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RESEARCH

Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis


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Abstract

Objective To assess the effect of tranexamic acid on blood transfusion, thromboembolic events, and mortality in surgical patients.

Design Systematic review and meta-analysis.

Data sources Cochrane central register of controlled trials, Medline, and Embase, from inception to September 2011, the World Health Organization International Clinical Trials Registry Platform, and the reference lists of relevant articles.

Study selection Randomised controlled trials comparing tranexamic acid with no tranexamic acid or placebo in surgical patients. Outcome measures of interest were the number of patients receiving a blood transfusion; the number of patients with a thromboembolic event (myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism); and the number of deaths. Trials were included irrespective of language or publication status.

Results 129 trials, totalling 10 488 patients, carried out between 1972 and 2011 were included. Tranexamic acid reduced the probability of receiving a blood transfusion by a third (risk ratio 0.62, 95% confidence interval 0.58 to 0.65; P<0.001). This effect remained when the analysis was restricted to trials using adequate allocation concealment (0.68, 0.62 to 0.74; P<0.001). The effect of tranexamic acid on myocardial infarction (0.68, 0.43 to 1.09; P=0.11), stroke (1.14, 0.65 to 2.00; P=0.65), deep vein thrombosis (0.86, 0.53 to 1.39; P=0.54), and pulmonary embolism (0.61, 0.25 to 1.47; P=0.27) was uncertain. Fewer deaths occurred in the tranexamic acid group (0.61, 0.38 to 0.98; P=0.04), although when the analysis was restricted to trials using adequate concealment there was considerable uncertainty (0.67, 0.33 to 1.34; P=0.25). Cumulative meta-analysis showed that reliable evidence that tranexamic acid reduces the need for transfusion has been available for over 10 years.

Conclusions Strong evidence that tranexamic acid reduces blood transfusion in surgery has been available for many years. Further trials on the effect of tranexamic acid on blood transfusion are unlikely to add useful new information. However, the effect of tranexamic acid on thromboembolic events and mortality remains uncertain. Surgical patients should be made aware of this evidence so that they can make an informed choice.

Introduction

In October 2011 the *BMJ* published a randomised controlled trial on the effect of tranexamic acid on blood transfusion in patients undergoing radical retropubic prostatectomy.[1] The authors pointed out that this was the first trial to assess the effect of tranexamic acid on blood transfusion in this particular operation. While this may be the case, it was not the first trial to examine the effect of tranexamic acid on blood transfusion in surgery more generally. A systematic review published in 2001 presented data from 18 clinical trials and showed that tranexamic acid reduces the probability of blood transfusion in elective surgery by 34%.[2]

We assessed the current evidence for the effect of tranexamic acid on blood transfusion, thromboembolic events, and mortality in surgical patients. To examine how the evidence has changed over time we used cumulative meta-analyses.

Methods

Although we specified and documented the methods of the analysis and inclusion criteria for this systematic review in advance, the protocol was not registered. We searched for all randomised controlled trials that compared tranexamic acid with no tranexamic acid or placebo in elective and emergency surgery. No age restriction was applied. Potentially eligible trials were identified by searching the Cochrane central register of controlled trials (2011, issue 3), Medline (1950 to September 2011), and Embase (1980 to September 2011), using a combination of subject headings and text words to identify

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Medline (Ovid) search strategy, 1950 to September 2011
Summary of the risk of bias judgments for each methodological quality domain
Forest plots of effects of tranexamic acid in surgery on risk of blood transfusion, thromboembolic events, and mortality

randomised controlled trials of any antifibrinolytic drug (see supplementary file for Medline search strategy). Searches were not restricted by language or publication status. To identify ongoing or unpublished trials we searched the WHO International Clinical Trials Registry Platform. We also examined the reference lists of eligible trials and reviews. Two authors independently screened the search output to identify records of potentially eligible trials, the full texts of which were retrieved and assessed for inclusion.

Outcome data

Outcome measures of interest were the number of patients receiving a blood transfusion; the number of patients with a thromboembolic event (myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism); and the number of deaths. We contacted trial authors to obtain any missing outcome data.

Data extraction and risk of bias assessment

We extracted data on the age and sex of trial participants, type of surgery, dose and timing of tranexamic acid, type of comparator, and outcome data. We also collected information on whether a systematic review had been conducted to support the trial rationale and whether a systematic review was cited in the trial report. We assessed the risk of bias associated with the method of sequence generation, allocation concealment, blinding, and the completeness of outcome data. As the risk of bias for blinding may vary according to outcome, we assessed this separately for each outcome. We rated the risk of bias as being low, unclear, or high according to established criteria.[3]

Statistical analysis

For each outcome we calculated risk ratios and 95% confidence intervals. We pooled these using a fixed effect model. Subgroup analyses were carried out to examine whether the effect of tranexamic acid on blood transfusion varied by type of surgery. Sensitivity analyses were done to quantify the effect of tranexamic acid on all outcomes when restricted to trials with adequate allocation concealment and blinded outcome assessment. We carried out a cumulative meta-analysis of the effect of tranexamic acid on blood transfusion based on the date of publication, and, when restricted to trials with adequate concealment, cumulative meta-analyses of the effect of tranexamic acid on blood transfusion, myocardial infarction, and mortality. Heterogeneity was examined by visual inspection of forest plots, the I^2 statistic, and the χ^2 test. We inspected funnel plots for the presence of small study effects. Statistical analyses were carried out using Stata version 11 and RevMan version 5.[4 5]

Results

Overall, 127 articles[1 6-131] describing 129 randomised controlled trials and totalling 10 488 patients were included; 5484 of these patients were allocated to tranexamic acid and 5004 to a control group (fig 1⇓). The median sample size was 60 (range 10-660) patients. In total, 126 (98%) trials were in elective surgery and three (2%) in emergency surgery. Eleven (8%) trials involved children.

The authors of 86 trials were contacted for missing data, 39 of whom provided additional information. Data were available on blood transfusion from 95 (74%) trials, on myocardial infarction from 73 (56%), on stroke from 71 (55%), on deep vein thrombosis from 72 (56%), on pulmonary embolism from 66 (51%), and on mortality from 72 (56%). Seven (5%) trials did not present any data on the outcome measures of interest to this review or reported data in a format that was unsuitable for inclusion in the analyses.

A further 14 ongoing trials were identified,[132-145] with a median planned sample size of 130 patients. The 14 trials were in orthopaedic (n=5), cardiac (n=4), cranial (n=2), hepatic (n=1), ear, nose, and throat (n=1), and gynaecological (n=1) surgery. In 12 of the 14 trials blood transfusion was a main outcome measure.

Risk of bias

Overall, 44 (34%) trials were judged to be at low risk of bias for sequence generation and five (4%) to be at high risk (see the supplementary file for the risk of bias judgments for each methodological quality item for the included trials). The risk of bias in the remaining 80 (62%) trials was unclear owing to lack of information. Allocation was adequately concealed in 36 trials (28%) and inadequately concealed in six (5%), with the other 87 (67%) presenting insufficient information to allow judgment. Of the 95 trials with data on blood transfusion, 69 (73%) were judged at low risk of blinding, four (4%) at high risk, and 22 (23%) were unclear. The risk of bias for blinding was similar for thromboembolic outcomes (myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism), with about 70% judged to be at low risk, 5% at high risk, and 25% at unclear risk. All 72 trials with mortality outcomes were judged to be at low risk of bias for blinding. Of 115 trials reporting eligible outcome data, 72 (63%) were at low risk of bias for incomplete outcome data, 17 (15%) at high risk, and 26 (23%) did not describe adequate information to permit judgment.

Quantitative data synthesis

Table 1⇓ presents the results of the meta-analysis.

Risk of blood transfusion

Data on blood transfusion were available for 95 trials, including a total of 7838 patients. Tranexamic acid reduced the probability of receiving a blood transfusion by 38% (pooled risk ratio 0.62, 95% confidence interval 0.58 to 0.65; P<0.001). When the analysis was restricted to the 32 adequately concealed trials involving 3408 patients, tranexamic acid reduced the risk of receiving a blood transfusion by 32% (0.68, 0.62 to 0.74; P<0.001). When the analysis was restricted to the 69 trials involving 5968 patients with adequate blinding for this outcome, tranexamic acid reduced the risk of blood transfusion by 37% (0.63, 0.59 to 0.68; P<0.001).

The trials with blood transfusion data involved cardiac (n=42), orthopaedic (n=36), cranial and orthognathic (n=7), gynaecological (n=5), hepatic (n=2), urological (n=2), and vascular (n=1) surgery. Blood transfusion was statistically significantly reduced in cardiac, orthopaedic, cranial and orthognathic, hepatic, and urological surgery (table 2⇓). The pooled estimates for blood transfusion were consistent with a reduction in the tranexamic acid group among trials in vascular and gynaecological surgery, although the results were imprecise. There was moderate heterogeneity in magnitude of the effects of tranexamic acid by type of surgery, although the direction of the effects was largely consistent.

Thromboembolic events

There was uncertainty about the effect of tranexamic acid on myocardial infarction (risk ratio 0.68, 95% confidence interval

0.43 to 1.09; P=0.11), stroke (1.14, 0.65 to 2.00; P=0.65), deep vein thrombosis (0.86, 0.53 to 1.39; P=0.54), and pulmonary embolism (0.61, 0.25 to 1.47; P=0.27). The results were similar when the analyses were restricted to trials with adequate allocation concealment and those with blinded outcome assessment.

Mortality

Fewer deaths occurred in the tranexamic acid group (risk ratio 0.61, 95% confidence interval 0.38 to 0.98; P=0.04), although there was uncertainty about this effect, particularly when the analysis was restricted to the 28 trials with adequate concealment (0.67, 0.33 to 1.34; P=0.25).

Cumulative meta-analyses

The supplementary file shows the results of the cumulative meta-analysis of the 95 trials with data on blood transfusion. A statistically significant effect of tranexamic acid on blood transfusion was first observed after publication of the third trial in 1993 (0.59, 0.43 to 0.80; P=0.001). Although subsequent trials have increased the precision of the point estimate, no substantive change has occurred in the direction or magnitude of the treatment effect.

Figures 2-4⇓⇓⇓ shows the cumulative meta-analyses of the effect of tranexamic acid on blood transfusion, myocardial infarction, and mortality among the trials with adequate allocation concealment. A statistically significant effect of tranexamic acid on blood transfusion was consistently observed after publication of the 10th trial in 2001.

Small study effects

Inspection of the funnel plot (fig 5⇓) for the outcome blood transfusion suggested the presence of small study effects favouring tranexamic acid. The other outcomes showed no clear asymmetry in the funnel plots.

Citation of previous systematic reviews

Between 1994 and 2011, 30 systematic reviews have been published on the effects of tranexamic acid in surgery.[2 89 146-175] Assuming a 12 month publication time lag, 98 of the 116 (84%) included trial reports published as full journal articles were published when at least one systematic review was available. Examination of the reference lists of these reports indicated that 45 (46%) did not cite any of the available systematic reviews. The authors of two of the 116 trial reports had carried out a systematic review and presented the findings within the final trial publication.

Discussion

Reliable evidence that tranexamic acid reduces blood transfusion in surgical patients has been available for many years. The treatment effect varies somewhat according to the type of surgery, but the effect is consistently large and remains so when the analysis is restricted to trials with adequate allocation concealment. The effect of tranexamic acid on thromboembolic events and mortality has not been adequately assessed by clinical trials in surgery and remains uncertain. In view of the evidence, those planning further placebo controlled trials should explain why they think that tranexamic acid might not reduce the risk of blood transfusion in the particular group of surgical patients under consideration and focus their efforts on resolving the uncertainties about the effect of tranexamic acid on thromboembolic events and mortality.

Strengths and weaknesses of the review

The inferences that can be made from the included trials depend on their quality, and many had methodological limitations. However, the large and statistically significant effect on blood transfusion remained when the analysis was restricted to trials with adequate allocation concealment and with adequate blinding.

We systematically searched a range of databases for published and unpublished trials. However, we cannot exclude the possibility that some were missed. Indeed, the observed asymmetry in the funnel plot could be explained by publication bias. If many unpublished trials show little or no effect of tranexamic acid on blood transfusion, then this meta-analysis may have overestimated the treatment effect. Although some degree of overestimation is likely, it seems improbable that publication bias could account for all of the observed effect.

Although mortality and thromboembolic outcomes showed no obvious asymmetry in the funnel plots, publication and other reporting biases remain a potential threat to the validity of the effect estimates. Mortality data were reported in only a third of the included trials, and less than half reported data on myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism. Inadequate reporting of adverse events is not unusual in reports of clinical trials and hinders the reliable estimation of treatment effects.[176 177] After contacting the trial authors we obtained some missing data and were able to include mortality data for three quarters of the included trials and data on myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism for about half of the trials. However, the effect of outcome reporting bias in this review remains open to question. Even if there was no significant bias, the precision of the estimates is low and the data are compatible with either a moderate increase or a moderate decrease in the risk of thromboembolic events.

Implications of the findings

The evidence in this review suggests that the uncertainty about the effect of tranexamic acid on blood transfusion in surgical patients was resolved over a decade ago; however, uncertainties about its effect on thromboembolic events and mortality persist. Despite this, trials of tranexamic acid continue to assess the effect on blood transfusion. One reason may be a reluctance to generalise the evidence across surgery types, although there is no evidence that the relative effect of tranexamic acid on blood transfusion varies by type of surgery. A second reason may be that trialists are unaware of the existing evidence when initiating a new trial. Our observation that only half of the trials cited one or more of the available systematic reviews and just two carried out their own systematic review, does suggest that many trialists are indeed failing to adequately consider the existing evidence.

Blood is a scarce and costly resource and blood transfusion is not without risk. The cost of a unit of red cells to the National Health Service has increased from £78 (€96; $126) in 2000 to £125 in 2011, and blood transfusion has several rare but serious adverse effects. Worldwide, most people do not have access to safe blood. Globally the most important transfusion related risks are HIV, hepatitis B virus, and hepatitis C virus, due to their high prevalence. That tranexamic acid safely reduces the need for blood transfusion in surgery has important health and economic implications in high, middle, and low income countries. The evidence that tranexamic acid reduces the need for blood transfusion is strong but the safety of routine use of tranexamic acid in surgical patients remains uncertain. A modest increase in the risk of thromboembolic effects could outweigh

the benefits of reduced blood use. Although some increased risk might be expected on theoretical grounds, recent evidence from the CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) trial of tranexamic acid in bleeding trauma patients showed a statistically significant reduction in mortality with no increase in thromboembolic effects. Indeed, there was a statistically significant reduction in the risk of myocardial infarction in trauma patients who received tranexamic acid.[178]

Further small trials of tranexamic acid in surgical patients considered in isolation will not resolve the uncertainties about the effects on thromboembolic events and mortality. Because thromboembolic events are relatively rare, such trials lack statistical power to detect clinically important increases in risk, and a meta-analysis of small trials remains vulnerable to publication bias. The ongoing Aspirin and Tranexamic Acid for Coronary Artery Surgery trial[179] with a planned sample size of 4300 high risk patients undergoing coronary artery surgery, should contribute importantly to resolving the uncertainty about the effect of tranexamic acid on mortality and thromboembolic events in this specific group. We urge investigators involved in all ongoing trials of tranexamic acid in surgery to collect data on thromboembolic events and mortality for inclusion in a prospective meta-analysis until the uncertainties are resolved. However, a need remains for a large pragmatic clinical trial of the effect of routine use of tranexamic acid in a heterogeneous group of surgical patients. The possibility that tranexamic acid might reduce mortality without any increase in the risk of thromboembolic events would justify the effort and expenditure involved.

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Data sharing: No additional data available.

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What is already known on this topic

Small trials on the effect of tranexamic acid (TXA) on blood transfusion in surgical patients continue to be carried out and published in the medical literature

What this study adds

Evidence that TXA reduces blood transfusion in surgical patients has been available for over a decade, yet the effect on thromboembolic events and mortality remains uncertain

Further trials on the effect of TXA on blood transfusion are unlikely to add useful new information

A large pragmatic clinical trial of TXA in a heterogeneous group of surgical patients is needed to resolve the uncertainties about the effects on thromboembolic events and mortality

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Tables

Table 1| Meta-analysis of effect of tranexamic acid on blood transfusion, thromboembolic events, and mortality

				Heterogeneity	
Outcomes	**Events (tranexamic acid/control)**	**Pooled risk ratio (95% CI)**	**P value***	**I^2 (%)**	**P value**
Blood transfusion:					
All trials	1067/1520	0.62 (0.58 to 0.65)	<0.001	69	<0.001
Well concealed trials	459/ 609	0.68 (0.62 to 0.74)	<0.001	55	<0.001
Adequate blinding	847/1182	0.63 (0.59 to 0.68)	<0.001	54	<0.001
Myocardial infarction:					
All trials	23/35	0.68 (0.42 to 1.09)	0.11	0	0.90
Well concealed trials	16/25	0.70 (0.39 to 1.25)	0.22	0	0.82
Adequate blinding	18/33	0.59 (0.36 to 0.98)	0.04	0	0.81
Stroke:					
All trials	23/16	1.14 (0.65 to 2.00)	0.65	0	0.92
Well concealed trials	5/4	1.18 (0.36 to 3.83)	0.78	0	0.92
Adequate blinding	23/16	1.14 (0.65 to 2.00)	0.65	0	0.92
Deep vein thrombosis:					
All trials	25/29	0.86 (0.53 to 1.39)	0.54	0	0.96
Well concealed trials	13/14	0.92 (0.45 to 1.85)	0.81	0	0.81
Adequate blinding	18/22	0.82 (0.46 to 1.44)	0.49	0	0.98
Pulmonary embolism:					
All trials	4/8	0.61 (0.25 to 1.47)	0.27	0	0.96
Well concealed trials	1/3	0.52 (0.10 to 2.75)	0.44	0	0.80
Adequate blinding	4/6	0.70 (0.26 to 1.87)	0.48	0	0.91
Mortality:					
All trials	20/34	0.61 (0.38 to 0.98)	0.04	0	0.97
Well concealed trials	9/15	0.67 (0.33 to 1.34)	0.25	0	0.85
Adequate blinding	20/34	0.61 (0.38 to 0.98)	0.04	0	0.97

*Test for effect.

Table 2| **Meta-analysis of effect of tranexamic acid on risk of blood transfusion, stratified by type of surgery**

Type of surgery	No of events (tranexamic acid/control)	Pooled risk ratio (95% CI)	P value*	Heterogeneity	
Cardiac	622/835	0.65 (0.60 to 0.70)	<0.001	60	<0.001
Orthopaedic	298/462	0.55 (0.49 to 0.61)	<0.001	83	<0.001
Hepatic	29/54	0.52 (0.39 to 0.68)	<0.001	93	<0.001
Urological	40/60	0.66 (0.48 to 0.91)	0.01	2	0.31
Vascular	11/19	0.58 (0.34 to 0.99)	0.05	—	—
Gynaecological	17/50	0.86 (0.48 to 1.54)	0.61	65	0.06
Cranial and orthognathic	52/76	0.63 (0.45 to 0.86)	0.004	46	0.12

*Test for effect.

Figures

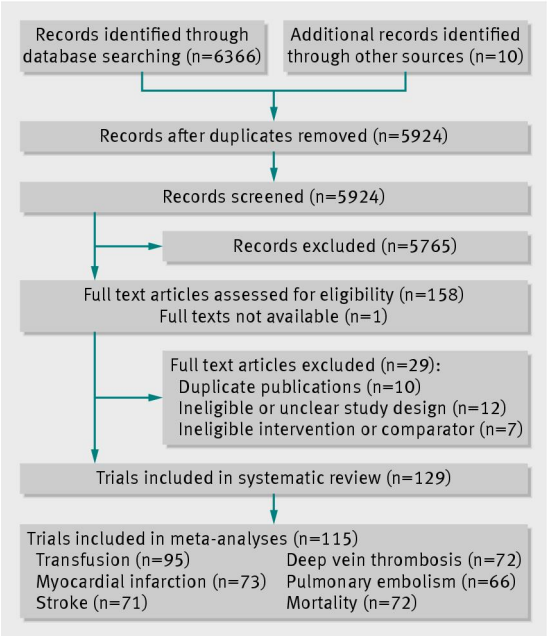

Fig 1 Selection of trials for review

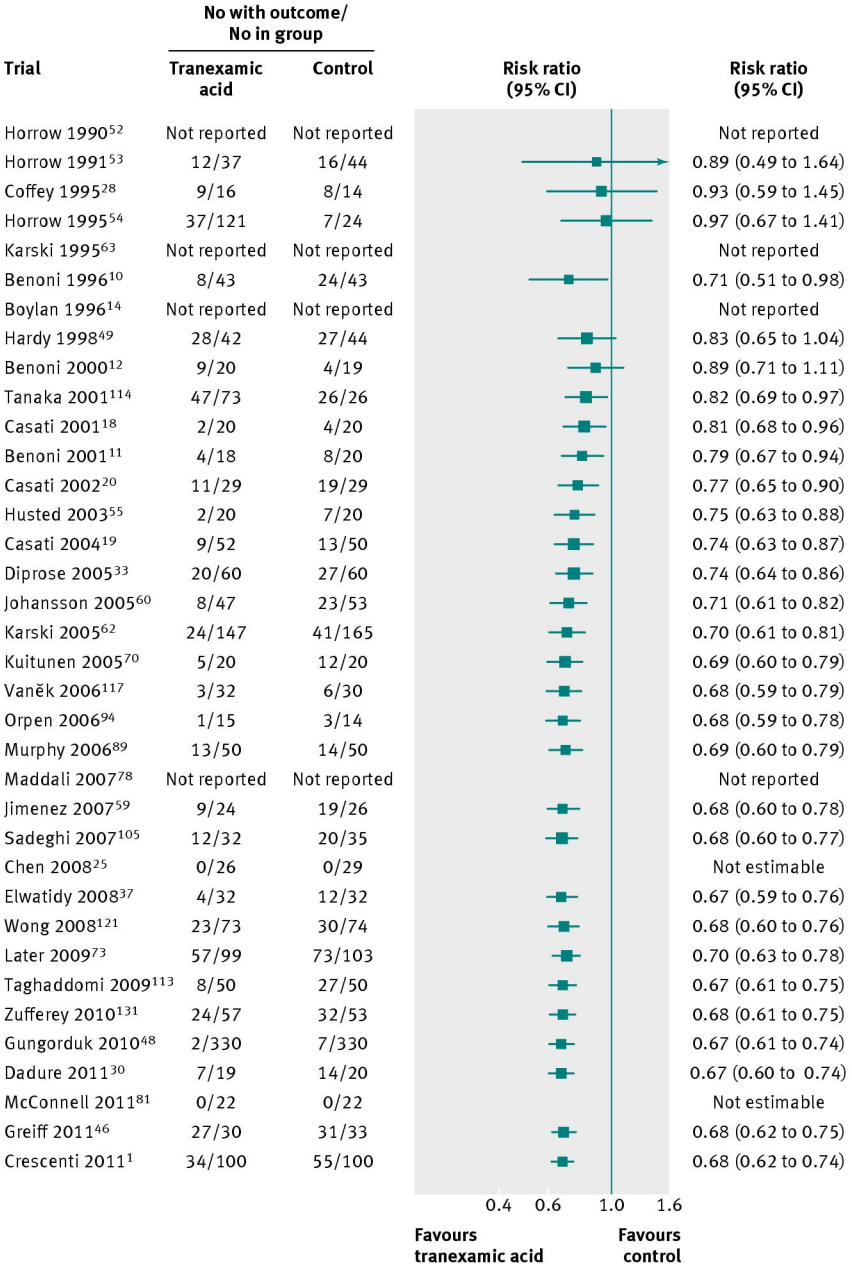

Fig 2 Cumulative meta-analysis of the effect of tranexamic acid in surgery on risk of blood transfusion in adequately concealed trials

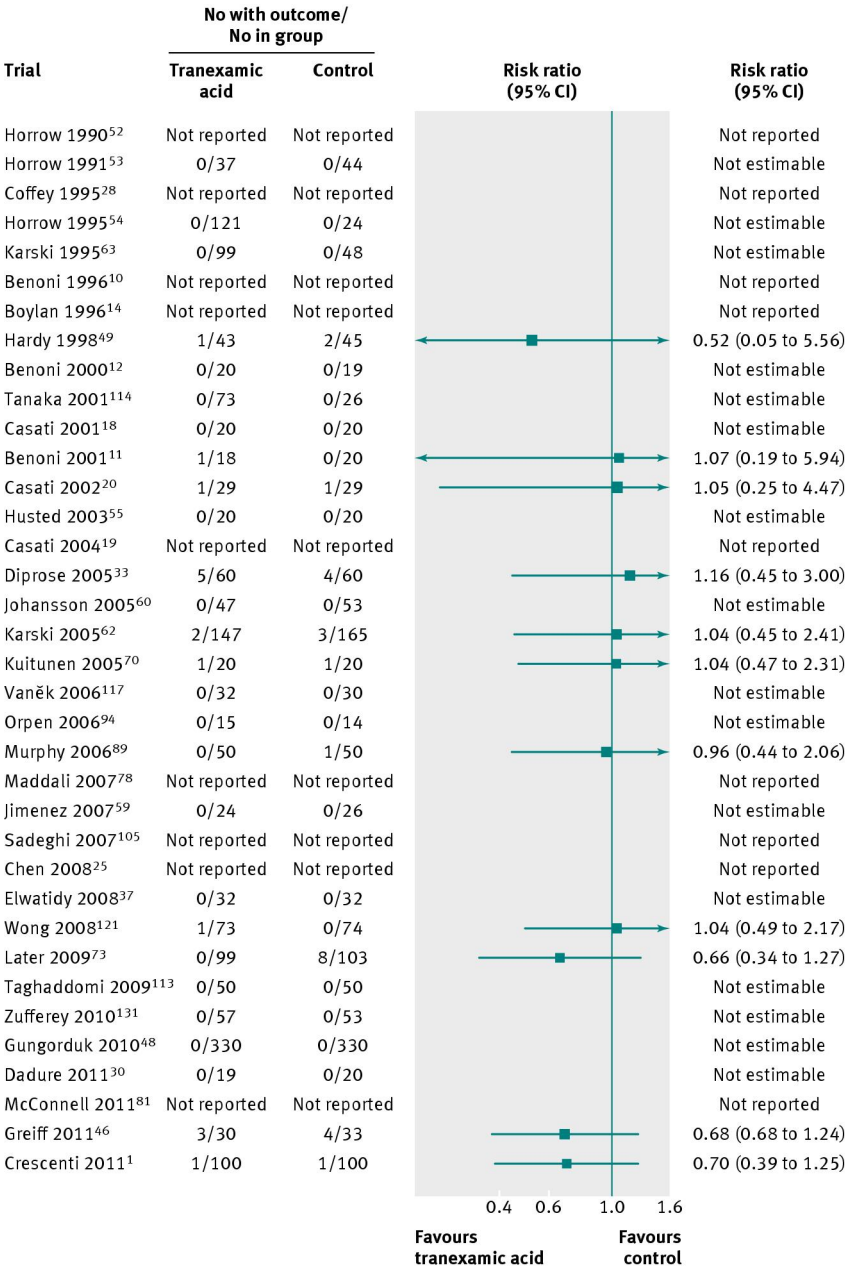

Fig 3 Cumulative meta-analysis of the effect of tranexamic acid in surgery on risk of myocardial infarction in adequately concealed trials

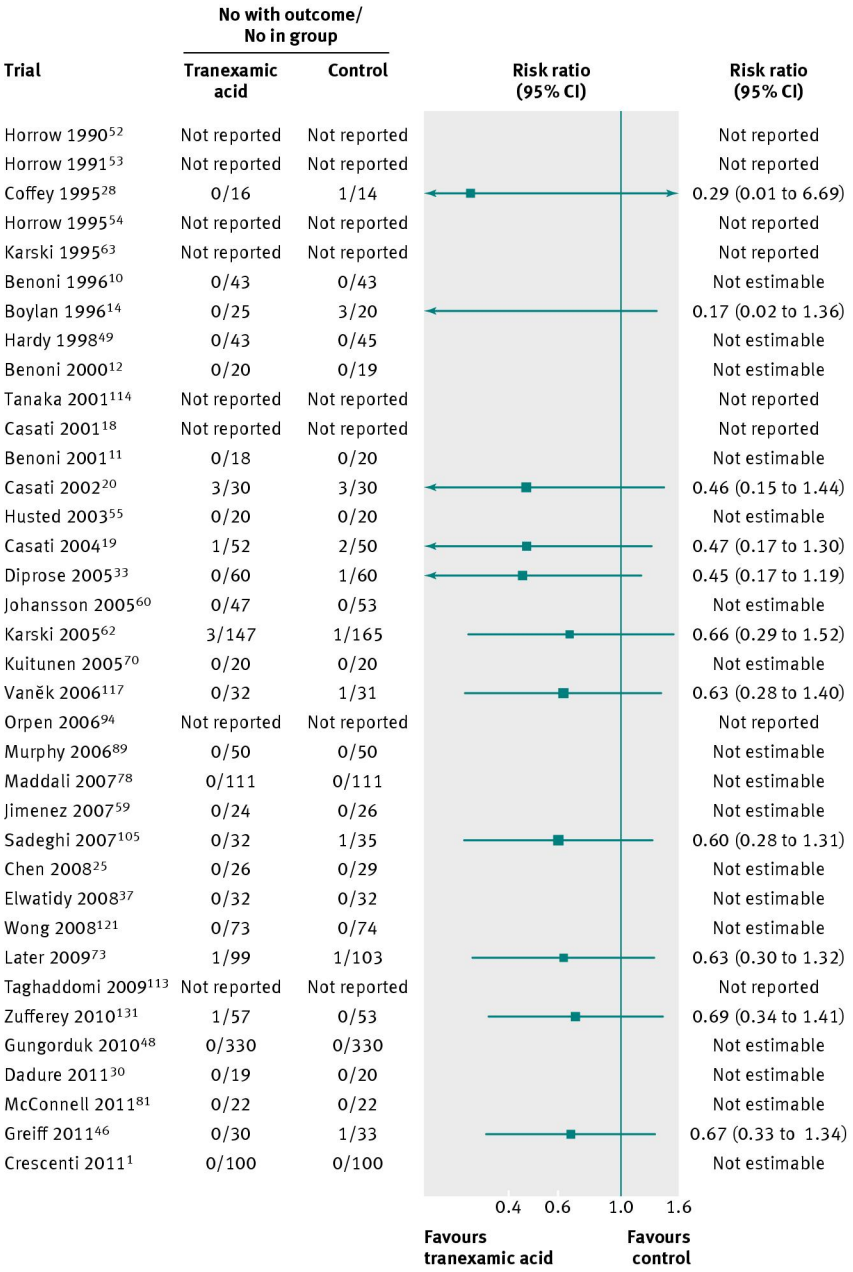

Fig 4 Cumulative meta-analysis of the effect of tranexamic acid in surgery on risk of death in adequately concealed trials

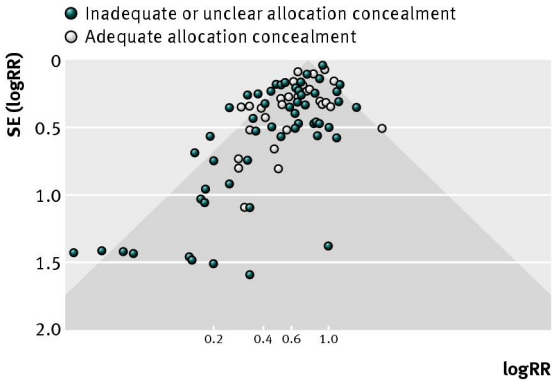

Fig 5 Funnel plot with pseudo 95% confidence limits for meta-analysis on effect of tranexamic acid on risk of blood transfusion