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A randomized trial of tranexamic acid in combination with cell salvage plus a meta-analysis of randomized trials evaluating tranexamic acid in off-pump coronary artery bypass grafting

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Supplemental material is available online.

Objectives: We sought to evaluate the effectiveness of tranexamic acid in off-pump coronary artery bypass grafting surgery, either when used in combination with mechanical cell salvage or when used alone.

Methods: One hundred patients were randomized to either 2 g of tranexamic acid as an intravenous bolus before sternotomy or to placebo. Intraoperative and postoperative cell salvage was used in all patients. The primary end point was early postoperative blood loss (within 4 hours). To evaluate the efficacy of tranexamic acid in isolation, we also performed a meta-analysis of 4 randomized trials identified from a systematic literature search. The primary end point of the meta-analysis was red cell transfusion.

Results: In our randomized trial patients in the tranexamic acid group had a significant reduction in early postoperative blood loss, (median difference, 50 mL; 95% confidence interval, 15-100 mL; $P < .01$); however, there was no reduction in the frequency of blood component transfusion. Patients in the placebo group received a significantly larger volume of autotransfused red cells (median difference, 120 mL; 95% confidence interval, 0-220 mL; $P = .02$). The meta-analysis demonstrated a significant reduction in red cell transfusions in patients receiving tranexamic acid compared with those receiving placebo (risk ratio, 0.48; 95% confidence interval, 0.24-0.97; $P = .041$). There was also a reduction in the frequency of any allogeneic blood component transfusion, as well as a highly significant reduction in postoperative blood loss, in patients receiving tranexamic acid ($P < .001$).

Conclusions: Tranexamic acid reduces blood loss and transfusion requirements in off-pump coronary artery bypass grafting surgery. A reduction in allogeneic blood transfusion was not evident in the presence of perioperative cell salvage. These data support the routine use of tranexamic acid in off-pump coronary artery bypass grafting surgery.

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The evidence base for the development of multimodality blood conservation protocols that minimize transfusion risk is incomplete. Transfusion of blood components increase health care costs both directly through the use of an increasingly scarce commodity and indirectly because of transfusion-associated morbidity attributed to immunosuppression, end-organ dysfunction, and the better-known but rare complications, such as viral transmission.[1-3] Off-pump coronary artery bypass grafting (OPCAB) surgery has been shown in a meta-analysis of randomized trials[4] to reduce the need for allogeneic blood component transfusion compared with conventional coronary artery bypass grafting (CABG); however, up

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Abbreviations and Acronyms
CABG = coronary artery bypass grafting
CI = confidence interval
ICU = intensive care unit
OPCAB = off-pump coronary artery bypass grafting

to a quarter of patients in OPCAB studies[5-7] still receive a transfusion. We have previously demonstrated that mechanical cell salvage and autotransfusion reduces allogeneic blood transfusion rates in OPCAB surgery.[8] There is also evidence from several small randomized trials that tranexamic acid might reduce postoperative blood loss in OPCAB surgery.[9-12] The aim of the present randomized trial was to assess whether the combination of perioperative mechanical cell salvage plus the antifibrinolytic agent tranexamic acid results primarily in a significant reduction in postoperative blood loss and secondarily in a reduction in transfusion requirements compared with perioperative cell salvage plus placebo in patients undergoing OPCAB surgery. We also sought to establish whether the observed reductions in blood loss associated with tranexamic acid use translates into a reduction in red cell transfusions in a larger cohort by performing a meta-analysis of randomized trials that evaluated the efficacy of tranexamic acid alone versus placebo in OPCAB surgery.

Patients and Methods

Study Population and Patient Allocation

Of 153 consecutive patients undergoing isolated OPCAB surgery at the Clinica Montevergine, Mercogliano, Avellino, Italy, over a 6-month period, 100 patients consented to enrollment in the study, 26 refused consent, and a further 27 were judged unsuitable according to the inclusion-exclusion criteria. Inclusion criteria were any male or female patients aged 18 years or older who were undergoing nonemergency first-time OPCAB surgery. Exclusion criteria included advanced chronic renal insufficiency (creatinine >2 mg/dL, n = 12), active chronic hepatitis or cirrhosis (n = 8), neurologic dysfunction (n = 4), and hematologic disorders (n = 1). Patients treated with aspirin or heparin, but not clopidogrel (n = 5), before the operation were enrolled (some patients met more than one exclusion criteria). The study received local ethics committee approval. Patients were assigned in a 1:1 ratio in a double-blind fashion to one of 2 randomized groups: a treatment group (50 patients) who received tranexamic acid as a bolus of 2 g over 20 minutes after the induction of anesthesia but before skin incision and a placebo control group (50 patients) who received a bolus of saline. Allocations were generated by a card system and concealed in sealed opaque envelopes. Both the staff of the operating room and that of the intensive care unit (ICU) were blinded regarding the treatment by the use of identical unmarked syringes for drug or placebo administration. The primary end point for the study was early postoperative blood loss (within 4 hours postoperatively). Given that mean blood loss 4 hours after OPCAB surgery is approximately 250 mL (standard deviation, 120 mL),[9-12] this study was powered to detect a 30% reduction in early blood loss (ie, a mean difference of 75 mL) with an α value of .05 and a power of 0.8. Secondary end points included total blood loss defined as blood loss at the time of drain removal, frequency of red cell transfusion, and frequency of any blood component transfusion. This, as well as clinical outcome data, were collected prospectively on preprinted leaflets and transferred to a computerized database (Microsoft Access 2003; Microsoft Corp, Seattle, Wash).

Operative Technique

The anesthetic technique, including heparin dose (150 IU/kg), target activated clotting time of greater than 300 seconds, and protamine dose (1:1 ratio), was standardized for all patients and has been reported previously.[13] The method of exposure and stabilization used to perform the anastomoses has been described previously.[14] The target vessel was snared proximally before arteriotomy, and an intracoronary shunt (Anastoflo Intravascular Shunt; Research Medical Inc, Midvale, Utah) was used to perform each anastomosis to reduce blood loss.[14] No patient had predonated autologous blood for use perioperatively. All patients underwent perioperative cell salvage (Fresenius C.A.T.S Continuous AutoTransfusion System; Fresenius Kabi Ltd, Warrington, United Kingdom) with autotransfusion of washed salvaged red cells at the completion of the operative procedure. After closure of the sternum, postoperative mediastinal drainage was achieved with 28F single-lumen rigid sump drains (1-3 in number) to a 1000-mL sterile collection chamber connected to 20 cm H_2O wall suction through an underwater seal, from which subsequent shed mediastinal fluid loss was then recorded. In accordance with unit protocols, where sufficient mediastinal loss occurred in any patient (>400 mL), the shed fluid was processed and washed, and shed cells were autotransfused at 6 hours postoperatively or sooner in the event of heavier blood loss. Chest drains were removed when bleeding was less than 100 mL in the preceding 4 hours.

Allogeneic Blood Component Transfusion

Perioperatively, all patients were administered homologous packed red cells as blood replacement therapy, according to predefined unit protocols. The threshold for transfusion of homologous blood was a hemoglobin concentration of less than 8.5 g/dL or a hematocrit value of less than 0.25. As part of routine postoperative care, haemoglobin concentration and hematocrit value were measured on arrival in the ICU and then at 2-hour intervals or as clinically indicated through the indwelling arterial cannula. In patients with excessive blood loss and cardiovascular instability, packed red cells were given at the discretion of anesthetic or ICU staff. Clotting products and platelets were administered at the discretion of the ICU staff in response to bleeding in the presence of coagulopathy or diminished platelet count. We also performed a comparison of hematologic and clotting pathway parameters in the postoperative period (Appendix E1).

Meta-analysis

The MEDLINE and PubMed databases (1966 through November 2004) were searched by using the medical subject headings for "Coronary artery bypass" or the text words "OPCAB" or "off pump" or "beating heart" or "randomized controlled trial" or

"coronary arteriosclerosis" or "myocardial revascularization" combined with the text words "tranexamic acid" or "hemostatics" or "antifibrinolytic agents." In addition, the reference lists from relevant articles, abstracts, and reviews were also searched for additional trials. Study selection was as described in Figure E1.[9-12] Studies were assessed and selected by a single observer (GJM) if they met the following criteria: (1) comparison of tranexamic acid with placebo; (2) patients undergoing OPCAB surgery; (3) prospective randomized controlled methodology; and (4) reporting of postoperative transfusion rates and postoperative blood loss. This identified 3 studies.[9-11] The primary end point for analysis was the frequency of red cell transfusion. Where these data were missing,[11] authors of the study were contacted individually to provide missing data (Table E1). This correspondence also resulted in the identification of a further randomized trial before its publication. This has subsequently been published.[12] A scoring system was not used, and all 4 studies were entered into the meta-analysis. Secondary end points included frequency of any blood component transfusion (early and total blood loss [reported in milliliters]) and the frequency of thromboembolic complications (venous thrombosis, thromboembolism, myocardial infarction, or stroke). In one study[9] data on the total number of patients receiving any blood product were missing, and in this case the figures for the total number of patients receiving red cells were used in the meta-analysis. In 2 of the randomized trials[9,12] data were extracted from studies in which tranexamic acid versus placebo in OPCAB surgery comprised 2 of a total of 3[12] or 4[9] randomized groups, respectively. The thresholds for allogeneic blood transfusion were broadly similar in all of the studies (hemoglobin, 8-8.5 g/dL), and the dose of tranexamic acid administered was the same, a 1-g bolus at anesthetic induction followed by a continuous infusion of 400 mg/h. Data from the present randomized trial were not included because of the significant differences in methodology, such as the use of cell salvage, that were likely to interact with the primary outcome.

Statistical Analysis

Continuous measurements were assessed for normality of distribution. If skewed, data are summarized as a median and interquartile range; otherwise, a mean and standard deviation are given. Data for the 2 groups were compared by using the Mann-Whitney test, and effect sizes are expressed as a median difference or hazard ratio (time measurements). Categoric data were reported as the number and percentage and were compared by using the Pearson χ^2 test or the Fisher exact test (if expected frequencies were <5), and the odds ratio was used to quantify the effect of tranexamic acid for binary variables. Hazard ratios were used to quantify effect sizes for time to event variables. All effect sizes are reported with 95% confidence intervals (CIs).

Meta-analysis was used to combine results from trials examining the effect of tranexamic acid on outcome. A fixed-effects model was chosen because only 4 trials were found. Study results were combined by using the Mantel-Haenszel method (transfusion requirement) or the inverse variance method (blood loss). Blood loss followed a skewed distribution and was transformed to the logarithmic scale for analysis. Results are presented as a risk ratio (transfusion requirement) or as a standardized mean difference (ln[blood loss]). Heterogeneity between studies was assessed by using the χ^2 test. Data analysis was performed with SPSS for Windows, Version 9.0 (Chicago, Ill) and SAS version 8.2 (SAS Institute, Inc, Cary, NC; mixed regression models) and Stata, Version 8.2 (Stata Corporation, College Station, Tex) (meta-analysis) software packages. No correction was made for the number of outcomes compared. Our interpretation of the findings is based on the consistency of the findings and their magnitude, as well as their statistical significance.

Results

Randomized Trial of Tranexamic Acid Versus Placebo in OPCAB Surgery

Preoperative and operative characteristics are shown in Table E2. The 2 groups were balanced preoperatively with respect to demographics and comorbidity, except for a higher proportion of triple-vessel disease in the tranexamic acid group (82% vs 62%, $P = .026$), although the number of grafts performed was similar. EuroSCOREs were similar for the 2 groups ($P = .20$, Table E2). Intraoperative characteristics were also well matched, apart from a longer median operation time in the placebo group (median, 240 [interquartile range, 205-270] vs 210 [interquartile range, 180-240]; $P = .002$). No patients were withdrawn from the study, and there was no crossover between the groups.

There was a significant reduction in blood loss at 4 hours in the patients receiving tranexamic acid compared with those receiving placebo (median difference, 50 mL; 95% CI, 15-100 mL; $P < .01$); however, there was no difference in total blood loss (Table 1). There was no difference in the frequency of allogeneic red cell or other blood component transfusion (odds ratio [tranexamic acid vs placebo], 0.90; 95% CI, 0.37-2.19; $P = .82$). There was no difference between the groups in the frequency of salvaged red cell autotransfusion; however, the median volume of cells autotransfused was significantly higher in the placebo group (median difference, 120 mL; 95% CI, 0-220 mL; $P = .02$). Ventilation time, ICU stay, hospital stay, and the frequency of serious morbidity were similar across the groups (Table 1). There was no difference in the level of postoperative hemodilution between the groups (Table 1). There was no statistically significant difference between the groups at any time point for hematocrit value, platelet count, serum creatinine level, serum fibrinogen level, or tests of coagulation pathway function (Table E3).

Meta-analysis of 4 Randomized Trials of Tranexamic Acid Versus Placebo in OPCAB Surgery

The meta-analysis included a total of 153 patients (Table E1)[9-12] and demonstrated a significant reduction in the frequency of exposure to red cell transfusion (risk ratio, 0.48; 95% CI, 0.24-0.97; $P = .041$) in patients receiving tranexamic acid versus placebo (Figure 1).[9-12] Analysis of secondary end points also demonstrated a significant reduction in the transfusion of any allogeneic blood component (risk

TABLE 1. Postoperative outcome and homologous blood product requirements

Outcome	Placebo (n = 50)	Tranexamic acid (n = 50)	Median difference (95% CI), placebo-autotransfusion	Odds ratio/hazard ratio (95% CI)	*P* value
Homologous RBC transfusion	14 (28%)	13 (26%)		0.90 (0.37 to 2.19)	.82
No. of units					
1	11 (22%)	10 (20%)			
2	3 (6%)	1 (2%)			
3	0	1 (2%)			
4	0	1 (2%)			
Total	17	19			
Platelets–clotting products	0	0			
Drainage, 4 h (mL)	225 (175 to 350)	175 (100 to 250)	50 (15 to 100)		.01
Drainage, total (mL)	460 (325 to 625)	390 (300 to 600)	45 (−30 to 125)		.30
Postoperative cell salvage	31 (62%)	23 (46%)		0.52 (0.23 to 1.16)	.11
No. of patients autotransfused	13 (26%)	12 (24%)		0.90 (0.36 to 2.22)	.82
Volume autotransfused (mL)	400 (300 to 520)	300 (90 to 400)	120 (0 to 220)		.02
Fluid infused, 24 h (mL)	2325 (1490 to 3000)	2500 (1681 to 2950)	−130 (−563 to 265)		.60
In-hospital deaths	0	0			
Ventilation time (h)	9.0 (8.0 to 12.0)	9.0 (8.0 to 11.3)		0.86 (0.58 to 1.23)	.46
Intensive therapy unit stay (d)	1.0 (1.0 to 2.0)	1.0 (1.0 to 2.0)		1.05 (0.71 to 1.56)	.81
Total hospital stay (d)	6.0 (6.0 to 7.0)	6.0 (5.0 to 6.0)		0.99 (0.66 to 1.48)	.95
Postoperative inotropic support	7 (14%)	8 (16%)		1.17 (0.39 to 3.52)	.78
Postoperative vasodilators	9 (18%)	7 (14%)		0.74 (0.25 to 2.17)	.59
Resternotomy	0	1 (2%)			>.99
Arrhythmia	6 (12%)	2 (4%)		0.31 (0.06 to 1.59)	.26
Pulmonary complication	0	0			
Stroke	0	0			
Infective complication	1 (3%)	2 (7%)		2.14 (0.18 to 25.0)	.61
Renal complication	0	1 (2%)			.99
Myocardial infarction	1 (2%)	0			.99

One unit of packed (hematocrit value, 0.6) homologous red cells is approximately 280 mL. *CI*, Confidence interval; *RBC*, leukodepleted packed red blood cells.

ratio, 0.50; 95% CI, 0.26-0.94; $P = .032$; Figure E2). The standardized mean difference for ln(blood loss) for tranexamic acid versus placebo at 4 hours was −1.72 (95% CI, −2.05 to −1.39; Figure E3). There was evidence to suggest heterogeneity between studies for blood loss ($P = .041$). The zero frequency of thromboembolic events in some of the studies did not permit a meta-analysis of these data (Table E1).

Discussion

The main finding of our randomized controlled trial was that tranexamic acid, when used in combination with perioperative cell salvage, results in a significant reduction in early blood loss after OPCAB surgery. There was no difference in the frequency of allogeneic blood component transfusion between the groups. The meta-analysis of randomized trials comparing tranexamic acid with placebo in OPCAB surgery demonstrated a significant reduction in transfusion risk in patients receiving tranexamic acid versus placebo, as well as confirming a significant reduction in postoperative blood loss with tranexamic acid.

Several observations should be considered when reviewing these results; first, in the randomized trial there was a longer operation time in the placebo group, despite similar numbers of bypass grafts between the groups. Prolonged operating times in CABG surgery are associated with greater blood loss and subsequently with blood transfusion.[15] We also cannot discount that this time difference could have been attributable to more bleeding from the operative field, with longer closing times in the placebo group. The magnitude of the time difference was small, however, and there was no difference between the groups with regard to the decrease in hematocrit values between preoperative and immediate postoperative values. We therefore consider it unlikely that this affected our results. Second, median reduction in blood loss in the tranexamic acid group was 50 mL, which suggests a small treatment effect. When one also considers that the median difference in autotransfusion volumes was 120 mL, or approximately half a unit of packed leukodepleted red cells, (patients with only small volume losses over 6 hours were not autotransfused), one can surmise that the treatment effect might be more

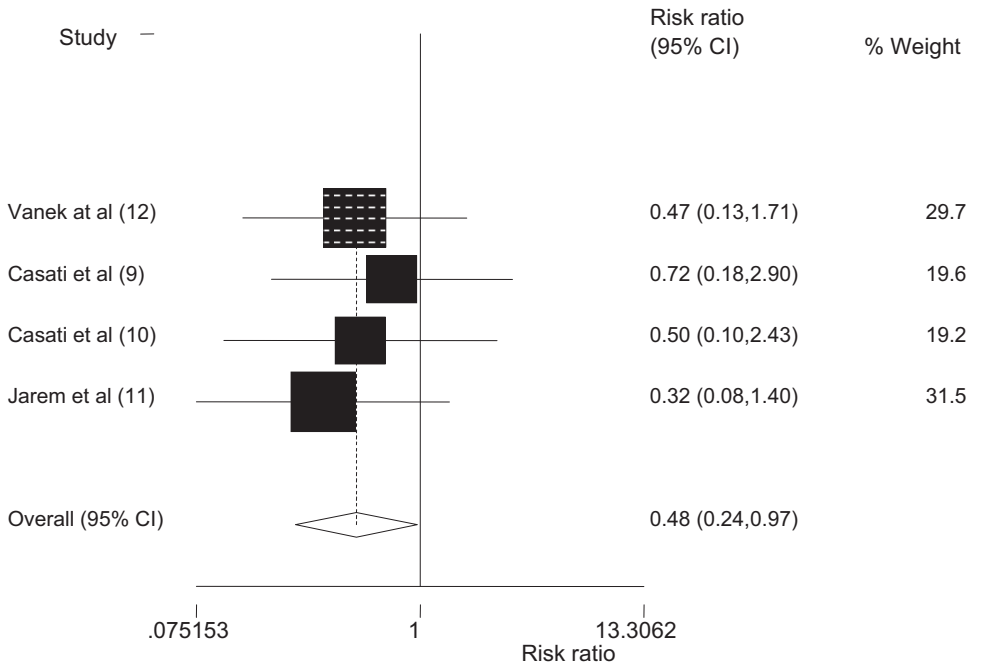

Figure 1. Effect of tranexamic acid on red cell transfusion after OPCAB surgery. Tranexamic acid significantly reduced red cell transfusion. There was no evidence of heterogeneity between the studies (heterogeneity test, 0.61; $P = .90$). *95% CI*, 95% confidence interval.

CSP

clinically significant than this figure suggests, however. By extrapolating from pharmacokinetic studies in patients undergoing conventional CABG,[16] this 2-g bolus dose, approximately 25 mg/kg per patient, should be sufficient to inhibit fibrinolysis in vitro; however, when one considers that the effective half-life of tranexamic acid in patients with normal renal function is approximately 2 hours,[17] this effect might not be sustained.[16] It is noteworthy that total blood loss was not different between treatment and placebo in the current study, unlike those studies cited in the meta-analysis,[9-12] in which an infusion was maintained intraoperatively. Although our data suggest that that higher blood loss in the placebo group was counterbalanced by larger autotransfusions, resulting in equivalent rates of allogeneic transfusion, we cannot exclude the possibility that a larger tranexamic acid dose or an intraoperative infusion might have produced a different result. Third, the randomized study presented here excluded many high-risk patients and is not absolutely representative of the patient population at this institution. Similar criticisms can be made of the studies incorporated into the meta-analysis, where the cohorts recruited appeared to have generally low transfusion risks (few female subjects, relatively high mean body mass, and young patients with good ventricles undergoing nonemergency operations). Whether the observations made either in our randomized trial or in the meta-analysis would also apply in higher-risk cases cannot be extrapolated from these data. Another limitation of the meta-analysis is the small sample size. As well as limiting the power of our observations, it also prevents us from commenting on the safety of tranexamic acid in this setting, given the relative rarity of thromboembolic complications. We have previously calculated that any clinical study powered to detect a significant reduction (10%) in the frequency of allogeneic blood exposure in our OPCAB practice (overall allogeneic transfusion rate, 23%; power, 0.9; α value, 0.05) would require more than 600 patients.[8] This meta-analysis therefore represents the best available evidence to date supporting the efficacy of tranexamic acid in OPCAB surgery. Finally, in the meta-analysis there was heterogeneity between the studies for postoperative blood loss. This can be attributed to different transfusion risks among cohorts in different trials. For example preoperative aspirin within 5 days of the operation, a recognized risk factor for postoperative bleeding and blood transfusion,[18] varied from approximately 25% in one study to 47% in another.[9,11] That this did not translate into heterogeneity between the trials for blood transfusion rates presumably reflects the large differences in blood loss required to alter transfusion rates.

In conclusion, we have previously demonstrated a reduction in postoperative blood loss with the use of mechanical cell salvage in OPCAB surgery. The meta-analysis presented here demonstrates a significant reduction in blood transfusion rates when tranexamic acid is used in isolation. Our randomized trial suggests that tranexamic acid reduces blood loss when combined with perioperative cell salvage; however, there is no reduction in the frequency of allogeneic transfusion. Larger trials are required to confirm these findings and develop more comprehensive multimodality protocols for reducing exposure to allogeneic blood products.

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Appendix E1

Laboratory Measurements of Clotting Pathway Function

Measurement of hematocrit values, platelet counts, clotting pathway function (prothrombin time and international normalized ratio of the prothrombin time, measurement of the extrinsic and common clotting pathways, and measurement of activated partial thromboplastin time expressed as the activated partial thromboplastin time ratio to a normalized control value, a measure of the intrinsic and common clotting pathways), and serum fibrinogen levels were performed preoperatively, immediately postoperatively on admission to the ICU, and then at 24 and 48 hours postoperatively.

Statistical Analysis

Postoperative measurements of hematocrit values, platelet count, clotting parameters, and renal function were compared by using a mixed regression model, with adjustment for preoperative readings. A variety of models describing the correlation between repeated measurements on the same patient were examined, and the structure leading to the lowest value for the Schwarz's Bayesian information criterion was chosen in each case. Creatinine measurements followed a skewed distribution and were transformed to the logarithmic scale for analysis. Changes in treatment effect over time were assessed by using the F test, and if statistically significant at the 10% level, the treatment difference is reported separately at each time point; otherwise, an overall effect of treatment is given (estimate of common difference). Results are presented as least squares means and as difference between means with 95% confidence intervals. Creatinine results are presented as geometric means and as a ratio of geometric means.

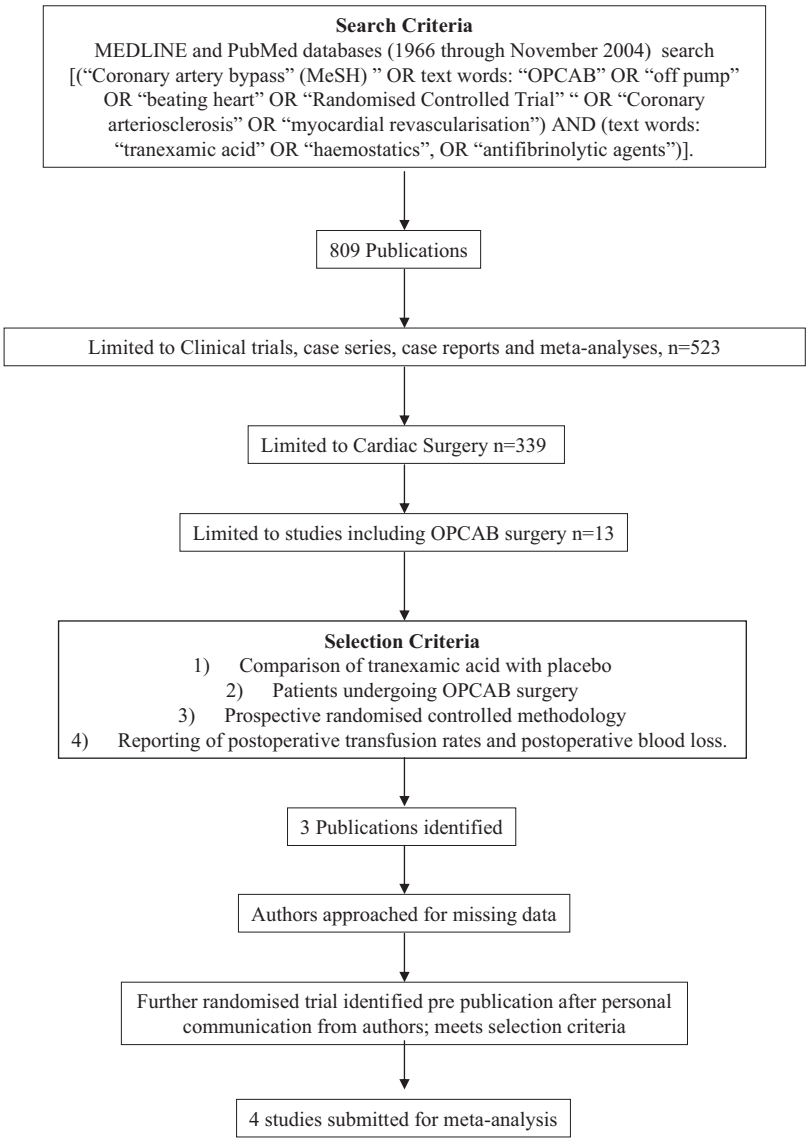

Figure E1. Systematic literature search and study selection for meta-analysis. *OPCAB*, Off-pump coronary artery bypass grafting.

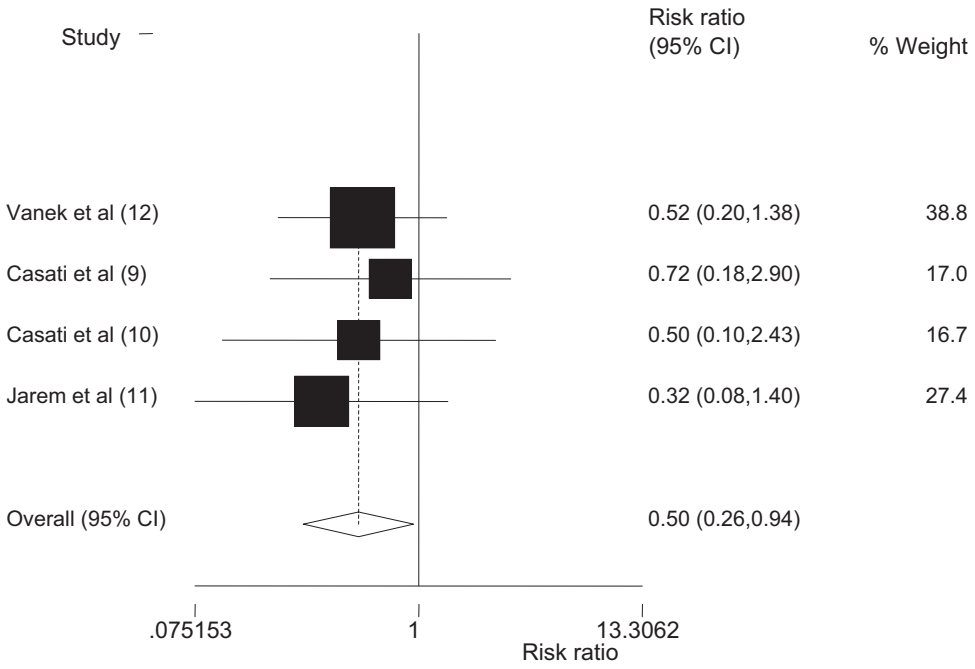

Figure E2. Effect of tranexamic acid on the frequency of any blood component transfusion after off-pump coronary artery bypass grafting surgery. Tranexamic acid significantly reduced exposure to any allogeneic blood product (heterogeneity test, 0.61; $P = .895$). *CI*, Confidence interval.

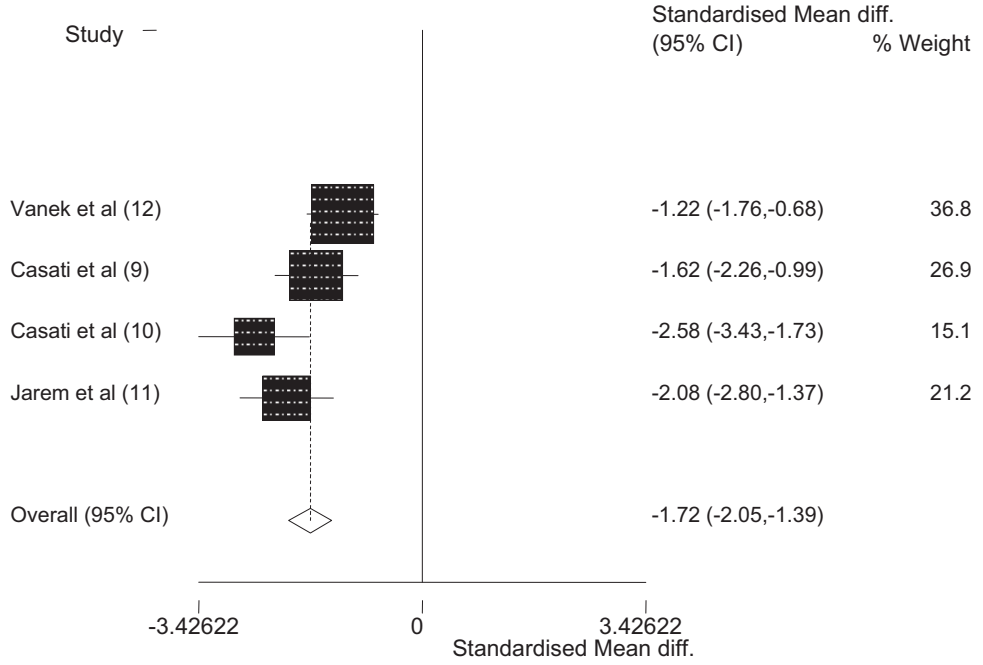

Figure E3. Effect of tranexamic acid on 4-hour blood loss after off-pump coronary artery bypass grafting surgery. Distributions for blood loss followed a skewed distribution and were transformed to the logarithmic scale for meta-analysis. Values represent the standardized mean difference (ln[blood loss]) for tranexamic acid versus placebo. There was evidence to suggest heterogeneity between studies (heterogeneity test, 8.23; $P = .041$). *CI*, Confidence interval.

TABLE E1. Summary of randomized trials of tranexamic acid versus placebo in OPCAB surgery

	Total no. of patients		No. transfused		No. transfused RBC only		Units of RBC transfused	
	Placebo	TA	Placebo	TA	Placebo	TA	Placebo	TA
Vanek and coworkers[12]	30	32	9	5	6	3	14	6
Casati and coworkers[10]	25	26			4	3	11	6
Casati and coworkers[9]	20	20	4	2	4	2	11	4
Jares and coworkers[11]	25	22	7	2	7	2	16	6

RBC, Leukodepleted packed red blood cells; *IQR*, interquartile range; *TA*, tranexamic acid.

CSP

Early blood loss, median (IQR)		24-h Blood loss, median (IQR)		Thromboembolic complications	
Placebo	TA	Placebo	TA	Placebo	TA
192.3 (151.8 to 243.5)	89.3 (72.7 to 109.8), geometric mean (95% CI)	619.8 (524.3 to 732.8)	410.3 (337.6 to 498.6)	0	0
311 (255 to 450)	150 (100 to 190)	654 (510 to 820)	375 (356 to 550)	1	1
375 (295 to 450)	150 (100 to 170)	650 (550 to 875)	400 (338 to 485)	0	0
230 (170 to 260)	115 (92 to 148)	550 (500 to 650)	420 (330 to 523)	1	1

TABLE E2. Patient characteristics

Variable	Placebo (n = 50)	Tranexamic acid (n = 50)
Age (y)	65.8 (8.7)	64.9 (7.0)
Tranexamic acid dose (mg/kg)	0	26.8 (21.9 to 30.1)
Male sex	37 (74%)	42 (84%)
Body mass index (kg/m^2)	28.6 (4.49)	27.3 (4.35)
Diabetes		
Diet	0	2 (4%)
Insulin	8 (16%)	6 (12%)
Oral	14 (28%)	17 (34%)
Hypertension	38 (76%)	37 (74%)
Hyperlipidemia	24 (48%)	26 (52%)
Current smoker	11 (22%)	13 (26%)
COPD	15 (30%)	17 (34%)
Baseline serum creatinine (mg/dL)	0.96 (0.85 to 1.05)	1.01 (0.83 to 1.22)
Renal impairment	1 (2%)	5 (10%)
Previous stroke/neurologic dysfunction	1 (2%)	1 (2%)
Peripheral vascular disease	4 (8%)	4 (8%)
Aspirin within 5 d of operation	2 (4%)	1 (2%)
CCS class (angina)		
0/1	18 (36%)	16 (32%)
2	22 (44%)	27 (54%)
3	8 (16%)	7 (14%)
4	2 (4%)	0
NYHA score (dyspnea)		
I	13 (26%)	13 (26%)
II	30 (60%)	32 (64%)
III	7 (14%)	5 (10%)
MI <1 mo of operation	23 (46%)	24 (48%)
Congestive cardiac failure	2 (4%)	0
Vessels diseased		
2	19 (28%)	9 (18%)
3	31 (62%)	41 (82%)
Ejection fraction <30%	2 (4%)	2 (4%)
Urgent	5 (10%)	6 (12%)
Heparin infusion preoperatively	1 (2%)	3 (6%)
EuroSCORE	3.0 (2.0 to 5.0)	4 (2.75 to 6.0)
No. of grafts	3.0 (2.0 to 3.0)	3.0 (2.0 to 3.0)
Intraoperative inotropes	7 (14%)	3 (6%)
Intraoperative vasodilators	16 (32%)	11 (22%)
Operation time (min)	240 (205 to 270)	210 (180 to 240)

Values represent numbers of patient with percentages, except for continuous variables, where values are means (standard deviations) for normally distributed data and medians (interquartile ranges) for skewed data. *COPD*, Chronic obstructive pulmonary disease; *CCS*, Canadian Cardiovascular Society; *NYHA*, New York Heart Association; *MI*, myocardial infarction.

TABLE E3. Haemoglobin concentration, platelet count, and measures of clotting pathway and renal function: Response over time and effect sizes

Variable	Randomized to tranexamic acid, mean* (SE)	Randomized to placebo, mean* (SE)	Difference	95% CI	*P* value
HCT					
Preoperative	39.39 (0.69)	40.25 (0.58)			
Postoperative	30.14 (0.40)	29.72 (0.41)	+0.42	−0.74 to 1.57	.48
24 h	29.14 (0.42)	29.59 (0.37)	−0.45	−1.57 to 0.67	.43
48 h	26.79 (0.43)	27.89 (0.40)	−1.09	−2.26 to 0.07	.065
Test for common difference		$P = .036$			
Platelets ($\times 10^9$/L)					
Preoperative	221.7 (9.16)	230.5 (8.94)			
Postoperative	168.4 (3.89)	162.1 (3.53)	+6.30	−4.07 to 16.66	.23
24 h	174.9 (4.33)	166.2 (3.96)	+8.78	−2.80 to 20.37	.14
48 h	153.3 (4.42)	159.1 (5.33)	−5.89	−19.44 to 7.85	.40
Test for common difference		$P = .046$			
Creatinine† (mg/dL)					
Preoperative	1.08 (1.06)	0.94 (1.03)			
Postoperative	0.84 (1.02)	0.82 (1.02)	1.027		
24 h	0.94 (1.02)	0.96 (1.02)	0.984		
48 h	0.98 (1.02)	0.95 (1.02)	1.032		
Test for common ratio		$P = .12$			
Estimate of common ratio			1.014	0.968 to 1.062	.55
APTT					
Preoperative	33.18 (0.94)	34.96 (1.22)			
Postoperative	36.17 (0.74)	35.25 (0.79)	+0.92	−1.22 to 3.06	.40
24 h	36.46 (1.01)	37.76 (1.22)	−1.30	−4.43 to 1.83	.41
48 h	46.00 (1.55)	50.60 (1.84)	−4.60	−9.32 to 0.12	.056
Test for common difference		$P = .087$			
PT (s)					
Preoperative	95.40 (1.10)	95.90 (1.03)			
Postoperative	75.09 (1.10)	72.11 (1.19)	+2.98		
24 h	79.50 (1.02)	78.72 (1.16)	+0.78		
48 h	82.39 (0.96)	81.06 (0.89)	+1.33		
Test for common difference		$P = .44$			
Estimate of common difference			+1.70	−0.59 to 3.98	.14
INR					
Preoperative	1.06 (0.012)	1.05 (0.010)			
Postoperative	1.27 (0.014)	1.29 (0.012)	−0.028		
24 h	1.21 (0.012)	1.23 (0.014)	−0.021		
48 h	1.20 (0.012)	1.21 (0.009)	−0.007		
Test for common difference		$P = .58$			
Estimate of common difference			−0.019	−0.045 to 0.007	.15
Fibrinogen (g/L)					
Preoperative	390.3 (15.9)	406.2 (18.2)			
Postoperative	247.9 (6.9)	245.6 (11.3)	+2.34		
24 h	371.2 (13.1)	372.0 (13.4)	−0.73		
48 h	573.2 (17.8)	600.0 (18.2)	−26.79		
Test for common difference		$P = .45$			
Estimate of common difference			−8.39	−39.52 to 22.73	.59

The F test was used to compare the treatment effect (difference between placebo and tranexamic acid) over time (ie, test of an interaction with time). If the difference between placebo and tranexamic acid is similar over time, the treatment effect is pooled over the 3 time points to give one overall estimate of the difference between treatments; otherwise, the effect is reported separately for each time point. There was variation ($P < .10$) in the magnitude of the difference (treatment effect) over the 3 postoperative time points for hematocrit value, platelet count, and activated partial thromboplastin time but not for the other measures. With the possible exception of the hematocrit value and activated partial thromboplastin time at 48 hours ($P = .065$ and $P = .056$, respectively), no significant differences between the 2 groups were found. *SE*, Standard error; *CI*, confidence interval; *HCT*, hematocrit; *APTT*, activated partial thromboplastin time; *PT*, prothrombin time; *INR*, international normalized ratio. *Means for measurements after surgical intervention are adjusted for the preoperative value. †Geometric means and ratio of geometric means. SEs have been transformed back to the original measurement scale. Confidence intervals are calculated as follows: mean/$(SE)^{1.96}$ to mean $\times$ $(SE)^{1.96}$.