Review

Lessons from aprotinin: is the routine use and inconsistent dosing of tranexamic acid prudent? Meta-analysis of randomised and large matched observational studies

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Received 30 September 2009; received in revised form 15 November 2009; accepted 18 November 2009; Available online 1 February 2010

Summary

In view of the safety concerns that led to the withdrawal of aprotinin, should antifibrinolytics be used indiscriminately in cardiac surgery? This meta-analysis examines the efficacy and safety profile of tranexamic acid, and in comparison to aprotinin. We identified randomised trials and large observational studies investigating the use tranexamic acid from January 1995 to January 2009 using Pubmed/Cochrane search engine and included them in a two-tier meta-analysis. There were 25 randomised trials and four matched studies with a total of 5411 and 5977 patients, respectively, reporting tranexamic acid use in varying dosages. Tranexamic acid is administered intravenously either as single dose, infusion or both, sometimes added to pump prime or applied topically. Total intravenous dose of tranexamic acid varies from 1 g to 20 g, administered over a period of 20 min to 12 h. Compared with placebo, tranexamic acid is associated with a lower mean difference in blood loss (random effect 298 ml, 95% confidence [CI] 367 to 229, p < 0.001) and decease in rates of re-operation for bleeding by 48%, transfusion of packed red cell by 47% and use of haemostatic blood products by 67%. A non-significant tendency for postoperative neurological events but a decrease in operative mortality was observed in patients treated with tranexamic acid compared with non-treatment group. Compared to aprotinin, tranexamic acid has less effective blood-conserving effect and mortality risk. Given the potential to increase neurological complications, the current trend towards indiscriminate use of tranexamic acid for all cardiac patients needs to be re-evaluated. Further studies are needed to clarify the neurological risk, appropriate indications and dosing of tranexamic acid.

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Keywords: Tranexamic acid; Cardiac surgery; Risk (morbidity, mortality)

'One’s first step in wisdom is to question everything — and one’s last is to come to terms with everything.’
Georg Christoph Lichtenberg (1742—1799)

1. Introduction

Postoperative bleeding after cardiac surgery, often due to deranged coagulation and fibrinolysis, contributes both directly and indirectly to adverse outcomes. Antifibrinolytic agents are therefore frequently used as a complementary strategy for haemostasis in patients undergoing cardiac surgery. Until recently, aprotinin was preferentially used till reports linked it with poor outcomes [1—4]. To some, it remains to be conclusively resolved whether aprotinin caused more harm than good in cardiac surgery, and opinions are still divided about the harmful effects of aprotinin [5—9]. Even though this may be circumstantially relevant, it is practically futile since aprotinin has now been withdrawn from routine clinical practice. Tranexamic acid (TA), the replacement for aprotinin, is notably cheaper with comparable antifibrinolytic and haemostatic potencies and a better safety profile.

TA, a synthetic analogue of the amino acid lysine, exerts its antifibrinolytic activity by competitive blockade of lysine-binding sites on plasminogen to prevent its activation, and at higher concentrations, causes non-competitive inhibition of plasmin. There are major similarities in the usage of TA and aprotinin, and like aprotinin, most studies (randomised and observational) focus on the antifibrinolytic and haemostatic efficacies, both of which are no longer in doubt. As a result, these studies are not powered to detect small differences in mortality, non-fatal myocardial infarction and neurological events. Following reports of adverse neurological outcomes with TA [10—13] and the recent aprotinin controversies, the rationale for a non-discriminatory, routine use of TA in cardiac surgery is open to discussion. This is the premise of
our meta-analysis. In order to increase the sample size, and in recognition of the profound influence of large observational studies in the withdrawal of aprotinin, we performed analyses of randomised trials and matched observational studies.

2. Methods

2.1. Search strategy

We conducted this meta-analysis using a format based on the QUOROM statement checklist [14]. MEDLINE database (public domain database) was searched using Pubmed (web-based search engine) to identify randomised and observational studies from January 1995 through July 2009. Keywords used were tranexamic acid, cyklokapron, antifibrinolytic, cardiac surgery, coronary artery bypass, heart valve, aortic valve and mitral valve surgery. Both primary and re-do operations were included. We further searched the references of selected papers, reviews and editorials. The search produced 48 randomised trials (Fig. 1) and nine observational studies (Fig. 2).

2.2. Study selection

Studies that report outcomes including re-operation for bleeding, myocardial infarction, neurological complications and mortality after cardiac surgery, with or without post-operative blood loss and blood product transfusion, were considered. We selected randomised trials with 15 or more patients in each group and observational studies with more than 150 patients treated with TA matched to aprotinin or no treatment (control) group using propensity scoring or other robust matching strategy.

2.3. Data abstraction

Data relating to study design, TA treatment regime and outcomes were collated from the studies and recorded on a spreadsheet. Treatment variables were; route of administration, drug doses for loading, pump prime and infusion, and duration of infusion. When indicated, the total dose of drug administered was noted. Outcome data retrieved included the amount of postoperative bleeding in millilitres, number of patients who had the following: transfusion of packed red blood cells, transfusion of blood products like fresh frozen plasma, platelets and cryoprecipitate, re-opening for bleeding, postoperative myocardial infarction, neurological complications (e.g., stroke, delirium, seizures) and operative mortality.

2.4. Statistical analyses

The primary objectives of this meta-analysis are to examine: (1) the influence of TA on the following outcomes of cardiac surgery: (i) postoperative blood loss, (ii) packed red cell transfusion, (iii) transfusion of haemostatic blood products such as fresh frozen plasma, platelets and cryoprecipitate, (iv) re-sternotomy for bleeding, (v) postoperative myocardial infarction, (vi) postoperative neurological events and (vii) operative mortality, and (2) the dosing of TA. The secondary objective is to compare these outcomes between patients treated with TA and aprotinin.

All analysis is done using Comprehensive Meta-Analysis 2 (CMA2) (Biostat Inc., 2006, Englewood, NJ, USA) and Stata 10 (StataCorp LP, 2009, College Station, TX, USA). For dichotomous outcomes such as mortality, the meta-analysis is performed by combining odds ratios. Heterogeneity is tested and the $I^2$ statistic computed. The fixed effects model is used where possible, and random effects model used when $I^2 > 50\%$ or $p < 0.10$. The analysis for randomised trials and observational studies are carried out separately, and then combined using a further meta-analysis. All results are presented as odds ratios, so for TA versus control, an odds ratio $>1$ means more events with TA.

For the continuous variables such as outcome blood loss, the meta-analysis is done using mean difference in blood loss. To do this, an estimate of standard deviation is required. Some studies do not report means and standard deviations. There is no generally accepted standard method for dealing with this and many reviewers omit studies without this information. One study provided standard errors. We multiply these by the square root of the sample size and regard that as equivalent to a given standard deviation. Some studies provide medians and either interquartile ranges, ranges or both. For these, we use the method described by Hozo et al. [15], which provides estimates of mean and standard deviation from median and range, and a method we
(MB) have developed to provide improved estimates when the quartiles are available (Bland, submitted for publication). Both these methods produce upwardly biased estimates of mean and of standard deviation for positively skew data. However, as it is argued in that paper, the bias in the means may not be important, as it will be present in both means and so should cancel out. The bias in the standard deviation will inflate the standard error of the difference, but this should be inflated anyway to take into account the estimation process.

We know of no method to produce an estimate of the standard deviation when the minimum and maximum are not available. For such studies, we use the other studies to estimate a standard deviation and then calculate the square root of the mean of the squares of the observed standard deviations. Because of the uncertainty in the methods for estimating standard deviations, we performed the meta-analysis for those studies with standard deviations or standard errors reported, then added the studies with estimated standard deviations as a second step.

### 3. Results

Twenty-nine studies \([1,2,13,16–41]\) are included in the meta-analysis; four of these \([2,13,18,22]\) are observational studies (see Table 1). In 21 of the randomised trials, TA is given intravenously, and used topically in four \([16,20,23,33]\). TA is compared with placebo (control) in 13 randomised trials, with aprotinin in five and in a two-way comparison with both in seven. In the observational studies, TA is compared with aprotinin in three and with both aprotinin and no treatment (control) in one manuscript. From all the studies, a total of 4634 patients received TA, 4350 were given aprotinin and 2404 had no antifibrinolytic treatment. There are 5411 patients in randomised trials (2571 TA, 1810 aprotinin, and 1030 placebo) and 5977 in the observational studies (2063 TA, 2540 aprotinin, and 1374 no treatment). The major focus of the studies comparing TA with control (no treatment and placebo) group are postoperative bleeding and blood transfusion.

#### 3.1. Tranexamic acid dosing

TA is administered topically in four trials in single doses ranging from 1000 mg to 2500 mg. The doses of intravenous TA are either calculated per kg body weight or given as uniform dose for all patients. Of 21 studies using TA intravenously, only in six is the cardiopulmonary bypass circuit primed with TA in doses of 500–2500 mg; in one study, a calculated dose of 2 mg kg\(^{-1}\) is used. The loading dose is given in all patients before the skin incision and ranges from

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<th>Study author (year)</th>
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Re-op: re-operation; MI: myocardial infarction; neuro-event: neurological event.
1000 mg to 10 000 mg or from 10 mg kg\(^{-1}\) to 100 mg kg\(^{-1}\). Continuous infusion of the treatment drug is further given in 15 studies using three different regimes: uniform doses of 500–10 000 mg or 200–1000 mg h\(^{-1}\), or calculated doses of either 1 mg kg\(^{-1}\) or 1 mg kg\(^{-1}\) h\(^{-1}\) to 16 mg kg\(^{-1}\) h\(^{-1}\). The duration of drug infusion varies from zero to 12 h after surgery. Termination of treatment is not dependent on any set criteria.

### 3.2. Postoperative bleeding

Twenty-four randomised and two observational studies report postoperative blood loss, and all studies uniformly record a reduction in mean postoperative blood loss with TA (Fig. 3). Based on the tests of heterogeneity, we use the random effects model for the mean difference in blood loss. In 12 randomised trials, the mean blood loss \(\pm SD\) is given and for these, the mean difference in blood loss with TA compared with control is \(-298\text{ ml} (95\% \text{ CI}: -367 \text{ to } -229, p < 0.001)\). Including eight trials for which we calculated the mean \(\pm SD\), we estimate the mean difference in blood loss to be \(-294\text{ ml} (95\% \text{ CI}: -353 \text{ to } -234, p < 0.001)\). Only the observational study of Mangano et al. reports blood loss: mean difference between TA and control is \(-283\text{ ml} (95\% \text{ CI}: -346 \text{ to } -220, p < 0.001)\) for TA.

On the contrary, we estimate that the mean blood loss is significantly greater with TA than aprotinin from 11 randomised trials (effect 114 ml, 95% CI: 47–180, \(p < 0.001\)) but not from two observational studies (effect 27 ml, 95% CI: -231 to 176, \(p = 0.80\)). Combination randomised and observational studies yields a mean difference in blood loss of \(-231\text{ ml} (95\% \text{ CI}: -298 \text{ to } -164, p < 0.001)\) for TA.

### 3.3. Packed red cell transfusion

The requirement for packed red cell transfusion is reported in 24 papers \((n = 22\) randomised). Packed red cell transfusion is compared between patients who received TA and a control group in 17 papers (all randomised trials), and TA versus aprotinin in 14 \((n = 12\) randomised). Tests of heterogeneity favour random effects estimate for the odds ratio (OR) of separate randomised and observational studies, and fixed effects estimate for the OR of the combined study types.

For TA versus control, most of the trials report a decrease in packed red cell transfusion except three, as shown in Fig. 4. The OR of randomised trials is 0.53 (95% CI: 0.38–0.75, \(p < 0.001\)). Compared with TA, aprotinin causes a greater decrease in packed red cell transfusion (OR 0.70, 95% CI: 0.54–0.92, \(p = 0.01\)) in the randomised trials but not in the observational studies (OR 0.90, 95% CI: 0.70–1.15, \(p = 0.40\)) and when both study designs are combined (OR 0.72, 95% CI: 0.56–1.08, \(p = 0.08\)).

### 3.4. Blood product transfusion

Ten randomised trials compare blood product transfusion between TA and placebo, while four randomised and two observational studies compare TA versus aprotinin. The fixed effects estimates are reported for the analyses, unless otherwise stated.

Usage of haemostatic blood products (e.g., fresh frozen plasma, platelets and cryoprecipitate) is reduced with TA than with placebo (OR 0.33, 95% CI: 0.24–0.46, \(p < 0.001\)). TA compares well with aprotinin in reducing blood product transfusion in randomised trials (OR 0.75, 95% CI: 0.49–1.15, \(p = 0.20\)), observational studies (random effects estimate 0.68, 95% CI: 0.21–2.23, \(p = 0.50\)) and the combined study types (OR 0.81, 95% CI: 0.54–1.21, \(p = 0.37\)).

### 3.5. Re-operation for bleeding

Of 21 studies \((n = 18\) randomised), 13 randomised trials compare TA with placebo, while eight randomised trials and three observational studies compare TA with aprotinin. Tests of heterogeneity favour the fixed effects estimates for most comparisons. TA reduces re-operation for bleeding by 48% (OR 0.52, 95% CI: 0.29–0.95, \(p = 0.03\)) compared with placebo. Aprotinin, however, is more effective than TA for preventing re-operation (OR 0.70, 95% CI: 0.49–0.99, \(p = 0.04\)) in randomised trials, but has similar effect to TA in observational studies (OR 1.10, 95% CI: 0.79–1.52).
3.6. Myocardial infarction

Postoperative myocardial infarction is recorded in 18 papers (n = 15 randomised). In eight randomised trials and one observational study, TA is compared to placebo and, in seven randomised trials and three observational studies TA is compared with aprotinin. Based on tests of heterogeneity, the fixed effects estimates are considered appropriate for these comparisons.

Compared to control, TA does not significantly affect the incidence of postoperative myocardial infarction in randomised trials (Fig. 5). The small number of events in both TA and control groups (n = 13 in each) results in a wide confidence interval in the meta-analysis (OR 0.90, 95% CI: 0.40–2.02, p = 0.80). Similarly, the observational study of Mangano et al. [2] did not find a significant difference in the incidence of postoperative myocardial infarction with the use of TA (OR 1.00, 95% CI: 0.77–1.29, p = 1.0). The OR for the combined study types is 0.99 (95% CI: 0.78–1.26, p = 0.90).

The effect of TA is comparable to aprotinin in the randomised studies (OR 1.00, 95% CI: 0.68–1.49, p = 1.00), but in observational studies aprotinin increased the risk of postoperative myocardial infarction compared with TA (OR 1.34, 95% CI: 1.06–1.68, p = 0.01); an effect maintained when both study types are combined (OR 1.24, 95% CI: 1.02–1.51, p = 0.03).

3.7. Neurological complication

Postoperative neurological event described as stroke, transient ischaemic attack or delirium is investigated in 17 studies (n = 13 randomised, see Fig. 6). Five randomised trials and one observational study examined this outcome with TA and no treatment. The fixed effect estimates are reported.

Neurological events are recorded in small numbers of patients (n = 10 treated with TA, n = 3 treated with placebo) in the randomised trials. TA does not significantly increase the risk of neurological event in any of these trials. The estimated OR for the meta-analysis comparing TA to no treatment is 2.19 (95% CI: 0.69–6.94, p = 0.20). The OR from the only observational study of Mangano et al. [2] is 1.36 (95% CI: 0.85–2.17, p = 0.20) and the combined study design is 1.45 (95% CI: 0.94–2.24, p = 0.09).

This outcome is compared between aprotinin and TA in four randomised and four observational studies. The risk of neurological events is similar for aprotinin and TA in randomised trials (OR 0.85, 95% CI: 0.51–1.43, p = 0.50), observational studies (random effect OR 1.03, 95% CI: 0.57–1.85, p = 0.90) and the combined study designs (OR 0.92, 95% CI: 0.63–1.36, p = 0.70).

3.8. Mortality

Operative mortality is reported in 22 papers (n = 18 randomised); 10 (all randomised trials) compare TA with placebo, seven (n = 4 randomised) compare TA with aprotinin and five (n = 4 randomised) compare TA, aprotinin and no treatment. For all comparisons, heterogeneity was not significant so the fixed effects estimates are chosen. TA does not increase the risk of operative death compared to no treatment (Fig. 7) and results in a significantly lower mortality risk than aprotinin.

For TA versus control, the OR of operative death from randomised trials is 0.50 (95% CI: 0.20–1.25, p = 0.10). There
are few deaths; seven in the TA and 16 in ‘no treatment’ group, hence the wide confidence interval. The mortality risk for TA from the only observational study [2] is 0.99 (95% CI: 0.53–1.85, \( p = 0.98 \)). Combining both randomised and observational studies yield an OR of 0.80 (95% CI: 0.48–1.34, \( p = 0.40 \)).

Aprotinin increases the risk of operative death compared to TA: OR 1.48 (95% CI: 1.00–2.20, \( p = 0.05 \)) from analysis of randomised trials and 1.34 (95% CI: 0.99–1.82, \( p = 0.06 \)) from observational studies. The substantial mortality risk with aprotinin is maintained in the analysis of combined study designs (OR 1.39, 95% CI: 1.10–1.77, \( p = 0.007 \)).

4. Discussion

In this meta-analysis we adopted a methodology of performing separate analyses for randomised trials and robustly matched observational studies to explore the influence of TA on outcome of cardiac surgery in comparison to another anti-inflammatory and haemostatic agent, aprotinin, which has fallen out of favour because of its strong association with adverse operative results. We then compared the results and combined them to determine the impact on the outcome effect size. This style of analysis seems credible and gives recognition to the major role the findings of large observational studies played in determining the use of antifibrinolytic agents in cardiac surgery.

4.1. Tranexamic acid dosing

There is major inconsistency and wide variability in the dosing of TA in randomised trials, and even more so for observational studies where it is often difficult to determine. This is captured in the paper of Mangano et al. [2], which include patients who had ‘any dose’ of TA. The dissimilarities in TA dose regimes between the different studies include routes of administration, amount of drug given as loading dose, pump prime, infusion and duration of infusion. In the majority of cases, the chosen regime is not informed by pharmacokinetic studies. In most studies, a uniform or calculated loading dose of TA is administered intravenously followed by a calculated infusion dose given over a variable length of time. There are few studies that relate the dosage of TA with plasma concentrations. Fiechtner et al. [42] showed that plasma levels are maintained over the therapeutic level for most of the duration of cardiopulmonary bypass with a regime of 10 mg kg\(^{-1}\) loading dose followed by an infusion of 1 mg kg\(^{-1}\) h\(^{-1}\) for up to 2 h after arrival in intensive care unit. By combining their findings with the results of other pharmacokinetic studies, they calculate a recommended dose of 5.4 mg kg\(^{-1}\) load, 40–50 mg pump prime, followed by an infusion of 5 mg kg\(^{-1}\) h\(^{-1}\). That study reveals higher plasma levels in renal insufficiency. Lambert et al. [43] investigated the efficacy of three different intravenous dose regimes: low (20 mg kg\(^{-1}\)), medium (50 mg kg\(^{-1}\)) and high (100 mg kg\(^{-1}\)), administered as a single dose before skin incision and report no difference in the primary outcomes of postoperative blood loss and transfusion between the doses.

The dosing of TA is important because its side effects are dose related. In fact, three of the studies with relatively higher rates of neurological events use a bolus dose of at least 10 000 mg of TA [36,38,41].

4.2. Comparison of tranexamic acid with no treatment

The use of TA in cardiac surgery patients significantly decreases the volume of postoperative bleeding. We estimate that the mean chest tube drainage after cardiac surgery is less by about 283 ml (95% CI: 220–346, \( p < 0.001 \)) when TA is administered, compared to no treatment. Consequently, re-operation for bleeding and the requirement for transfusion of packed red cells and blood products is considerably less. Our meta-analysis estimates a decrease in the risk of re-operation for bleeding by 48%, transfusion of packed red cell by 47% and use of haemostatic blood products by 67%. The blood-conserving property of TA is uniformly reported by randomised and observational studies included in this meta-analysis, and this is consistent with other meta-analyses [44,45].

In general, our meta-analysis does not reveal a statistically significant increased risk of adverse operative outcome, such as postoperative myocardial infarction, neurological events or mortality, with TA. However, the numbers of patients experiencing these adverse outcomes in randomised trials are small, and only one observational study reports the incidence of all these outcomes. Both observational and randomised studies are discordant in showing no elevated risk of postoperative myocardial infarction with TA, and a non-statistically significant tendency to increased risk of postoperative neurological events. This tendency is maintained in the analysis of combined study types and is further discussed below. The vast majority of studies, randomised and observational, separately and collectively demonstrate a non-incremental risk of mortality with TA. Our meta-analysis of randomised trials show that TA may indeed have a beneficial effect in reducing operative mortality, as suggested in a previous meta-analysis [45], even though this effect is not consistent with observational studies.

4.3. Comparison of tranexamic acid with aprotinin

Aprotinin causes a more remarkable reduction in postoperative blood loss than TA, and consequently fewer requirements for packed red cell (but not haemostatic blood product) transfusion and re-operation for bleeding. This difference in blood-conservation between both drugs is replicated in observational studies. This variation between studies is perhaps because of differences in the transfusion thresholds in different centres and the clinical judgement for re-sternotomy for bleeding. However, it is important to stress that for the objective assessment of the volume of blood loss following surgery, TA is less effective than aprotinin.

There is discrepancy in the risk of postoperative myocardial infarction between randomised and observational studies. A weaker risk of postoperative myocardial infarction with TA compared to aprotinin in observational studies is not reproduced by the analysis of randomised trials, probably because the outcome is observed in small numbers of patients as reflected by the wide confidence interval. However, our analysis of randomised trials is in agreement with other reports [44,45].
Our meta-analysis reveals a lower mortality risk with TA than with aprotinin. This difference in the risk of death between both antifibrinolytic agents is consistent for observational and randomised studies with no evidence of heterogeneity. The meta-analysis of combined study types show that compared to TA, aprotinin substantially increases mortality risk. We estimate that aprotinin increases the mortality risk by 48% compared to TA. These findings are consistent with the meta-analyses of Takagi et al. [46] and Henry et al. [45], unlike the analysis of Brown et al. [44] that reported no difference in mortality risk between both antifibrinolytic agents. It has to be said that Brown’s paper did not include the large multi-centre (BART) trial [1], which exerts a major effect.

4.4. Safety of tranexamic acid

The present meta-analysis, like previous analyses, does not show any increased risk of postoperative myocardial infarction or mortality with the use of TA. By conserving blood and reducing transfusion and re-operation, it decreases the risk of adverse outcomes relating to these interventions. It may, in fact, reduce the risk of operative mortality. Although our meta-analysis does not demonstrate a statistically significant risk for adverse events with TA, the consistent but weak evidence in both randomised and observational studies linking the use of TA with a tendency toward an increased risk of postoperative neurological events gives some concern about its safety needs to be further investigated. The small number of patients with postoperative neurological events in these studies, not primarily designed to investigate this outcome measure may explain the inability of this meta-analysis to detect a significant risk. The possibility of an association between TA and postoperative neurological dysfunction has been raised by some authors who observed higher incidence of seizures in both adult and paediatric cardiac patients treated with TA [10,13]. It is therefore vital to emphasise that the meta-analysis may not have found a strong association between TA and postoperative neurological events because the studies included in the analysis predominantly report postoperative stroke rather than postoperative complications including seizures, which are more relevant. A matter of interest and deserving of further examination is perhaps the additive risk for patients at high risk for neurological complications by reason of other factors such as advanced age or previous cerebrovascular disease. The relation-ship of high TA dosage and postoperative neurological events, referred to earlier, is also worthy of close scrutiny. Lambert et al. [43] also report neurological complications in three out of 72 patients who received high-dose TA (100 mg kg⁻¹), compared with one out of 74 patients who had low-dose regime (20 mg kg⁻¹) after primary coronary artery bypass grafting. The clinical implication of this potential risk associated with TA is that perhaps TA should be used with caution in patients at high risk for postoperative neurological complications like octogenarians and those with a history of stroke.

5. Conclusion

TA is an effective blood-conserving agent with signifi-
cantly lower risk of death, and possibly a lower propensity to cause postoperative myocardial infarction, than aprotinin. Its indiscriminate use and inconsistent dosing regimes can potentially increase the likelihood of postoperative neurological complications especially in high-risk patients. Further studies are needed to clarify the association between TA and neurological dysfunction and to determine the appropriate dosage in cardiac patients.

References


Appendix A. Conference and discussion

Dr D. Pagano (Birmingham, United Kingdom): I have a number of points and comments to make which I’ll do on a point-by-point basis so that we can have an answer to each.

First of all, I have some methodological problems to raise. I’m sure you’re aware that in 2007 there was a large and very sophisticated review from the Cochrane group on the use of antifibrinolitics. The conclusions of that review are a little bit at odds with yours, particularly in the field of comparing aprotinin and tranexamic acid. And in fact, for those in the audience that may not have read the Cochrane review at the time, there was absolutely no difference in safety parameters. So these studies have been largely designed for efficacy rather than safety. There was not an increase in mortality with aprotinin. And most importantly, there was no convincing evidence that the tranexamic acid would reduce re-operation for bleeding while it was effective in reducing blood loss at time of surgery and transfusion. How do you explain that difference?

Dr Ngaage: The Cochrane review has been updated recently. It has been updated by J. Brown and Dr Ferguson as well. And I think what makes the difference is the randomized trial that was done by Ferguson and his group from Canada. If you exclude that trial, you will find that it will affect the conclusion. But that was a very big trial and it did have a major impact.

Dr Pagano: Well, it’s good you raise that, because that’s exactly what I want to talk about is the BART trial. The BART trial has got very serious faults statistically. In the BART trial they used in the analysis multiple testing, and they really reduced the half-expanding power from 0.050 to 0.017. They did not take into account a p value in their manuscript. But when we calculate that p value, it’s 0.026. So none of their conclusions were reaching conventional statistical significance.

It is important to note that that trial, together with the politics and the legal system, has changed completely the way we use antifibrinolitics. So I think that is a point that is worth making in your manuscript.

I just wanted to ask you a little bit more about your methodology about using observational studies. As you just said, you just need to add one study and you change the result. There are large observational studies where actually aprotinin has been shown not to be ineffective, to be very effective, and not deleterious. You have included the Mangano paper. The problem with aprotinin is that there is a tremendous bias in the population. In North America it’s used only for patients at high risk. There is no propensity score matching system and no conventional statistics that can adjust for those huge differences. Why did you exclude some papers which were actually favourable to aprotinin?

Dr Pagano: We included studies that had tranexamic acid with aprotinin or placebo groups.

I am aware that you have also done a study, as we have, about antifibrinolitics. But in those studies there was no tranexamic acid group. Now, the advantage of this study is the separate reporting of the analysis for randomized trials, observational studies and the combined study designs so you can look at the different designs and make your own conclusion. But I think what is important is, as you have pointed out, that the large observational studies were actually the main reason why Trasylol was withdrawn. And I do agree with you that there were problems with the BART trial, which we have all
highlighted, but it still remains that it is a trial that was published in a very reputable journal and still exerts an influence and influences political decisions as well.

Dr Pagano: One more point of question to you. We are not left with using an agent, as you quite rightly say, that we don’t know what dose to use, we don’t know what efficacy it really has and what’s the safety profile. What’s your practice? What do you advise?

Dr Ngaage: I think that there are very few pharmacokinetic studies looking at tranexamic acid dosing. And those studies have made some recommendations. It does appear to me that tranexamic acid in small doses is effective. And I would be inclined to use tranexamic acid as recommended by these pharmacokinetic studies in the dosage of 10 mg/kg body weight as a loading dose with or without pump prime and then run an infusion of 1 mg/kg up to 2 hours after coming off bypass.

Now, having said that, I would prefer that a large, randomized study, multicentre trial preferably, is done to look at the safety of tranexamic acid and provide compelling evidence that will not later on be challenged and we get into the same situation as we did with Trasylol.

Dr Pagano: One minor point which I think is very important. In light of your analysis, which patient would you use tranexamic acid for, everybody or just high-risk patients? What criteria would you use?

Dr Ngaage: I would initially avoid patients at risk of neurological events, especially people, as I did show yesterday, who have preoperative neurological events. I would use with caution in patients with renal impairment, who usually have very high plasma levels. The dose would need to be adjusted in patients with in renal impairment.

Dr Pagano: But you’d use it for everybody else?

Dr Ngaage: Yes.