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RESEARCH

Risks of harms using antifibrinolytics in cardiac surgery: systematic review and network meta-analysis of randomised and observational studies

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Abstract

Objective To estimate the relative risks of death, myocardial infarction, stroke, and renal failure or dysfunction between antifibrinolytics and no treatment following the suspension of aprotinin from the market in 2008 for safety reasons and its recent reintroduction in Europe and Canada.

Design Systematic review and network meta-analysis.

Data sources A Cochrane review of antifibrinolytic treatments was chosen as the starting point for this systematic review. Medline, Embase, and the Cochrane register of trials were searched with no date restrictions for observational evidence.

Study selection Propensity matched or adjusted observational studies with two or more of the interventions of interest (aprotinin, tranexamic acid, epsilon-aminocaproic acid, and no treatment) that were carried out in patients undergoing cardiac surgery.

Data analysis Network meta-analysis was used to compare treatments, and odds ratios with 95% credible intervals were estimated. Meta-analyses were carried out for randomised controlled trials alone and for randomised controlled trials with observational studies.

Results 106 randomised controlled trials and 11 observational studies (43 270 patients) were included. Based on the results from analysis of randomised controlled trials, tranexamic acid was associated on average with a reduced risk of death compared with aprotinin (odds ratio 0.64, 95% credible interval 0.41 to 0.99). When observational data were incorporated, comparisons showed an increased risk of mortality with aprotinin on average relative to tranexamic acid (odds ratio 0.71, 95% credible interval 0.50 to 0.98) and epsilon-aminocaproic acid (0.60, 0.43 to 0.87), and an increased risk of renal failure or dysfunction on average relative to all comparators: odds ratio 0.66 (95% credible interval 0.45 to 0.88) compared with no treatment, 0.66 (0.48 to 0.91) versus tranexamic acid, and 0.65 (0.45 to 0.88) versus epsilon-aminocaproic acid.

Conclusion Although meta-analyses of randomised controlled trials were largely inconclusive, inclusion of observational data suggest concerns remain about the safety of aprotinin. Tranexamic and epsilon-aminocaproic acid are effective alternatives that may be safer for patients.

Introduction

In 2008, aprotinin (Trasylol; Bayer, Germany), an antifibrinolytic drug used to reduce blood loss and exposure to transfusion in patients undergoing cardiac surgery, was voluntarily withdrawn by the manufacturer. This decision occurred after the early stopping of the Blood conservation using Antifibrinolytics in a Randomized Trial (BART) study, a trial comparing aprotinin with a pair of lysine analog drugs (tranexamic acid and epsilon-aminocaproic acid) owing to concerns of an increased risk of deaths related to aprotinin.[1] Since then, tranexamic acid and epsilon-aminocaproic acid have been used to manage patients at risk of bleeding from cardiac surgery. Some have suggested that the withdrawal of aprotinin has been detrimental to patient care because of increased adverse outcomes from surgery and increased use of blood products,[2-4] whereas others have suggested a relatively minimal change in clinical practice.[5]

Most recently the European Medicines Agency has recommended the lifting of the suspension of aprotinin for use in cardiac surgery.[6] In September of 2011, following

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Supplementary materials

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deliberations by an expert committee convened by Health Canada, aprotinin was made available again to clinicians. Health Canada has requested additional warnings, taking note of studies that have found an increased risk of kidney problems and death associated with use of non-indicated aprotinin. Given the history of aprotinin, the extent to which it may be used by clinicians is unclear, with recent surveys of cardiac anaesthesiologists illustrating divided opinions.[2]

To explore further the relative safety of aprotinin compared with alternative treatments, we carried out network meta-analyses for the outcomes of death, myocardial infarction, stroke, and renal failure or dysfunction using all available evidence. We used data from both randomised controlled trials and observational studies, and to permit simultaneous comparisons between all treatments we made use of network meta-analysis.

Methods

Inclusion criteria

We sought studies that enrolled patients undergoing cardiac surgery using cardiopulmonary bypass. No restrictions were set for surgical history (primary or repeat), urgency (elective or emergent), or type (coronary artery bypass graft, valve, or other cardiac procedures). We considered randomised controlled trials to be eligible for inclusion if at least two of the following treatments of interest were compared: aprotinin, tranexamic acid, epsilon-aminocaproic acid, or no treatment (including placebo). No restrictions on drug dose were applied. We only chose studies reporting results for death, myocardial infarction, stroke, or renal failure or dysfunction. Propensity matched and adjusted observational studies were also included. Although observational studies cannot be considered to be as free of confounding and selection bias as randomised controlled trials, including data from them can help to offset limitations of analysing rare outcomes such as harms using only randomised controlled trials,[7-9] and may also help increase generalisability.

Study identification

Given its rigorous methods, we chose the most recent update of the Cochrane review[10] of antifibrinolytic treatments as the starting point for this systematic review; we removed trials carried out in patient populations other than those requiring cardiac surgery. This review was based on a search of three databases using a peer reviewed search strategy, with independent screening and data collection by two reviewers. We also carried out a literature search of Medline, Embase, and the Cochrane register of controlled trials to find trials or propensity matched or propensity adjusted observational studies not included in the Cochrane review (see supplementary tables 1 and 2 for the search strategy). Two researchers (BH, DM) screened citations independently for further studies and classified them as relevant or irrelevant.

Data collection

Data on outcome and quality assessment from randomised controlled trials in the 2011 Cochrane review were subjected to double data extraction, but for the purposes of this study were extracted by one researcher (BH). The same reviewer was also responsible for extraction of data from additional studies. Where observational studies consisted of analyses based on propensity matched samples as well as larger, unmatched samples, we collected the information from the propensity matched sample. The Cochrane review used as a basis for our work assessed trial quality using the Cochrane risk of bias scale, which considers sequence generation, allocation concealment, and blinding. The Newcastle Ottawa scale[11] was used to assess the quality of observational studies; for cohort studies this scale assigns points for representativeness of the exposed and control groups, adequate ascertainment of exposure, clarity of the absence of outcomes at study start, comparability of groups based on study design and analysis, blinded assessment or record linkage to confirm study outcomes, sufficiency of follow-up duration to observe the outcomes of interest, and reporting of a sufficiently low withdrawal rate that would not threaten a great risk of bias to the study. A maximum of nine points can be assigned.

Evidence synthesis

We used a two stage approach to evidence synthesis: in the first stage we used data from randomised controlled trials alone and in the second stage we added data from propensity matched or adjusted studies, allowing for the assessment of the additional contribution from observational studies. Sensitivity analyses were carried out wherein we removed randomised controlled trials from the network of treatments that were not scored as having both adequate allocation concealment and double blinding in the Cochrane review[10], removed studies that used propensity scores in ways other than matching of patients in competing intervention groups (such studies may have greater residual confounding compared with propensity matched studies), and where we considered these two restrictions simultaneously.

For each of the four clinical outcomes of interest (death, myocardial infarction, stroke, renal failure or dysfunction) we carried out the mixed treatment comparisons approach for network meta-analysis.[12] To estimate posterior densities for unknown variables we used Markov Chain Monte Carlo methods through WinBUGS software (version 1.4.3, MRC Biostatistics Unit, Cambridge, UK). Given that the safety of aprotinin was of primary interest, we chose aprotinin as the reference group for all analyses. We used vague prior distributions throughout, allowing the data to drive inferences.

A hierarchical model was used to examine the four clinical outcomes of interest. For each outcome, the total number of events in the j^{th} study for intervention k is denoted by r_{jk}, and the corresponding number of participants is given by n_{jk}. Together, this data gives information on the probability of an event (p_{jk}) for each intervention group in each included study. A logistic regression model was used wherein each study is assigned a reference intervention arm, b_j, and a corresponding log-odds for the outcome denoted by μ_j. Based on this set-up, we assumed a log-odds ratio (denoted by $\varphi_{j,k}$) for intervention k relative to intervention b_j to follow a normal density with mean log-odds ratio (d_k-d_{bj}), and between study standard deviation, τ, where d_k is the mean log-odds ratio of outcome for intervention compared with usual care (so that d_1=0). The model can be expressed as log-odds($p_{j,k}$)=μ_j if intervention b_j, and log-odds($p_{j,k}$)=μ_j if intervention k; $\varphi_{j,k}$ ~Normal((d_k-d_{bj}), τ^2). The between study variability of treatment effects was assigned a uniform (0, 2) prior density and assumed to be the same for all pairwise comparisons.

As recommended by previous researchers, when carrying out meta-analyses we excluded trials involving 0 events in all treatment arms.[13] All results are reported with point estimates and 95% credible intervals for the average treatment effects of interest; we also estimated 95% predictive intervals for all comparisons to assess the intervention effects in a single study setting, as described elsewhere (see supplementary table 4 for

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this information).[14 15] We estimated the average ranking of each treatment, the probability of each odds ratio being larger than 1, and the probability of a treatment being associated with the lowest risk of harm. To present the respective probabilities for each combination of outcome and intervention we used bar plots and cumulative probability plots (see supplementary figures 1 and 2).[16] To assess model convergence we used trace plots and the Brooks-Gelman-Rubin statistic.[17] For each analysis we fit two chains, each employing 50 000 or more iterations, with a burn-in of 50 000 iterations. We assessed model fit by comparing the residual deviance from each model with the total number of unconstrained data points (that is, the number of treatment arms across all studies) to ensure these quantities were about equal.[13] When carrying out network meta-analysis, checking consistency of direct and indirect data is of interest, as large differences related to the type of evidence may suggest the presence of important differences between data sources. We assessed consistency between direct and indirect evidence as described previously, which involved comparison of deviance information criteria between our primary mixed treatment comparison models and alternative node splitting models.[18] In the supplementary material we also report estimates from meta-analyses of head to head data only for comparison purposes to further enable consideration of inconsistencies between direct and indirect evidence.

Results

Overall, 106 eligible randomised controlled trials were identified from the Cochrane review (see supplementary list). The remaining 67 trials in patients undergoing cardiac surgery were excluded because they did not report data on relevant harms. The electronic literature search identified 96 citations for review (155 before removal of duplicates); 15 of these were chosen for full text screening and 11 were retained for final inclusion.[19-29] All were observational studies and no additional randomised controlled trials were included. Two studies were of interest, but could not be acquired: one of aprotinin compared with tranexamic acid and with epsilon-aminocaproic acid (90 patients) and one of aprotinin compared with tranexamic acid (243 patients).[30 31] Figure 1⇓ presents a summary of the study identification process. Sample sizes from individual trials were generally small (median 80, range 18-2329; 63.2% enrolled fewer than 100 patients).

Nine observational studies used propensity matching algorithms[20 21 23-29] and two were propensity adjusted.[19 22] In our analyses, using propensity matched samples where available, these studies contributed data from an additional 26 577 participants (median 1544, range 438-9598).

Figure 2⇓ presents a diagram of studies and treatments for this systematic review, and table 1⇓ presents the evidence available for each clinical outcome (see supplementary table 3 for characteristics of the newly included studies). Overall, the quality of the randomised studies included in the Cochrane review[10] was judged partially limited by a lack of transparency in the reporting of the generation of allocation sequences (78 were judged adequate, 2 inadequate, and 172 unclear), although double blinding was considered adequate in 170/252 of trials. Among the randomised controlled trials in patients undergoing cardiac surgery included in this review, 35 had adequate allocation concealment and were double blinded. Based on the Newcastle Ottawa scale, the included observational studies were judged to be of high quality for measures to protect against selection bias and detection bias (see supplementary table 3 for a summary of the quality assessment findings of observational studies).

Outcomes

Mortality

In total, 82 randomised studies (14 773 patients) were included in the analysis. Compared with aprotinin, on average tranexamic acid was associated with a reduced risk of mortality (odds ratio 0.64, 95% credible interval 0.41 to 0.99), whereas epsilon-aminocaproic acid and no treatment were associated with wide and inconclusive 95% credible intervals (table 2⇓). The corresponding credible intervals for all other pairwise treatment comparisons were wide and inconclusive (see supplementary table 5 for analyses restricted to randomised controlled trials), although on average tranexamic acid was associated with a potentially important reduced risk of death relative to no treatment (odds ratio 0.64, 95% credible interval 0.41 to 1.02). Tranexamic acid was estimated to have a 73.4% probability of being the lowest risk of treatment, followed by epsilon-aminocaproic acid (24.0%), aprotinin (0.9%), and no treatment (1.7%). The between study standard deviation for this analysis was estimated to be 0.23.

When eligible cohort studies were incorporated into the analysis (11 studies and 26 577 patients), credible intervals narrowed. Relative to aprotinin, tranexamic acid (odds ratio 0.71, 95% credible interval 0.50 to 0.98) and epsilon-aminocaproic acid (0.60, 0.43 to 0.87) were both on average associated with a reduction in risk of mortality compared with aprotinin; the comparison with no treatment remained inconclusive (table 2, fig 3⇓). Epsilon-aminocaproic acid was associated on average with a reduced risk of death relative to no treatment (odds ratio 0.66, 95% credible interval 0.45 to 1.00), whereas the comparisons between tranexamic acid and no treatment as well as tranexamic acid and epsilon-aminocaproic acid were inconclusive (fig 3). Ranking probabilities were most favourable for epsilon-aminocaproic acid and tranexamic acid (table 2 and supplementary figure 1a), and the odds ratios comparing each of these treatments with aprotinin were associated with probabilities of 99.0% and 98.2% of lower mortality. Prediction intervals from all pairwise comparisons based on the available data were wide and included 1 (see supplementary table 4), suggesting that observed increases in risk may not be present in all settings or patients. The between study standard deviation for this analysis was estimated to be 0.32.

Myocardial infarction

Overall, 67 randomised controlled trials (12 390 patients) were included for analysis. Compared with aprotinin, all other treatments were associated with wide and inconclusive 95% credible intervals (table 2). When all pairwise comparisons among the three alternative interventions were reviewed, none fully excluded a possible null difference (see supplementary table 5). Epsilon-aminocaproic acid was associated with a 69.2% probability of being associated with the lowest risk of myocardial infarction, followed by tranexamic acid (20.1%), aprotinin (8.9%), and no treatment (1.9%). The between study standard deviation for this analysis was estimated to be 0.18.

Addition of data from eligible cohort studies (eight studies, 14 304 patients) resulted in narrowed 95% credible intervals. Comparisons of the three alternatives with aprotinin were inconclusive (table 2 and fig 4⇓); epsilon-aminocaproic acid approached a conclusive benefit (odds ratio 0.78, 95% credible interval 0.60 to 1.03), whereas the probabilities in favour of epsilon-aminocaproic acid and tranexamic acid were estimated

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to be 96.6% and 86.2% (table 2). Comparisons among the three remaining alternatives were also inconclusive, although epsilon-aminocaproic acid approached an average benefit compared with no treatment (odds ratio 0.80, 95% credible interval 0.60 to 1.04; table 2 and fig 4). Ranking probabilities were most favourable for epsilon-aminocaproic acid (table 2 and supplementary figure 1b). Prediction intervals from all pairwise comparisons based on the available data were also wide and included 1 (see supplementary table 4). The between study standard deviation for this analysis was estimated to be 0.17.

Stroke

Overall, 40 randomised controlled trials (7421 patients) were included for analysis. Compared with aprotinin, all of the alternative treatments were associated with wide and inconclusive 95% credible intervals (table 2), and this remained true for all possible comparisons among the three remaining alternatives (see supplementary table 5). Epsilon-aminocaproic acid was associated with the largest probability of being the safest treatment (59.6%), followed by aprotinin (15.7%), tranexamic acid (13.2%), and no treatment (11.5%) (table 2). The between study standard deviation for this analysis was estimated to be 0.67.

Changes occurred in summary estimates when observational data were added (10 studies and 24 585 patients), but clinical interpretations were relatively unchanged (table 2 and fig 5⇓). Compared with aprotinin, all three alternatives were associated with estimates that failed to rule out a null difference, and this was also true for all possible pairwise comparisons among them. Ranking probabilities (table 2 and supplementary figure 1c) suggested tranexamic acid and epsilon-aminocaproic acid to be the two safest treatments (probabilities to be safest were 52.7% and 33.6%, whereas probabilities to be the second safest were 28% and 31%, respectively). Prediction intervals from all pairwise comparisons based on the available data were wide and included 1 (see supplementary table 4). The between study standard deviation for this analysis was estimated to be 0.54.

Renal failure or dysfunction

Overall, 28 randomised controlled trials (7656 patients) were included for analysis. Compared with aprotinin, all of the alternatives were found to be associated with favourable average summary estimates but with wide and inconclusive 95% credible intervals (table 2), and the same was true for all possible pairwise comparisons between the three alternatives (see supplementary table 5). The estimated probabilities that aprotinin could be associated with greater renal harms relative to no treatment, tranexamic acid, and epsilon aminocaproic acid were estimated to be 77.8%, 73.2%, and 82.6%. Epsilon-aminocaproic acid was associated with the largest probability of being safest (42.9%), followed by tranexamic acid (24.2%) and no treatment (24.0%). The between study standard deviation for this analysis was estimated to be 0.39.

When observational data were added (nine studies, 23 903 patients), the average summary estimates as well as corresponding clinical interpretations changed. Compared with aprotinin, no treatment (odds ratio 0.66, 95% credible interval 0.45 to 0.88), tranexamic acid (odds ratio 0.66, 95% credible interval 0.48 to 0.91), and epsilon-aminocaproic acid (odds ratio 0.65, 95% credible interval 0.45 to 0.88) were associated with summary average effects that represented reductions in the risk of renal failure or dysfunction (table 2 and fig 6⇓), whereas all possible pairwise comparisons between the three alternatives were inconclusive (fig 6). Exploration of ranking probabilities showed comparable likelihoods of being the safest therapy for epsilon-aminocaproic acid (36.5%), no treatment (33.5%), and tranexamic acid (30.3%), and the same was true for corresponding probabilities of being second most and third most safe (see supplementary figure 1d). Prediction intervals from all pairwise comparisons based on the available data were wide and included the null value of 1 (see supplementary table 4), suggesting that observed increases in risk may not be present in all settings or patients. The between study standard deviation for this analysis was estimated to be 0.30.

Sensitivity analyses, model fit, and assessment of inconsistency

Restriction of studies to all high quality observational studies and randomised trials reduced the number of studies in the analyses of mortality to 41 (33 262 patients), myocardial infarction to 31 (n=19 407), stroke to 28 (n=28 835), and renal failure or dysfunction to 23 (n=29 274). In these analyses, point estimates for all outcomes consistently showed equivalent or stronger benefits for no treatment, tranexamic acid, and epsilon-aminocaproic acid compared with aprotinin, although with some increase in uncertainty owing to the reduced number of studies (see supplementary table 6). On average, the conclusive benefit on mortality in favour of epsilon-aminocaproic acid remained present, as did benefits regarding renal failure or dysfunction for all three comparators.

Analyses carried out to explore the effect of excluding the two studies[19 22] that used propensity scores either as a variable in a multivariable model[19] or for data stratification[22] were generally associated with improvement of the risk profile for aprotinin (see supplementary table 6). However, a conclusive mortality benefit favouring epsilon-aminocaproic acid compared with aprotinin remained, and tranexamic acid also maintained its conclusive benefit regarding the occurrence of renal failure or dysfunction. When both low quality randomised controlled trials and propensity adjusted studies were excluded simultaneously, findings were largely similar to those observed in this analysis.

The residual deviances from all analyses in this review were comparable to the number of unconstrained data points in all cases, suggesting adequate model fit (see supplementary table 7). When deviance information criteria were assessed from node splitting models, which were fit to assess the potential for inconsistency between direct and indirect evidence, values were comparable to those observed with primary analyses, suggesting no improvement in model fit. Estimates from pairwise meta-analyses of head to head evidence were comparable to those generated from network meta-analysis (see supplementary table 8).

Discussion

Following withdrawal from the market in 2008 because of concerns about safety, aprotinin has been reintroduced in both Europe (2012) and Canada (2011). Given these recent developments, we considered a comprehensive synthesis of all evidence to be worthwhile. Based on our findings from network meta-analyses, synthesis of evidence from randomised trials alone generally produced inconclusive estimates of the relative risks of death, myocardial infarction, stroke, or renal failure or dysfunction associated with using the antifibrinolytic aprotinin in cardiac surgery compared with no treatment, tranexamic acid, and epsilon-aminocaproic acid (although tranexamic acid was associated with a lower risk of mortality). Subsequent to inclusion of data from observational studies, our summary

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estimates suggested aprotinin to be associated on average with clinically important increased risks of mortality and renal failure or dysfunction in our work, although corresponding prediction intervals suggest that variations in patients' comorbidities, surgical history, or type of procedure play a part. From a decision making perspective, although several of the summary estimates from our meta-analyses were associated with inconclusive credible intervals, corresponding probabilities presented in this work can be used to help inform choices.[16] In most cases the active alternatives of tranexamic acid and epsilon-aminocaproic acid were associated with increased safety on average. To our knowledge, this work represents the first application of network meta-analysis to combine data from randomised and observational studies to assess drug safety, an approach that may be particularly helpful for assessment of data on harms. Such an approach can be implemented sequentially to assess how observational evidence contributes to overall findings.

How the return of aprotinin to the market in Europe and Canada will be received by cardiac surgeons and anaesthesiologists is unclear. Several authors have addressed whether practice has changed since Bayer stopped the marketing of aprotinin, and whether those changes have been associated with expected changes in clinical outcomes. One review[32] summarised several such studies that explored the implications associated with the use compared with non-use of aprotinin after its withdrawal.[2-4 28] Based on these studies, the reviewer noted that while recent reports have documented increases in lengths of hospital stay, extent of bleeding, rates of reoperation, and usage of other costly blood products (including fresh frozen plasma and factor VII), reports suggesting improvements in patients' clinical outcomes and reductions in costs are still lacking. In contrast, researchers[5] recently suggested that withdrawal of aprotinin had little impact on practice or patient outcomes, noting that their research showed there had been no important changes in the proportion of patients receiving a red blood cell transfusion, and that there were no changes in rates of reoperation, readmission to hospital within one month, or 30 day mortality.

Comparisons with other studies

Meta-analyses of aprotinin in cardiac surgery have clearly shown the benefits of this drug compared with placebo for reduction of blood loss and exposure to transfusion.[10 33-35] However, our data suggest the potential for increased risk of renal dysfunction or failure, and thus the risk-benefit ratio of aprotinin is unclear. Systematic reviews have shown clinical benefits of the drug alternatives tranexamic acid and epsilon-aminocaproic acid[10 33 36]; whereas their impacts on blood loss and exposure to transfusion may be smaller than those of aprotinin (the effect of epsilon-aminocaproic acid perhaps being smallest), they remain clinically important, and findings from this systematic review suggest more favourable safety profiles for both treatments. Given these findings, use of tranexamic acid or epsilon-aminocaproic acid in place of aprotinin may prove more clinically attractive to physicians given the potential benefits for increased patient safety.

Strengths and limitations of this review

Our review has limitations. Although observational studies increased our sample sizes and in some comparisons led to strong results, even propensity adjusted and matched studies may have residual confounding. Raw data from two propensity adjusted studies were used in place of their adjusted odds ratios. We addressed this concern by carrying out a sensitivity analysis with these studies omitted, and still observed important differences between treatments. Additionally, some of the observational research captured varied doses of the treatments studied. Data extraction for articles was done by one reviewer; however, in the case of most included studies derived from the Cochrane review, data had previously been collected in duplicate.

Conclusions

Results from our network meta-analyses of randomised and observational studies suggest that on average concerns about the safety of aprotinin use in patients undergoing cardiac surgery still remain. Clinicians need to be mindful of the benefits and risks surrounding the use of aprotinin in their practice, as alternative drugs are available that may offer greater safety to their patients.

Contributors: BH, LJ, and DF developed the study design. All authors interpreted the data and critically reviewed drafts of the manuscript. BH and CDM carried out the review of citations from the literature search for study selection. BH collected and analysed the data and prepared the manuscript. BH is guarantor.

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Ethical approval: Not required.

Data sharing: No additional data available.

1 Fergusson DA, Hebert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 2008;358:2319-31.
2 McMullan V, Alston RP. The effect of the suspension of the license for aprotinin on the care of patients undergoing cardiac surgery: a survey of cardiac anesthesiologists' and surgeons' opinions in the United Kingdom. *Cardiothorac Vasc Anesth* 2010;24:418-21.
3 Sniecinski RM, Chen EP, Makadia SS, Kikura M, Bolliger D, Tanaka KA. Changing from aprotinin to tranexamic acid results in increased use of blood products and recombinant factor VIIa for aortic surgery requiring hypothermic arrest. *J Cardiothorac Vasc Anesth* 2010;24:959-63.
4 Strouch Z, Drum M, Chaney M. Aprotinin use during cardiac surgery: recent alterations and effects on blood product utilization. *J Clin Anesth* 2009;21:502-7.
5 Bennett-Guerrero E, Song HK, Zhao Y, Ferguson TB Jr, Gammie JS, Peterson ED, et al. Temporal changes in the use of blood products for coronary artery bypass graft surgery in North America: an analysis of the Society of Thoracic Surgeons Adult Cardiac Database. *J Cardiothorac and Vasc Anesth* 2010;24:814-6.
6 European Medicines Agency. European Medicines Agency recommends lifting of suspension of aprotinin. 2012. www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/02/WC500122914.pdf.
7 Bradburn M, Deeks J, Berlin J, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-anaytical methods with rare events. *Stat Med* 2007;26:53-77.
8 Sweeting MJ, Sutton A, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med* 2004;23:1351-75.
9 Sutton A, Cooper N, Lambert P, Jones D, Abrams K, Sweeting M. Meta-analysis of rare and adverse event data. *Expert Rev Pharmacoecon Outcomes Res* 2002;2:367-79.
10 Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2011;16(3):CD001886.
11 Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2012. www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
12 Lu G, Ades A. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004;23:3105-24.
13 Dias S, Welton N, Sutton A, Ades A. NICE DSU Technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. Last updated Aug 2011. www.nicedsu.org.uk. 2011.
14 Riley R, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;342.d549.
15 Dias S, Sutton AJ, Welton NJ, Ades AE. NICE DSU Technical support document 3: heterogeneity: subgroups, meta-regression, bias and bias-adjustment. Last updated April 2012. www.nicedsu.org.uk. 2011.
16 Salanti G, Ades AE, Ioannidis J. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64:163-71.

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What is already known on this topic

After suspension from the market in 2008 related to trial findings, aprotinin has been put back on the market in Canada (2011) and Europe (2012)

Important observational evidence about the safety of antifibrinolytics warrants consideration in syntheses of the evidence to study the safety of these drugs

What this study adds

Although meta-analyses of randomised controlled trials were largely inconclusive, inclusion of observational data suggest concerns remain about the safety of aprotinin in cardiac surgery

Tranexamic and epsilon-aminocaproic acid are effective alternatives that may be safer for patients

17 Gelman A, Carlin JB, Stern HS, Rubin DB. Bayesian data analysis, 2nd edn. Chapman and Hall, 2003.
18 Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010;29:932-44.
19 Mangano DT, Tudor JC, Dietzel C. The risk associated with aprotinin in cardiac surgery. *N Engl J Med* 2006;354:353-65.
20 Karkouti K, Beattie WS, Dattilo KM, McCluskey SA, Ghannam M, Hamdy A, et al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion* 2006;46:327-38.
21 Karkouti K, Wijeysundera D, Yau T, McCluskey S, Tait G, Beattie W. The risk-benefit profile of aprotinin versus tranexamic acid in cardiac surgery. *Anesth Analg* 2010;110:21-9.
22 Olenchock SA Jr, Lee PH, Yehoshua T, Murphy SA, Symes J, Tolis G Jr. Impact of aprotinin on adverse clinical outcomes and mortality up to 12 years in a registry of 3,337 patients. *Ann Thorac Surg* 2008;86:560-6; discussion 566-7.
23 Shaw AD, Stafford-Smith M, White WD, Phillips-Bute B, Swaminatham M, Milano C, et al. The effect of aprotinin on outcome after coronary artery bypass grafting. *N Engl J Med* 2008;358:784-93.
24 Schneeweiss S, Seeger JD, Landon J, Walker AM. Aprotinin during coronary artery bypass grafting and risk of death. *N Engl J Med* 2008;358:771-83.
25 Stamou S, Reames M, Skipper E, Stiegel RM, Nussbaum M, Geller R, et al. Aprotinin in cardiac surgery patients: is the risk worth the benefit? *Eur J Cardiothorac Surg* 2009;36:869-75.
26 Ngaage DL, Cale AR, Cowen ME, Griffin S, Guvendik L. Aprotinin in primary cardiac surgery: operative outcome of propensity score-matched study. *Ann Thorac Surg* 2008;86:1195-202.
27 Jakobsen C, Sondergaard F, Hjortdal V, Johnsen S. Use of aprotinin in cardiac surgery: effectiveness and safety in a population-based study. *Eur J Cardiothorac Surg* 2009;36:863-8.
28 Wang X, Zheng Z, Ao H, Zhang S, Wang Y, Zhang H, et al. Effects of aprotinin on short-term and long-term outcomes after coronary artery bypass grafting surgery. *Ann Thorac Surg* 2010;89:1489-95.
29 Gillespie EL, Gryskiewicz K, White M, Kluger J, Humphrey C, Horotwitz S, et al. Effect of aprotinin on the frequency of postoperative atrial fibrillation or flutter. *Am J Health Syst Pharm* 2005;62:1370-4.
30 Rahman Z, Hoque R, Ali A, Rahman M, Rahman MS. Blood conservation strategies for reducing peri-operative blood loss in open heart surgery. *Mymensingh Med* 2011;20:45-53.
31 Muedra V, Delas F, Villalonga V, Gomez M, Sanchez F, Llopis JE. Transfusion requirements, morbidity and mortality in cardiac surgery and the use of antifibrinolytic agents: a comparison of aprotinin and tranexamic acid. *Rev Esp Anestesiol Reanim* 2011;58:140-6.
32 Spiess BD. Transfusion of blood products affects outcome in cardiac surgery. *Vasc Anesth* 2004;8:267-81.
33 Brown J, Birkmeyer N, O'Connor G. Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. *Circulation* 2007;115:2801-13.
34 Levi M, Cromheecke M, de Jonge E, Prins M, de Mol BJ, Briet E, et al. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. *Lancet* 1999;354:1940-7.
35 Laupacis A, Fergusson D. Drugs to minimize perioperative blood loss in cardiac surgery: meta-analyses using perioperative blood transfusion as the outcome. The International Study of Peri-operative Transfusion (ISPOT) Investigators. *Anesth Analg* 1997;85:1258-67.
36 Carless P, Moxey AJ, Stokes BJ, Henry D. Are antifibrinolytic drugs equivalent in reducing blood loss and transfusion in cardiac surgery? A meta-analysis of randomized head-head trials. *BMC Cardiovasc Disord* 2005;5:19.

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Tables

Table 1| Amount of data available for meta-analyses, by outcome

Clinical outcome by study design	No of studies (No of patients)
Mortality:	
Randomised controlled trials	82 (14 773)
Observational studies	11 (26 577)
Myocardial infarction:	
Randomised controlled trials	67 (12 390)
Observational studies	8 (14 304)
Stroke:	
Randomised controlled trials	40 (7 421)
Observational studies	10 (24 585)
Renal failure or dysfunction:	
Randomised controlled trials	28 (7656)
Observational studies	9 (23 903)

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Table 2| Summary of results from network meta-analysis

Treatment	Findings from syntheses of RCTs			Findings from syntheses of RCTs and observational studies		
	Odds ratio (95% CrI)	P(safest)* (%), average rank of treatment†	P(odds ratio <1)‡ (%)	Odds ratio (95% CrI)	P(safest)* (%), average rank of treatment†	P(odds ratio <1)‡ (%)
Mortality:						
Aprotinin	Reference group	0.9; 3.29	Reference group	Reference group	0; 3.76	Reference group
No treatment	0.99 (0.72 to 1.36)	1.7; 3.23	51.7	0.91 (0.71 to 1.16)	0.7; 3.11	78.1
Tranexamic acid	0.64 (0.41 to 0.99)	73.4; 1.30	97.6	0.71 (0.50 to 0.98)	22.7; 1.88	98.2
Epsilon-aminocaproic acid	0.79 (0.47 to 1.55)	24.0; 2.19	79.2	0.60 (0.43 to 0.87)	76.6; 1.26	99.0
Myocardial infarction:						
Aprotinin	Reference group	8.9; 2.61	Reference group	Reference group	1.2; 3.42	Reference group
No treatment	1.14 (0.89 to 1.47)	1.9; 3.55	17	0.98 (0.81 to 1.20)	2.2; 3.13	59.8
Tranexamic acid	0.95 (0.66 to 1.44)	20.1; 2.36	60.9	0.89 (0.73 to 1.11)	15.1; 2.20	86.2
Epsilon-aminocaproic acid	0.79 (0.50 to 1.30)	69.2; 1.49	83.1	0.78 (0.60 to 1.03)	81.5; 1.25	96.6
Stroke:						
Aprotinin	Reference group	15.7; 2.64	Reference group	Reference group	8.0; 2.76	Reference group
No treatment	1.05 (0.40 to 2.23)	11.5; 2.83	44.8	1.14 (0.68 to 1.89)	5.7; 3.32	30.3
Tranexamic acid	1.06 (0.33 to 2.63)	13.2; 2.82	45.1	0.81 (0.48 to 1.40)	52.7; 1.73	79.5
Epsilon-aminocaproic acid	0.72 (0.15 to 2.02)	59.6; 1.72	73.7	0.89 (0.48 to 1.59)	33.6; 2.18	66.5
Renal failure or dysfunction:						
Aprotinin	Reference group	2.7; 3.38	Reference group	Reference group	0; 3.98	Reference group
No treatment	0.83 (0.50 to 1.37)	24.0; 2.48	77.8	0.66 (0.45 to 0.88)	33.5; 2.04	99.0
Tranexamic acid	0.82 (0.31 to 1.68)	24.2; 2.43	73.2	0.66 (0.48 to 0.91)	30.3; 2.04	99.0
Epsilon-aminocaproic acid	0.74 (0.23 to 1.43)	42.9; 2.03	82.6	0.65 (0.45 to 0.88)	36.0; 1.94	99.6

RCT=randomised controlled trial.

*Value (possible range 0-100%) was estimated by counting the number of times out of the sampling iterations that treatment was associated with the odds ratio most suggestive of largest reduced risk of the outcome.

†Average rank (possible score range 1-4) was estimated by averaging the rank assigned across the sampling iterations from the simulation done to estimate pairwise odds ratios. A higher average rank suggests a lesser risk of the outcome.

‡Probability that aprotinin is associated with an increased risk of the clinical outcome relative to its comparator—that is, a higher probability is unfavourable for aprotinin.

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Figures

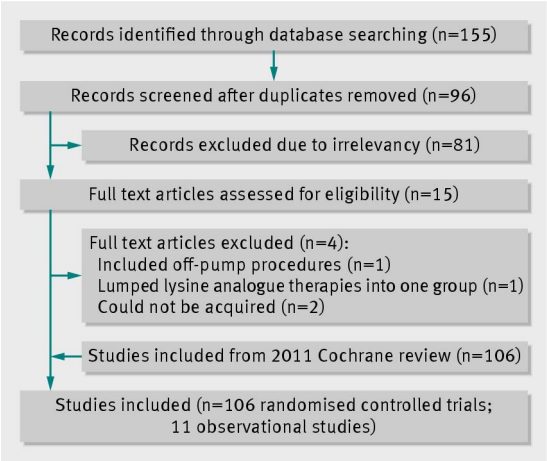


Fig 1 Flow diagram of study identification process

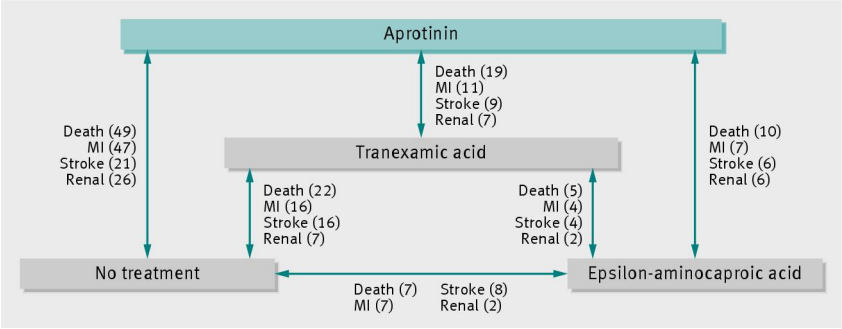


Fig 2 Network of amounts of available evidence for clinical outcomes of interest in both randomised and observational studies. MI=myocardial infarction; renal=renal failure or dysfunction

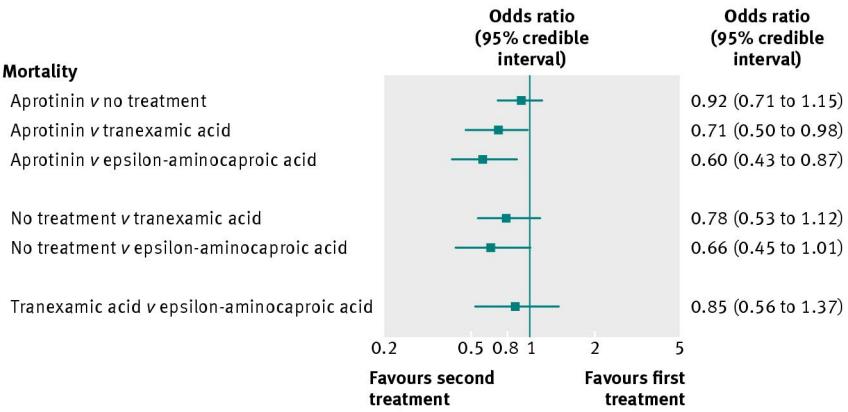


Fig 3 Summary of findings from mixed treatment comparisons meta-analysis of data on mortality (estimated between study standard deviation 0.32)

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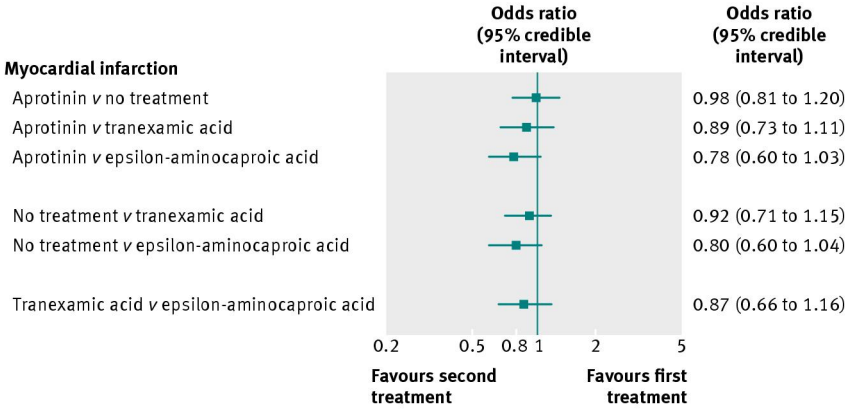


Fig 4 Summary of findings from mixed treatment comparisons meta-analysis of data on myocardial infarction (estimated between study standard deviation 0.17)

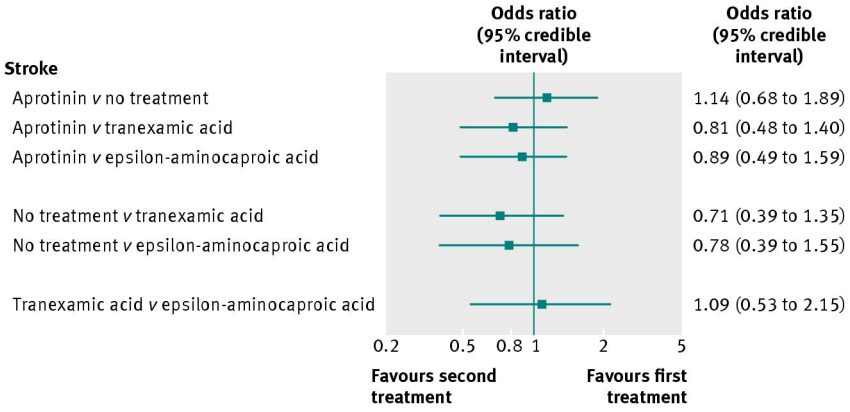


Fig 5 Summary of findings from mixed treatment comparisons meta-analysis of data on stroke (estimated between study standard deviation 0.54)

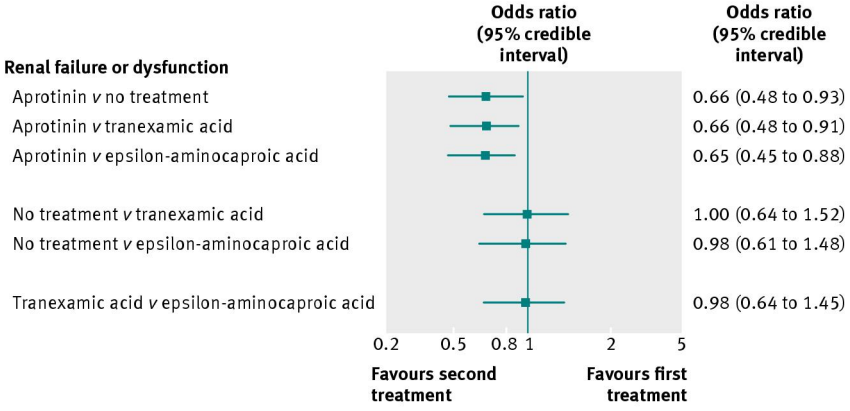


Fig 6 Summary of findings from mixed treatment comparisons meta-analysis of data on renal failure or dysfunction (estimated between study standard deviation 0.30)

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