Comparison of Two Doses of Tranexamic Acid in Adults Undergoing Cardiac Surgery with Cardiopulmonary Bypass

Stéphanie Sigaut, M.D., Benjamin Tremey, M.D., Alexandre Ouattara, M.D., Ph.D., Roland Couturier, M.D., Christian Taberlet, M.D., Stanislas Grassin-Delyle, Pharm.D., Ph.D., Jean-Francois Dreyfus, M.D., Ph.D., Sylvie Schlumberger, M.D., Marc Fischler, M.D.

ABSTRACT

Background: The optimal dose of tranexamic acid (TA) is still an issue. The authors compared two doses of TA during cardiac surgery in a multicenter, double-blinded, randomized study.

Methods: Patients were stratified according to transfusion risk, then randomized to two TA doses: 10 mg/kg bolus followed by 1 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion (low dose) until the end of surgery or 30 mg/kg bolus followed by 16 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion (high dose). The primary endpoint was the incidence of blood product transfusion up to day 7. Secondary ones were incidences of transfusion for each type of blood product and amounts transfused, blood loss, repeat surgery, TA-related adverse events, and mortality.

Results: The low-dose group comprised 284 patients and the high-dose one 285. The primary endpoint was not significantly different between TA doses (63% for low dose *vs.* 60% for high dose; $P = 0.3$). With the high dose, a lower incidence of frozen plasma (18 *vs.* 26%; $P = 0.03$) and platelet concentrate (15 *vs.* 23%; $P = 0.02$) transfusions, lower amounts of blood products (2.5 ± 0.38 *vs.* 4.1 ± 0.39; $P = 0.02$), fresh frozen plasma (0.49 ± 0.14 *vs.*1.07 ± 0.14; $P = 0.02$), and platelet concentrates transfused (0.50 ± 0.15 *vs.* 1.13 ± 0.15; $P = 0.02$), lower blood loss (590 ± 50.4 *vs.* 820 ± 50.7; $P = 0.01$), and less repeat surgery (2.5 *vs.* 6%; $P = 0.01$) were observed. These results are more marked in patients with a high risk for transfusion.

Conclusions: A high dose of TA does not reduce incidence of blood product transfusion up to day 7, but is more effective than a low dose to decrease transfusion needs, blood loss, and repeat surgery. **(ANESTHESIOLOGY 2014; 120:590-600)**

ONE of the most common complications of cardiac surgery is excessive bleeding mainly caused by fibrinolysis induced by cardiopulmonary bypass (CPB) during and after cardiac surgery.[1,2] Therefore, antifibrinolytic agents are used during cardiac surgery with CPB to prevent excessive blood loss during and after surgery and to minimize transfusion requirements.[3] Three antifibrinolytic agents have been used in this indication: aprotinin, and two lysine analogs, tranexamic and aminocaproic acids. A meta-analysis of 138 randomized, controlled clinical studies showed that blood loss sparing with any of these agents is approximately 300 ml although the number of patients requiring transfusion is decreased.[4] Tranexamic acid (TA) is a synthetic derivative of lysine, and exerts its antifibrinolytic effect through the reversible blockade of lysine-binding sites on plasminogen molecules. Although its use is common, the optimal mode of its administration is still under discussion.

Many modes have been reported in the literature and clinical practice: TA may be administered before or after initiating CPB, as a bolus immediately after anesthesia induction or as a continuous infusion *via* the CPB bypass; similarly, doses administered vary from 10 to 100 mg/kg and are not always adjusted for body weight.

What We Already Know about This Topic

- Bleeding remains a common complication of cardiac surgery, however, the optimal dose of tranexamic acid remains to be clarified
- This study randomized clinical trial compared two dosing regimens of tranexamic acid targeted at 10 or 100 μg/ml

What This Article Tells Us That Is New

- The incidence of blood product transfusion up to postoperative day 7 did not differ significantly between the tranexamic acid doses (63% for low dose *vs.* 60% for high dose)

Most studies conducted over the past 40 yr, based on an *in vitro* study from 1968,[5] stated that the effective antifibrinolytic TA plasma concentration should be stable and greater than 10 μg/ml (64 μM).[6–11] However, analyses on tissue extracts have shown that that concentrations as high as

Submitted for publication October 5, 2012. Accepted for publication June 26, 2013. From the Department of Anesthesiology (S.Sigaut, B.T., S. Schlumberger, M.F.), Clinical Research Unit (J.-F.D.), Hôpital Foch, Suresnes, France; Department of Anesthesiology and Critical Care 2 (A.O.), University Hospital, Bordeaux, France; Department of Anesthesiology, Centre Chirurgical Marie Lannelongue (R.C.), Le Plessis-Robinson, France; Department of Anesthesiology and Critical Care (C.T.), University Hospital, Besançon, France; and Laboratory of Pharmacology and Toxicology (S.G.-D.), Centre Hospitalier Universitaire Raymond Poincaré, Garches, France.

 Anesthesiology 2014; 120:590-600

100 μg/ml may be required to inhibit fibrinolysis.[5] These results corroborate studies showing that higher doses are more effective in decreasing bleeding.[12,13]

Given the limited and conflicting evidence regarding the optimum administration regimen of TA during cardiac surgery with CPB, we conducted a randomized clinical trial comparing the effectiveness of two TA dosing schedules during cardiac surgery: a low-dose regimen, according to Horrow *et al.*,[10] aiming at a stable 10 μg/ml TA plasma concentration, and a higher dose, according to Dowd *et al.*,[13] aiming at a stable plasma concentration greater than 100 μg/ml as used in the Blood Conservation Using Antifibrinolytics in a Randomized Trial study.[14] For each dose group, data are presented in two strata (high and low) of transfusion risk.

Materials and Methods

Study Design

This study was a multicenter, double-blinded, randomized controlled study, comparing two dose levels of TA as an antifibrinolytic agent during cardiac surgery. Patients enrolled at four French teaching-hospital clinical centers (Hôpital Foch, Suresnes; Centre Chirurgical Marie Lannelongue, Le Plessis Robinson; Hôpital Haut-Lévêque, Pessac; Hôpital Jean Minjoz, Besançon) underwent scheduled cardiac surgery with CPB.

In accordance with the French regulations, the study was approved by the relevant French authorities and the Comité de Protection des Personnes Ile-de-France VIII (Boulogne-Billancourt, Hauts-de-Seine, France) acting as a central ethics committee. All patients received detailed oral and written information during the preanesthetic consultation and gave their written informed consent.

This institutional study was sponsored solely by Hôpital Foch without any involvement of drug manufacturers; in particular, TA (Exacyl®, Sanofi, Paris, France), was purchased according to the normal routine of the hospital pharmacy of each clinical center; the protocol was registered with the European clinical trials database (2008-003831-20), and ClinicalTrials.gov (NCT00809393) and conducted according to the Good Clinical Practices guidelines and in compliance with European and French laws and regulations.

Study Population

From February 2009 to January 2011, patients aged more than 18 yr scheduled for cardiac surgery, and requiring CPB, including coronary artery bypass graft, valve surgery, aortic surgery, and intracardiac tumors, were enrolled. Patients at both high and low risk for transfusion were eligible. Patients were considered at high risk for transfusion if they were receiving a dual antiplatelet at any time within 5 days of surgery, or in the following cases: repeat coronary artery bypass graft, repeat valve surgery (replacement or repair), combined coronary artery bypass graft and valve surgery, multiple valve surgery, surgery of the aorta, intracardiac tumor ablation, and surgery for endocarditis. All other cardiac surgery procedures were considered low risk.

Noneligibility criteria were as follows: emergency surgery, pregnancy (a pregnancy test was performed in all patients of child-bearing potential), known allergy to TA or any of the Exacyl® excipients, history of arterial or venous thrombosis or embolism, history of seizure, antifibrinolytic or thrombolytic treatment within 5 days of surgery, and chronic hemostasis abnormality (prothrombin ratio <50% or international normalized ratio >2, platelet count $<50 \times 10^9$ l^{-1}, fibrinogen <1 g/l). We also excluded patients with chronic liver disease (grade B or C of the Child-Pugh classification), severe chronic kidney disease with creatinine clearance less than 30 ml/min, patients who refused blood transfusion, and those who participated in another clinical study.

Procedures

After preoperative stratification according to the expected risk for transfusion, the anesthesiologist in charge randomly allocated patients to one of the two TA dose levels. Sequentially numbered sealed envelopes were used to this effect, prepared by the sponsor's statistician for each transfusion risk stratum (as determined preoperatively) and for each center. A computer-generated random sequence with blocks of size 2, 4, and 6 was used. Patients, anesthesiologists, and clinical staff were blinded to the dose. Syringes were prepared by a pharmacist not involved in clinical care. Low-dose TA consisted of a 10 mg/kg bolus administered 15 min after anesthesia induction, followed by a 1 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion; high-dose TA consisted of a 30 mg/kg bolus followed by a 16 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion. Infusion of TA was ended when the wound dressings were placed and the anesthesiologist agreed to take the patient to the intensive care unit. In addition, the low-dose and high-dose groups received, respectively, 1 and 2 mg/kg with the priming solution in the venous reservoir just before the beginning of the CPB period. The low-dose regimen was based on the dosing protocol of Horrow *et al.*,[10] and the high-dose regimen on the pharmacokinetic model of Dowd *et al.*[13]

The study drug was injected in a central or peripheral venous line, using a syringe driver. The initial bolus was a 100 ml isotonic solution (TA concentration: low dose = 0.1 $mg \cdot kg^{-1} \cdot ml^{-1}$; high dose = 0.3 $mg \cdot kg^{-1} \cdot ml^{-1}$). Infusion (TA concentration: low dose = 0.2 $mg \cdot kg^{-1} \cdot ml^{-1}$; high dose = 3.2 $mg \cdot kg^{-1} \cdot ml^{-1}$) was administered from a 50 ml syringe at a 5 ml/h rate. The dose injected through the CPB tubing was a 20 ml isotonic solution (TA concentration: low dose = 0.05 $mg \cdot kg^{-1} \cdot ml^{-1}$; high dose = 0.1 $mg \cdot kg^{-1} \cdot ml^{-1}$).

Either an opioid-based anesthetic supplemented with volatile agents, or total intravenous anesthesia with propofol, remifentanil, and muscle relaxants was used. Monitoring included an indwelling arterial catheter and a central venous catheter. Heparin dosing and maintenance was guided in all centers by the same strict protocol. Before CPB all patients received a 300 U/kg dose of heparin, and if necessary

additional doses were injected to achieve and maintain an activated clotting time greater than 480 s during CPB. The CPB pump flow was adjusted to maintain a mean arterial pressure greater than 60 mmHg. All patients underwent median sternotomy and myocardial preservation. After discontinuation of CPB, heparin was reversed with protamine sulfate to return the activated clotting time to within 10% of the preheparin level (dose based on blood heparin levels measured by Hepcon® HMS [Medtronic, Minneapolis, MN]). A blood salvage device was used in all patients. Blood samples were collected as usual for hemoglobin and activated clotting time monitoring.

Transfusion was guided at all centers by the same transfusion algorithm: packed erythrocytes if hemoglobin less than 80 g/l (or 60 g/l during CPB), fresh frozen plasma (FFP) when prothrombin ratio was less than 50%, platelet concentrate (PC) when platelet count was less than 70×10^9 l^{-1}, and fibrinogen when fibrinogen less than 1 g/l. Transfusion was performed only in presence of these results and when obvious clinical bleeding was present as determined by physicians.

Measurements/Endpoints

The primary study endpoint was the incidence of overall blood transfusion during surgery and up to 7 days after surgery. Secondary endpoints were: incidence of packed erythrocytes, frozen plasma, and PC transfusion during surgery and for up to 7 days after surgery; number of packed erythrocytes, frozen plasma, and PC administered on the first 7 days after surgery; blood loss during the first 24 h; repeat surgery because of bleeding; required doses of fibrinogen; and 7- and 28-day mortality. Creatinine and coagulation parameters were recorded, and adverse events were noted as they occurred.

Statistical Methods

Sample Size. The 2007 database of the Department of Anesthesiology of Hôpital Foch included 249 cardiac surgical patients. Among them, 131 patients belonged to the high-risk stratum for transfusion during surgery and up to 7 days after surgery and 233 to the low-risk stratum. The transfusion proportion was 69.4% in the high-risk group and 50.6% in the low-risk stratum. The sample size of 245 patients per group was calculated so as to provide a power of 0.8 to detect a reduction of 13% of transfused patients in overall population, *i.e.*, a final transfusion proportion of 44% with a bilateral α risk of 0.05 (based on a reduction by 20 and 10% of the proportion of transfused high-risk and low-risk patients, respectively). A sample size of 300 patients per group, *i.e.*, a total of 600 patients, was recommended to allow for an attrition rate of up to 10% and for one interim analysis, which required the addition of 17 patients based on an analog of O'Brien spending function.

Interim Analysis. An interim analysis for futility was performed when 300 patients had been treated. The independent statistician recommended that the study be continued. As safety was considered acceptable, recruitment was continued up to the planned 600 patients.

Final Statistical Analysis. The primary analysis was an intent-to-treat analysis in which patients were analyzed in the group to which they had been randomly assigned regardless of the actual dose of TA they had received. Routine descriptive analyses were performed in accordance with the statistical plan. For all inferential statistical procedures, a 0.05 bilateral α risk was used. A full log-linear model was fitted over qualitative variables' frequencies for doses, risks, and centers. When a significant interaction term was present, relevant cell counts were summed and Fisher exact test was performed providing a *P* value for summed counts. For quantitative variables, a generalized linear model was used with center, dose, and risk as fixed factors. All interaction terms were analyzed to determine whether results could be generalized across factor levels. Safety data (adverse effect incidence) were compared using Fisher exact test between dose groups. Statistical tests used for each variable are detailed in the table footnotes.

Data analysis was performed with NCSS 2007 (Kaysville, UT) and R 2.12.0 (The R Foundation for Statistical Computing, Vienna, Austria) running on a computer using Windows 7 (Microsoft Corp., Seattle, WA). Data are presented as mean ± SEM or number (%) of total patients in each group.

Results

Study Population

From February 2009 to January 2011, we obtained consent from 596 patients, of which 27 did not undergo randomization. Among the remaining 569 patients, 311 were considered preoperatively at low risk for transfusion, and 258 were considered at high risk for transfusion. In the low-risk stratum, 156 patients were randomized in the low-dose group, and 155 in the high-dose group. In the high-risk stratum, 128 patients were randomized in the low-dose group, and 130 in the high-dose group. In total, 284 patients were randomized to the low-dose group and 285 patients to the high-dose group. Twenty patients (3.5%) did not receive the assigned dose but were included in our intent-to-treat analysis. Thirty-nine patients (6.9%) had a surgery that was of a different risk class than the one for which they were randomized. In order to be clinically relevant, the statistical analysis was performed according to the real risk, and not to the preoperative estimate risk used for randomization. The flowchart summarizes the distribution of patients (fig. 1). For one of the centers (Hôpital Haut-Lévêque, Pessac), deaths were not recorded after day 7.

Study groups were similar at baseline (table 1), the only significant differences being a higher incidence of type 1 diabetes mellitus (3.4 *vs.* 7.6%; $P = 0.03$), a higher preoperative creatinine level (90.4 ± 1.5 μM *vs.* 95.7 ± 1.5 μM; $P = 0.04$), and a higher international normalized ratio (1.1 ± 0.01 *vs.* 1.4 ± 0.01; $P < 0.0001$) in the high-dose group.

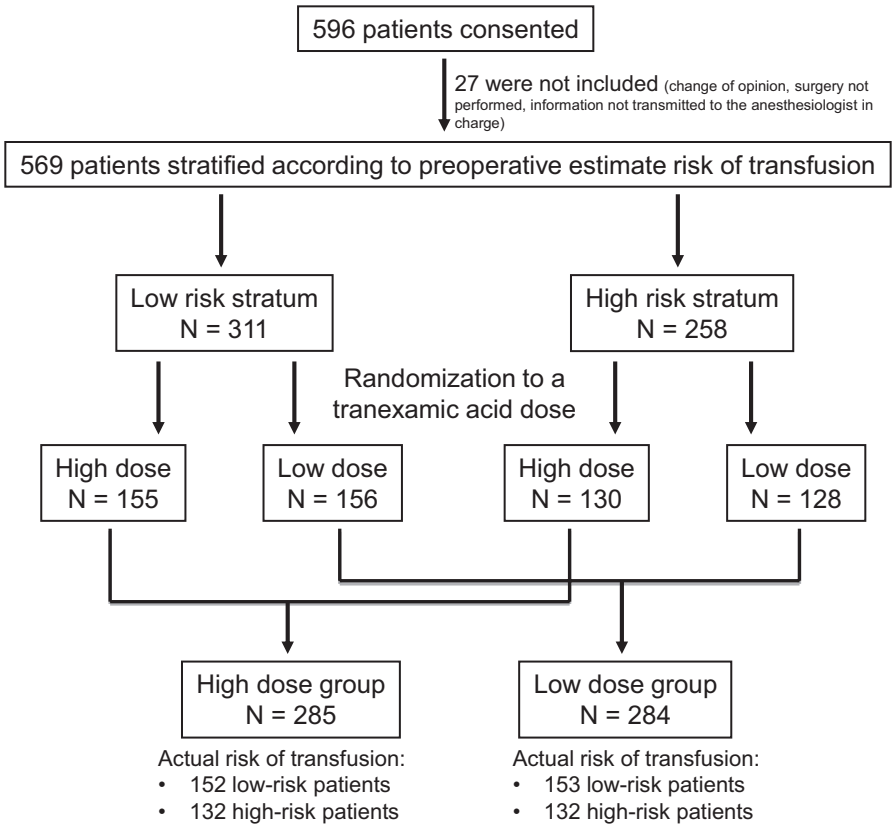

Fig. 1. Trial profile.

No significant between-dose group difference existed as regards preoperative treatment (table 2).

Surgery-related data are displayed in table 3, and operative data in table 4. Patients receiving bypass had a significantly higher number of bypasses in the high-dose group than in the low-dose group (2.9 ± 0.8 *vs.* 2.5 ± 0.7; $P = 0.005$).

In some cases, the center factor and dose × center and dose × risk × center interaction terms were found to be significant. Some of them are outlined in the Discussion, as they represent a limitation to direct extrapolation of these results to every center.

Blood Product Transfusion

On the primary endpoint, the number of patients who received at least 1 unit of blood product during the first postoperative week (including intraoperative period), the difference between low- and high-dose groups was not statistically significant (180 [63%] in the low-dose group, *vs.* 170 [60%] in the high-dose group; table 5).

The incidence of at least one FFP administration during surgery and up to 7 days after surgery was significantly lower in the high-dose group (26 *vs.* 18%; $P = 0.03$). The same was true for the administration of PC (23% in the low-dose group *vs.* 15% in the high-dose group; $P = 0.02$). The difference of incidence for packed erythrocyte transfusion was not significant (59% in the low-dose group *vs.* 56% in the high-dose group; $P = 0.4$).

The mean amount of blood products transfused during surgery and up to 7 days after surgery was significantly lower in the high-dose group: 4.1 ± 0.39 *versus* 2.5 ± 0.38; $P = 0.02$. The mean amount of FFP administered was also significantly lower in the high-dose group (1.1 ± 0.14 *vs.* 0.5 ± 0.14; $P = 0.02$), as was that of PC (1.1 ± 0.15 *vs.* 0.5 ± 0.15; $P = 0.02$), but there was no significant difference concerning the amount of packed erythrocytes transfused (2.1 ± 0.18 *vs.* 1.6 ± 0.18; $P = 0.07$). Furthermore, the incidence of fibrinogen administration was significantly lower in the high-dose group (2.8 *vs.* 0.4%; $P = 0.02$). As to transfusions that occurred during surgery, the only significant between-dose difference was a lower incidence and a lower amount of PC transfused in the high-dose group (table 6). Results for each center are presented in the appendix.

Blood Loss and Repeat Surgery because of Bleeding

In the high-dose group, blood loss during the first 24 h after surgery was significantly lower than in the low-dose group (820 ± 50.7 *vs.* 590 ± 50.4 ml; $P = 0.01$). Similarly, the incidence of bleeding-related repeat surgery was significantly lower in the high-dose group (6.2 *vs.* 2.5%; $P = 0.03$; table 7).

Death and Other Adverse Events

There was no statistically significant difference between the two dose regimens regarding mortality at 7 days (3.2% for the low-dose group and 1.4% for the high-dose group) and

Table 1. Demographic and Preoperative Characteristics of the Patients

	Low Dose n = 284	High Dose n = 285
Age (yr)	67.3 ± 0.70	67.7 ± 0.69
Male sex	199 (69.1)	212 (72.9)
Weight (kg)	75.8 ± 0.92	76.7 ± 0.90
Height (cm)	167.8 ± 0.49	168.7 ± 0.51
Hypertension	172 (60.6)	179 (62.8)
Diabetes mellitus (type 1 + type 2)	62 (21.8)	59 (20.7)
Ejection fraction (%)	58.7 ± 0.63	58.9 ± 0.62
EuroSCORE	5.1 ± 0.17	4.9 ± 0.17
Endocarditis	8 (2.8)	8 (2.8)
Creatinine (μM)	90.4 ± 1.47	95.7 ± 1.47
Hemoglobin (g/dl)	13.4 ± 0 .09	13.4 ± 0.10
Platelet count (10^9 l^{-1})	226.6 ± 4.28	235.4 ± 4.24
Prothrombin ratio (%)	90.4 ± 0.78	88.5 ± 0.77
APTT ratio	1.1 ± 0.01	1.1 ± 0.01
Fibrinogen (g/l)	3.8 ± 0.08	3.7 ± 0.08

Data are presented as mean ± SEM or number (%) of patients.
APTT = activated partial thromboplastin time.

28 days (5.2% for the low-dose group and 3.0% for the high-dose group; table 7).

The incidence of adverse events, including renal dysfunction (defined as creatinine higher than twice its initial value or >150 μM), thromboembolic events (stroke, pulmonary embolism, and deep venous thrombosis), and seizures were not different between the high- and low-dose groups (table 8).

Postoperative Biological Results

There were no significant between-dose differences in the laboratory parameters recorded postoperatively (highest creatinine concentration during first week after surgery, and hemoglobin concentration, platelet counts, prothrombin ratio, activated partial thromboplastin time ratio, and fibrinogen concentration on the first day after surgery; table 9).

Table 2. Preoperative Drug Therapy

	Low Dose n = 284	High Dose n = 285
β-blocker	143 (50.4)	157 (55.1)
ACE inhibitor	159 (56.0)	150 (52.6)
Calcium-channel blocker	60 (21.1)	66 (23.2)
Nitrates	28 (9.9)	31 (10.9)
Anticoagulant		
Heparin	29 (10.2)	29 (10.2)
Warfarin	25 (8.8)	24 (8.4)
Antiplatelet agent		
Aspirin	157 (55.3)	167 (58.6)
Clopidogrel	39 (13.7)	34 (11.9)
Glycoprotein IIa/IIIb inhibitor	3 (1.1)	5 (1.8)
Dual antiplatelet therapy	27 (9.5)	25 (8.8)

Data are presented as number (%) of patients.
ACE = angiotensin-converting enzyme.

Table 3. Surgical Procedures

	Low Dose N = 284	High Dose N = 285
Low-risk group		
CABG	67 (23.6)	81 (28.4)
Valve replacement	72 (25.4)	60 (21.1)
Valve plasty	13 (4.6)	12 (4.2)
High-risk group		
Repeat CABG	1 (0.4)	4 (1.4)
CAGB and double antiplatelet agents	24 (8.5)	19 (6.7)
CABG + valve surgery	38 (13.4)	34 (11.9)
Repeat valve surgery	6 (2.1)	4 (1.4)
Valve surgery and double antiplatelet agents	0 (0)	2 (0.7)
Multiple valve surgery	8 (2.8)	6 (2.1)
Aorta surgery	37 (13.0)	47 (16.5)
Repeat aorta surgery	3 (1.1)	1 (0.4)
CABG + aorta surgery	5 (1.8)	4 (1.4)
Cardiac tumor surgery	2 (0.7)	1 (0.4)
Endocarditis surgery	8 (2.8)	8 (2.8)
Other*	0 (0)	2 (0.7)

Data are presented as number (%) of patients.
* One case of sinus of valsalva rupture and one surgery for left ventricular aneurism.
CABG = coronary artery bypass graft.

Risk Strata Analysis

There was a significant risk × dose interaction for the mean number of total blood products transfused during the first week; the between-dose difference for this amount did not differ in the low-risk stratum (low dose: 2.2 ± 0.52, high dose: 2.2 ± 0.52) but was significantly lower in the high-risk stratum with the high dose (low dose: 6.0 ± 0.59, high dose: 2.8 ± 0.57; P = 0.05). In other cases of significant dose × risk interaction, dissimilar outcomes for dose effects were also noted between the high- and low-risk strata for FFP

Table 4. Operative Data

	Low Dose n = 284	High Dose n = 285
Duration of surgery, min	265.2 ± 5.05	259.8 ± 5.03
Duration of CPB, min	88.0 ± 2.35	91.4 ± 2.33
Duration of aortic clamp, min	66.9 ± 1.96	69.5 ± 1.94
Tranexamic acid, total dose, mg	1,177 ± 323	7,669 ± 2,319
Heparin, total dose, U	27,958 ± 405	28,622 ± 403
Protamine, total dose, mg	29,175 ± 476	30,416 ± 472
ACT before heparin, s	121 ± 1.2	126 ± 1.2
ACT after heparin, s	477 ± 5.4	473 ± 5.4
ACT after protamine, s	126 ± 0.9	125 ± 0.9

Data are presented as mean ± SEM.
ACT = activated clotting time; CPB = cardiopulmonary bypass.

Table 5. Transfusion during the First Week, Including Intraoperative Period, Between-dose Comparisons

	Low Dose n = 284	High Dose n = 285	*P* Value
Transfusion during the first week; all patients			
Blood transfusion (yes)	180 (63.4)	170 (59.6)	0.3†
Packed erythrocyte transfusion (yes)	167 (58.8)	160 (56.1)	0.4†
FFP transfusion (yes)	74 (26.1)	53 (18.6)	0.03†
PC transfusion (yes)	64 (22.5)	43 (15.1)	0.02†
Fibrinogen (yes)	8 (2.8)	1 (0.4)	0.02†
Blood products (number of units)	4.10 ± 0.39	2.49 ± 0.38	0.02*
Packed erythrocytes (number of units)	2.14 ± 0.18	1.57 ± 0.18	0.07*
FFP (number of units)	1.07 ± 0.14	0.49 ± 0.14	0.02*
PC (number of units)	1.13 ± 0.15	0.50 ± 0.15	0.02*
Transfusion during the first week; patients transfused			
Packed erythrocytes (number of units)	3.61 ± 0.24	2.81 ± 0.25	0.08*
FFP (number of units)	4.99 ± 0.38	2.90 ± 0.45	0.04*
PC (number of units)	5.45 ± 0.42	4.34 ± 0.53	0.3*

Data are presented as mean ± SEM or number (%) of patients.

* General linear model with dose, risk, and center as main factors; dose effect. † Log-linear model with dose, risk, center as main factors; dose effect.

FFP = fresh frozen plasma; PC = platelet concentrate.

and PC (incidence and amounts). In all cases the low dose led to small differences, if any, in the low-risk stratum but to more marked differences in the high-risk stratum (table 10).

Concerning bleeding and mortality, between-dose comparisons in low and high risk for transfusion strata are presented in table 11. The only significant result is less blood loss during the first 24 h with the high-dose group in the low-risk stratum.

Discussion

The withdrawal of aprotinin from the market has increased the use of TA to reduce perioperative bleeding during cardiac surgery with CPB, and has highlighted the need for an optimal dose regimen. The results of the current study show that our primary endpoint, the proportion of patients receiving blood products up to day 7 postoperatively, did not differ between the two regimens. However, the higher-dose regimen infusion decreased the incidence of FFP and PC transfusion and the amount of total blood products, FFP, and PC administered. Furthermore, postoperative bleeding and the need for reoperation for hemostasis control decreased with this regimen. This set of findings on secondary outcomes has important clinical implications.

In a randomized clinical trial Horrow *et al.*[10] reported that high doses were unnecessary for reducing blood loss and that a 10 mg/kg bolus dose followed by 1 $mg \cdot kg^{-1} \cdot h^{-1}$ for 12 h was effective and sufficient to decrease postoperative bleeding. A more recent study comparing the regimen of Horrow *et al.* with a higher dose (loading dose of 6.6 mg/kg followed by 6 $mg \cdot kg^{-1} \cdot h^{-1}$ and a 40 mg priming in the CPB tubing)[11] showed

Table 6. Transfusion during the First Day, Including Intraoperative Period, Between-dose Comparisons

	Low Dose n = 284	High Dose n = 285	*P* Value
Transfusion during the first day; all patients			
Blood transfusion (yes)	111 (39.0)	107 (37.5)	0.6†
Packed erythrocyte transfusion (yes)	91 (32.0)	95 (33.3)	0.9†
FFP transfusion (yes)	35 (12.3)	24 (8.4)	0.09†
PC transfusion (yes)	35 (12.3)	17 (6.0)	0.01†
Packed erythrocytes (number of units)	0.9 ± 0.08	0.9 ± 0.08	>0.9*
FFP (number of units)	0.4 ± 0.07	0.2 ± 0.07	0.11*
PC (number of units)	0.5 ± 0.08	0.2 ± 0.08	0.02*
Transfusion during the first day; patients transfused			
Packed erythrocytes (number of units)	2.6 ± 0.1	2.3 ± 0.1	0.4*
FFP (number of units)	3.2 ± 0.3	2.4 ± 0.4	0.4*
PC (number of units)	2.1 ± 0.3	5.0 ± 0.48	0.11*

Data are presented as mean ± SEM or number (%) of patients.

* General linear model with dose, risk, and center as main factors; dose effect. † Log-linear model with dose, risk, and center as main factors; dose effect.

FFP = fresh frozen plasma; PC = platelet concentrate.

Table 7. Bleeding and Mortality, Between-dose Comparisons

	Low Dose n = 284	High Dose n = 285	*P* Value
Blood loss during day 1 (ml)	820 ± 50.7	590 ± 50.4	0.01*
Return to surgery for hemostasis	17 (6.0)	7 (2.5)	0.03†
Mortality from day 0 to day 7	9 (3.2)	4 (1.4)	0.2†
Mortality from day 0 to day 28	14 (4.9)	8 (2.8)	0.2†

Data are presented as mean ± SEM or number (%) of patients.

* General linear model with dose, risk, and center as main factors; dose effect. † Log-linear model with dose, risk, and center as main factors; dose effect.

Table 9. Postoperative Results

	Low Dose N = 284	High Dose N = 285	*P* Value
Creatinine, μM	93.4 ± 1.7	97.6 ± 1.6	0.2*
Hemoglobin, g/dl	10.6 ± 0.09	10.7 ± 0.09	0.8*
Platelet count, 10^9 l^{-1}	141.8 ± 3.2	146.8 ± 3.1	0.4*
PR, %	60.5 ± 0.6	60.7 ± 0.6	0.9*
APTT, s	42 ± 1	39 ± 1	0.2*
Fibrinogen, g/l	2.3 ± 0.04	2.4 ± 0.04	0.4*

Creatinine is the highest creatinine level measured the week after surgery. Data are presented as mean ± SEM.

* General linear model with dose, risk, and center as main factors, dose effect.

APTT = activated partial thromboplastin time; PR = prothrombin ratio.

that postoperative mediastinal blood loss and transfusion requirements did not significantly differ between groups. Conversely, Karski *et al.*[12] reported the superiority of a single dose of 100 mg/kg compared with 50 mg/kg to decrease postoperative blood transfusion. Nevertheless, it is difficult to compare these studies because of differences in the administration of TA (bolus *vs.* bolus followed by continuous infusion). Our results show a benefit of a higher dose when given as a bolus followed by continuous infusion during surgery. Under physiological conditions, fibrinolysis occurs after tissue plasminogen activator is released from endothelium, which triggers the conversion of plasminogen to plasmin, the active protease that cleaves fibrin. During CPB, activation of coagulation factors induces the release of tissue plasminogen activator from endothelial cells and consequent hyperfibrinolysis.[2] TA antifibrinolytic effects are related to its reversible blockade of lysine-binding sites on plasminogen molecules, which, while still allowing their conversion to plasmin, prevents their binding to fibrin and subsequent fibrin degradation. However, data on a TA concentration–effect relationship are rather sparse, and all published pharmacodynamic studies refer to one study[5] to justify the need for target TA plasma concentrations greater than 10 μg/ml. Interestingly, the same study showed with regard to several tissues such as lung, kidney, or prostate that concentrations as high as 100 μg/ml may be required to achieve a 98% fibrinolysis inhibition. Moreover, the authors indicated that the duration of 80% inhibition of fibrinolysis in tissues lasted from 4 to approximately 17 h after the last TA dose. A similar dual time- and organ-dependent plasmin-inhibition profile was recently demonstrated with TA in an *in vivo* pig model.[15] Such variability may, at least in part, be explained by the high compound's hydrophilicity, which prevents biological membranes crossing and diffusion process and translates into poor tissue distribution, as shown in a pharmacokinetic study performed in the same subject population demonstrating a volume of distribution of approximately 7 l.[16] Taken together, these considerations raise questions about the actual plasma TA concentration needed to obtain an effective and durable systemic antifibrinolytic effect. This point was previously addressed by Dowd *et al.*,[13] who recommended maintaining concentrations greater than 126 μg/ml for high-risk bleeding patients in cardiac surgery with CPB. One may wonder whether even higher doses would not provide additional benefits. However, there are growing concerns about the safety of TA.[17] Its massive use since aprotinin discontinuation has highlighted its weaknesses, especially with regard to neurological morbidity.[18] There have even been reports of higher mortality and lower efficiency with TA than with aprotinin.[19,20] These concerns, in part, have led Canadian and European health authorities to reauthorize aprotinin. In our study, we did not detect an increase in adverse events with the higher dose. But the incidence of adverse events was very low, so our cohort is actually too small to be properly powered for this outcome. No conclusion can thus be drawn of our results concerning adverse events.

Table 8. Adverse Events

	Low Dose N = 284	High Dose N = 285	*P* Value
Renal dysfunction	57 (20.1)	58 (20.4)	>0.9
Seizures during the first week	2 (0.7)	4 (1.4)	0.7
Seizures up to 28 days	3 (1.1)	5 (1.8)	0.8
Pulmonary embolism	2 (0.7)	1 (0.4)	0.7
Deep venous thrombosis	2 (0.7)	1 (0.4)	0.7
Stroke	9 (3.2)	10 (3.5)	>0.9
Any complication	34 (12.0)	42 (14.7)	0.4

Data are presented as number (%) of patients.

All *P* values obtained with Fisher exact test.

Seizures are now a well-known adverse event of TA.[21,22] The neuronal hyperexcitability induced by TA is thought to be due to inhibition of γ-aminobutyric acid[23] and glycine[24] receptors, both major inhibitor receptors in the brain. Its reported incidence ranges from 2.7 to

Table 10. Transfusion during the First Week, Including Intraoperative Period, Between-dose Comparisons in Low- and High-risk for Transfusion Strata

	Low-risk Stratum			High-risk Stratum		
	Low Dose	High Dose	*P* Value	Low Dose	High Dose	*P* Value
Transfusion during the first week; all patients						
Blood transfusion (yes)	86 (56.6)	83 (54.2)	±	94 (75.8)	87 (68.0)	*
Packed erythrocyte transfusion (yes)	84 (55.3)	79 (51.3)	*	83 (65.9)	81 (63.3)	*
FFP transfusion (yes)	20 (13.2)	23 (14.9)	0.8†	54 (42.9)	30 (23.4)	0.002†
PC transfusion (yes)	15 (9.9)	15 (9.7)	>0.9†	49 (38.9)	28 (21.9)	0.005†
Fibrinogen (yes)	5 (3.3)	1 (0.6)	0.12†	3 (2.4)	0 (0)	0.12†
Blood products (number of units)	2.2±0.52	2.2±0.52	>0.05‡	6.0±0.59	2.8±0.57	<0.05‡
Packed erythrocytes (number of units)	1.7±0.24	1.4±0.24	*	2.6±0.27	1.7±0.26	*
FFP (number of units)	0.6±0.19	0.4±0.19	>0.05‡	1.5±0.21	0.6±0.20	<0.05‡
PC (number of units)	0.5±0.20	0.4±0.20	>0.05‡	1.8±0.23	0.6±0.22	<0.05‡
Transfusion during the first week; patients transfused						
Packed erythrocytes (number of units)	3.2±0.34	2.7±0.35	*	4.0±0.34	2.9±0.35	*
FFP (number of units)	5.8±0.75	2.9±0.68	<0.05‡	4.1±0.45	2.9±0.60	>0.05‡
PC (number of units)	4.97±0.90	4.28±0.84	*	5.94±0.48	4.41±0.68	*

Data are presented as mean ± SEM or number (%) of patients.

* Not calculated as main term was not significant. † Fisher exact test; the between-dose difference was significant (table 5). ‡ Between-dose difference with Bonferroni–Simes correction; globally, the between-dose difference was significant (table 5).

FFP = fresh frozen plasma; PC = platelets concentrate.

7.6%,[20,25–27] being dose-dependent, with doses of TA of 100 mg/kg and above associated with an increased risk of seizures.[22] In most of these studies TA was administered in a single bolus. Interestingly, a recent article showed that peak TA concentration in the cerebrospinal fluid occurred after termination of drug infusion.[24] Occurrence of a seizure is not trivial, especially after cardiac surgery: seizure patients have an increased rate of postoperative neurological complications, such as delirium or stroke, increased length of stay in intensive care unit, and increased intensive care unit mortality.[28] In our study, the overall incidence of seizures for 1 month after surgery was 1.1% in the low-dose group (95% CI, 0.4–3.0) and 1.8% (95% CI, 0.8–4.0) in the high-dose group, which is lower than in previous reports. Although TA has been reported to have a decreased risk of myocardial infarction and stroke compared with aprotinin,[29] there are now some publications showing that TA use is not exempt from vascular accidents. In a recent article, ischemic strokes occurred after TA administration in two patients with a particular genotype.[30] Acute myocardial infarction[31] and venous thromboembolism[32] may also occur. In our study, the rate of thromboembolic accidents was low and was not higher with the high dose of TA: there were three cases of pulmonary embolism (0.5%), three of deep vein thrombosis (0.5%), and 19 of stroke (3.3%). No myocardial infarction occurred during the study.

Our study has some limitations. First, our results are presented according to low or high doses of TA and to low or high risk for transfusion. Definition for the latter relied on only two elements: use of dual antiplatelet treatment and complex surgical procedure. Other elements presented as predictive factors by several major studies, particularly advanced age,[33–35] low preoperative erythrocyte

Table 11. Bleeding and Mortality, Between-dose Comparisons in Low and High Risk for Transfusion Strata

	Low-risk Stratum			High-risk Stratum		
	Low Dose	High Dose	*P* Value	Low Dose	High Dose	*P* Value
Blood loss during day 1 (ml)	798±67.8	561±68.2	<0.05‡	843±76.5	619±74.6	>0.05‡
Return to surgery for hemostasis	7 (4.6)	3 (2.0)	0.4†	10 (8.2)	4 (3.1)	0.10†
Mortality from day 0 to day 7	4 (2.6)	2 (1.3)	*	5 (4.0)	2 (1.5)	*
Mortality from day 0 to day 28	5 (3.4)	4 (2.8)	*	9 (7.4)	4 (3.2)	*

Data are presented as mean ± SEM or number (%) of patients.

* Not calculated as main term (generalized linear model) or main interaction term (log-linear model) was not significant. † Fisher exact test; the between-dose difference was significant (table 7). ‡ Between-dose difference with Bonferroni–Simes correction; globally, the between-dose difference was significant (table 7).

volume,[33,34] and noncardiac patient comorbidities,[34] were not included in our definition. Another definition of the high-risk stratum could have given other results. However, there were a few instances in which a significant difference was shown to be more marked in the high-risk stratum with the higher dose. Patients who were expected to be at high risk for transfusion had indeed significantly more transfusions than low-risk patients, and the effect of high doses of TA was superior in this group, with a reduction in incidence of blood product transfusion of 75.8–68.0% in this stratum, whereas the reduction was only of 56.6–54.2% in the low-risk stratum. This difference of effect probably explains the negative result of our primary outcome in the global population. However the absence of a significant difference in the low-risk stratum may be due to a lack of power. Thus, conclusions on the low-risk stratum should be interpreted with caution. Second, the recruitment objective of 600 patients was missed by approximately 5%, but as this objective took into account an estimated 10% attrition rate, it cannot be said that results were hampered due to underpowering. Moreover, most patients were included in one center, Hôpital Foch; despite strict standardization of transfusion procedures that were set up in the protocol to limit variations in transfusion practices, this center was found to significantly different from the others with a higher incidence of blood product administration and a higher mean number of blood products used. This may be explained by a higher mean blood loss, possibly due to the higher prevalence of anticoagulant and antiplatelet drugs given preoperatively; there were also some differences regarding surgery, *e.g.*, more aortic surgery. Finally, despite the rather large sample size, dose groups were slightly different: lower number of bypasses in coronary artery bypass graft patients, less type 1 diabetes, and lower preoperative creatinine and international normalized ratio in the low-dose group. One would expect such differences, however minor, to enhance results in the low-dose group thus leading to a reduction of the between-dose difference. The lower international normalized ratio is probably a biased value due to 25% missing data for this variable; in fact, there was no between-group difference concerning the prothrombin ratio.

In conclusion, this work is the first double-blind, randomized study comparing two regimens for TA with a loading dose followed by continuous infusion (30 mg/kg bolus followed by 16 $mg \cdot kg^{-1} \cdot h^{-1}$ *vs.* 10 mg/kg bolus followed by 1 $mg \cdot kg^{-1} \cdot h^{-1}$) during cardiac surgery with CPB in a large cohort of patients. The incidence of blood products transfused during the first week, our primary outcome, was not different between the two doses, but we observed differences favoring the higher dose on some secondary outcomes, especially on blood loss, in return to surgery for hemostasis, and in incidence and amount of frozen plasma and PC transfused during the first postoperative week.

Acknowledgments

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Fischler: Service d'Anesthésie, Hôpital Foch, 40 Rue Worth, 92150 Suresnes, France. m.fischler@hopital-foch.org.

References

1. Levi M, Cromheecke ME, de Jonge E, Prins MH, de Mol BJ, Briët E, Büller HR: Pharmacological strategies to decrease excessive blood loss in cardiac surgery: A meta-analysis of clinically relevant endpoints. Lancet 1999; 354:1940–7
2. Hartmann M, Sucker C, Boehm O, Koch A, Loer S, Zacharowski K: Effects of cardiac surgery on hemostasis. Transfus Med Rev 2006; 20:230–41
3. Carless PA, Moxey AJ, Stokes BJ, Henry DA: Are antifibrinolytic drugs equivalent in reducing blood loss and transfusion in cardiac surgery? A meta-analysis of randomized head-to-head trials. BMC Cardiovasc Disord 2005; 5:19
4. Brown JR, Birkmeyer NJ, O'Connor GT: Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. Circulation 2007; 115: 2801–13
5. Andersson L, Nilsoon IM, Colleen S, Granstrand B, Melander B: Role of urokinase and tissue activator in sustaining bleeding and the management thereof with EACA and AMCA. Ann N Y Acad Sci 1968; 146:642–58
6. Eriksson O, Kjellman H, Pilbrant A, Schannong M: Pharmacokinetics of tranexamic acid after intravenous administration to normal volunteers. Eur J Clin Pharmacol 1974; 7:375–80
7. Pilbrant A, Schannong M, Vessman J: Pharmacokinetics and bioavailability of tranexamic acid. Eur J Clin Pharmacol 1981; 20:65–72
8. Puigdellívol E, Carral ME, Moreno J, Plà-Delfina JM, Jané F: Pharmacokinetics and absolute bioavailability of intramuscular tranexamic acid in man. Int J Clin Pharmacol Ther Toxicol 1985; 23:298–301
9. Soslau G, Horrow J, Brodsky I: Effect of tranexamic acid on platelet ADP during extracorporeal circulation. Am J Hematol 1991; 38:113–9
10. Horrow JC, Van Riper DF, Strong MD, Grunewald KE, Parmet JL: The dose-response relationship of tranexamic acid. Anesthesiology 1995; 82:383–92
11. Nuttall GA, Gutierrez MC, Dewey JD, Johnson ME, Oyen LJ, Hanson AC, Oliver WC Jr: A preliminary study of a new tranexamic acid dosing schedule for cardiac surgery. J Cardiothorac Vasc Anesth 2008; 22:230–5
12. Karski JM, Dowd NP, Joiner R, Carroll J, Peniston C, Bailey K, Glynn MF, Teasdale SJ, Cheng DC: The effect of three different doses of tranexamic acid on blood loss after cardiac surgery with mild systemic hypothermia (32 degrees C). J Cardiothorac Vasc Anesth 1998; 12:642–6
13. Dowd NP, Karski JM, Cheng DC, Carroll JA, Lin Y, James RL, Butterworth J: Pharmacokinetics of tranexamic acid during cardiopulmonary bypass. Anesthesiology 2002; 97:390–9

14. Fergusson DA, Hébert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, Teoh K, Duke PC, Arellano R, Blajchman MA, Bussières JS, Côté D, Karski J, Martineau R, Robblee JA, Rodger M, Wells G, Clinch J, Pretorius R; BART Investigators: A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med 2008; 358:2319–31
15. Reust DL, Reeves ST, Abernathy JH III, Dixon JA, Gaillard WF II, Mukherjee R, Koval CN, Stroud RE, Spinale FG: Temporally and regionally disparate differences in plasmin activity by tranexamic acid. Anesth Analg 2010; 110:694–701
16. Grassin-Delyle S, Tremey B, Abe E, Fischler M, Alvarez JC, Devillier P, Urien S: Population pharmacokinetics of tranexamic acid in adults undergoing cardiac surgery with cardiopulmonary bypass. Br J Anaesth. 2013; Jul 23 [Epub ahead of print]
17 Royston D: Tranexamic acid in cardiac surgery: Is there a cause for concern? Crit Care 2010; 14:194
18. Berman M, Cardone D, Sharples L, Vuylsteke A, Klein A, Gerrard C, Dunning J, Tsui S, Jenkins D: Safety and efficacy of aprotinin and tranexamic acid in pulmonary endarterectomy surgery with hypothermia: Review of 200 patients. Ann Thorac Surg 2010; 90:1432–6
19. Karkouti K, Wijeysundera DN, Yau TM, McCluskey SA, Tait G, Beattie WS: The risk-benefit profile of aprotinin *versus* tranexamic acid in cardiac surgery. Anesth Analg 2010; 110:21–9
20. Sander M, Spies CD, Martiny V, Rosenthal C, Wernecke KD, von Heymann C: Mortality associated with administration of high-dose tranexamic acid and aprotinin in primary open-heart procedures: A retrospective analysis. Crit Care 2010; 14:R148
21. Murkin JM, Falter F, Granton J, Young B, Burt C, Chu M: High-dose tranexamic Acid is associated with nonischemic clinical seizures in cardiac surgical patients. Anesth Analg 2010; 110:350–3
22. Kalavrouziotis D, Voisine P, Mohammadi S, Dionne S, Dagenais F: High-dose tranexamic acid is an independent predictor of early seizure after cardiopulmonary bypass. Ann Thorac Surg 2012; 93:148–54
23. Furtmüller R, Schlag MG, Berger M, Hopf R, Huck S, Sieghart W, Redl H: Tranexamic acid, a widely used antifibrinolytic agent, causes convulsions by a gamma-aminobutyric acid(A) receptor antagonistic effect. J Pharmacol Exp Ther 2002; 301:168–73
24. Lecker I, Wang DS, Romaschin AD, Peterson M, Mazer CD, Orser BA: Tranexamic acid concentrations associated with human seizures inhibit glycine receptors. J Clin Invest 2012; 122:4654–66
25. Martin K, Wiesner G, Breuer T, Lange R, Tassani P: The risks of aprotinin and tranexamic acid in cardiac surgery: A one-year follow-up of 1188 consecutive patients. Anesth Analg 2008; 107:1783–90
26. Keyl C, Uhl R, Beyersdorf F, Stampf S, Lehane C, Wiesenack C, Trenk D: High-dose tranexamic acid is related to increased risk of generalized seizures after aortic valve replacement. Eur J Cardiothorac Surg 2011; 39:e114–21
27. Martin K, Knorr J, Breuer T, Gertler R, Macguill M, Lange R, Tassani P, Wiesner G: Seizures after open heart surgery: Comparison of ε-aminocaproic acid and tranexamic acid. J Cardiothorac Vasc Anesth 2011; 25:20–5
28. Manji RA, Grocott HP, Leake J, Ariano RE, Manji JS, Menkis AH, Jacobsohn E: Seizures following cardiac surgery: The impact of tranexamic acid and other risk factors. Can J Anaesth 2012; 59:6–13
29. Mangano DT, Tudor IC, Dietzel C; Multicenter Study of Perioperative Ischemia Research Group; Ischemia Research and Education Foundation: The risk associated with aprotinin in cardiac surgery. N Engl J Med 2006; 354:353–65
30. Nardi K, Pelone G, Bartolo M, Di Ruzza MR, Storto M, Notte A, Grillea G, Colonnese C, Lembo G, Vecchione C: Ischaemic stroke following tranexamic acid in young patients carrying heterozygosity of MTHFR C677T. Ann Clin Biochem 2011; 48(Pt 6):575–8
31. Sirker A, Malik N, Bellamy M, Laffan MA: Acute myocardial infarction following tranexamic acid use in a low cardiovascular risk setting. Br J Haematol 2008; 141:907–8
32. Sundström A, Seaman H, Kieler H, Alfredsson L: The risk of venous thromboembolism associated with the use of tranexamic acid and other drugs used to treat menorrhagia: A case-control study using the General Practice Research Database. BJOG 2009; 116:91–7
33. Karkouti K, O'Farrell R, Yau TM, Beattie WS; Reducing Bleeding in Cardiac Surgery Research Group: Prediction of massive blood transfusion in cardiac surgery. Can J Anaesth 2006; 53:781–94
34. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Ferraris SP, Saha SP, Hessel EA II, Haan CK, Royston BD, Bridges CR, Higgins RS, Despotis G, Brown JR; Society of Cardiovascular Anesthesiologists Special Task Force on Blood Transfusion, Spiess BD, Shore-Lesserson L, Stafford-Smith M, Mazer CD, Bennett-Guerrero E, Hill SE, Body S: Perioperative blood transfusion and blood conservation in cardiac surgery: The Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline. Ann Thorac Surg 2007; 83:S27–86
35. Vuylsteke A, Pagel C, Gerrard C, Reddy B, Nashef S, Aldam P, Utley M: The Papworth Bleeding Risk Score: A stratification scheme for identifying cardiac surgery patients at risk of excessive early postoperative bleeding. Eur J Cardiothorac Surg 2011; 39:924–30

Appendix. Between-dose Comparison: Data Relative to Each Center

Hôpital Foch

	Low Dose N = 164	High Dose N = 162
Transfusion during first week		
Blood transfusion (yes)	110 (67.1)	104 (64.2)
Packed erythrocyte transfusion (yes)	104 (63.4)	100 (61.7)
FP transfusion (yes)	51 (31.1)	37 (22.8)
PC transfusion (yes)	40 (24.4)	25 (15.4)
Blood loss during day 1 (ml)	988 ± 68	837 ± 66
Return to surgery for hemostasis (yes)	8 (4.9)	5 (3.1)
Mortality at day 7 (yes)	7 (4.3)	2 (1.2)
Mortality at day 28 (yes)	11 (6.7)	5 (3.1)

Data are presented as mean ± SEM or number (%) of patients.
FP = frozen plasma; PC = platelet concentrate.

Centre Chirurgical Marie Lannelongue

	Low Dose N = 40	High Dose N = 42
Transfusion during first week		
Blood transfusion	17 (42.5)	16 (38.1)
Packed erythrocyte transfusion (yes)	16 (40)	12 (28.6)
FP transfusion (yes)	8 (20)	6 (14.3)
PC transfusion (yes)	4 (10)	4 (9.5)
Blood loss during day 1 (ml)	707 ± 132	618 ± 128
Return to surgery for hemostasis (yes)	3 (7.5)	0 (0)
Mortality at day 7	1 (2.5)	1 (2.4)
Mortality at day 28	1 (2.5)	2 (4.8)

Data are presented as mean ± SEM or number (%) of patients.
FP = frozen plasma; PC = platelet concentrate.

Hôpital Jean Minjoz

	Low Dose N = 43	High Dose N = 43
Transfusion during first week		
Blood transfusion	27 (62.8)	23 (53.5)
Packed erythrocyte transfusion (yes)	25 (58.1)	21 (48.8)
FP transfusion (yes)	9 (20.9)	6 (13.9)
PC transfusion (yes)	12 (27.9)	8 (18.6)
Blood loss during day 1 (ml)	1,080 ± 132	467 ± 132
Return to surgery for hemostasis (yes)	5 (11.6)	2 (4.6)
Mortality at day 7 (yes)	1 (2.3)	1 (2.3)
Mortality at day 28 (yes)	1 (2.3)	1 (2.3)

Data are presented as mean ± SEM or number (%) of patients.
FP = frozen plasma; PC = platelet concentrate.

Hôpital Haut-Lévêque

	Low Dose N = 37	High Dose N = 38
Transfusion during first week		
Blood transfusion	26 (70.3)	27 (71)
Packed erythrocyte transfusion (yes)	22 (59.4)	25 (65.8)
FP transfusion (yes)	6 (16.2)	4 (10.5)
PC transfusion (yes)	8 (21.6)	6 (15.8)
Blood loss during day 1 (ml)	506 ± 138	439 ± 142
Return to surgery for hemostasis (yes)	1 (2.7)	0 (0)
Mortality at day 7	0 (0)	0 (0)
Mortality at day 28	1 (2.7)	0 (0)

Data are presented as mean ± SEM or number (%) of patients.
FP = frozen plasma; PC = platelet concentrate.