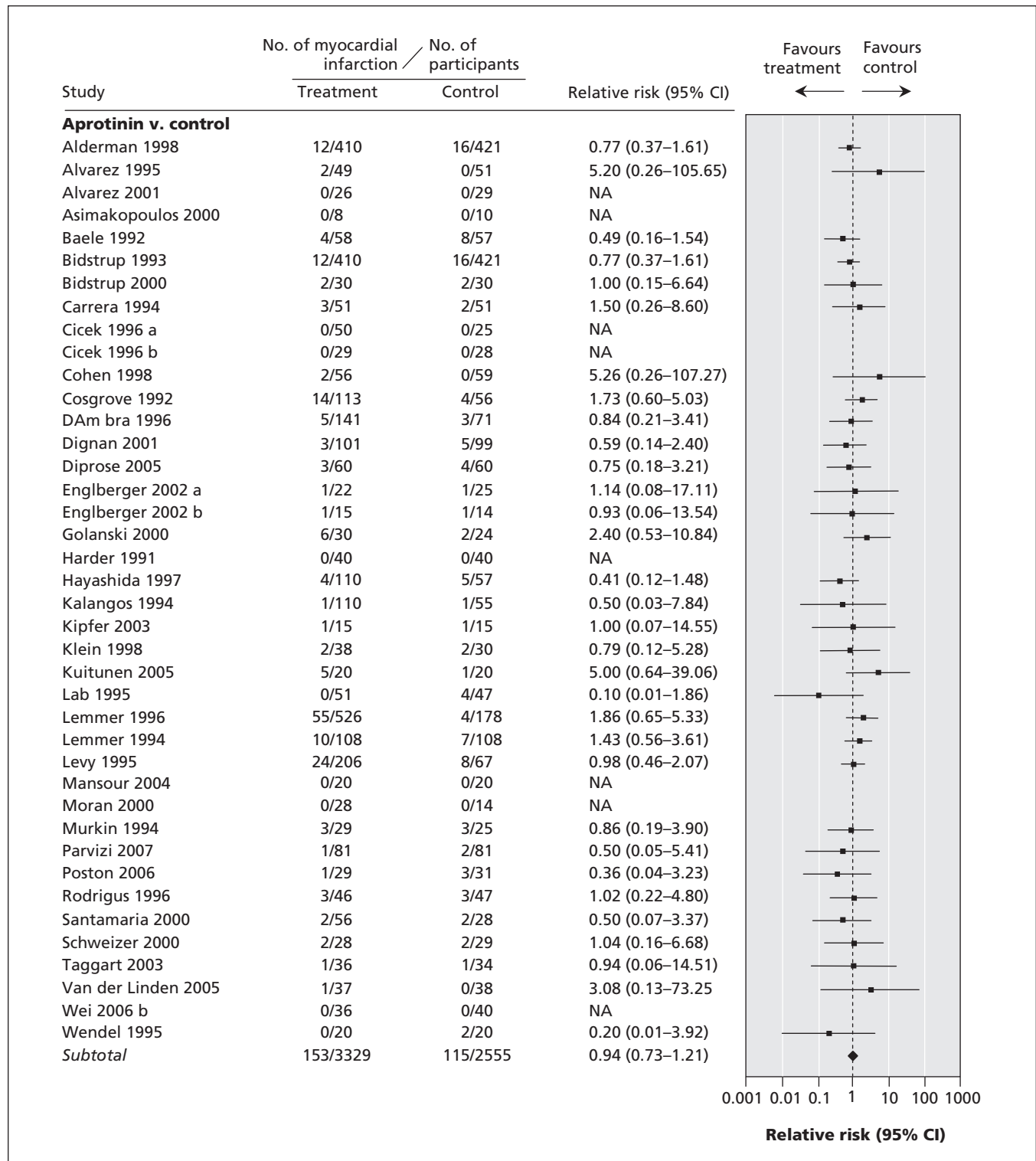


Figure 2: Meta-analyses of myocardial infarction in placebo or inactive randomized controlled trials of the use of aprotinin in cardiac surgery ($I^2 = 0\%$, $Z = 0.46$). References available in Appendix 1 (www.cmaj.ca/cgi/content/full/180/2/183/DC2). Note: CI = confidence interval, NA = not applicable.

of blood transfusions. Thus, the reporting of the number of deaths and myocardial infarctions in the head-to-head trials of aprotinin and tranexamic acid was virtually complete. Data on deaths and myocardial infarction in the trials that included epsilon aminocaproic acid were sparse. From the 5 placebo or inactive controlled trials that included data on deaths (672 patients), there were 10 deaths reported. The head-to-head comparison of epsilon aminocaproic acid with aprotinin was dominated by 1 large trial.¹³

Blood transfusions and reoperation because of bleeding

Compared with no active treatment, all 3 drugs reduced the number of allogeneic blood transfusions (aprotinin RR 0.66, 95% CI 0.61–0.72; tranexamic acid 0.70, 95% CI 0.61–0.80, epsilon aminocaproic acid 0.75, 95% CI 0.58–0.96). These drugs also reduced the need for reoperation because of continued or recurrent bleeding, although this effect was only statistically significant for aprotinin

(aprotinin RR 0.48, 95% CI 0.34–0.67; tranexamic acid 0.67, 95% CI 0.41–1.12; epsilon aminocaproic acid 0.35, 95% CI 0.11–1.17).

Indirect comparisons suggested that there was no difference between aprotinin, tranexamic acid and epsilon aminocaproic acid in reducing the need for allogeneic blood transfusion (aprotinin v. tranexamic acid RR 0.94, 95% CI 0.80–1.11; aprotinin v. epsilon aminocaproic acid RR 1.0, 95% CI 0.81–1.27). The need for reoperation was not significantly reduced with the use of aprotinin compared with the use of tranexamic acid (RR 0.71, 95% CI 0.39–1.31) or epsilon aminocaproic acid (RR 1.37, 95% CI 0.40–4.7).

In contrast, when the use of aprotinin and tranexamic acid or epsilon aminocaproic acid were directly compared, aprotinin reduced the need for allogeneic transfusion (aprotinin v. tranexamic acid RR 0.87, 95% CI 0.72–1.03; aprotinin v. epsilon aminocaproic acid RR 0.81, 95% CI 0.75–0.88). The use of aprotinin also reduced the need for reoperation (aprotinin v. tranexamic acid RR 0.74, 95% CI 0.54–1.02; aprotinin

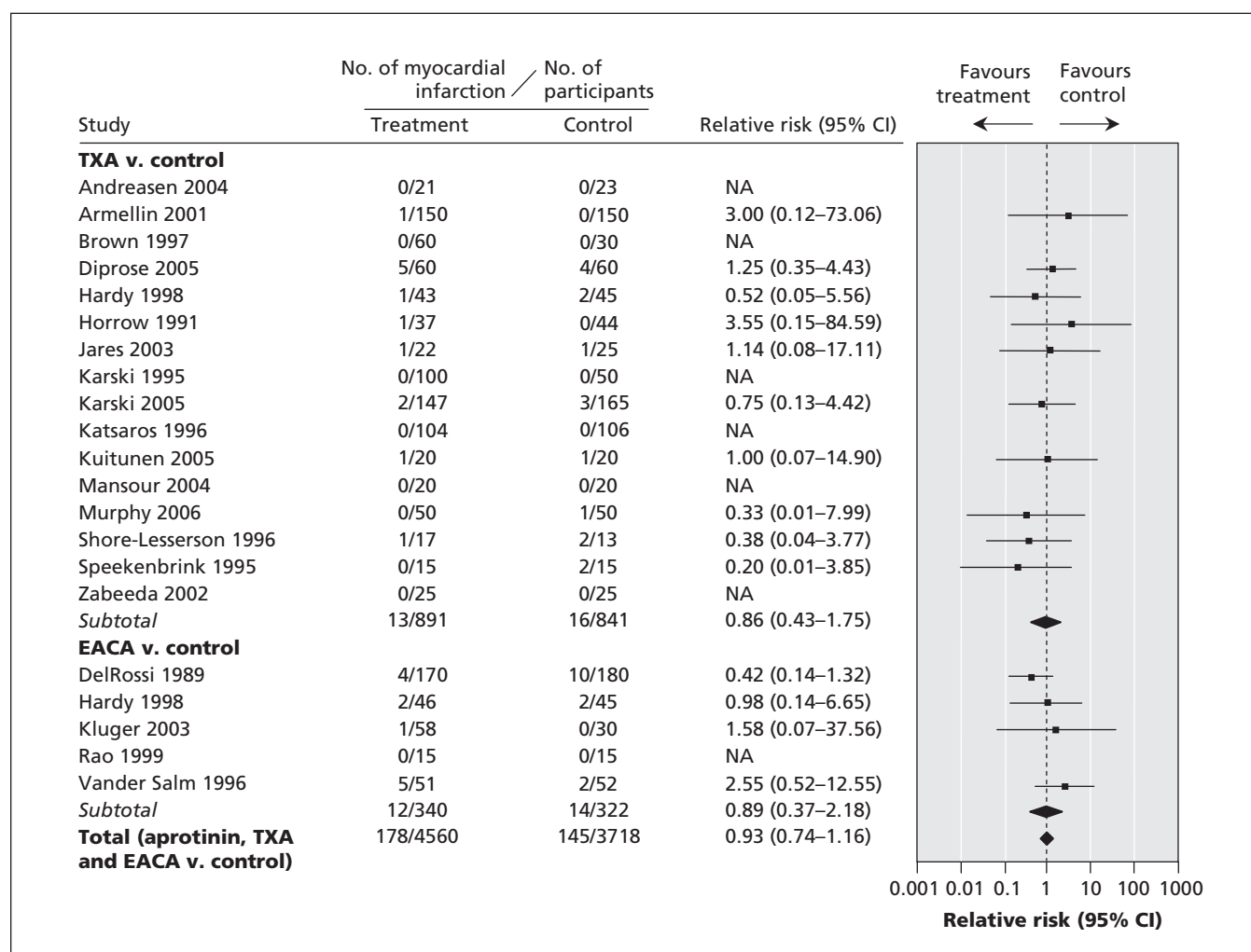


Figure 3: Meta-analyses of myocardial infarction in placebo or inactive randomized controlled trials of the use of tranexamic acid (TXA) and epsilon aminocaproic acid (EACA) in cardiac surgery (TXA v. control $I^2 = 0\%$, $Z = 0.41$; EACA v. control $I^2 = 12.4\%$, $Z = 0.25$; aprotinin, TXA and EACA v. control $I^2 = 0\%$, $Z = 0.66$). References available in Appendix 1 (www.cmaj.ca/cgi/content/full/180/2/183/DC2). Note: CI = confidence interval, NA = not applicable.

tinin v. epsilon aminocaproic acid RR 0.72, 95% CI 0.51–1.03). These direct comparisons were heavily influenced by the inclusion of 1 large trial.¹³

Myocardial infarction

In total, 81 placebo or inactive controlled trials of the use of aprotinin included 9139 participants. Of these, 40 trials reported 268 myocardial infarctions in 5884 participants (summary RR 0.94, 95% CI 0.73–1.21) (Figure 2). The RR from the 16 placebo or inactive controlled trials that included tranexamic acid (1732 participants) was 0.86 (95% CI 0.43–1.75), and the RR from 5 trials that included epsilon aminocaproic acid (662 participants) was 0.89 (95% CI 0.37–2.18) (Figure 3).

In the indirect comparison of aprotinin with tranexamic acid or epsilon aminocaproic acid, the RR for myocardial infarction was 1.1 (95% CI 0.52–2.3) for tranexamic acid and 1.1 (95% CI 0.42–2.7) for epsilon aminocaproic acid.

There were 11 head-to-head trials that compared aprotinin with tranexamic acid, which included a total of 3252 participants and reported 123 myocardial infarctions (Figure 4). There was no difference in the risk of myocardial infarction with the use of aprotinin or tranexamic acid (summary RR 1.0, 95% CI 0.71–1.43). Only 3 trials compared the use of aprotinin and epsilon aminocaproic acid. These trials included a total of 1617 participants and reported 69 myocardial infarctions, and there was no difference in the risk of myocardial infarction (summary RR 1.17, 95% CI 0.74–1.86). These analyses were heavily influenced by the results of the BART study.¹³ This study accounted for 51% of the statistical weight in the comparison of aprotinin and tranexamic acid and 88% of the weight in the comparison of aprotinin and epsilon aminocaproic acid.

Mortality

Forty-nine trials of aprotinin, which included 7439 participants, reported 182 deaths. The summary RR for death with the use of aprotinin compared with the use of a placebo or an inactive control was 0.93 (95% CI 0.69–1.25) (Figure 5). The results were not different when the analysis was restricted to the 11 trials that included more than 100 patients in the aprotinin group (5030 participants total, average of 260 patients in the aprotinin group, 140 deaths total) (summary RR 0.90, 95% CI 0.64–1.28). All but 2 of the larger trials^{26,27} recruited patients at high risk of perioperative mortality (second or subsequent revascularization procedure, valve surgery or combined procedures). The observed effects of aprotinin were not related to trial quality, as reflected in the adequacy of allocation concealment.

There were 31 trials that compared tranexamic acid with placebo, with a total of 2617 participants. Of these trials, 19 (1802 participants) reported 24 deaths (summary RR 0.55, 95% CI 0.24–1.25) (Figure 6). Five trials of epsilon aminocaproic acid included a total of 672 participants with a total of 10 deaths (summary RR 1.65, 95% CI 0.50–5.43) (Figure 6). The indirect estimate of RR was 1.69 (95% CI 0.70–4.10 for aprotinin versus tranexamic acid and 0.56 (95% CI 0.16–1.93) for aprotinin versus epsilon aminocaproic acid.

Thirteen trials compared aprotinin directly with tranexamic acid (3537 participants). There were 107 deaths reported in these trials (Figure 7). The summary RR for death with the use of aprotinin versus tranexamic acid was 1.43 (95% CI 0.98–2.08). Four trials compared the use of aprotinin and epsilon aminocaproic acid. These trials included 1840 participants and reported 85 deaths. The RR for death with the use of aprotinin versus epsilon aminocaproic acid was 1.49 (95% CI 0.98–2.28) (Figure 8). These analyses

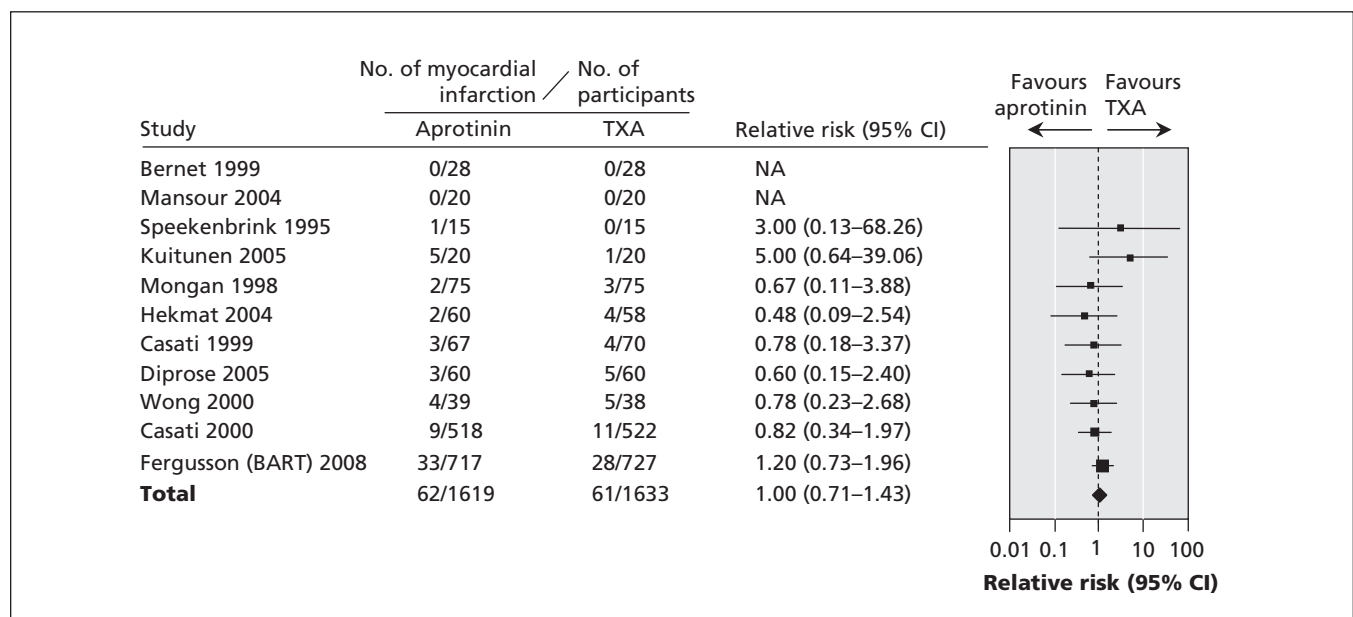


Figure 4: Meta-analyses of myocardial infarction in head-to-head randomized controlled trials of the use of aprotinin and tranexamic acid (TXA) in cardiac surgery ($I^2 = 0\%$, $Z = 0.02$). References available in Appendix 1 (www.cmaj.ca/cgi/content/full/180/2/183/DC2). Note: CI = confidence interval, NA = not applicable.

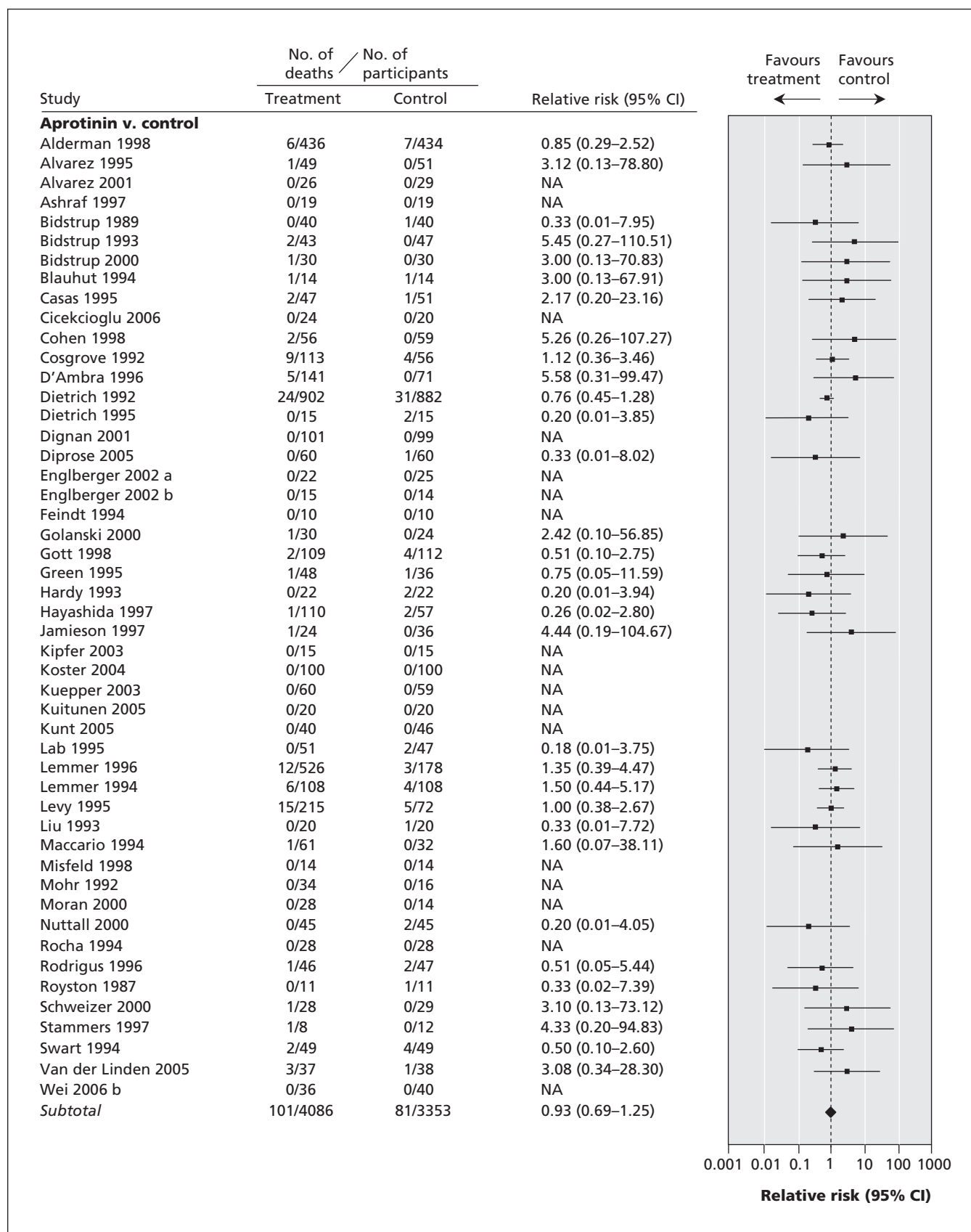


Figure 5: Meta-analyses of mortality in randomized placebo or inactive controlled trials of aprotinin ($I^2 = 0\%$, $Z = 0.49$). References available in Appendix 1 (www.cmaj.ca/cgi/content/full/180/2/183/DC2). Note: CI = confidence interval, NA = not applicable.

were dominated by the inclusion of 1 large trial,¹³ which accounted for 71% of the statistical weight in the comparison of aprotinin and tranexamic acid and 91% in the comparison of aprotinin and epsilon aminocaproic acid. None of the other new trials included in this updated review contributed significant statistical weight to the analysis of the direct comparisons.

We found no significant heterogeneity in any of the meta-analyses of myocardial infarctions or deaths.

Interpretation

We found that there was a moderate increase in the risk of death among patients who received aprotinin. Although all confidence intervals for mortality included 1, the results were consistent in both direct and indirect comparisons. It appears that meta-analyses of direct and indirect comparisons agree that aprotinin increases the risk of death compared to lysine analogues. How-

ever, this conclusion is not as clear if we consider the clinical events that might cause an increase in the risk of death. Although there was an increase in cardiac death among patients who received aprotinin in the BART study, there was no increase in myocardial infarction, stroke or renal failure either in this trial or in our indirect and direct comparison meta-analyses. In addition, both our 2007 review and our current meta-analyses comparing aprotinin with placebo did not show increased mortality.² These meta-analyses also did not show increases in myocardial infarction, stroke, or renal dysfunction or failure.²

Ray and Stein⁷ suggested that the failure to detect an increase in death in the placebo controlled trials of aprotinin in our 2007 meta-analysis may have been because of under-reporting of infrequent events that were not the primary outcomes of small trials. However, deaths were reported in most of these trials, and the mortality analysis included more than 80% of the patients included in all eligible placebo controlled trials of aprotinin. To account for the

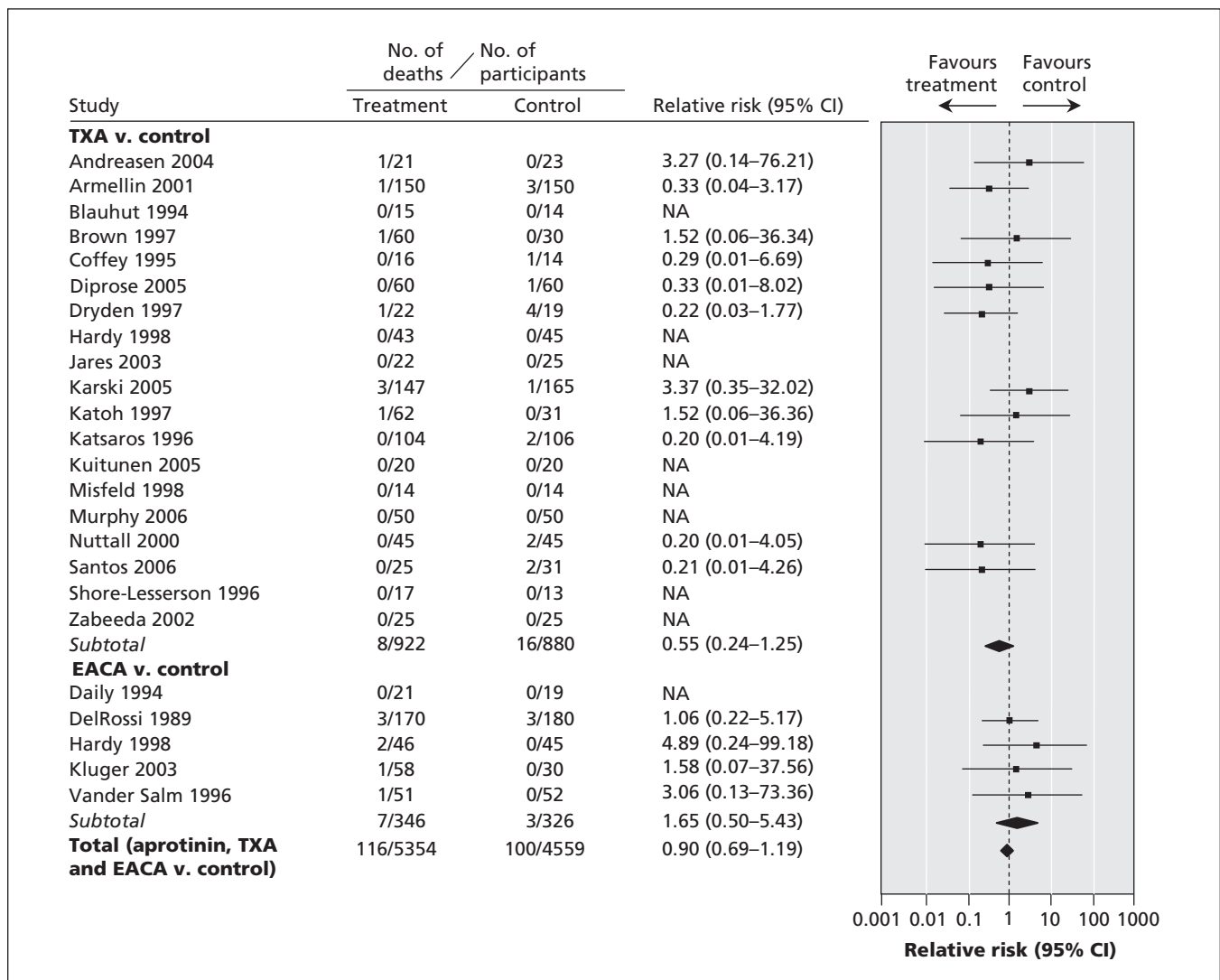


Figure 6: Meta-analyses of mortality in randomized placebo or inactive controlled trials of tranexamic acid (TXA) and epsilon aminocaproic acid (EACA) (TXA v. control $I^2 = 0\%$, $Z = 1.43$; EACA v. control $I^2 = 0\%$, $Z = 0.83$; aprotinin, TXA and EACA v. control $I^2 = 0\%$, $Z = 0.73$). References available in Appendix 1 (www.cmaj.ca/cgi/content/full/180/2/183/DC2). Note: CI = confidence interval, NA = not applicable.

possibility that underreporting of deaths in small trials diluted an adverse effect of aprotinin, we restricted our analysis to the 11 largest placebo controlled trials. These trials included more than 100 patients in the aprotinin arms. All but 2 of these trials included patients at high risk of death (defined as those having their second or subsequent revascularization procedure, valve surgery or combined procedures). Thus, the participants in these trials were similar to those in the recently published BART study. However, the sensitivity analysis of larger trials with predominantly high-risk patients found no increase in death with the use of aprotinin compared to use of an inactive control. We accept

that death after admission to hospital is seldom reported in these trials, and we may have missed a late effect. However, in the largest comparative trial, the separation in survival curves occurred early and the curves appear parallel from 5 to 30 days after surgery.¹³ The observational study by Schneeweiss and colleagues also found an early increase in mortality with use of aprotinin.⁹

The use of tranexamic acid appeared to reduce mortality; however, the effect was not statistically significant. As a consequence, the increased relative risk of death seen in the indirect comparison of aprotinin and tranexamic acid is because of lower mortality with the use of tranexamic acid, rather than

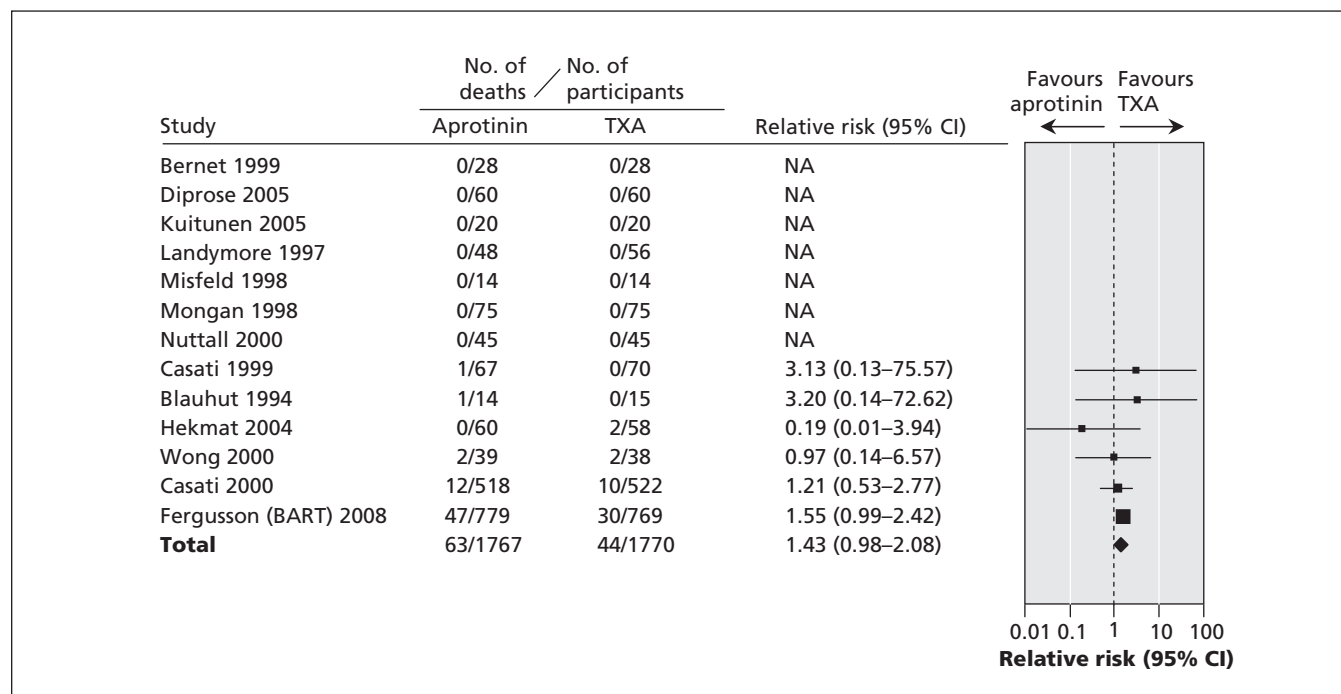


Figure 7: Meta-analyses of mortality in head-to-head randomized controlled trials of the use of aprotinin and tranexamic acid (TXA) in cardiac surgery ($I^2 = 0\%$, $Z = 1.85$). References available in Appendix 1 (www.cmaj.ca/cgi/content/full/180/2/183/DC2). Note: CI = confidence interval, NA = not applicable.

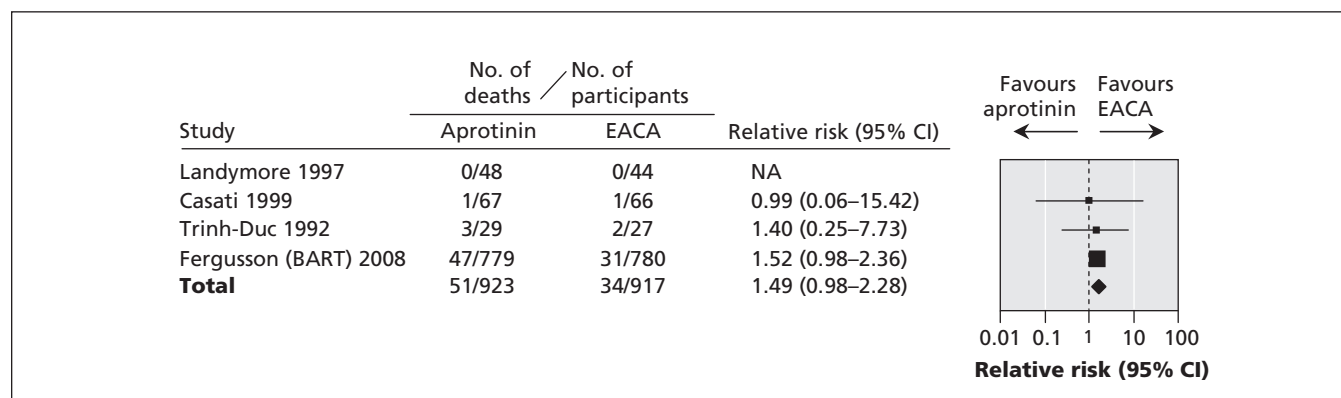


Figure 8: Meta-analyses of mortality in head-to-head randomized controlled trials of the use of aprotinin and epsilon aminocaproic acid (EACA) in cardiac surgery ($I^2 = 0\%$, $Z = 1.86$). References available in Appendix 1 (www.cmaj.ca/cgi/content/full/180/2/183/DC2). Note: CI = confidence interval, NA = not applicable.

an adverse effect of aprotinin. In contrast to aprotinin and tranexamic acid, the indirect and direct comparisons of mortality between aprotinin and epsilon aminocaproic acid gave qualitatively different results (RR 0.56 and 1.49 respectively, neither of which was statistically significant). However, there were only 7 deaths reported in the epsilon aminocaproic acid group and 3 in the control group, which makes the results of the indirect comparisons unstable and unreliable.

In our 2007 Cochrane review,² we addressed the issue of heterogeneity, which will not be discussed at length here. Briefly, we found significant heterogeneity among the trials of antifibrinolytic drugs in cardiac surgery that included bleeding and the need for transfusion as clinical outcomes. However, there was no significant heterogeneity among trials that included clinical outcomes (surgery for re-bleeding, myocardial infarction and death). The heterogeneity for bleeding outcomes is likely because of the subjective nature of clinical judgment about blood loss and need for transfusion against a background of often unblinded trials. Varying drug doses could also have contributed to heterogeneity in bleeding outcomes.

As reported in our Cochrane review,² we found evidence of publication bias in the trials of aprotinin, which led to a probable overestimation of the blood sparing effect of aprotinin. However, we did not find publication bias in relation to the clinical outcomes of death and myocardial infarction.

Several controlled observational studies have examined the putative adverse effects of aprotinin. One large observational study by Mangano and colleagues,²⁸ which found an approximate 50% relative increase in 5-year mortality with use of aprotinin, was criticized for being based on registry data and because of the possibility that selection bias (the use of aprotinin in high-risk patients) might have confounded the association between use of aprotinin and adverse effects.^{7,11,12} Later studies, which appear to have been better controlled than the study by Mangano and colleagues, reported a lower but still elevated risk of death from all causes when the use of aprotinin was compared to lysine analogues or placebo.^{9,10} The overall relative risk for death was similar to that observed in the BART study and to the results of the direct and indirect meta-analyses in this article. However, the latter analyses found no increase in stroke, myocardial infarction or renal failure, in contrast to the results of observational studies.^{10,28}

Limitations

The main limitation of this meta-analysis is the relatively small number of deaths and myocardial infarctions. Even with the addition of the BART study, there were only 63 deaths among patients who received aprotinin and 44 deaths among those who received tranexamic acid in the head-to-head trials. None of these trials was designed to measure changes in the rates of death and thrombosis, and underreporting of adverse events may, in part, account for our previous failure to detect an increase in mortality. Thus, although the trend toward increased mortality among those who received aprotinin compared with those who received a lysine analogue is worrying (and convinced the data safety monitoring board and investigators of the BART study to stop randomly allocating patients

to receive aprotinin), this meta-analysis should not be interpreted as providing definitive evidence that aprotinin increases the risk of death. However, because of evidence that lysine analogues decrease the frequency of transfusion compared with no treatment, as well as their lower cost and the increased mortality with use of aprotinin, it is unlikely that another large randomized trial will be designed to directly compare mortality with use of these drugs.

Conclusions

The conclusions of our updated review conflict with those of our published Cochrane review.² In our 2007 review, we included trials that compared the use of antifibrinolytic drugs in all types of surgery, not just cardiac procedures. Our conclusions about the safety of antifibrinolytic drugs compared with placebo or no treatment remains the same — there was no increase in the risk of death or myocardial infarction in either review.

However, there is an important change in the conclusion based on the results of the direct comparisons of aprotinin, tranexamic acid and epsilon aminocaproic acid. The addition of data from the BART study increased the relative risk of death with the use of aprotinin compared with the use of either tranexamic acid or epsilon aminocaproic acid. The balance of evidence now favours the use of lysine analogues over aprotinin. This represents a shift in the conclusions of our Cochrane review, which was last updated in 2007.² Compared with aprotinin, lysine analogues are almost as effective, are cheaper and do not appear to increase mortality.

This article has been peer reviewed.

Competing interests: Dean Fergusson was a principal investigator of the BART trial. Andreas Laupacis was chair of the BART Data Safety Monitoring Board. None declared for David Henry or Paul Carless.

Paul Hébert, editor-in-chief of *CMAJ*, was a principal investigator of the BART trial. He was not involved in the editorial decision-making process for this article.

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