

Efficacy and Safety Profile of Low-Dose Tranexamic Acid Regimen in Cardiac Surgery: A Meta-Analysis

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ABSTRACT

Introduction: Various dosing regimens of tranexamic acid have been reported to exhibit varying efficacy and safety profiles. Herein, we conducted a meta-analysis to evaluate the efficacy and safety of low-dose regimens in open-heart surgery.

Methods: Three databases were systematically searched for randomized trials examining the bleeding reduction effect of tranexamic acid in open-heart surgery. The pooled data of the low-dose group was then compared with the control, high-dose, and epsilon aminocaproic acid groups. The boundary between the low- and high-dose groups was a bolus of 30 mg/kg followed by 16 mg/kg/hour.

Results: The meta-analysis included 81 studies. The low-dose tranexamic acid regimen was associated with a decreased incidence of reoperation (risk ratio: 0.52; 95% confidence interval: 0.39–0.69; high quality of evidence), perioperative myocardial infarction (risk ratio: 0.64; 95% confidence interval: 0.43–0.95; high

quality of evidence), the amount of postoperative bleeding in 24 hours, and the need for transfusion of packed red cells compared to control, without increasing the rates of mortality, venous thromboembolism, or stroke. Compared with the high-dose group, the low-dose group had a lower incidence of seizures and stroke. The low-dose of tranexamic acid group also showed significantly reduced postoperative bleeding; however, the cost of an increased risk of seizure events was higher in the low-dose group than in the epsilon aminocaproic acid group.

Conclusion: Low-dose tranexamic acid effectively reduced bleeding, the risk of reoperation, and myocardial infarction without increasing the risk of adverse events.

Keywords: Tranexamic Acid. Hemorrhage. Thoracic Surgery. Myocardial Infarction. Venous Thromboembolism. Meta-Analysis.

Abbreviations, Acronyms & Symbols

ASD	= Atrial septal defect	OR	= Odds ratio
BART	= Blood Conservation Using Antifibrinolytics in a Randomized Trial	PRC	= Packed red cell
CABG	= Coronary artery bypass grafting	PRISMA	= Preferred Reporting Items for Systematic Reviews and Meta-Analyses
CPB	= Cardiopulmonary bypass	RCTs	= Randomized controlled trials
CI	= Confidence interval	RR	= Risk ratio
EACA	= Epsilon aminocaproic acid	SD	= Standard deviation
GRADE	= Grading of Recommendations Assessment, Development and Evaluation	SE	= Standard error
Hb	= Hemoglobin	SMD	= Standardized mean difference
Hct	= Hematocrit	VTE	= Venous thromboembolic events
IV	= Intravenous	QOE	= Quality of evidence

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INTRODUCTION

Administration of tranexamic acid is recommended to reduce bleeding and the need for blood product transfusion after cardiac surgery. However, its administration increases the risk of seizures, as indicated by a meta-analysis of randomized and observational studies^[1]. Furthermore, the incidence of seizures has been shown to be dose-dependent.

Although the benefits of tranexamic acid have been well-established, there is a significant knowledge gap regarding the optimal dosing regimen for cardiac surgery. Various dosing regimens have been reported to exhibit varying efficacy and safety profiles. In terms of the existing research, one prior meta-analysis performed subgroup analyses comparing low- and high-dose regimens of tranexamic acid, with dosing thresholds set at 10 mg/kg + 1 mg/kg/hour for a combined bolus and continuous infusion regimen, and 50 mg/kg for bolus administration alone^[2]. Another pharmacokinetic study compared the outcomes of low-dose (10 mg/kg followed by a continuous infusion of 1 mg/kg/hour throughout the surgery, with an additional 1 mg/kg administered into the cardiopulmonary bypass [CPB]) and high-dose (30 mg/kg initially, followed by a continuous infusion of 16 mg/kg/hour, with 2 mg/kg administered into the CPB) tranexamic acid regimens^[3].

These discrepancies in dosing regimens have led to divergent opinions within the medical community regarding the most effective and safe approach for utilizing tranexamic acid in cardiac surgery. In our meta-analysis, we defined low- and high-dose regimens based on the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) regimen, that is, a cutoff of a bolus of tranexamic acid 30 mg/kg followed by 16 mg/kg/hour intraoperatively and 2 mg/kg administered in the priming solution^[4]. Using this definition, this meta-analysis of trials aims to assess the efficacy and safety profile of low-dose regimens in open-heart surgery compared to control group, high-dose regimens, and epsilon aminocaproic acid (EACA).

METHODS

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (or PRISMA) statement. Three databases — PubMed®, Clarivate Web of Science, and Cochrane Central Register of Controlled Trials (or CENTRAL) — were systematically searched until November 25, 2022, using the search strategy outlined in Supplementary Table 1. Subsequently, two authors independently screened all identified randomized trials examining the bleeding-reducing effect of tranexamic acid in open-heart surgery based on the specified inclusion criteria. Open-heart surgery encompasses coronary artery bypass grafting (CABG) (on- or off-pump), valve surgery, aortic surgery, congenital surgery, or a combination of elective and emergency procedures. A third author resolved any differences of opinion between the two authors.

The full text of all included studies was searched, and data were extracted, including the type of surgery, number of participants, average age of participants, criteria for packed red cell (PRC) transfusion, and data collected according to the intended outcomes. We excluded studies that did not have the desired outcomes and those that did not compare low-dose regimen with control or high-dose regimen.

We compared the pooled data of the low-dose vs. control groups and low-dose vs. high-dose groups. As stated above, the boundary between the low-dose and high-dose groups was defined by the regimen used in the BART study (bolus 30 mg/kg followed by 16 mg/kg/hour intraoperatively, with an additional 2 mg/kg added to the priming solution)^[4]. A high-dose regimen was defined as administration of a 30 mg/kg bolus or 2.5 g more than once. When a study included more than one group, classified as either low- or high-dose group, we combined the data using the formula described in the Cochrane handbook.

The primary outcomes of this meta-analysis included safety outcomes, specifically the incidence of adverse events, including mortality, bleeding-associated reoperation, myocardial infarction, venous thromboembolic events (VTE), stroke, and seizures. These adverse events were confined to occurrences within 30 days or during the treatment period. Secondary outcomes included efficacy considerations in the form of the amount of bleeding within 24 hours and number of participants receiving PRC unit transfusions within 24 hours. Outcomes were evaluated in terms of the risk ratio (RR) for dichotomous data and standardized mean difference (SMD) for continuous data. Data initially presented as medians and interquartile ranges were converted into means and standard deviations using the method outlined by Wan et al.^[5].

All pooled data were analyzed using the Mantel-Haenszel fixed effects method for dichotomous data or the inverse variance random effects method for continuous data using RevMan 5.4.1 program. Heterogeneity between the studies was assessed using the χ^2 test. A subgroup analysis was performed for each type of surgery. Sensitivity analysis was further conducted by excluding studies that did not report data in the form of mean $\pm$ standard deviation for continuous outcomes, as well as studies with a high risk of bias. Another sensitivity analysis was conducted by excluding studies that did not exclude patients still taking antiplatelet medications for a minimum of five days, or studies that did not specify exclusion criteria for the consumption of antiplatelet or anticoagulant medications.

Two reviewers independently evaluated the risk of bias in the included studies using the Cochrane Collaboration tool, which is designed to assess the risk of bias in randomized controlled trials (RCTs). A risk of bias assessment was further conducted for outcomes categorized into two groups: bleeding- and non-bleeding-related outcomes. Bleeding-related outcomes included the transfusion rate and postoperative bleeding. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to evaluate the quality of evidence (QOE) for each outcome. For outcomes involving > 10 studies in the meta-analysis, tests for funnel plot asymmetry were performed. The results of these tests were interpreted in conjunction with a visual inspection of the funnel plot. In addition, a contour-enhanced funnel plot was generated to identify the potential causes of any observed asymmetry.

RESULTS

Initially, we identified 549 studies through the systematic search of three databases, as well as additional nine studies from searching for the references of the included studies. After removing duplicates, 426 abstracts were screened based on the inclusion criteria. The initial screening yielded 153 articles for full-text review,

which were further screened based on exclusion criteria. Finally, 81 studies were included in our meta-analysis^[6–86]. The screening process is summarized in Figure 1.

The baseline characteristics of the included studies are shown in Supplementary Table 2. Among these studies, seven involved the pediatric population^[16,20,34,67,79,80,82], 336 focused solely on on-pump CABG^[9–12,14,15,21,25,27,28,30,32,33,35,42,45,49–52,54,56,57,59,61–66,70,74,76–78,83], 10 specifically addressed off-pump CABG^[7,17,19,39,48,71–73,75,86], five concentrated on valve surgery^[22,46,47,55,84], and three targeted aortic surgery^[18,53,85]. Subsequently, we conducted a subgroup analysis based on the type of surgery.

Studies that did not implement double-blinding were judged to have a high risk of bias in measuring bleeding-related outcomes (Table 1). This judgment was based on the notion that knowledge of the intervention likely influenced the assessment of these outcomes. However, when measuring non-bleeding-related outcomes (Supplementary Table 3), these studies were judged to have a low risk of bias.

We determined that studies that excluded participants from the analysis due to surgical-origin bleeding complications during or

after surgery raised concerns regarding bias in the missing outcome data. However, a high risk of bias was considered if the reason for exclusion was not bleeding of surgical origin. Nevertheless, for the overall risk of bias, we judged that the majority of the included studies were not at high risk, except for two^[14,58].

The GRADE evaluations of the included studies are shown in Table 2. We considered some inconsistencies in all continuous outcomes of the low-dose vs. control comparison and the postoperative bleeding outcomes of the low-dose vs. high-dose comparison due to substantial heterogeneity. Therefore, we downgraded these outcomes to one level. There were no issues with indirectness in any of the outcomes. We further downgraded some outcomes for imprecision when the upper or lower confidence limit crossed the SMD of 0.5, for continuous outcomes, or a RR reduction of 25% for dichotomous outcomes in either direction. We downgraded two levels if the 95% confidence interval (CI) crossed a relative risk increase > 100%.

We did not conduct a test for funnel plot asymmetry for the high-dose vs. low-dose group and low-dose vs. EACA comparisons because fewer than 10 studies were included for all outcomes.

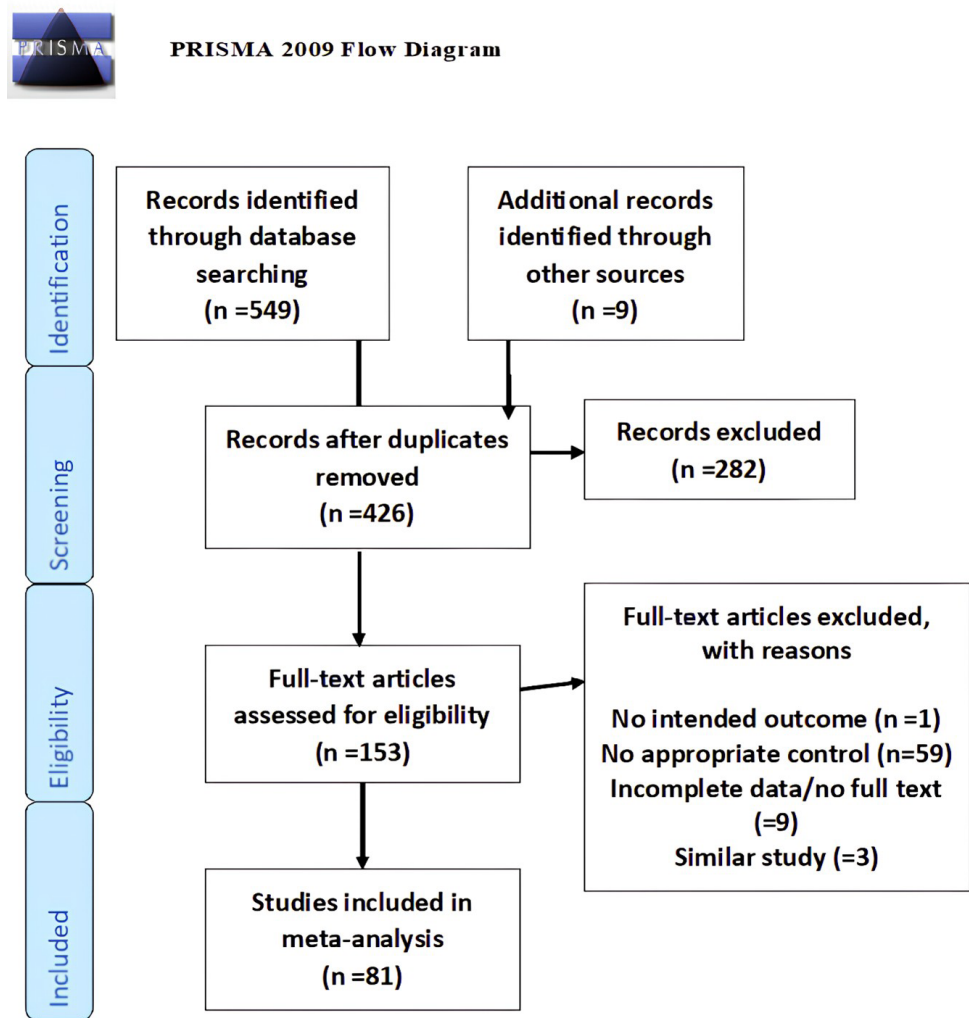


Fig. 1 - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of this study.

Table 1. Risk of bias of included studies for bleeding-related outcomes.						
Studies	Randomization	Adhering to intervention	Missing outcome data	Measurement	Reporting	Overall
Abul-Azm, 2006 ⁶						
Ahn, 2011 ⁷						
Ali Shah, 2015 ⁸						
Altun, 2017 ⁹						
Andreasen, 2004 ¹⁰						
Armellin, 2004 ¹¹						
Banihashem, 2019 ¹²						
Baric, 2007 ¹³						
Blauhut, 1994 ¹⁴						
Brown, 1997 ¹⁵						
Casati 1999 ⁸¹						
Casati, 2001 ¹⁷						
Casati, 2001 ¹⁸						
Casati, 2004 ¹⁹						
Chaudhary, 2018 ²⁰						
Chauhan, 2004 (2) ⁸⁰						
Chauhan, 2004 (1) ⁷⁹						
Chen, 2013 ²¹						
Choudhuri, 2015 ²²						
Coffey, 1995 ²³						
Corbeau, 1995 ²⁴						
De Bonis, 2000 ²⁵						
Du, 2014 ²⁶						
El Baser, 2021 ⁸²						
Esfandiari, 2013 ²⁷						
Fakher-e-Fayaz, 2014 ²⁸						
Faraoni, 2014 ²⁹						
Fawzy, 2009 ³⁰						
Greiff, 2012 ³¹						
Hardy, 1998 ³²						
Hashemi, 2011 ³³						
Hatami, 2020 ³⁴						
Hekmat, 2004 ³⁵						
Horrow, 1990 ³⁶						
Horrow, 1991 ³⁷						
Horrow, 1995 ³⁸						
Hosseini, 2014 ³⁹						
Iribarren, 2008 ⁴⁰						
Jimenez, 2007 ⁴¹						
Kuitunen, 2005 ⁴²						
Lambert, 1998 ⁴³						
Landymore, 1997 ⁸³						

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Later, 2009 ⁴⁴						
Maddali, 2007 ⁴⁵						
Madershahian, 2015 ⁴⁶						
Makhija, 2013 ⁸⁵						
Mansouri, 2012 ⁴⁷						
Mehr-Aein, 2007 ⁴⁸						
Menichetti, 1996 ⁴⁹						
Mirmohammad-sadeghi, 2018 ⁵⁰						
Mirmohammad-sadeghi, 2020 ⁵¹						
Misfeld, 1998 ⁵²						
Monaco, 2020 ⁵³						
Mongan, 1998 ⁵⁴						
Moret, 2007 ⁵⁵						
Murphy, 2006 ⁵⁶						
Nouraei, 2013 ⁵⁷						
Nuttall, 2000 ⁵⁸						
Ozal, E, 2002 ⁵⁹						
Penta de Peppo, 1995 ⁶⁰						
Pinosky, 1997 ⁶¹						
Pleym, 2003 ⁶²						
Rao, 2018 ⁶³						
Santos, 2006 ⁶⁴						
Shi, 2013 ⁶⁵						
Shi, 2013 ⁶⁶						
Shi, 2022 ⁶⁷						
Shore-Lesserson, 1996 ⁶⁸						
Sigaut, 2014 ⁶⁹						
Singh, 2022 ⁸⁴						
Speekenbrink, 1995 ⁷⁰						
Taghaddomi, 2009 ⁷¹						
Vanek, 2005 ⁷²						
Verma, 2020 ⁸⁶						
Wang, 2012 ⁷³						
Wang, 2017 ⁷⁴						
Wei, 2006 ⁷⁵						
Yanartas, 2015 ⁷⁶						
Zabeeda, 2002 ⁷⁷						
Zhang, 2018 ⁷⁸						



Table 2. GRADE evaluation of included studies.

Outcomes	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias
Low-dose vs. control group comparison					
Mortality	No issue	No issue	No issue	Downgrade 1 level	No issue
Reoperation	No issue	No issue	No issue	No issue	No issue
Myocardial infarction	No issue	No issue	No issue	No issue	No issue
VTE	No issue	No issue	No issue	Downgrade 2 levels	Not applicable
Stroke	No issue	No issue	No issue	Downgrade 1 level	No issue
Seizure	No issue	No issue	No issue	Downgrade 2 levels	Not applicable
Transfusion rate	No issue	Downgrade 1 level	No issue	No issue	Downgrade 1 level
Postoperative bleeding	No issue	Downgrade 1 level	No issue	No issue	No issue
Low-dose vs. high-dose group comparison					
Mortality	No issue	No issue	No issue	Downgrade 1 level	Not applicable
Reoperation	No issue	Downgrade 1 level	No issue	Downgrade 1 level	Not applicable
Myocardial infarction	No issue	No issue	No issue	No issue	Not applicable
VTE	No issue	No issue	No issue	Downgrade 1 level	Not applicable
Stroke	No issue	No issue	No issue	Downgrade 1 level	Not applicable
Seizure	No issue	No issue	No issue	No issue	Not applicable
Transfusion rate	No issue	No issue	No issue	No issue	Not applicable
Postoperative bleeding	No issue	Downgrade 1 level	No issue	No issue	Not applicable
Low-dose group vs. EACA comparison					
Mortality	No issue	No issue	No issue	Downgrade 2 levels	Not applicable
Reoperation	No issue	No issue	No issue	Downgrade 2 levels	Not applicable
Myocardial infarction	No issue	No issue	No issue	Downgrade 2 levels	Not applicable
VTE	No issue	No issue	No issue	Downgrade 2 levels	Not applicable
Stroke	No issue	No issue	No issue	Downgrade 2 levels	Not applicable
Seizure	No issue	No issue	No issue	Downgrade 2 levels	Not applicable
Transfusion rate	No issue	No issue	No issue	Downgrade 1 level	Not applicable
Postoperative bleeding	No issue	Downgrade 1 level	No issue	No issue	Not applicable

EACA=epsilon aminocaproic acid; GRADE=Grading of Recommendations Assessment, Development and Evaluation; VTE=venous thromboembolic events

Conversely, for the low-dose vs. control group comparison, we assessed asymmetry in the funnel plot test for transfusion rates and postoperative bleeding (Figure 2). However, after inspecting the enhanced contour funnel plot of the postoperative bleeding outcomes (Figure 3), we found indications of missing studies on the top-left side of the plot. As this area primarily contained regions of high statistical significance, we concluded that the likely cause of the asymmetry was not publication bias. True heterogeneity stemming from differences in the dose regimen of tranexamic acid or variations in the underlying risk of surgery between studies is

considered a plausible explanation for the funnel plot asymmetry. Publication bias was detected in transfusion rate outcomes. In terms of the safety profile (Table 3), the low-dose regimen of tranexamic acid significantly decreased the incidence of reoperation (RR: 0.52; 95% CI: 0.39–0.69; $P<0.01$; high QOE) and perioperative myocardial infarction (RR: 0.64; 95% CI: 0.43–0.95; $P=0.03$; high QOE) compared to the control. The low-dose regimen of tranexamic acid did not increase mortality, VTE, or stroke rates compared to the control. However, the low-dose regimen of tranexamic acid increased the incidence of seizures (RR: 1.72;

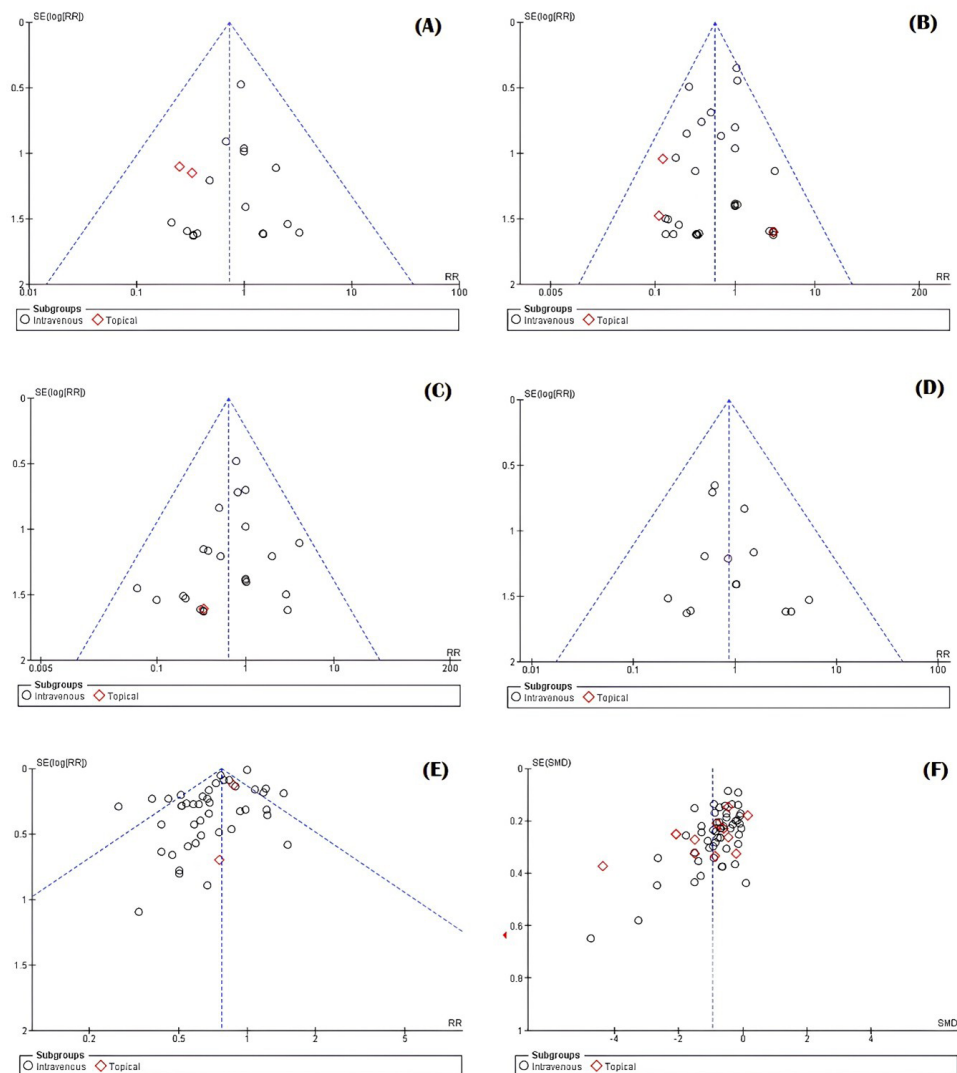


Fig. 2 - Funnel plot test of low-dose vs. control group comparison for (A) mortality; (B) reoperation; (C) myocardial infarction; (D) stroke; (E) transfusion rate; (F) postoperative bleeding. RR=risk ratio; SE=standard error; SMD=standardized mean difference.

95% CI: 0.61–4.86; $P=0.30$, low QOE). Our confidence in the effect estimate of seizure outcomes was limited, indicating that the actual effect may differ substantially from the estimated effect. In terms of the efficacy profile, a low-dose regimen of tranexamic acid was able to reduce the proportion of participants requiring PRC transfusion (RR: 0.77; 95% CI: 0.72–0.81; $P<0.01$; low QOE) and the number of perioperative hemorrhages in 24 hours (SMD: -0.98; 95% CI: -1.16 – -0.80; $P<0.01$; moderate QOE). Conducting a sensitivity analysis, either by excluding studies that did not report mean data, as demonstrated in Supplementary Table 4, or trials that did not adequately account for the absence of antiplatelet agents, as indicated in Supplementary Table 5, did not change the direction of the effect estimates. Further, this analysis did not result in an improvement in heterogeneity except for transfusion rate outcomes.

In terms of the safety profile, as shown in Table 4, the low-dose regimen of tranexamic acid decreased the incidence of seizures (RR: 0.54; 95% CI: 0.26–1.10; $P=0.09$, high QOE) and stroke (RR: 0.84; 95% CI: 0.45–1.55; $P=0.58$, moderate QOE) compared to a high-dose regimen of intravenous tranexamic acid. The low-dose tranexamic acid regimen also showed no differences in myocardial infarction events or VTE. However, the low-dose group increased the needs for transfusion (RR: 1.13; 95% CI: 1.03–1.23; $P<0.01$; high QOE), mortality rate, and postoperative bleeding with moderate QOE. Sensitivity analyses that did not report mean data did not change the direction of effect estimates, and further did not improve heterogeneity, as shown in Supplementary Table 4. Performing a sensitivity analysis by excluding studies that did not consider adequate abstinence of antiplatelet agents did not alter the direction of the effect estimates for all outcomes. However,

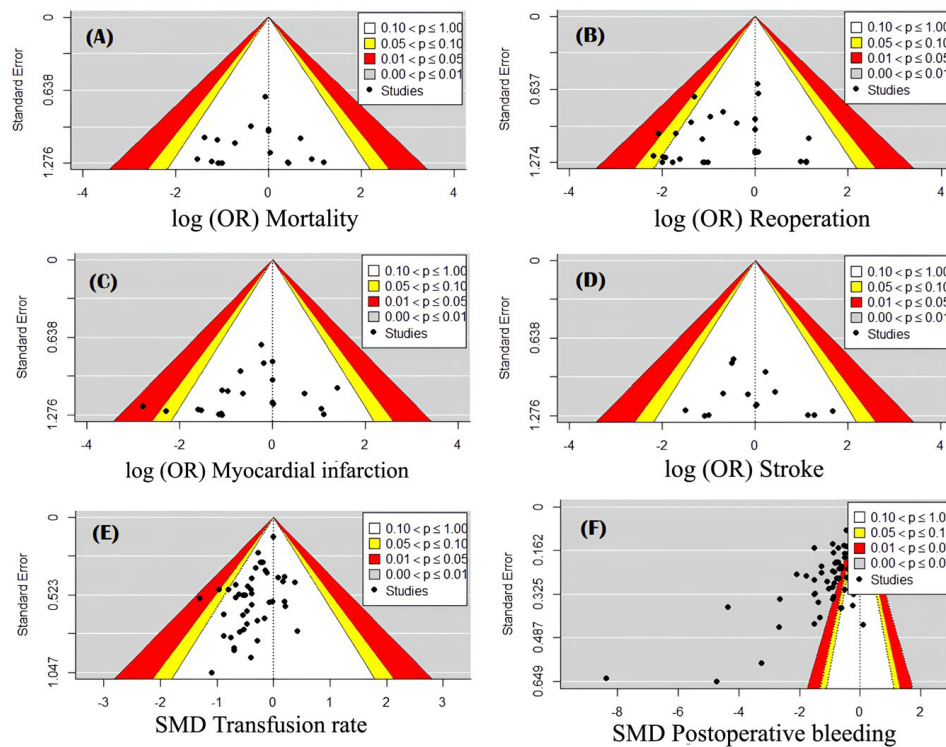


Fig. 3 - Enhanced-contour funnel plot test for low-dose vs. control group comparison for (A) mortality; (B) reoperation; (C) myocardial infarction; (D) stroke; (E) transfusion rate; (F) postoperative bleeding. OR=odds ratio; SMD=standardized mean difference.

it enhanced precision in reoperation (RR: 2.60; 95% CI: 1.13–5.95; $P=0.02$) and reduced precision in transfusion rate outcomes (SMD: 1.05; 95% CI: 0.93 – 1.19; $P=0.43$), as indicated in Supplementary Table 6. However, this analysis did not improve heterogeneity. Compared to EACA (Table 5), a low-dose regimen of tranexamic acid was able to significantly reduce postoperative bleeding (SMD: -0.58; 95% CI: -1.02 – -0.14; $P<0.01$; moderate QOE). However, the low-dose tranexamic acid group had low-quality evidence in increasing the incidence of reoperation (RR: 1.60; 95% CI: 0.61–4.18; $P=0.34$) and seizure (RR: 3.46; 95% CI: 0.73–16.29; $P=0.12$). Our confidence in the effect estimates for reoperation and seizure outcomes is limited, and the true effect may be substantially different from the estimated effect.

When compared with a control, a low-dose regimen of tranexamic acid was shown to significantly reduce the incidence of bleeding-associated reoperation in on-pump CABG (RR: 0.52; 95% CI: 0.33–0.82; $P<0.01$), valve surgery (RR: 0.39; 95% CI: 0.16–0.99; $P=0.05$), and congenital surgery (RR: 0.17; 95% CI: 0.05–0.54; $P<0.01$), but the decrease was not significant in off-pump CABG and aortic surgeries (Supplementary Table 7). Regarding other adverse events, the low-dose regimen did not significantly increase the incidence of stroke in on-pump CABG surgery other than seizures compared with the control. The need for transfusion and the amount of postoperative hemorrhage were significantly reduced in the low-dose regimen group compared with the control group in all types of surgery.

For the subgroup analysis based on surgery type for low-dose vs. high-dose comparisons, as presented in Supplementary Table 8, there was only one study investigating off-pump CABG and one study on congenital surgery. Therefore, meta-analyses could not be performed on these subgroups. For on-pump CABG, the analysis was performed only for postoperative bleeding outcomes. The results showed that a high-dose regimen of tranexamic acid decreased postoperative bleeding compared with a low-dose regimen. However, evidence was only obtained from two studies with low levels of imprecision accompanied by inconsistency^[11,28].

DISCUSSION

A total dose of tranexamic acid less than a regimen consisting of a 30 mg bolus dose followed by a continuous infusion at 16 mg/kg/hour was sufficient to reduce postoperative bleeding and other bleeding-related outcomes without increasing the risk of adverse events compared with controls. A higher dose of tranexamic acid can reduce bleeding in cardiac surgery compared with lower doses; however, it is associated with an elevated risk of seizures and stroke. This indicates that caution should be exercised, and high doses of tranexamic acid should be avoided.

Low-dose topical administration was effective at reducing postoperative bleeding and other bleeding-related outcomes, without increasing the risk of adverse events compared with controls. However, analysis of seizures could not be conducted

Table 3. Summary findings of low-dose vs. control group comparison.

Outcomes	No. of studies	No. of participants	Effect estimates (95% CI), P-value	Heterogeneity	Quality of the evidence (GRADE)
Mortality	42	4752	0.73 [0.46, 1.18], P=0.20	I ² = 0%, P=0.99	Moderate
Intravenous	36	4201	0.83 [0.50, 1.38], P=0.48	I ² = 0%, P=1.00	
Topical	6	551	0.28 [0.06, 1.34], P=0.11	I ² = 0%, P=0.86	
Reoperation	48	5239	0.52 [0.39, 0.69], P<0.01	I ² = 0%, P=0.68	High
Intravenous	41	4750	0.55 [0.41, 0.73], P<0.01	I ² = 0%, P=0.76	
Topical	7	489	0.23 [0.07, 0.79], P=0.02	I ² = 37%, P=0.21	
Myocardial infarction	38	4460	0.64 [0.43, 0.95], P=0.03	I ² = 0%, P=0.93	High
Intravenous	35	4302	0.64 [0.43, 0.96], P=0.03	I ² = 0%, P=0.91	
Topical	3	158	0.33 [0.01, 7.72], P=0.49	Not applicable	
Venous thromboembolic events	22	2306	0.71 [0.18, 2.87], P=0.63	I ² = 0%, P=0.85	Low
Intravenous	21	2235	0.71 [0.18, 2.87], P=0.63	I ² = 0%, P=0.85	
Topical	1	71	Not estimable	Not applicable	
Stroke	35	4371	0.87 [0.51, 1.51], P=0.63	I ² = 0%, P=0.96	Moderate
Intravenous	33	4220	0.87 [0.51, 1.51], P=0.63	I ² = 0%, P=0.96	
Topical	2	151	Not estimable	Not applicable	
Seizure	15	1781	1.72 [0.61, 4.86], P=0.30	I ² = 0%, P=0.75	Low
Intravenous	13	1617	1.72 [0.61, 4.86], P=0.30	I ² = 0%, P=0.75	
Topical	1	80	Not estimable	Not applicable	
Transfusion rate	45	4964	0.77 [0.72, 0.81], P<0.01	I ² = 87%, P<0.01	Low
Intravenous	43	4731	0.76 [0.72, 0.81], P<0.01	I ² = 88%, P<0.01	
Topical	2	233	0.86 [0.67, 1.11], P=0.24	I ² = 0%, P=0.83	
Postoperative bleeding	67	6877	-0.98 [-1.16, -0.80], P<0.01	I ² = 91%, P<0.01	Moderate
Intravenous	56	5920	-0.95 [-1.13, -0.76], P<0.01	I ² = 91%, P<0.01	
Topical	11	957	-1.14 [-1.72, -0.55], P<0.01	I ² = 94%, P<0.01	

CI=confidence interval; GRADE=Grading of Recommendations Assessment, Development and Evaluation

Table 4. Summary findings of low-dose vs. high-dose group comparison.

Outcomes	No. of studies	No. of participants	Effect estimates (95% CI), P-value	Heterogeneity	Quality of the evidence (GRADE)
Mortality	7	4333	1.30 [0.73, 2.29], P=0.37	I ² = 0%, P=0.74	Moderate
Intravenous	6	4255	1.30 [0.73, 2.29], P=0.37	I ² = 0%, P=0.74	
Topical	1	78	Not estimable	Not applicable	
Reoperation	6	4200	1.41 [0.89, 2.23], P=0.14	I ² = 66%, P=0.03	Low
Myocardial infarction	4	4011	0.99 [0.81, 1.21], P=0.91	I ² = 0%, P=0.50	High
Venous thromboembolic events	4	3701	0.90 [0.46, 1.76], P=0.75	I ² = 6%, P=0.30	Moderate
Intravenous	3	3623	0.90 [0.46, 1.76], P=0.75	I ² = 6%, P=0.30	
Topical	1	78	Not estimable	Not applicable	
Stroke	5	4019	0.84 [0.45, 1.55], P=0.58	I ² = 0%, P=0.96	Moderate
Seizure	5	3876	0.54 [0.26, 1.10], P=0.09	I ² = 0%, P=0.64	High
Intravenous	4	3798	0.47 [0.23, 1.02], P=0.06	I ² = 0%, P=0.78	
Topical	1	78	Not estimable	Not applicable	
Transfusion rate	7	4376	1.13 [1.03, 1.23], P<0.01	I ² = 0%, P=0.85	High
Postoperative bleeding	10	4664	0.62 [-0.18, 1.42], P=0.13	I ² = 99%, P<0.01	Moderate
Intravenous	9	4586	0.67 [-0.20, 1.54], P=0.13	I ² = 99%, P<0.01	
Topical	1	78	0.11 [-0.33, 0.55], P=0.63	Not applicable	

CI=confidence interval; GRADE=Grading of Recommendations Assessment, Development and Evaluation

because of the absence of events in one study that reported seizure outcomes. This implies that topical administration may be considered an alternative to a low-dose intravenous regimen. Furthermore, our findings indicate that low-dose tranexamic acid reduces the risk of perioperative myocardial infarction by 36% compared to controls. This contradicts evidence from a previous meta-analysis (RR: 0.89, 95% CI: 0.77–1.04)^[2]. Other meta-analyses specific to CABG surgeries also reported no significant difference in myocardial infarction incidence (RR: 0.90; 95% CI: 0.78–1.05)^[87]. The positive impact of tranexamic acid on myocardial infarction alleviates concerns about prothrombotic effects that could potentially result in graft blockage. The low incidence of myocardial infarction could be attributed to the minimal occurrence or duration of anemia, particularly due to a reduction in postoperative bleeding.

We observed that tranexamic acid effectively reduced bleeding and the need for transfusions in valve, on-pump CABG, and off-pump CABG surgeries. The effects of on-pump and off-pump CABG were nearly identical. Given that heparin exposure increases the risk of bleeding during off-pump CABG surgery, the administration of tranexamic acid could be beneficial for these patients. However, we were regrettably unable to determine whether the reduction in bleeding in off-pump surgery justified the associated risks.

The low-dose group exhibited a pooled RR estimate of 1.72 for seizure events; however, this result was not statistically significant. Overall, seizures were reported in only five studies, with a total incidence of eight (0.9%) of 845 participants in the low-dose group and four (0.5%) of 852 in the control group. The incidence of seizures in the control group in our meta-analysis

Table 5. Summary findings of low-dose group vs. EACA comparison.

Outcomes	No. of studies	No. of participants	Effect estimate (95% CI), P-value	Heterogeneity	Quality of the evidence (GRADE)
Mortality	4	390	0.80 [0.20, 3.24], P=0.75	I ² = 16%, P=0.30	Low
Reoperation	6	496	1.60 [0.61, 4.18], P=0.34	I ² = 0%, P=0.80	Low
Myocardial infarction	4	365	0.83 [0.27, 2.55], P=0.75	I ² = 0%, P=0.68	Low
Venous thromboembolic events	2	216	0.32 [0.01, 7.60], P=0.48	Not applicable	Low
Stroke	4	286	1.41 [0.29, 6.96], P=0.67	I ² = 0%, P=0.82	Low
Seizure	3	197	3.46 [0.73, 16.29], P=0.12	I ² = 0%, P=0.81	Low
Transfusion rate	5	296	1.19 [0.87, 1.63], P<0.27	I ² = 0%, P=0.61	Moderate
Postoperative bleeding	9	696	-0.58 [-1.02, -0.14], P=0.01	I ² = 87%, P<0.01	Moderate

CI=confidence interval; EACA=epsilon aminocaproic acid; GRADE=Grading of Recommendations Assessment, Development and Evaluation

was comparable to that in the control group in a broader meta-analysis combining RCT and observational studies, with 53 cases (0.6%) in 8,726 participants^[1].

In general, a minimum of 300 events is typically required to assess rare events. Obtaining precise results for seizure outcomes poses a challenge, as all meta-analyses reporting seizure outcomes have yielded no more than 30 events. Therefore, caution must be exercised when drawing conclusions from this study. Two studies in our low-dose group with high body weight employed a 10 mg/kg bolus, followed by 10 mg/kg/hour after induction. This dosage exceeded the recommended 20 mg/kg single bolus or 10 mg/kg bolus followed by 1 mg/kg/hour to reduce seizure incidence based on a model-based meta-analysis^[3]. However, the intravenous low-dose vs. high-dose comparison in this meta-analysis reported that the risk for seizure events was reduced by 46% in the low-dose group relative to the high-dose group.

Patients who undergo heart surgery are often provided long-term treatment with antiplatelet or anticoagulant agents. The studies included in our meta-analysis varied in terms the associated cessation periods, and some did not discontinue the antiplatelet agents. Discontinuation or continuation should be considered when assessing the benefit of reducing the risk of thrombotic events compared with the increased risk of major bleeding, including the need for reoperation. The administration of tranexamic acid is an effective strategy to reduce the risk of bleeding and bleeding-related complications in patients who are still experiencing the effects of antiplatelet or anticoagulant agents during surgery. This

fact was confirmed in our study, in which low-dose tranexamic acid administration significantly reduced the risk of bleeding (SMD: -0.79, 95% CI: -1.06 – -0.53; P<0.01) and reoperation (RR: 0.29, 95% CI: 0.11–0.74; P<0.01) compared to controls among the subset of patients who were still on antiplatelet or anticoagulant therapy (Supplementary Table 7). Additionally, the sensitivity analysis in our meta-analysis indicated that discontinuation of antiplatelet or anticoagulant therapy for a minimum of five days did not increase the risk of stroke and, in fact, reduced the incidence of myocardial infarction.

Limitations

This meta-analysis had several limitations. First, unavoidable heterogeneity arises from clinical diversity, encompassing variations in the dose regimen of tranexamic acid, duration of antiplatelet or anticoagulant use before surgery, and different types of surgeries. This diversity may affect the reliability of the results, particularly in terms of outcomes related to transfusion and blood loss. Despite the division into two groups, the range of dose variations within each group was extensive. In addition to dose variations, factors such as the method of administration (bolus or continuous) and timing of administration (pre-incision, during CPB, or after protamine reversal) also exhibited variability. Second, relatively few undesirable events were identified in this meta-analysis. Consequently, the small study effect could have potentially influenced the findings concerning the safety profile outcomes of this study.

CONCLUSION

Overall, the present meta-analysis revealed that a dose regimen of no more than two administrations of 30 mg/kg or a single bolus of 30 mg/kg followed by no more than 16 mg/kg/hour of tranexamic acid was effective in reducing postoperative bleeding and the risk of reoperation, without increasing the risk of adverse events. Additionally, the administration is associated with a reduction in the incidence of perioperative myocardial infarction.

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Authors' Roles & Responsibilities

AW	Substantial contributions to the conception or design of the work; and the analysis and interpretation of data for the work; revising the work; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published
CG	Substantial contributions to the acquisition, analysis, or interpretation of data for the work; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published
AN	Substantial contributions to the acquisition and analysis of data for the work; drafting the work; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published
NCPK	Substantial contributions to the acquisition and analysis of data for the work; drafting the work critically for important intellectual content; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published
JN	Substantial contributions to interpretation of data for the work; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published

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Supplementary Table 1 - Searching strategy.
1. Cochrane Central Register of Controlled Trials (or CENTRAL) database
"tranexamic acid" OR "aminocaproic acid" OR "antifibrinolytic agent" in All Text AND "coronary bypass graft" OR "coronary bypass surgery" OR "cardiac surgery" OR "heart valve surgery" in All Text AND "controlled clinical trial" OR "double blind study" OR "clinical trial" in All Text - (Word variations have been searched)
2. Clarivate Web of Science database
(ALL=(tranexamic acid)) OR ALL=(antifibrinolytic agents) OR ALL=(aminocaproic acid)) AND (((ALL=(coronary bypass artery surgery)) OR ALL=(coronary bypass artery grafting)) OR ALL=(cardiac surgery)) OR ALL=(heart valve surgery) AND (ALL=(controlled clinical trial) OR ALL=(double blind study) OR ALL=(clinical trial))
3. PubMed® database
((("aminocaproic acid"[MeSH Terms]) OR (tranexamic acid[MeSH Terms] AND (randomizedcontrolledtrial[Filter]))) OR (antifibrinolytic agents[MeSH Terms] AND (randomizedcontrolledtrial[Filter])) AND (randomizedcontrolledtrial[Filter])) AND (("cardiac surgical procedures"[MeSH Terms]) OR (thoracic surgery[MeSH Terms]) AND (randomizedcontrolledtrial[Filter])) Filters: Randomized Controlled Trial

Supplementary Table 2 - Baseline characteristic of included studies.						
Author, year	Age (mean ± SD)	Sex, male (%)	Type of surgery (%)	Dose of tranexamic acid	Trigger for transfusion of PRC	Antiplatelet or anticoagulant discontinued before surgery
Abul-Azm & Abdullah, 2006 ⁶	58 ± 23 vs. 55 ± 26	52	CABG (on-pump): 26	2 g, topical, before sternal closure	Hb < 8 or Hct < 24%	Antiplatelet < 7 days
			Valve: 65			
			Combined: 9			
Ahn et al., 2012 ⁷	69 ± 7 vs. 67 ± 7	53.9	CABG (off-pump): 100	1 g, IV bolus, after induction, continued by infusion at 200 mg/h during surgery	Hb < 8.5 g/dL	Antiplatelet < 5 days
Ali Shah et al., 2015 ⁸	51 ± 13 vs. 49 ± 12	79	CABG (on-pump): 69	2.5 g, topical, before sternal closure	No information	Antiplatelet < 7 days
			Valve: 27			
			Combined: 4			
Altun et al., 2017 ⁹	65 ± 29	87	CABG (on-pump): 100	10 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h for 10 h	Hct < 24%	Dual antiplatelet was not discontinued
Andreasen & Nielsen, 2004 ¹⁰	62 ± 10 vs. 64 ± 8	84.1	CABG (on-pump): 100	1.5 g, IV bolus, after induction, continued by infusion at 200 mg/h until 1.5 g	Hct < 25%	Antiplatelet < 7 days

Armellin et al., 2004 ¹¹	66 ± 8 vs. 64 ± 9	83.9	CABG (on-pump): 100	15 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h	Hb < 9 g/dL	Not reported
				vs.		
				30 mg/kg, IV bolus, after induction and 30 mg/kg on priming of CPB		
Banihashem et al., 2019 ¹²	58 ± 10 vs. 58 ± 12	67.5	CABG (on-pump): 100	10 mg/kg, IV bolus, after induction and 10 mg/kg, IV bolus, after reversal	Hct < 24%	Not reported
Baric et al., 2007 ¹³	61 ± 11 vs. 61 ± 10	75.1	CABG (on-pump): 68.3	2.5 g, topical, prior to sternal closure	Hct < 30% and Hb < 9 g/dL	Antiplatelet < 5 days
			Valve: 16.4			
			Combined: 7.8			
			Other: 7.5			
Blauhut et al., 1994 ¹⁴	63 ± 2 vs. 63 ± 3	82.2	CABG (on-pump): 100	10 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h	Hct < 30%	Any recent aspirin consumption was excluded
Brown et al., 1997 ¹⁵	62 ± 9 vs. 59 ± 7	81.1	CABG (on-pump): 100	15 mg/kg, IV bolus, after induction or 15 mg/kg, IV bolus, after reversal, continued by infusion at 1 mg/kg/h	Hb < 8/dL	Not reported
Casati et al., 1999 ⁸¹	62 ± 10 vs. 59 ± 10	80.8	CABG (on-pump): 83.3	1 g, IV bolus, after induction, continued by infusion at 400 mg/h during surgery and 500 mg added to priming solution	Hb < 8 g/dL and Hct < 24%	Antiplatelet was not discontinued
			Valve: 11.8			
			Combined: 8.9			
Casati, Bellotti, et al., 2001 ¹⁶	56 ± 49 vs. 56 ± 49	65.4	CABG (on-pump): 45.4	Continuous infusion 1 mg/kg/h or 2 mg/kg/h for 12 h	Hb < 8 g/dL and Hct < 24%	Not reported
			Valve: 31.8			
			Combined: 15.7			
			ASD: 1.6			
Casati, Gerli, et al., 2001 ¹⁷	64 ± 13 vs. 62 ± 11	80	CABG (off-pump): 100	1 g, IV bolus, after induction, continued by infusion at 400 mg/h during surgery	Hb < 8 g/dL or Hct < 24%	Antiplatelet was not discontinued

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Casati et al., 2002 ¹⁸	59 ± 13 vs. 63 ± 11	70	Aortic surgery: 100	1 g, IV bolus, after induction, continued by infusion at 400 mg/h during surgery and 500 mg on priming of CPB	Hb < 8 g/dL and Hct < 24%	Antiplatelet was not discontinued
Casati et al., 2004 ¹⁹	64 ± 11 vs. 61 ± 10	84.3	CABG (on-pump): 50	1 g, IV bolus, after induction, continued by infusion at 400 mg/h during surgery and 500 mg on priming of CPB	Hb < 8 g/dL and Hct < 24%	Antiplatelet was not discontinued
			CABG (off-pump): 50			
Chaudhary et al., 2018 ²⁰	18 ± 31 months	64	Congenital: 100	2 g, topical, prior to sternal closure	No information	Not reported
Chauhan, Das, et al., 2004 ⁷⁹	4.1 ± 2.4 vs. 4.3 ± 2.3 vs. 4.2 ± 2.1	70	Congenital: 100	10 mg/kg, IV bolus, after induction, added by 10 mg/kg on priming of CPB and 10 mg/kg, IV bolus, after reversal	Hct < 33%	Not reported
				vs.		
				EACA: 100 mg/kg, IV bolus, after induction, added by 100 mg/kg on priming of CPB and 100 mg/kg, IV bolus, after reversal		
Chauhan, Bisoi, et al., 2004 ⁸⁰	3.3 ± 2.9 vs. 4.2 ± 4.0 vs. 3.0 ± 4.3 vs. 2.9 ± 5.0 vs. 4.3 ± 3.3	80	Congenital: 100	10 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h for 8 h or 10 mg/kg, IV bolus, after induction, added by 10 mg/kg on priming of CPB and 10 mg/kg, IV bolus, after reversal or 20 mg/kg, IV bolus, after induction, added by 20 mg/kg, IV bolus, after reversal	No information	Antiplatelet was not discontinued
				vs.		
				50 mg/kg, IV bolus, after induction		
Chen et al., 2013 ²¹	50 vs. 50	45	CABG (on-pump): 100	15 mg/kg, IV bolus, after induction, continued by infusion at 15 mg/kg/h	No information	Not reported

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Choudhuri & Biswas, 2015 ²²	36 ± 12 vs. 39 ± 13	55.1	Valve: 100	10 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h	Hct < 25%	Any recent aspirin consumption was excluded
Coffey et al., 1995 ²³	64 vs. 65	33.3	CABG (on-pump): 93.3	10 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h for 12 h	No information	Not reported
			Combined: 6.7			
Corbeau et al., 1995 ²⁴	62 vs. 63	72.1	CABG (on-pump): 52.9	15 mg/kg on priming of CPB and 15 mg/kg, IV bolus, after reversal	Hct < 25%	Antiplatelet < 10 days
			Valve: 47.1			
De Bonis et al., 2000 ²⁵	62 ± 7 vs. 60 ± 6	87.5	CABG (on-pump): 100	1 g, topical, prior to sternal closure	Hct < 24% or Hb < 7.5 g/dL	Antiplatelet < 14 days
Du et al., 2014 ²⁶	51 ± 12 vs. 51 ± 12	48.6	Valve: 92.6, Combined: 7.4	10 mg/kg, IV bolus, after induction, continued by infusion at 2 mg/kg/h during surgery and 400 mg on priming of CPB	Hb < 9 g/dL or Hct < 27%	Coumadin < 7 days
				vs.		
				30 mg/kg, IV bolus, after induction, continued by infusion at 16 mg/kg/h during surgery and 2 mg/kg on priming of CPB		
El Baser et al., 2021 ⁸²	34 ± 24 vs. 34 ± 30 months	54.8	Congenital: 100	6.4 mg/kg, IV bolus, after induction, continued by infusion at 3 mg/kg/h	Hct < 25%	Not reported
					Hb < 10 g/dl	
Esfandiari et al., 2013 ²⁷	54 ± 10 vs. 55 ± 10	80	CABG (on-pump): 100	10 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h	Hct < 24%	Not reported
Fakher-e-Fayaz et al., n.d. ²⁸	56 vs. 54	87.7	CABG (on-pump): 100	10 mg/kg, IV bolus, after reversal, continued by infusion at 10 mg/kg/h or 20 mg/kg, IV bolus, after reversal, continued by infusion at 15 mg/kg/h	Hct < 26%	Antiplatelet < 7 days
				vs.		
				30 mg/kg, IV bolus, after reversal, continued by infusion at 20 mg/kg/h		

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Faraoni et al., 2014 ²⁹	61 ± 10 vs. 62 ± 14 vs. 71 ± 14	66.7	CABG (on-pump): 42.4	5 mg/kg, IV bolus, after induction, continued by infusion at 5 mg/kg/h	Hb < 8.5 g/dL	Not reported
			Valve: 39.4	vs.		
			Combined: 18.2	30 mg/kg, IV bolus, after induction, continued by infusion at 16 mg/kg/h		
Fawzy et al., 2009 ³⁰	55 ± 11 vs. 60 ± 7	94.7	CABG (on-pump): 100	1 g, topical, prior to sternal closure	Hb < 8 g/dL	Antiplatelet < 2 days
Greiff et al., 2012 ³¹	77 ± 4 vs. 77 ± 5	58.7	Combined: 100	10 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h	No information	Any recent aspirin consumption was excluded
Hardy et al., 1998 ³²	No information	74.6	CABG (on-pump): 100	10 mg/kg, IV bolus, after induction	Hb < 8 g/dL	Not reported
Ghaffari Nejad et al., 2012 ³³	55 ± 9	77	CABG (on-pump): 100	1 g on priming of CPB and 1 g, IV bolus, after reversal	Hct < 30%	Not reported
Hatami et al., 2020 ³⁴	4 ± 4	52.1	Congenital: 100	20 mg/kg on priming of CPB and 20 mg/kg, IV bolus, after reversal	Hb < 8 g/dL	Any recent anticoagulant consumption was excluded
				vs.		
				50 mg/kg, topical, prior to sternal closure		
Hekmat et al., 2004 ³⁵	63 ± 8	94.9	CABG (on-pump): 100	500 mg, IV bolus, after induction, 500 mg on priming of CPB, 1 g, IV bolus, after induction	Hb < 8 g/dL	Antiplatelet was not discontinued
Horrow et al., 1990 ³⁶	66 ± 10 vs. 62 ± 9	No information	No information	10 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h	No information	Antiplatelet < 7 days
Horrow et al., 1991 ³⁷	65 ± 11 vs. 64 ± 10	No information	CABG (on-pump): 80.7	10 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h	Hct < 24%	Antiplatelet < 7 days
			Valve: 12.6			
			Combined: 5			
			Other: 3.3			

Horrow et al., 1995 ³⁸	64 ± 3	81.8	No information	2.5 or 5 or 10 or 20 mg/kg, IV bolus, after induction, continued by infusion at 0.25 or 0.5 or 1 or 2 mg/kg/h	No information	Antiplatelet < 7 days
				vs.		
				40 mg/kg, IV bolus, after induction, continued by infusion at 4 mg/kg/h		
Hosseini et al., 2014 ³⁹	61 ± 11	74.6	CABG (off-pump): 100	1 g, topical, prior to sternal closure	Hb < 8 g/dL	Any recent antiplatelet consumption was excluded
Iribarren et al., 2008 ⁴⁰	67 ± 6 vs. 68 ± 12	54	CABG (on-pump): 50	2 g, IV bolus, after induction and 2 g on priming of CPB	No information	Antiplatelet < 5 days
			Valve: 38			
			Combined: 12			
Jimenez et al., 2007 ⁴¹	66 vs. 67	54	CABG (on-pump): 50	2 g, IV bolus, after induction and 2 g, IV bolus, after reversal	Hb < 8 g/dL	Antiplatelet < 5 days
			Valve: 38			
			Combined: 12			
Kuitunen et al., 2005 ⁴²	63 ± 2 vs. 65 ± 2	No information	CABG (on-pump): 100	15 mg/kg, IV bolus, after induction, continued by infusion at 15 mg/kg/h during surgery and 15 mg/kg on priming of CPB	Hct < 30%	Antiplatelet < 5 days
Lambert et al., 1998 ⁴³	No information	No information	No information	20 mg/kg, IV bolus, after induction	No information	Warfarin < 7 days
				vs.		
				50 or 100 mg/kg, IV bolus, after induction		
Landymore et al., 1997 ⁸³	No information	No information	CABG (on-pump): 100	10 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h	No information	Antiplatelet < 2 days
				vs.		
				EACA: 5 g, IV bolus, after induction, continued by infusion at 1 g/h		

Later et al., 2009 ⁴⁴	64 ± 13 vs. 65 ± 11	71.8	CABG (on-pump): 34.2	1 g, IV bolus, after induction and 500 mg on priming of CPB, continued by infusion at 400 mg/h	Hb < 8.1 g/dL	Antiplatelet < 5 days
			Valve: 29.2			
			Combined: 36.6			
Maddali & Rajakumar, 2007 ⁴⁵	No information	No information	CABG (on-pump): 100	10 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h during surgery	Hb < 6 g/dL	Antiplatelet < 7 days
Madershahian et al., 2015 ⁴⁶	82 ± 7	38	Valve: 100	1 g, IV bolus, after induction, continued by infusion at 400 mg/h during surgery	Hb < 8 g/dL	Not reported
Makhija et al., 2013 ⁸⁵	39 ± 12 vs. 41 ± 11	90.2	Aorta: 100	10 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h	Hct < 30%	Any recent antiplatelet consumption was excluded
				vs.		
				EACA: 50 mg/kg, IV bolus, after induction, continued by infusion at 25 mg/kg/h		
Mansouri et al., 2012 ⁴⁷	48 ± 16 vs. 48 ± 14	No information	Valve: 100	30 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h during surgery	Hb < 9 g/dL	Antiplatelet < 5 days
Mehr-Aein et al., 2007 ⁴⁸	44 ± 10	59.1	CABG (off-pump): 100	15 mg/kg, IV bolus, on priming of CPB and 15 mg/kg, IV bolus, after reversal	Hb < 7 g/dL	Antiplatelet < 7 days
Menichetti et al., 1996 ⁴⁹	55 vs. 61	52.1	CABG (on-pump): 100	10 mg/kg, IV bolus, after induction, continued by infusion at 3 mg/kg/h during surgery and 10 mg/kg on priming of CPB	Hct < 30%	Not reported
Mirmohammad-sadeghi et al., 2018 ⁵⁰	63 ± 8 vs. 63 ± 9	80	CABG (on-pump): 100	1 g, topical, prior to sternal closure	No information	Aspirin < 3 days; clopidogrel < 5 days
Mirmohammad-sadeghi & Asadollahi, 2020 ⁵¹	58 ± 11 vs. 53 ± 10	84	CABG (on-pump): 100	200 mg, topical, prior to sternal closure	No information	Antiplatelet < 5 days
Misfeld et al., 1998 ⁵²	56 ± 7 vs. 59 ± 10	92.9	CABG (on-pump): 42	10 mg/kg, bolus on priming of CPB, continued by infusion at 1 mg/kg/h	Hb < 8 g/dL	Antiplatelet < 5 days
Monaco et al., 2020 ⁵³	69 ± 9 vs. 70 ± 7	93	Aortic: 100	500 mg, IV bolus, after induction, continued by infusion at 250 mg/h	Hb < 8 g/dL	Not reported

Mongan et al., 1998 ⁵⁴	61 ± 11 vs. 59 ± 7	80	CABG (on-pump): 100	15 mg/kg, IV bolus, after induction, continued by infusion at 2 mg/kg/h	Hb < 8 g/dL	Aspirin was not discontinued
Moret et al., 2007 ⁵⁵	69 ± 10 vs. 66 ± 13	42.1	Valve: 100	1 g, IV bolus, after induction, continued by infusion at 400 mg/h during surgery and 500 mg on priming of CPB or 30 mg/kg on priming of CPB	Hct < 25%	Antiplatelet or anticoagulant < 10 days
Murphy et al., 2006 ⁵⁶	No information	No information	CABG (on-pump): 100	2 g, IV bolus, after induction	Hb < 8.5 g/dL	Aspirin was not discontinued, but clopidogrel was excluded
Nouraei et al., 2013 ⁵⁷	60 ± 10 vs. 60 ± 10	67.5	CABG (on-pump): 100	2 g, topical, prior to sternal closure	Hb < 8 g/dL	Anticoagulant < 5 days
Nuttall et al., 2000 ⁵⁸	66 ± 31 vs. 59 ± 41	81.7	Not specified	10 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h	Hb < 8 g/dL	Not reported
Özal et al., 2002 ⁵⁹	59 ± 4 vs. 61 ± 7	73	CABG (on-pump): 100	10 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h	Hct < 25%	Antiplatelet < 10 days
Penta de Peppo et al., 1995 ⁶⁰	62 ± 9	83.3	CABG (on-pump): 81.7	10 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h	Hb < 8.5 g/dL	Antiplatelet < 1 day
			Valve: 13.3			
			Other: 5			
Pinosky et al., 1997 ⁶¹	63 ± 2 vs. 61 ± 3	72.9	CABG (on-pump): 100	15 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h	Hct < 20 %	Antiplatelet < 7 days
Pleym et al., 2003 ⁶²	64 ± 10 vs. 62 ± 9	83.5	CABG (on-pump): 100	30 mg/kg, bolus on priming of CPB	Hct < 25 %	Aspirin was not discontinued but other antiplatelet or anticoagulant was excluded
Rampure Vittal Rao & Anakapalli, 2018 ⁶³	58 ± 8 vs. 60 ± 8	81.7	CABG (on-pump): 100	2 g, topical, prior to sternal closure	Hb < 9 g/dL	Antiplatelet < 7 days
Santos et al., 2006 ⁶⁴	62 ± 9 vs. 59 ± 9	71.7	CABG (on-pump): 100	10 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h for 5 h	Hb < 7 g/dL, Hb < 10 g/dL (> 70 years)	Antiplatelet < 7 days
Shi, Wang, et al., 2013 ⁶⁵	60 ± 8 vs. 60 ± 10	80.3	CABG (on-pump): 100	15 mg/kg, IV bolus, after induction and 15 mg/kg, IV bolus, after reversal	Hb < 8 g/dL, Hb < 9 g/dL (> 70 years)	Antiplatelet < 7 days

Shi, Ji, et al., 2013 ⁶⁶	60 ± 9 vs. 60 ± 9	76.8	CABG (on-pump): 100	10 mg/kg, IV bolus, after induction, continued by infusion at 10 mg/kg/h	Hb < 8 g/dL	Antiplatelet < 7 days
Shi et al., 2022 ⁶⁷	53 ± 12 vs. 53 ± 12	61.9	CABG: 16.4	10 mg/kg, IV bolus, after induction, continued by infusion at 2 mg/kg/h and 1 mg/kg, bolus on priming of CPB	Hb < 8 g/dL	Not reported
			Valve: 36.7	vs.		
			Combined: 11.6	30 mg/kg, IV bolus, after induction, continued by infusion at 16 mg/kg/h and 2 mg/kg, bolus on priming of CPB		
			Congenital: 6.5			
			Other: 28.7			
Shore-Lesserson et al., 1996 ⁶⁸	68 ± 13 vs. 63 ± 6	66.7	CABG (on-pump): 66.7	20 mg/kg, IV bolus, after induction, continued by infusion at 2 mg/kg/h throughout surgery	Hct < 25%	Not reported
			Valve: 20			
			Combined: 13.3			
Sigaut et al., 2014 ⁶⁹	67 ± 1 vs. 68 ± 1	72.2	CABG (on-pump): 34.5	10 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h and 1 mg/kg, bolus on priming of CPB	Hb < 8 g/dL	Antiplatelet < 5 days
			Valve: 32.2	vs.		
			Combined: 14.6	30 mg/kg, IV bolus, after induction, continued by infusion at 16 mg/kg/h and 2 mg/kg, bolus on priming of CPB		
			Aortic: 14.8			
			Other: 2.8			
Singh et al., 2022 ⁸⁴	29 ± 10 vs. 32 ± 12	35.9	Valve: 100	20 mg/kg, IV bolus, after induction, continued by infusion at 2 mg/kg/h	No information	Antiplatelet < 7 days
				vs.		
				EACA: 100 mg/kg, IV bolus, after induction, continued by infusion at 20 mg/kg/h		

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Speekenbrink et al., 1995 ⁷⁰	61 ± 11 vs. 57 ± 12	91.1	CABG (on-pump): 100	10 mg/kg, IV bolus, after induction continued by infusion at 1 mg/kg/h	No information	Aspirin < 2 to 4 days
Taghaddomi et al., 2009 ⁷¹	55 ± 11 vs. 60 ± 10	72	CABG (off-pump): 100	1 g, IV bolus, after induction, continued by infusion at 400 mg/h	Hct < 27% or Hb < 9 g/dL	Not reported
Vanek et al., 2005 ⁷²	68 ± 6 vs. 69 ± 5	63.7	CABG (off-pump): 100	1 g, IV bolus, after induction, continued by infusion at 200 mg/h	Hct < 26% or Hb < 8.5 g/dL	Antiplatelet < 5 days
Verma et al., 2020 ⁸⁶	64 ± 2 vs. 63 ± 3	68.4	CABG (off-pump): 100	10 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h	Hb < 8 g/dL	Antiplatelet < 5 days
				vs.		
				EACA: 100 mg/kg, IV bolus, after induction, continued by infusion at 10 mg/kg/h		
G. Wang et al., 2012 ⁷³	61 ± 8 vs. 60 ± 9	84.4	CABG (off-pump): 100	1 g, IV bolus, after induction, continued by infusion at 400 mg/h throughout surgery	Hb < 9 g/dL	Antiplatelet < 5 days
J. Wang et al., 2017 ⁷⁴	62 ± 10 vs. 62 ± 9	72.5	CABG (on-pump): 100	10 mg/kg, IV bolus, after induction, continued by infusion at 10 mg/kg/h throughout the surgery	Hb < 7 g/dL	Antiplatelet < 3 days
Wei et al., 2006 ⁷⁵	63 ± 8 vs. 61 ± 8	No information	CABG (off-pump): 100	0.75 g, IV bolus, after induction, continued by infusion at 250 mg/h	Hb < 8.5 g/dL	Antiplatelet < 5/7 days
Yanartas et al., 2015 ⁷⁶	61 ± 9 vs. 63 ± 10	37.9	CABG (on-pump): 100	10 mg/kg, bolus on priming of CPB, continued by infusion at 1 mg/kg/h for 5 h	Hct < 25% or Hb < 9 g/dL	Antiplatelet < 5 days
Zabeeda et al., 2002 ⁷⁷	65 ± 13 vs. 66 ± 9	76	CABG (on-pump): 100	10 mg/kg, IV bolus, after induction, continued by infusion at 1 mg/kg/h	Hb < 10 g/dL	Not reported
Zhang et al., 2019 ⁸⁷	59 ± 9 vs. 58 ± 8	79.7	CABG (on-pump): 100	10 mg/kg, IV bolus, after induction, continued by infusion at 10 mg/kg/h	Hb < 8 g/dL or < 9 g/dL for elderly	Antiplatelet < 7 days

ASD=; CABG=coronary artery bypass grafting; CPB=cardiopulmonary bypass; EACA=epsilon aminocaproic acid; Hb=hemoglobin; Hct=hematocrit; IV=intravenous; PRC=packed red cell; SD=standard deviation

Supplementary Table 3. Risk of bias of included studies for non-bleeding-related outcomes.

Studies	Randomization	Adhering to intervention	Missing outcome data	Measurement	Reporting	Overall
Abul-Azm, 2006 ⁶						
Ahn, 2011 ⁷						
Ali Shah, 2015 ⁸						
Altun, 2017 ⁹						
Andreasen, 2004 ¹⁰						
Armellin, 2004 ¹¹						
Banihashem, 2019 ¹²						
Baric, 2007 ¹³						
Blauhut, 1994 ¹⁴						
Brown, 1997 ¹⁵						
Casati, 1999 ⁸¹						
Casati, 2001 ¹⁶						
Casati, 2001 ¹⁷						
Casati, 2002 ¹⁸						
Casati, 2004 ¹⁹						
Chaudhary, 2018 ²⁰						
Chauhan, 2004 (1) ⁸⁰						
Chauhan, 2004 (2) ⁷⁹						
Chen, 2013 ²¹						
Choudhuri, 2015 ²²						
Coffey, 1995 ²³						
Corbeau, 1995 ²⁴						
De Bonis, 2000 ²⁵						
Du, 2014 ²⁶						
El Baser, 2021 ⁸²						
Esfandiari, 2013 ²⁷						
Fakher-e-Fayaz, 2014 ²⁸						
Faraoni, 2014 ²⁹						
Fawzy, 2009 ³⁰						
Greiff, 2012 ³¹						
Hardy, 1998 ³²						
Hashemi, 2011 ³³						
Hatami, 2020 ³⁴						
Hekmat, 2004 ³⁵						
Horrow, 1990 ³⁶						
Horrow, 1991 ³⁷						
Horrow, 1995 ³⁸						
Hosseini, 2014 ³⁹						
Iribarren, 2008 ⁴⁰						
Jimenez, 2007 ⁴¹						
Kuitunen, 2005 ⁴²						

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Lambert, 1998 ⁴³						
Landymore, 1997 ⁸³						
Later, 2009 ⁴⁴						
Maddali, 2007 ⁴⁵						
Madershahian, 2015 ⁴⁶						
Makhija, 2013 ⁸⁵						
Mansouri, 2012 ⁴⁷						
Mehr-Aein, 2007 ⁴⁸						
Menichetti, 1996 ⁴⁹						
Mirmohammad-sadeghi, 2018 ⁵⁰						
Mirmohammad-sadeghi, 2020 ⁵¹						
Misfeld, 1998 ⁵²						
Monaco, 2020 ⁵³						
Mongan, 1998 ⁵⁴						
Moret, 2007 ⁵⁵						
Murphy, 2006 ⁵⁶						
Nouraei, 2013 ⁵⁷						
Nuttall, 2000 ⁵⁸						
Ozal, E, 2002 ⁵⁹						
Penta de Peppo, 1995 ⁶⁰						
Pinosky, 1997 ⁶¹						
Pleym, 2003 ⁶²						
Rao, 2018 ⁶³						
Santos, 2006 ⁶⁴						
Shi, 2013 ⁶⁵						
Shi, 2013 ⁶⁶						
Shi, 2022 ⁶⁷						
Shore-Lesserson, 1996 ⁶⁸						
Sigaut, 2014 ⁶⁹						
Singh, 2022 ⁸⁴						
Speekenbrink, 1995 ⁷⁰						
Taghaddomi, 2009 ⁷¹						
Vanek, 2005 ⁷²						
Verma, 2020 ⁸⁶						
Wang, 2012 ⁷³						
Wang, 2017 ⁷⁴						
Wei, 2006 ⁷⁵						
Yanartas, 2015 ⁷⁶						
Zabeeda, 2002 ⁷⁷						
Zhang, 2018 ⁷⁸						

Low risk of bias Some concerns High risk of bias

Supplementary Table 4. Summary findings of sensitivity analysis after taking out studies not reporting data in mean.				
Outcomes	No. of studies	No. of participants	Effect estimates	Heterogeneity
			(95% CI), <i>P</i> -value	
Low-dose vs. placebo group comparison				
Postoperative bleeding	48	4984	-1.19 [-1.43, -0.95], <i>P</i> <0.01	I ² = 93%, <i>P</i> <0.01
Low-dose vs. high-dose group comparison				
Postoperative bleeding	7	1337	0.80 [-0.63, 2.24], <i>P</i> =0.27	I ² = 99%, <i>P</i> <0.01
CI=confidence interval				

Supplementary Table 5. Sensitivity analysis of low-dose vs. placebo group comparison based on the adequate abstinence of antiplatelet agents.				
Outcomes	No. of studies	No. of participants	Effect estimates	Heterogeneity
			(95% CI), <i>P</i> -value	
Adequate abstinence of antiplatelet or anticoagulant agents				
Mortality	20	2472	0.58 [0.28, 1.20], <i>P</i> =0.14	<i>I</i> ² = 0%, <i>P</i> =0.94
Reoperation	21	2566	0.50 [0.34, 0.73], <i>P</i> <0.01	<i>I</i> ² = 0%, <i>P</i> =0.50
Myocardial infarction	20	2584	0.52 [0.30, 0.89], <i>P</i> =0.02	<i>I</i> ² = 0%, <i>P</i> =0.72
Venous thromboembolic events	11	1011	0.65 [0.09, 4.93], <i>P</i> = 0.68	<i>I</i> ² = 0%, <i>P</i> =0.66
Stroke	20	2536	0.88 [0.40, 1.96], <i>P</i> =0.76	<i>I</i> ² = 0%, <i>P</i> =0.74
Seizure	10	1426	1.72 [0.61, 4.86], <i>P</i> =0.30	<i>I</i> ² = 0%, <i>P</i> =0.75
Transfusion rate	22	2587	0.78 [0.72, 0.84], <i>P</i> <0.01	<i>I</i> ² = 22%, <i>P</i> =0.18
Postoperative bleeding	38	4001	-1.14 [-1.40, -0.88], <0.01	<i>I</i> ² = 93%, <i>P</i> <0.01
No withdrawal of antiplatelet or anticoagulant agents				
Mortality	5	361	0.74 [0.17, 3.17], <i>P</i> =0.68	<i>I</i> ² = 0%, <i>P</i> =0.64
Reoperation	6	481	0.29 [0.11, 0.74], <i>P</i> <0.01	<i>I</i> ² = 0%, <i>P</i> =0.43
Myocardial infarction	4	259	1.77 [0.25, 12.53], <i>P</i> =0.57	<i>I</i> ² = 0%, <i>P</i> =0.60
Venous thromboembolic events	4	259	Not estimable	Not applicable
Stroke	5	361	0.50 [0.05, 5.22], <i>P</i> =0.56	Not applicable
Seizure	0	0	Not estimable	Not applicable
Transfusion rate	4	307	0.47 [0.34, 0.66], <i>P</i> <0.01	<i>I</i> ² = 0%, <i>P</i> =0.69
Postoperative bleeding	4	322	-0.79 [-1.06, -0.53], <i>P</i> <0.01	<i>I</i> ² = 17%, <i>P</i> =0.31
CI=confidence interval				

Supplementary Table 6. Sensitivity analysis of low-dose vs. high-dose group comparison based on the adequate abstinence of antiplatelet or anticoagulant agents.

Outcomes	No. of studies	No. of participants	Effect estimates	Heterogeneity
			(95% CI)	
Adequate abstinence of antiplatelet or anticoagulant agents				
Mortality	4	1043	1.52 [0.68, 3.39], $P=0.31$	$I^2 = 0\%$, $P=0.35$
Reoperation	2	790	2.60 [1.13, 5.95], $P=0.02$	$I^2 = 0\%$, $P=0.60$
Myocardial infarction	2	744	Not estimable	Not applicable
Venous thromboembolic events	2	647	2.01 [0.37, 10.87], $P=0.42$	$I^2 = 6\%$, $P=0.30$
Stroke	3	965	0.86 [0.38, 1.96], $P=0.73$	$I^2 = 0\%$, $P=0.80$
Seizure	3	822	0.85 [0.27, 2.62], $P=0.77$	$I^2 = 0\%$, $P=0.66$
Transfusion rate	4	1086	1.05 [0.93, 1.19], $P=0.43$	$I^2 = 0\%$, $P=0.88$
Postoperative bleeding	6	1254	1.05 [-0.50, 2.61], $P=0.18$	$I^2 = 99\%$, $P<0.01$

CI=confidence interval

Supplementary Table 7. Subgroup analysis based on the type of surgery for low-dose vs. placebo group comparison.

Outcomes	No. of studies	No. of participants	Effect estimates	Heterogeneity
			(95% CI), <i>P</i> -value	
Mortality				
On-pump CABG	18	2071	0.66 [0.28, 1.56], <i>P</i> = 0.35	<i>I</i> ² = 0%, <i>P</i> = 0.93
Off-pump CABG	5	515	0.48 [0.04, 5.14], <i>P</i> = 0.54	<i>I</i> ² = 0%, <i>P</i> = 0.75
Valve surgery	2	355	1.05 [0.43, 2.55], <i>P</i> = 0.91	<i>I</i> ² = 0%, <i>P</i> = 0.53
Aortic surgery	2	160	1.00 [0.15, 6.64], <i>P</i> = 1.00	Not applicable
Congenital surgery	1	78	Not estimable	Not applicable
Reoperation				
On-pump CABG	21	2472	0.52 [0.33, 0.82], <i>P</i> < 0.01	<i>I</i> ² = 0%, <i>P</i> = 0.76
Off-pump CABG	4	439	0.28 [0.06, 1.33], <i>P</i> = 0.11	<i>I</i> ² = 0%, <i>P</i> = 0.96
Valve surgery	3	407	0.39 [0.16, 0.99], <i>P</i> = 0.05	<i>I</i> ² = 0%, <i>P</i> = 0.72
Aortic surgery	2	160	0.71 [0.15, 3.48], <i>P</i> = 0.68	<i>I</i> ² = 0%, <i>P</i> = 0.56
Myocardial infarction				
On-pump CABG	19	2397	0.75 [0.44, 1.28], <i>P</i> = 0.30	<i>I</i> ² = 0%, <i>P</i> = 0.88
Off-pump CABG	6	569	1.00 [0.14, 7.06], <i>P</i> = 1.00	<i>I</i> ² = 0%, <i>P</i> = 0.34
Valve surgery	1	209	0.10 [0.00, 2.08], <i>P</i> = 0.14	Not applicable
Aortic surgery	2	160	1.00 [0.21, 4.81], <i>P</i> = 1.00	<i>I</i> ² = 0%, <i>P</i> = 1.00
Venous thromboembolic events				
On-pump CABG	6	507	0.59 [0.08, 4.39], <i>P</i> = 0.61	<i>I</i> ² = 0%, <i>P</i> = 0.60
Off-pump CABG	6	611	Not estimable	Not applicable
Valve surgery	1	146	1.70 [0.11, 26.69], <i>P</i> = 0.70	Not applicable
Aortic surgery	2	160	Not estimable	Not applicable
Congenital surgery	1	78	Not estimable	Not applicable

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Stroke				
On-pump CABG	14	1919	1.63 [0.43, 6.10], $P=0.47$	$I^2=0\%$, $P=0.61$
Off-pump CABG	8	753	Not estimable	Not applicable
Valve surgery	3	415	0.68 [0.22, 2.09], $P=0.50$	$I^2=0\%$, $P=0.83$
Aortic surgery	1	60	0.50 [0.05, 5.22], $P=0.56$	Not applicable
Seizure				
On-pump CABG	5	1053	1.88 [0.61, 5.81], $P=0.27$	$I^2=0\%$, $P=0.62$
Off-pump CABG	3	242	Not estimable	Not applicable
Valve surgery	1	60	Not estimable	Not applicable
Aortic surgery	1	100	Not estimable	Not applicable
Congenital surgery	1	78	1.00 [0.06, 15.43], $P=1.00$	Not applicable
Transfusion rate				
On-pump CABG	19	2190	0.74 [0.69, 0.79], $P<0.01$	$I^2=95\%$, $P<0.01$
Off-pump CABG	8	753	0.63 [0.48, 0.83], $P<0.01$	$I^2=0\%$, $P=0.99$
Valve surgery	2	355	0.76 [0.59, 0.97], $P=0.03$	$I^2=65\%$, $P=0.09$
Aortic surgery	2	160	0.58 [0.36, 0.93], $P=0.02$	$I^2=0\%$, $P=0.99$
Postoperative bleeding				
On-pump CABG	26	2844	-1.13 [-1.44, -0.81], $P<0.01$	$I^2=93\%$, $P<0.01$
Off-pump CABG	8	753	-1.05 [-1.46, -0.64], $P<0.01$	$I^2=85\%$, $P<0.01$
Valve surgery	3	415	-0.72 [-0.99, -0.44], $P<0.01$	$I^2=39\%$, $P=0.20$
Aortic surgery	2	160	-0.42 [-0.89, 0.05], $P=0.08$	$I^2=52\%$, $P=0.15$
Congenital surgery	1	78	-0.40 [-0.85, 0.05], $P=0.08$	Not applicable

CABG=coronary artery bypass grafting; CI=confidence interval

Supplementary Table 8. Subgroup analysis based on the type of surgery for low-dose vs. high-dose group comparison.

Outcomes	No. of studies	No. of participants	Effect estimate	Heterogeneity
			(95% CI), <i>P</i> -value	
Mortality				
On-pump CABG	1	236	0.98 [0.14, 6.86], <i>P</i> = 0.99	Not applicable
Off-pump CABG	1	3031	1.13 [0.46, 2.76], <i>P</i> = 0.80	Not applicable
Reoperation				
On-pump CABG	1	236	Not estimable	Not applicable
Off-pump CABG	1	3031	1.33 [0.70, 2.54], <i>P</i> = 0.39	Not applicable
Myocardial infarction				
On-pump CABG	1	236	2.95 [0.12, 71.69], <i>P</i> = 0.51	Not applicable
Off-pump CABG	1	3031	0.98 [0.80, 1.20], <i>P</i> = 0.87	Not applicable
Venous thromboembolic events				
Off-pump CABG	1	3031	0.76 [0.36, 1.60], <i>P</i> = 0.47	Not applicable
Stroke				
Off-pump CABG	1	3031	0.81 [0.32, 2.05], <i>P</i> = 0.66	Not applicable
Seizure				
Off-pump CABG	1	3031	0.41 [0.16, 1.04], <i>P</i> = 0.06	Not applicable
Transfusion rate				
On-pump CABG	1	236	1.06 [0.75, 1.50], <i>P</i> = 0.75	Not applicable
Off-pump CABG	1	3031	1.19 [1.05, 1.35], <i>P</i> < 0.01	Not applicable
Postoperative bleeding				
On-pump CABG	2	326	0.64 [-0.17, 1.45], <i>P</i> = 0.12	<i>I</i> ² = 89%, <i>P</i> <0.01
Off-pump CABG	1	3031	0.12 [0.05, 0.19], <i>P</i> < 0.01	Not applicable

CABG=coronary artery bypass grafting; CI=confidence interval