USING e-ANNOTATION TOOLS FOR ELECTRONIC PROOF CORRECTION

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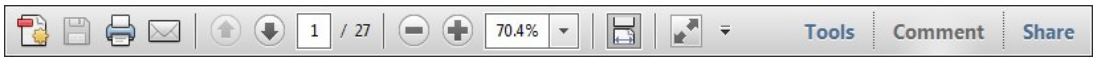
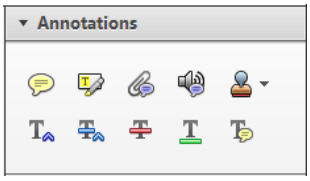
Once you have Acrobat Reader open on your computer, click on the Comment tab at the right of the toolbar:



This will open up a panel down the right side of the document. The majority of tools you will use for annotating your proof will be in the Annotations section, pictured opposite. We've picked out some of these tools below:

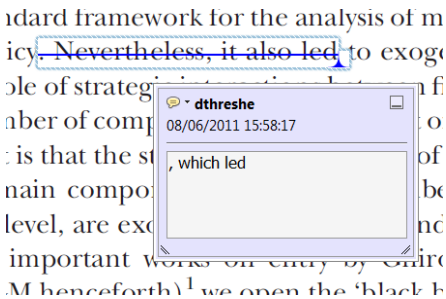


1. Replace (Ins) Tool – for replacing text.

Strikes a line through text and opens up a text box where replacement text can be entered.

How to use it

- Highlight a word or sentence.
- Click on the Replace (Ins) icon in the Annotations section.
- Type the replacement text into the blue box that appears.

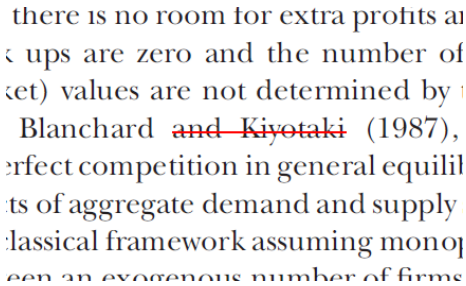


2. Strikethrough (Del) Tool – for deleting text.

Strikes a red line through text that is to be deleted.

How to use it

- Highlight a word or sentence.
- Click on the Strikethrough (Del) icon in the Annotations section.

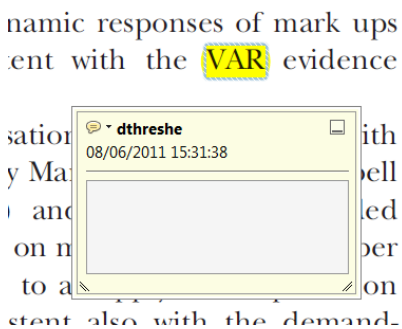


3. Add note to text Tool – for highlighting a section to be changed to bold or italic.

Highlights text in yellow and opens up a text box where comments can be entered.

How to use it

- Highlight the relevant section of text.
- Click on the Add note to text icon in the Annotations section.
- Type instruction on what should be changed regarding the text into the yellow box that appears.

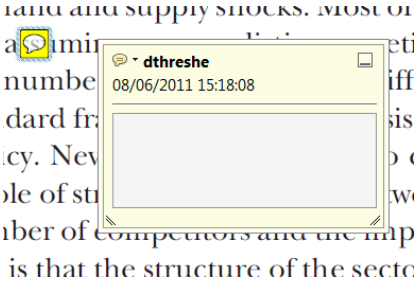


4. Add sticky note Tool – for making notes at specific points in the text.

Marks a point in the proof where a comment needs to be highlighted.

How to use it

- Click on the Add sticky note icon in the Annotations section.
- Click at the point in the proof where the comment should be inserted.
- Type the comment into the yellow box that appears.

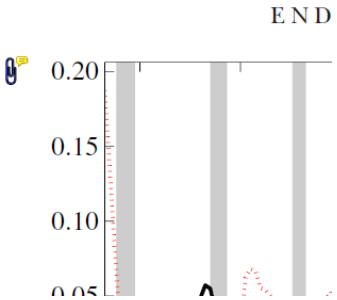


5. Attach File Tool – for inserting large amounts of text or replacement figures.

Inserts an icon linking to the attached file in the appropriate place in the text.

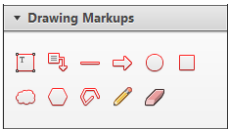
How to use it

- Click on the Attach File icon in the Annotations section.
- Click on the proof to where you'd like the attached file to be linked.
- Select the file to be attached from your computer or network.
- Select the colour and type of icon that will appear in the proof. Click OK.



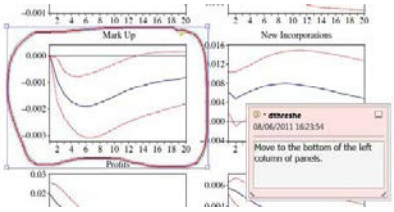
6. Drawing Markups Tools – for drawing shapes, lines and freeform annotations on proofs and commenting on these marks.

Allows shapes, lines and freeform annotations to be drawn on proofs and for comment to be made on these marks.



How to use it

- Click on one of the shapes in the Drawing Markups section.
- Click on the proof at the relevant point and draw the selected shape with the cursor.
- To add a comment to the drawn shape, move the cursor over the shape until an arrowhead appears.
- Double click on the shape and type any text in the red box that appears.



Desmopressin after cardiac surgery in bleeding patients. A multicenter randomized trial

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The authors have no conflict of interest to declare.

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Background: Previous studies showed that desmopressin decreases post-operative blood loss in patients undergoing cardiac surgery. These studies were small and never studied the effect of desmopressin in patients with active bleeding. Objective of the study was to determine whether desmopressin reduces red blood cells transfusion requirements in patients with active bleeding after cardiac surgery who had been pre-treated with tranexamic acid.
Methods: This multicenter, randomized, double-blind, placebo-controlled, parallel-group study randomized elective patients with bleeding after cardiac surgery despite pre-treatment with tranexamic acid, to receive placebo (saline solution) or a single administration of desmopressin (0.3 μg/kg in saline solution). The primary endpoint was the number of patients requiring red blood cells transfusion after randomization and during hospital stay. Secondary end points were: blood loss from chest tubes during the first 24 h after study drug administration, hours of mechanical ventilation, intensive care unit stay, and in-hospital mortality.
Results: The study was interrupted after inclusion of 67% of the planned patients for futility. The number of patients requiring red blood cells transfusion after randomization was 37/68 (54%) in desmopressin group and 33/67 (49%) in placebo group ($P = 0.34$) with no difference in blood loss: 575 (interquartile 422–770) ml in desmopressin group and 590 (476–1013) ml in placebo group ($P = 0.42$), mechanical ventilation, intensive care unit stay or mortality.
Conclusions: This multicenter randomized trial demonstrated that, in patients pre-treated with tranexamic acid, desmopressin should not be expected to improve treatment of patients who experience bleeding after cardiac surgery.

Editorial comment
Desmopressin is sometimes administered to perioperative patients in the hope of reducing perioperative bleeding. The findings from this clinical trial indicate that in patients treated with tranexamic acid before cardiac surgery who then have perioperative bleeding, the addition of desmopressin treatment probably will not reduce bleeding.

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Peri-operative bleeding and the need for blood transfusions are correlated with increased morbidity, mortality, and costs.[1–4] In cardiac surgery, patients often require transfusions of blood products and a surgical cause cannot be identified in many patients. Among non-surgical factors, hemostatic abnormalities are of paramount importance.

Pharmacological options to control peri-operative bleeding consist of topical agents, antifibrinolytic drugs, and drugs that improve primary and/or secondary hemostasis. Among the latter drugs, desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) has been extensively studied in several types of surgical intervention,[5] but mostly in patients undergoing cardiac surgery with extracorporeal circulation.[6,7] Desmopressin stimulate increases in plasma concentrations of factor VIII and von Willebrand factor and exerts other, less well-characterized pro-hemostatic effects.[8–10]

Several randomized controlled trials (RCTs)[11,12] and a meta-analysis of RCTs[5] suggested that prophylactic desmopressin reduces bleeding in surgical patients with a clinical effect of approximately 3–4 h.[13] Existing guidelines agree with the potential hemostatic properties of desmopressin, but do not give strong recommendations.[14,15] Notably, all the RCTs performed so far have a small sample size, none of them included patients with active post-operative bleeding, and only one of them was multicenter.

With the hypothesis that desmopressin might reduce the transfusion rate of red blood cells (RBC) in patients with excessive bleeding after cardiac surgery, we performed a multicenter RCT comparing a single dose infusion of desmopressin vs. placebo. We also investigated in-hospital mortality, blood loss/24 h, hours of mechanical ventilation, duration of intensive care unit, and hospital stay.

Methods

We performed a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial to determine if desmopressin could reduce the need for packed RBC transfusion after cardiac surgery in patients with excessive bleeding in the operating room or in the cardiac post-operative intensive care unit (ICU). The drug desmopressin is used in a way that is different from that described in the Food and Drug Administration-approved drug label ('off-label' use).

Three teaching centers participated to the study, all in Italy: IRCCS San Raffaele Scientific Institute, Milan; IRCCS Policlinico San Donato, Milan; and University Hospital of Pisa, Pisa.

The study was conceived in accordance with the Declaration of Helsinki and its amendments. The study protocol was approved by the Ethical Committees of the three teaching centers involved (Coordinating Center: Ospedale San Raffaele Ethical Committee, IRCCS San Raffaele Scientific Institute, via Olgettina 60, 20132 Milan; protocol n. DS/URC/ER/mm 151/DG; date of approval: March 13th, 2006), registered on ClinicalTrials.gov with the identifier NCT00337766 and the first patient was randomized on June 2006.

All patients aged 18 years or more undergoing elective cardiac surgery were asked to sign the informed consent before surgery and if they met the inclusion criteria they were randomized to receive either desmopressin or placebo, in the operating room or in the post-operative cardiac ICU.

Inclusion/exclusion criteria

The inclusion criterion in the operating room was diffuse bleeding without an identifiable surgical source from the surgical site ≥ 15 min after correct antagonization of heparin with protamine,[12] likely to require management with transfusion of platelets concentrates, fresh frozen plasma, and/or RBC. This was decided jointly by surgeons and anesthesiologists. The inclusion criterion in the ICU was excessive bleeding from chest tubes defined as 200 ml/h in 30 min or 2 ml/kg/h for at least 2 h.[16] Exclusion criteria were lack of informed consent, and recent (< 7 days) or ongoing acute myocardial infarction.

Randomization and experimental procedure

A computer-generated randomization sequence stratified by center with blocks of 20 was used.

Treatment allocation (1 : 1) prepared by an independent operator not otherwise involved in the trial was concealed by opaque, sealed envelopes that were sequentially numbered. Patients, managing physicians, and nurses were blinded to treatment assignment for the whole duration of the study. Desmopressin and placebo were prepared in a separate room, as colorless fluids in unlabeled bottles, by personnel who was not involved in patients' management and data collection. Desmopressin (Kedrion, Barga, Lucca, Italy) or an equivolume saline solution was administered intravenously over 20 min at a dose of 0.3 μg/kg diluted in a 50 ml saline solution. This dose was chosen because it was the most frequently used (35 out of 41) in previous RCTs performed in the peri-operative period.[5] Registration of blood loss was started after completing study drug administration. Data were collected by trained personnel who did not participate in patients' management and was blinded to the assigned treatment. No protocol violations were noted.

Clinical management

Enrolled patients were managed according to standardized institutional practice for cardiac surgery. This was a pragmatic trial and all patients received the standard treatment according to the anesthesiologist and the physician in charge of the ICU. In patients on treatment with double antiplatelet therapy, aspirin was maintained throughout the surgical procedure, while drugs inhibiting the platelet $P2Y_{12}$ receptor were discontinued at least 5 days before surgery. Patient monitoring included invasive radial artery blood pressure measurement, continuous electrocardiographic leads II and V5 monitoring with ST-segment monitoring, pulse oximetry, central venous pressure, capnometry, urine output and trans-esophageal echocardiography. All patients received an intravenous slow bolus of 1 g tranexamic acid before surgery, which was followed by a continuous infusion of 400 mg/h during the surgical intervention in one institution (San Raffaele Scientific Institute), or by a second intravenous 1 g bolus after the administration of protamine in the remaining two institutions. A further dose of 500 mg tranexamic acid was allowed after cardio pulmonary bypass (CPB). Aprotinin was never administered.

CPB management

Surgery was conducted either with CPB or off pump. Cardio pulmonary bypass was conducted mostly at moderate hypothermia (32–34°C). In CPB procedures, myocardial protection during aortic cross-clamping was obtained by antegrade and/or retrograde cold blood cardioplegia or antegrade crystalloid cardioplegia according to the local standard. Heparin was administered as intravenous bolus of 300 IU/kg to patients undergoing CPB, or 150 IU/kg to patients undergoing off pump procedures. Activated clotting time was maintained longer than 480 s during CPB and longer than 300 s during off pump procedures. Upon achievement of normothermia, extracorporeal circulation was discontinued and heparin was neutralized with protamine sulfate (1 mg per 100 IU heparin).

Intensive care management

Patients were transferred to the ICU, sedated with propofol 2 mg/kg/h for 4 h, and weaned from the ventilator as soon as they were hemodynamically stable with no major bleeding, normothermic, and achieved an adequate level of consciousness and analgesia. Intravenous morphine was administered to all patients for post-operative pain relief. In case of bleeding, the surgeon was summoned to decide if surgical revision was suitable. Criteria for ICU discharge to post-intensive cardiac surgery ward were respiratory and hemodynamic stability and no active bleeding from chest tubes.

Bleeding and transfusion management

The amount of blood loss from chest tubes was recorded hourly for 48 h after surgery or until chest tubes removal, whichever came first. The number of transfused platelet concentrates, fresh frozen plasma, and RBC were recorded. Transfusions were administered following a predefined protocol: if hemoglobin was < 8 g/dl, one RBC was transfused. In case of bleeding from chest tubes, if prothrombin time (INR) was ≤ 1.39, no fresh frozen plasma was infused,

if platelets count was > 100 × 10^9/l, no platelets concentrates were infused. In the operating room, advanced patient's age or hemodynamic instability were factors that allowed a lower threshold for RBC transfusion, according to the attending anesthesiologist.

Data collection

We collected data on need of re-thoracotomy due to excessive bleeding, length of mechanical ventilation and of ICU stay. All randomized patients were followed up till hospital discharge.

Laboratory-based hematological tests, including complete blood cells count, prothrombin time ratio, PTT ratio, and biochemistry tests, including serum creatinine, troponin I, transaminase, and plasma sodium concentration were done before and after surgery, on arrival in ICU and on the first post-operative day. The anticoagulant effect of heparin was monitored by kaolin-activated clotting time before and after CPB.

Endpoints

The pre-specified main outcome measure was the number of patients requiring RBC transfusion after randomization and during hospital stay. Secondary end points were: blood loss from chest tubes during the first 24 h after study drug administration, hours of mechanical ventilation, ICU stay, and in-hospital mortality.

Sample size calculation

On the basis of previous data[17,18] investigating post-operative RBC transfusion in patients at high risk of bleeding after cardiac surgery and on our experience, we anticipated a 65% frequency of transfusion of RBC in the standard treatment group and a reduction to 45% after treatment with desmopressin (we tested the hypothesis that desmopressin administration would reduce the need of RBC transfusion when compared to placebo with an absolute risk reduction of 20% and a relative risk reduction of 30%). Sample size calculations, based on a two-sided alpha error of 0.05 and 80% power, indicated that a sample size of 100 patients per group was necessary.

Ad interim analysis and study interruption

We experienced a low enrollment rate due to organizing problems and lack of funding and we decided to perform an unplanned ad interim analysis after enrolling 67% of the patients. As showed in supplemental material (Appendix S1, Figs S1 and S2) the trial was considered to have reached its goal of testing the null hypothesis with adequate statistical precision and was stopped for futility.

Statistical analyses

All data were analyzed according to the intention-to-treat principle. Data were stored electronically and analyzed by use of SAS software, version 9 (SAS Institute). All data analysis was carried out according to a pre-established analysis plan and results are presented as mean ± standard deviation, median (interquartile range), or number (percentage). Dichotomous data were compared using two-tailed Chi-square test with the Yates correction or Fisher's exact test when appropriate; 95% confidence interval estimation for the differences between independent proportions was performed with methods based on the Wilson score. Continuous measures were compared by analysis of variance (ANOVA) or the Mann–Whitney *U*-test when appropriate; 95% confidence interval estimate for the mean/median difference was performed. Two-sided significance tests were used throughout our data analysis.

Results

During the study period, 3552 patients signed the written informed consent. A total of 135 (3.8%) patients had excessive bleeding after cardiac surgery and were randomized to desmopressin (n = 68) or placebo (n = 67) (Fig. 1). The study was interrupted for futility at an ad interim analysis performed after enrolling 67% of the planned patients. All 135 included patients completed their hospital follow-up.

The two groups of patients had similar characteristics at baseline (Table 1). Mean age was 63 years, 100 (74%) were males and 54 (40%) were on treatment with antiplatelet drugs. Seventy-three patients (54%) were randomized

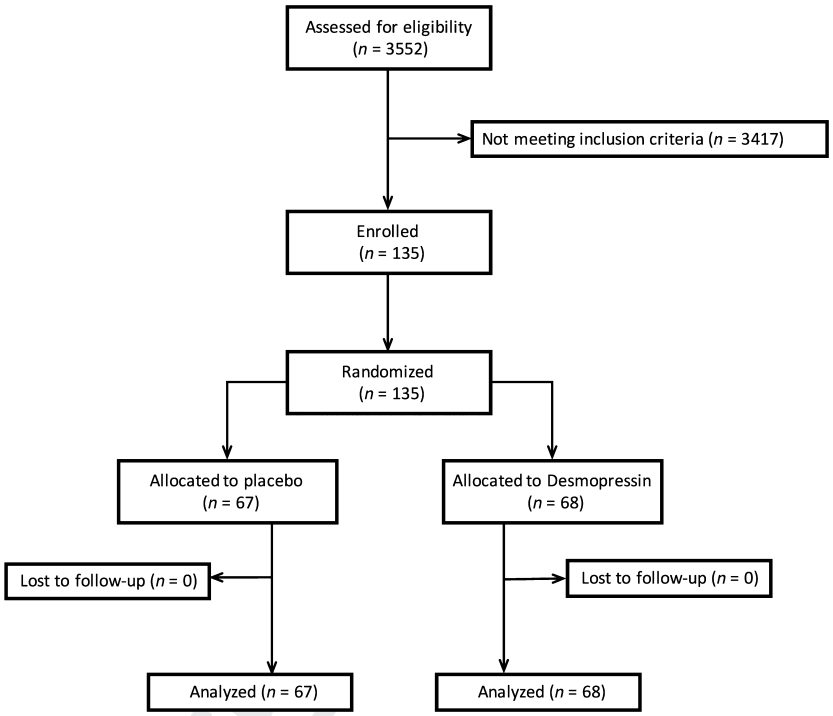

Fig. 1. Assessment, randomization and follow-up of study patients.

in the operating theater and 62 (46%) in the ICU after a median of 120 (60–180) min after arrival to ICU.

All patients received a single intravenous administration of placebo or desmopressin 0.3 μg/kg, without protocol deviations.

The number of patients receiving RBC transfusions after randomization was similar in the desmopressin (37/68, 54%) and in the placebo group (33/67, 49%) ($P = 0.34$) (Table 2).

No statistically significant differences were observed between the two treatment groups in terms of hours of mechanical ventilation, days in ICU and other outcomes (Table 2). Five patients (7.4%) in the desmopressin group and 4 (6.0%) in the placebo group died ($P = 0.99$).

Neither differences in bleeding nor RBC transfusion was observed in subanalyses of patients randomized in the theater (Table S1) and those randomized in the ICU (Table S2).

Discussion

In this multicenter, double-blind, placebo-controlled RCT, we found that desmopressin was not effective in reducing post-operative blood loss and RBC transfusion requirements in patients undergoing cardiac surgery who experienced excessive bleeding after successful heparin neutralization despite pre-treatment with tranexamic acid. Moreover, no statistically significant differences in mortality rates or in any other outcomes were observed, even if the power for these analyses was low. Transfusion of RBC did not differ significantly also in predefined subgroups. The study was interrupted for futility after enrolling 67% of the planned patients.

Previous studies evaluating the blood saving effects of desmopressin in patients undergoing cardiac surgery gave conflicting results. A meta-analysis of 17 studies[17] showed that desmopressin decreased post-operative blood loss by 34% in those trials in which the 24 h blood loss in the placebo-treated patients was in the upper third of distribution, suggesting that the drug may be clinically efficacious only in patients at risk of excessive post-operative bleeding.[17] The data of this meta-analysis were substantially confirmed in a later prospective, double-blind, placebo-controlled trial, in which the effects of desmopressin were compared to those of placebo in patients identified as being at high risk of post-operative bleeding with the point-of-care

Table 1 Baseline characteristics according to randomized group assignment (desmopressin vs. placebo).

Variable	Desmopressin (68 patients)	Placebo (67 patients)
Age, years	64 ± 13.3	62 ± 13.2
No. of patients aged > 75 years	15 (23%)	13 (20%)
Women	18 (27%)	17 (25%)
Weight, kg	73 ± 13.5	73 ± 13.8
Height, cm	169 ± 8.4	170 ± 8.1
Cirrhosis, no.	2 (3%)	1 (1.5%)
On antiplatelet drugs, no.	25 (38%)	29 (43%)
Acetylsalicylic acid, no.	21 (31%)	16 (24%)
Ticlopidine, no.	4 (5.9%)	5 (7.5%)
Clopidogrel, no.	8 (12%)	9 (13%)
Tirofiban, no.	1 (1.5%)	1 (1.5%)
Congenital defect of primary hemostasis, no.	1 (1.5%)	1 (1.5%)
Activated clotting time before surgery, seconds	147 ± 29.4	145 ± 24.4
Activated clotting time at end of CPB, seconds	140 ± 29.0	140 ± 20.7
Hemoglobin preoperative, g/dl	13.3 ± 1.85	13.4 ± 1.89
Hematocrit preoperative, %	39.3 ± 5.19	39.6 ± 5.15
Platelet count preoperative, $\times 10^3/mm^3$	204 ± 73.4	204 ± 60.5
PT ratio preoperative	1.2 ± 0.31	1.2 ± 0.53
PTT ratio preoperative	1.1 ± 0.25	1.2 ± 0.39
Serum creatinine preoperative, mg/dl	0.90 (0.79–1.08)	0.96 (0.82–1.1)
No. of patients whit preoperative creatinine > 1.5 mg/dl	7 (11%)	5 (7.6%)
Randomization in the operating theater, no.	37 (54%)	36 (54%)
Minutes between CPB weaning and randomization in the theater	60 (30–80)	50 (40–79.8)
Randomization in the ICU, no.	31 (46%)	31 (46%)
Minutes between ICU admission and randomization in the ICU	120 (60–157.5)	145 (60–240)
Supplemental dose of tranexamic acid, no.	35 (52%)	34 (51%)
No. of patients transfused with any blood product before randomization	31 (46%)	34 (51%)
No. of patients transfused with RBC before randomization	24 (35%)	28 (42%)
No. of RBC units transfused/patient before randomization	2 (1.75–3)	2 (1–3)
No. of patients transfused with FFP pre-randomization	20 (29%)	21 (31%)
No. of FFP units transfused/patient before randomization	2 (1.75–3.25)	2 (2–3)
No. of patients transfused with PLT pre-randomization	10 (15%)	9 (13%)
No. of PLT units transfused/patient before randomization	1 (1–1)	1 (1–1)

No., number; CPB, cardiopulmonary bypass; PT, prothrombin time; INR, international normalized ratio; PTT, partial thromboplastin time; Na, sodium; ICU, intensive care unit; RBC, red blood cell; FFP, fresh frozen plasma; PLT, platelets.

test hemoSTATUS.[12] The trial showed that the average 24 h blood loss in desmopressin-treated, high-risk patients was 39% lower than that in placebo-treated high-risk patients and was comparable to that of low risk, untreated patients. The most important difference between our study and previous studies is that as part of modern cardiac surgery[19,20] we used tranexamic acid in all patients included in the present trial. Interestingly, 1000 ml of blood loss in the first post-operative 24 h seems to be the cut-off value that identifies patients who may potentially benefit from this treatment.[19] Therefore, we speculate that, when an adequate prophylaxis with antifibrinolytic agents is administered to patients, excessive post-operative bleeding is not severe enough to benefit from the pro-hemostatic effect of desmopressin.

In a recent meta-analysis of 38 randomized placebo-controlled trials (2488 patients) in cardiac and non-cardiac surgery, Crescenzi et al. showed that desmopressin was associated with reduced requirements of blood product transfusion [standardized mean difference = −0.29 (−0.52 to −0.06) units per patient; $P = 0.01$], and with a non-statistically significant increase in thromboembolic adverse events (57/1002 = 5.7% in the desmopressin group vs. 45/979 = 4.6% in the

Table 2 Post-randomization data according to randomized group assignment (desmopressin vs. placebo).

Variable	Desmopressin (68 patients)	Placebo (67 patients)	*P* value
No. of patients transfused with RBC post-randomization	37 (54%)	33 (49%)	0.34
No. of RBC units transfused/patient post-randomization	2 (1–4)	2 (1–3)	0.74
No. of patients transfused with FFP post-randomization	24 (35%)	25 (37%)	0.62
No. of FFP units transfused/patient post-randomization	2.5 (2–4)	3 (2–3)	0.77
No. of patients transfused with PLT post-randomization	9 (13%)	10 (15%)	0.62
No. of PLT units transfused/patient post-randomization	1 (1–3)	1 (1–2)	0.90
No. of patients transfused with any blood product post-randomization	40 (59%)	35 (52%)	0.44
Chest tube blood loss in the first 12 h after study drug administration, ml	400 (267.5–700)	430 (325–800)	0.34
Chest tube blood loss in the first 24 h after study drug administration, ml	575 (422.5–770)	590 (476.25–1013.75)	0.42
Bleeding at drainage removal, ml	850 (600–1390)	1040 (565–1457.5)	0.69
Hemoglobin at ICU admission, g/dl	11.1 ± 1.74	11.1 ± 1.68	0.67
Hemoglobin in the 1st morning, g/dl	10.8 ± 1.36	11.1 ± 1.46	0.16
Hemoglobin in the 2nd morning, g/dl	10.6 ± 1.41	10.7 ± 1.23	0.78
Hematocrit at ICU admission, %	33.1 ± 4.70	33.1 ± 4.83	0.98
Hematocrit in the 1st morning, %	31.8 ± 4.08	32.7 ± 4.04	0.23
Hematocrit in the 2nd morning, %	31.0 ± 4.14	31.3 ± 3.90	0.68
Platelet count at ICU admission, $\times 10^3/mm^3$	136 ± 69.8	128 ± 47.6	0.47
Platelet count in the 1st morning, $\times 10^3/mm^3$	136 ± 62.4	140 ± 58.0	0.74
Platelet count in the 2nd morning, $\times 10^3/mm^3$	135 ± 68.1	128 ± 55.0	0.63
PT ratio at ICU admission	1.4 ± 0.32	1.4 ± 0.28	0.65
PT ratio in the 1st morning	1.3 ± 0.21	1.2 ± 0.18	0.61
PT ratio in the 2nd morning	1.4 ± 0.48	1.3 ± 0.25	0.94
PTT ratio at ICU admission	1.1 ± 0.27	1.2 ± 0.34	0.85
PTT ratio in the 1st morning	1.1 ± 0.12	1.0 ± 0.10	0.85
PTT ratio in the 2nd morning	1.1 ± 0.19	1.1 ± 0.15	0.66
Serum creatinine at ICU admission, mg/dl	0.97 (0.82–1.09)	0.89 (0.75–1.09)	0.23
Serum creatinine in the 1st morning, mg/dl	1.15 (0.95–1.4)	1.22 (0.89–1.56)	0.94
Serum creatinine peak level in the ICU, mg/dl	1.23 (1.02–1.71)	1.14 (0.95–1.57)	0.37
Serum troponin I at ICU admission, ng/l	4.1 (2.1–8.4)	5.1 (2.1–8.9)	0.73
Serum troponin I in the 1st morning, ng/l	6.8 (2.6–11.3)	5.8 (3.3–11.1)	0.97
Serum troponin I peak level, ng/l	8.4 (3.4–11.5)	7.5 (3.9–13.6)	0.70
Hypotension during study drug administration, no.	12 (18%)	4 (6.0%)	0.11
Hypotension requiring intervention, no.	3 (4.4%)	2 (3.0%)	0.90
Surgical revision, no.	8 (12%)	12 (18%)	0.39
Surgical source of bleeding in re-operated patients, no.	5/8 (62%)	5/12 (42%)	0.36
Mechanical ventilation, h	17 (11–34)	16 (10.75–31)	0.92
ICU stay, days	2 (1–4)	2 (1–4)	0.63
Thrombosis, no.	3 (4.4%)	2 (3.0%)	0.51
Hospital mortality, no.	5 (7.4%)	4 (6.0%)	0.99

No., number; ICU, intensive care unit; RBC, red blood cell; FFP, fresh frozen plasma; PLT, platelets; PT, prothrombin time; INR, international normalized ratio; PTT, partial thromboplastin time.

placebo group; $P = 0.3$).[6] Our study will also help to modify the message of the existing guidelines[14,15] for the peri-operative management of desmopressin. At the moment, they are both suggesting potential benefits in reducing blood loss in the presence of coagulopathy conditions, but they are based on small single-center trials or meta-analysis[21] performed in settings that did not routinely use tranexamic acid. In this multicenter randomized trial desmopressin did not translate into a reduced rate of patients requiring RBC transfusion among those with active bleeding after cardiac surgery who had been pre-treated with tranexamic acid.

Importantly, it is necessary to investigate further how to improve outcomes of patients with bleeding after surgery, which has a high mortality rate, as confirmed by the results of our

study: 6.7% in the patients included in this study vs. 2.2–3.4% published[22,23] mortality reported in the overall population undergoing cardiac surgery in our centers.

This trial was randomized and double-blinded in design with allocation concealment, thus reducing the risk of selection bias. It focused on patient-centered, objectively verifiable and clinically relevant outcomes, thus reducing ascertainment bias. The intervention had biological plausibility and was supported by a series of single-center studies with promising results and by meta-analyses, thus justifying the initial trial hypothesis. Our results likely carry external validity because patients were recruited in three different hospitals with the use of pragmatic inclusion criteria and few exclusion criteria. They are also likely to be highly reproducible, as the trial protocol was simple, with routine practice maintained throughout, except for desmopressin or placebo infusion.

A limitation of our study is that it was interrupted prematurely, after the enrollment of 135 of the planned 200 patients; even if this caused a reduction in power, the case for the futility of the intervention was clear. Despite its premature interruption, this is the largest multicenter RCT ever performed with desmopressin as a hemostatic agent in the peri-operative period and one of the few to study patients who were actively bleeding. This was a pragmatic trial and we did not change the routine of our centers to perform the protocol; at the same time we acknowledge that we did not collect some important data that could influence coagulability such as kind of surgery (e.g., off pump CABG); CPB duration, pH, calcium, and the number of patients operated under hypothermia or with normothermia. A possible limitation of our study is that the inclusion criteria in the theater might be considered less objective and relevant that the inclusion criteria in the ICU, but hemostasis is optimized in the operating rooms and other investigators randomized patients in this setting. Furthermore, results in the two groups (theater and ICU) were similar.

In conclusion, this multicenter randomized trial demonstrated that in patients pre-treated with tranexamic acid, desmopressin should not be expected to improve treatment of patients who experience bleeding after cardiac surgery. Therefore, also considering its potential side effects, the routine use of desmopressin as a blood saving agent in this setting is not justified.

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Supporting Information

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Appendix S1. Ad interim analyses results.
Figure S1. Point estimated and 99% confidence interval for the absolute risk reduction.
Figure S2. Point estimated and 99% confidence interval for the relative risk.
Table S1. Bleeding and transfusion in the subgroup of patients randomized in theater.
Table S2. Bleeding and transfusion in the subgroup of patients randomized in the ICU.

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