

Original Article

Comparison of Two Activated Clotting Time Targets During Cardiac Surgery With Cardiopulmonary Bypass: A Prospective Multicenter Randomized Controlled Trial



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Objectives: The present study was designed to investigate the equivalence of two target activated clotting time (ACT) values with regard to packed red blood cell (PRBC) transfusion in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). Secondary endpoints include postoperative blood loss, transfusion of other blood products, and postoperative laboratory parameters, including renal function, intensive care unit length of stay, postoperative thrombotic events, and other adverse events.

Design: Multicenter, randomized, single-blind, controlled equivalence trial. Patients were randomized to a lower target ACT of ≥ 400 seconds or a higher target ACT of ≥ 480 seconds.

Setting: Three tertiary and one university medical center in the Netherlands.

Participants: 1,021 patients ≥ 18 years of age scheduled for first-time elective cardiac surgery with CPB between November 2019 and December 2023.

Measurements and Main Results: PRBC transfusion was equivalent in both ACT groups (19.1% v 17.2% risk difference -0.029 ; 0.066). In the low ACT group, blood loss at 6 and 24 hours postoperative was significantly lower (median [interquartile range], 260 [245] v 300 [250] mL, $p = 0.003$ and 480 [363] v 550 [410] mL, $p = 0.007$) and the hemoglobin level at 6 hours and 1 day after surgery significantly higher (mean [95% confidence interval], 11.8 [11.6–11.9] v 11.6 [11.3–11.8] g/dL, $p = 0.017$ and 11.4 [11.1–11.6] v 11.1 [11.0–11.4] g/dL, $p = 0.045$) compared with the high ACT group, but lacking clinical relevance. The frequency of thromboembolic events was similar in both groups.

Conclusions: This study showed that a target ACT of ≥ 400 seconds is equivalent to a target ACT of ≥ 480 seconds in terms of intraoperative and postoperative PRBC transfusion rates in the modern cardiac surgery setting. This target range is considered comparable regarding the outcomes of patients undergoing cardiac surgery with CPB.

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PROFOUND ANTICOAGULATION IS REQUIRED in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). To prevent thrombin generation, caused by a

number of factors including the continuous interaction of the circulating blood with nonbiologic surfaces, surgical trauma, and the retransfusion of pericardial blood, unfractionated heparin is administered to the patient before and during CPB.^{1,2} While high doses of heparin reduce the risk of thrombus formation during CPB, excessive administration of heparin and subsequent protamine administration cause adverse effects on coagulation after termination of CPB, such as inhibition of thrombin and platelet function^{3–6} and activation of fibrinolysis.⁷ This may lead to increased postoperative blood loss and blood product transfusion requirements, which is an independent predictor of increased mortality and morbidity in cardiac surgery requiring CPB.⁸ The activated clotting time (ACT) is the most widely used test to monitor heparin anticoagulation during cardiopulmonary bypass.⁹ However, there is very little evidence on the optimal ACT target during CPB with regard to minimizing blood loss and transfusion requirements, and large randomized controlled trials (RCTs) are lacking.¹⁰

Nowadays, most centers consider a minimal target ACT between 400 and 480 seconds an adequate level of anticoagulation based on early studies from the 1970s.^{11,12} While an ACT target of 480 seconds is commonly used during CPB, it is unclear whether this target ACT remains appropriate in the modern cardiosurgical routine where biocompatible-coated CPB circuits have become the standard. Studies have shown that lower anticoagulation targets may be as safe as an ACT target of 480 seconds and are associated with reduced postoperative bleeding and transfusion requirements.^{13,14} Also, a recent systematic review and meta-analysis including 22 RCTs and 4 prospective cohort studies showed a significant correlation between the doses of heparin and protamine and postoperative blood loss.¹⁵ Other studies, however, do not show a difference in postoperative bleeding and transfusion requirements when comparing different ACT targets.^{16,19} Due to the lack of large RCTs in modern cardiosurgical settings, there is not enough evidence to conclude whether the different ACT targets that are currently used are equivalent with respect to postoperative transfusion rates following cardiac surgery. The present study was therefore designed to investigate the equivalence of a lower (≥ 400 seconds) and higher (≥ 480 seconds) target ACT with regard to packed red blood cell (PRBC) transfusion in patients undergoing cardiac surgery with CPB using biocompatible coated systems. Secondary endpoints include blood loss, transfusion of other blood products, postoperative laboratory parameters, including renal function, intensive care unit (ICU) length of stay, postoperative thrombotic events, and other adverse events.

Methods

This multicenter, randomized, single-blinded, controlled trial assessing the equivalence of a lower ACT of 400 seconds and a higher ACT of 480 seconds in relation to blood transfusion requirements was conducted between November 2019 and December 2023 at four hospitals in the Netherlands. The study protocol (18-683/D) was approved by the independent ethics committee of the University Medical Center Utrecht,

The Netherlands in August 2019. The study was performed in compliance with the Declaration of Helsinki and institutional regulations, including privacy rights. Written informed consent was obtained from each patient. The trial is registered in the Dutch database of the Central Committee on Research Involving Human Subjects (CCMO) under registry NL6474104118, and at the Dutch Trial Register under registry NL-OMON27592. The trial is reported following the Consolidation Of Standards Of Reporting Trials (CONSORT) guidelines for noninferiority and equivalence randomized trials.²⁰

Patients

Patients ≥ 18 years of age who were scheduled for coronary artery bypass grafting (CABG), heart valve repair or replacement, surgery of the aortic root or ascending aorta, surgery for hypertrophic obstructive cardiomyopathy, or combined procedures with the use of CPB, were eligible for inclusion. Exclusion criteria were as follows: reoperations, surgery requiring circulatory arrest, emergency surgery, the use of minimized extracorporeal circuits, planned body temperature during CPB below 32°C, patients with congenital or acquired coagulation factor abnormalities, patients with a preoperative hemoglobin value < 10.5 g/dL, infective endocarditis, and the preoperative use of unfractionated heparin. Patients who were withdrawn from the study prior to receiving the study treatment were replaced. Reasons for withdrawal were withdrawal of informed consent, change in the planned procedure, cancellation of surgery, or logistic problems due to last-minute changes in the operation schedule. There was no follow-up of withdrawn patients.

Demographic Variables

Baseline demographic variables recorded were age, sex, body weight and height, preoperative laboratory values for creatinine, platelets, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation and hemoglobin, presence of peripheral vascular disease, chronic obstructive pulmonary disease or diabetes mellitus, left ventricular ejection fraction, history of cerebrovascular accident (CVA), and recent myocardial infarction. Also, the use of preoperative antithrombotic medication, as documented in the patient's hospital file, was recorded.

Surgery and Extracorporeal Circulation

Patients received premedication and anesthesia according to routine local clinical practice. Surgical procedures and extracorporeal circulation techniques were performed according to local standards. The extracorporeal circuit consisted of a semi-permeable or diffusion membrane oxygenator, collapsible venous reservoir, hardshell cardiectomy reservoir, arterial centrifugal pump, and biocompatible coated tubing (Affinity Fusion, Medtronic Inc., Minneapolis, United States, or Quadrox-iD Adult, Maquet, Hirrlingen, Germany, or Inspire 6-8F M, LivaNova, Mirandola, Italy). Priming fluid consisted of a

balanced electrolyte solution combined with a colloid (Voluven, Fresenius Kabi, Bad Domburg, Germany, or Gelofusine, B Braun, Melsungen, Germany) or 15% mannitol; 200g/L albumin was added when indicated following hospital protocol. When the patient's volume status was sufficient, retrograde autologous priming was performed. Data on the intraoperative administration of antifibrinolytics as well as CPB characteristics were recorded in the case report form.

Study Intervention

Patients were randomly assigned to the low or high target ACT group. Randomization was stratified per hospital using the Castor EDC database (Ciwit B.V., Amsterdam, the Netherlands) and block sizes of four, six, and eight. The perfusionist and anesthesiologist were informed on the day of randomization. The cardiac surgeon and ICU personnel were blinded for group randomization.

Heparinization started with a single bolus of 250 or 350 IU/kg heparin (LEO Pharma BV, Amsterdam, the Netherlands) for the low ACT and high ACT groups, respectively, and was supplemented with 75 to 150 IU/kg heparin until the ACT test exceeded 400 or 480 seconds. A total of 7,500 IU and 10,000 IU unfractionated heparin were added to the priming of the CPB system in both groups, respectively. The detailed heparin dosing protocol is displayed in Fig 1. ACT measurements were performed with the Hemochron Signature whole blood microcoagulation system (Hemochron Signature Elite or Hemochron Jr. Signature Plus, Edison, NJ, USA). Heparin was reversed with protamine after termination of CPB. Protamine was dosed in a ratio of 0.8:1 protamine:

heparin (IUs), based on the heparin dose required to reach the minimal target ACT. From the start of the study until December 2021, protamine hydrochloride (Meda Pharma BV, Amstelveen, the Netherlands) was used, and protamine sulfate (LEO Pharma BV, Amsterdam, the Netherlands) was used from January 2022 until the end of the study.

Study Outcome

The main study parameter was the overall number of patients receiving a PRBC transfusion during hospitalization (during surgery and postoperatively during ICU stay, or 24-hour postsurgery in case the patient was not admitted to the ICU). The transfusion strategy followed the recommendations of the European Task Force on Patient Blood Management for Adult Cardiac Surgery.¹⁰ They state that the focus should be on balancing the patient's oxygen demand and consumption and the clinical circumstances rather than maintaining a specific hemoglobin level. Secondary study parameters were doses of heparin and protamine, postoperative blood loss, transfusion of autologous blood, overall transfusion requirements, postoperative laboratory parameters, and ICU length of stay. Safety parameters included thromboembolic events; ICU mortality; 30-day, 90-day, and 1-year mortality; rethoracotomies; new-onset atrial fibrillation, mediastinitis, respiratory infection, and prolonged mechanical ventilation (>24 hours). The thromboembolic events included observations of thrombus formation in the CPB system or pericardium intraoperatively or mention of a postoperative transient ischemic attack (TIA), CVA, MI, or pulmonary thromboembolism in the patient medical record.

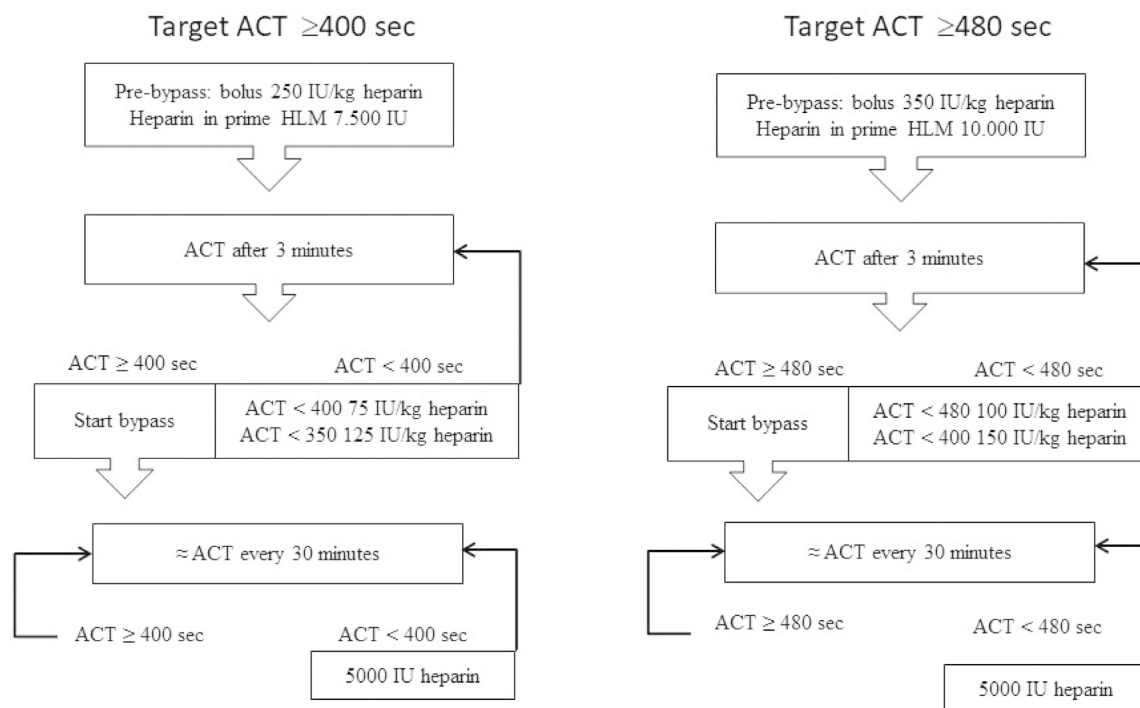


Fig 1. Study intervention flow chart. ACT, activated clotting time; HLM, heart-lung machine.

Statistical Analysis

The average PRBC transfusion rate in patients undergoing cardiac surgery is 40%.²¹ In this equivalence study design, a margin of 7% between groups was accepted as clinically equivalent. With a beta of 0.8 and alpha of 0.025, the required number of patients was 768 per group (total $n = 1,536$).

At the interim analysis, the average PRBC transfusion rate was 19.4%. The sample size was recalculated, with all other parameters remaining unchanged, which resulted in 505 patients per treatment group (total $n = 1,010$). The University Medical Center Utrecht internal Data Safety and Monitoring Board advised adopting the new sample size. The protocol was adjusted accordingly.

Data were analyzed according to the per-protocol (PP) principle for the primary outcome parameter because intention-to-treat (ITT) analysis tends to be anticonservative in demonstrating equivalence.²² Secondary parameters were analyzed according to the ITT principle, and safety parameters were analyzed according to the as-treated (AST) principle. Analyses were performed with IBM SPSS Statistics 29 software (SPSS Inc., Chicago, IL, USA) and SAS (SAS Enterprise Guide 8.2). For patient demographic data, procedural data, and safety data, only descriptive statistics are reported, and no formal statistical test was applied. For these data, continuous variables are presented as means with standard deviations (SDs) or medians with 25th–75th interquartile ranges (IQRs). Categorical variables are presented as absolute numbers with percentages.

Analysis of Primary Outcome

The primary analysis concerned a logistic regression model with treatment group and center as independent variables. Estimates for the risk difference (RD) with their 95% confidence intervals (CIs) were obtained. Proportions and 95% CIs for each group are reported. Equivalence could be concluded if this two-sided 95% CI lay entirely between the equivalence margins ($-7, +7$).²⁰ The two-sided 95% CI of the RD of the low ACT group versus the high ACT group was calculated using the Farrington and Manning method implemented in SAS (SAS Enterprise Guide 8.2) for the sensitivity analysis. The analysis of the primary outcome was repeated on the ITT population for the N analysis.

Analysis of Secondary Outcomes

Secondary endpoints were analyzed using a linear regression model with treatment group and center as independent variables. Mean and 95% CI or median and IQR for each group are reported. p -values < 0.05 for the differences between groups were considered significant. For the continuous variables, residuals were checked by examining the plots of residuals versus predicted values and the normal probability plot. If, from the analysis of the residuals, it became apparent that the analysis was not suitable for the data, nonparametric tests were applied, and the parameter center was excluded from the analysis. In case of convergence issues for binary

parameters due to a low number of events, the Firth's correction was applied. If the issue could not be solved in this way, the model was simplified by removing center.

Results

Study Participants

The flowchart of patients is shown in Fig 2. Between November 2019 and December 2022, 1,457 cardiac surgery patients were eligible for inclusion, of which 1,132 (78%) gave informed consent. One patient was excluded due to a postponed surgery before randomization. In each group, 55 patients did not receive the study treatment, mainly due to last-minute changes in the operation schedule (35 and 38 patients), and no data were collected. Other reasons can be found in Fig 2. From the ITT population, 8 patients in the lower ACT group and 11 patients in the higher ACT group were excluded from the PP analysis because of major protocol deviations, as described in the diagram. From the ITT population, six patients accidentally received the heparin dose of the other randomization group and were excluded from the AST analysis.

Baseline Data

Demographic data and medical record data were similar for both groups (Table 1). Antithrombotic medication was considered to be continued when used preoperatively, according to the patient medical record, beyond the duration described in the 2017 EACTS/EACTA guidelines on patient blood management.¹⁰

Procedural Data

Table 2 shows the types of surgical procedures performed in both ACT groups. Additional procedures include, but are not limited to, left atrial appendage closure or amputation, MAZE procedure for atrial fibrillation, and atrial septum defect closure. Table 2 also shows the CPB characteristics for all patients with a median lowest hemoglobin level during CPB of 9.2 g/dL in both groups and a comparable duration of CPB in both groups.

Heparin and Protamine Dosing

As per the protocol, patients in the higher ACT group received a significantly larger initial dose of heparin (Table 3). In this group, 60% of the patients reached the target of ≥ 480 seconds after this first dose compared with 65% in the low ACT group. Respectively, 52% and 56% of patients received one or more additional doses of 5,000 IU of heparin during the surgical procedure. The total amount of additional heparin was higher in the higher ACT group, as was the total dose of heparin received during the surgical procedure. Subsequently, patients in the higher ACT group received a significantly higher dose of protamine at the end of surgery. The mean ratio between the total dose of heparin received before CPB and the

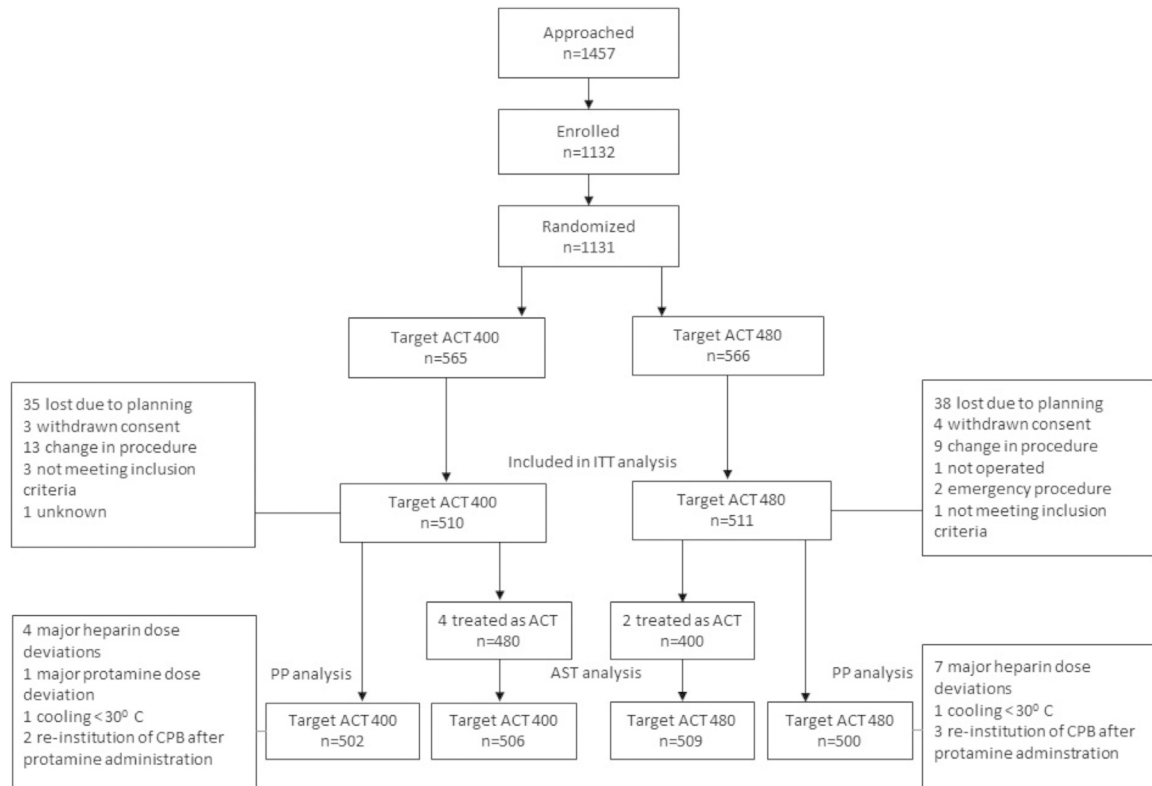


Fig 2. Flow of participants. ACT, activated clotting time; AST, as treated; CPB, cardiopulmonary bypass; ITT, intention to treat; PP, per protocol.

Table 1
Patient Demographics, Medical Record, and Continued Use of Preoperative Medication

	ACT ≥400 (n = 510) N=510	ACT ≥480 (n = 511) N = 511
Male sex, n (%)	390 (76)	396 (78)
Age, median [IQR], y	68 [12]	69 [13]
Height, mean (SD), cm	176 (9)	176 (9)
EuroSCOREII, median [IQR]	1.1 [1.0]	1.2 [1.0]
Preoperative creatinine, mean (SD), μmol/L	85 (19)	86 (19)
Preoperative platelets, mean (SD), number x10 ⁹ /L	237 (60)	238 (68)
Preoperative Hb, median [IQR], g/dL	14.5 [1.6]	14.3 [1.9]
Preoperative eGFR, n (%), mL/min/1.73m ²		
≥90	134 (26)	123 (24)
60-89	305 (60)	316 (62)
30-59	71 (14)	72 (14)
CVA, n (%)	42 (8)	33 (7)
Peripheral vascular disease, n (%)	36 (7)	42 (8)
Diabetes mellitus, n (%)	34 (7)	31 (6)
Recent myocardial infarction, n (%)	60 (12)	87 (17)
LVEF, n (%)		
>50%	411 (81)	398 (78)
30%-49%	85 (17)	101 (20)
<30%	13 (3)	12 (2)
COPD, n (%)	23 (4.5)	17 (3.4)
Continued use of preoperative antithrombotic medication, n (%)		
Platelet inhibitors		
Acetylsalicylic acid for noncoronary surgery	62 (15.5)	75 (15.5)
P2Y12 inhibitors	35 (8.8)	42 (8.8)
GPIIb/IIIa inhibitors	1 (0.2)	1 (0.2)
Anticoagulants		
Vitamin K antagonists	2 (0.4)	4 (0.8)
Direct oral anticoagulants	2 (0.6)	3 (0.6)
Low-molecular-weight heparin	1 (0.2)	1 (0.2)
Fondaparinux	0 (0)	1 (0.2)
Other	2 (0.6)	3 (0.6)

Abbreviations: ACT, activated clotting time; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; IQR, interquartile range; LVEF, left ventricular ejection fraction; SD, standard deviation.

Table 2
Type of Surgical Procedure and Cardiopulmonary Bypass Characteristics

	ACT ≥ 400 (n = 510)	ACT ≥ 480 (n = 511)
Type of surgical procedures, n (%)		
CABG	237 (46)	232 (45)
Single valve	170 (33)	178 (35)
CABG + single valve	66 (13)	68 (13)
Multiple valve	18 (4)	18 (4)
CABG + multiple valve	4 (1)	8 (2)
Aortic root repair/replacement	17 (3)	11 (2)
Ascending aorta replacement	12 (2)	12 (2)
Additional procedures		
Rhythm surgery	34 (7)	38 (7)
ASD closure	4 (1)	1 (0)
Other	26 (5)	19 (4)
CPB characteristics		
CPB time, mean [IQR], min	98 [49]	102 [55]
Cross-clamp time, mean [IQR], min	66 [39]	70 [42]
Lowest Hb during CPB, mean [IQR], g/dL	9.2 [2.1]	9.2 [1.9]
Lowest temperature during CPB, mean [IQR], °C	34 [3]	34 [3]
Use of intraoperative antifibrinolytics, n (%)	449 (88)	454 (89)
Separation of cardiomy suction, n (%)	81 (16)	81 (16)
Use of CO ₂ flush, n (%)	251 (51)	244 (52)
Type of cardioplegia, n (%)		
Crystallloid	357 (70)	348 (68)
Blood	102 (20)	115 (23)
Combination	50 (10)	47 (9)

Abbreviations: ACT, activated clotting time; ASD, atrium septum defect; CABG, coronary artery bypass grafting; CO₂, carbon dioxide; CPB, cardiopulmonary bypass; Hb, hemoglobin; IQR, interquartile range.

total dose of protamine was 0.8 for both groups. Considering the total amount of heparin administered during the procedure and total dose of protamine, the mean ratio between heparin and protamine was 0.6 for both groups.

Primary Outcome

The PRBC transfusion rate was 19.1% in the lower ACT group versus 17.2% in the higher ACT group. The 95% CI of the RD (RD 0.019, 95% CI –0.029 to 0.066) lies entirely

between the predefined margins of –7% to +7% which means that the PRBC transfusion rate was equivalent for both ACT groups. The equivalence was confirmed by the sensitivity analysis (RD 0.019, 95% CI –0.029 to 0.068) and the supplementary analysis (RD 0.017, 95% CI –0.032 to 0.065).

Secondary Outcomes

Results for the secondary outcomes are shown in Table 4 and Appendix A. Patients in the higher ACT group had significantly more postoperative blood loss at 6 hours ($p = 0.003$) and 24 hours ($p = 0.007$) compared with the lower ACT group (Fig 3). Postoperative hemoglobin levels were significantly higher in the lower ACT group at 6 hours ($p = 0.017$) and at 1 day after surgery ($p = 0.045$). There were no differences in the amount of autologous blood transfusion, postoperative CKMB and creatinine levels, or postoperative platelet count and ICU length of stay. The percentage of patients receiving a transfusion was higher in the higher ACT group for all products except for intraoperative PRBC transfusions. This difference was only significant when comparing patients receiving either one or a combination of PRBC, plasma, and platelet transfusions peri- or postoperative ($p = 0.045$).

Adverse Events

Result for the occurrence of adverse events can be found in Table 5. New-onset atrial fibrillation was the most reported adverse event. A total of 46 patients (9.1%) in the lower ACT group and 33 patients (6.5%) in the higher ACT group developed atrial fibrillation. The second most reported adverse events were rethoracotomies (5.1% and 4.7%), which were required mostly because of bleeding complications (severe blood loss or tamponade): 24 out of 26 in the lower ACT group and 22 out of 24 rethoracotomies in the higher ACT group. The cause of bleeding was apparently surgical in 58% and 59% of the cases, respectively. Mechanical ventilation lasting more than 24 hours was reported in 10 patients (2.0%) in the lower ACT group and in 15 patients (2.9%) in the higher ACT group. The rates of occurrence of other adverse events range

Table 3
Heparin and Protamine Dosing

	ACT ≥ 400 (n = 510)	ACT ≥ 480 (n = 511)	p-Value
First dose of heparin, mean (SD), IU	21,549 (4,056)	29,940 (5,435)	<0.001*
ACT after first dose of heparin, mean (SD), s	427 (73)	529 (129)	<0.001*
Target achieved after first dose, % (n)	65 (331)	60 (309)	0.143
Total dose of heparin for achieving ACT target, mean (SD), IU	24,418 (4,934)	33,768 (7,275)	<0.001*
Extra dose of heparin during CPB			
Patients, n (%)	265 (52)	286 (56)	0.199
Amount of heparin, mean (SD), IU	7,724 (4,566)	8,812 (6,398)	0.021*
Total dose of heparin, mean (SD), IU	35,182 (8,666)	47,346 (11,271)	<0.001*
Total dose of protamine, mean (SD), IU	20,167 (4,768)	27,634 (6,204)	<0.001*

Abbreviations: ACT, activated clotting time; CPB, cardiopulmonary bypass; SD, standard deviation.

* Significant at $p < 0.05$.

Table 4
Secondary Outcomes

	ACT ≥ 400 (n = 510 [*])	ACT ≥ 480 (n = 511 [*])	Missing	p-Value
Hemoglobin postoperative, mean (95% CI), g/dL				
ICU arrival (n = 510/510)	11.1 (11.0-11.3)	11.0 (10.8-11.1)	-/1	0.284
6 h (n = 456/457)	11.8 (11.6-11.9)	11.6 (11.3-11.8)	54/54	0.017 [†]
Next day	11.4 (11.1-11.6)	11.1 (11.0-11.4)	-	0.045 [†]
Postoperative blood loss, median [IQR], mL				
1 h (n = 507/510)	80 [70]	80 [90]	3/1	0.103
6 h (n = 509/509)	260 [245]	300 [250]	1/2	0.003 [†]
24 h (n = 508/511)	480 [363]	550 [410]	2/-	0.007 [†]
PRBC transfusion, % (95% CI)				
Intraoperative	12.3 (8.4-17.5)	9.1 (6.1-13.4)	-	0.098
Postoperative	9.8 (6.6-14.3)	11.4 (7.8-16.3)	-	0.425
Platelet transfusion, % (95% CI)				
Intraoperative	10.4 (6.1-16.9)	13.3 (8.0-21.1)	-	0.155
Postoperative	7.5 (6.1-16.9)	9.4 (5.5-15.6)	-	0.228
Total	17.2 (12.0-24.2)	21.7 (5.5-15.6)	-	0.079
Plasma transfusion, % (95% CI)				
Intraoperative	5.6 (3.1-9.9)	7.8 (4.4-13.3)	-	0.151
Postoperative	6.1 (2.9-12.6)	6.8 (3.2-13.9)	-	0.543
Total	10.0 (5.9-16.5)	12.6 (7.6-20.2)	-	0.157
PRBC and/or plasma and/or platelet transfusion total, % (95% CI)	31.9 (25.9-38.5)	38.3 (31.8-45.2)	-	0.045 [†]

Abbreviations: ACT, activated clotting time; CI, confidence interval; IQR, interquartile range; PRBC: packed red blood cell.

^{*} When no missing values are reported.[†] Significant at p < 0.05.

from 0% to 1.6%. There was no necessity to replace the CPB system parts due to thrombus formation. However, small thrombi were observed in the venous and cardiectomy reservoirs of the CPB system during or after weaning from bypass in 8 and 5 patients in the lower and higher ACT groups, respectively. There were no subsequent adverse events reported that were related to these observations of thrombus formation. The reasons for mortality can be found in Appendix A.

Discussion

In this multicenter RCT, PRBC transfusion was found to be equivalent whether targeting a lower ACT of ≥ 400 seconds or a higher ACT of ≥ 480 seconds for anticoagulation in patients undergoing first-time cardiac surgery with CPB. Despite the

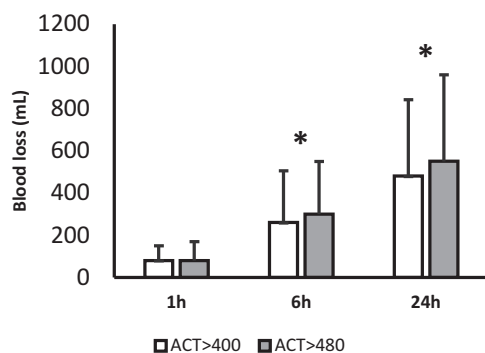


Fig 3. Blood loss at 1, 6, and 24 hours postoperative. *Significance at p < 0.005. ACT, activated clotting time.

Table 5
Adverse Events

	ACT ≥ 400 (n = 506)	ACT ≥ 480 (n = 509)
Mortality during ICU stay	4 (0.8)	2 (0.4)
Mortality at 30 d	7 (1.4)	4 (0.8)
Mortality at 90 d	7 (1.4)	8 (1.6)
Mortality at 1 y	8 (1.6)	9 (1.8)
TIA [*]	0 (0)	3 (0.6)
CVA [*]	6 (1.2)	3 (0.6)
Myocardial infarction [*]	3 (0.6)	2 (0.4)
Venous thromboembolism [*]	0 (0)	0 (0)
Pulmonary thromboembolism [*]	1 (0.2)	1 (0.2)
Rethoracotomies total [*]	26 (5.1)	24 (4.7)
For bleeding	24 (4.7)	22 (4.3)
Apparent surgical bleeding	14 (2.8)	13 (2.6)
Other/unknown	2 (0.4)	2 (0.4)
Thrombus in CPB circuit	8 (1.6)	5 (1.0)
Replacement of CPB parts	0 (0)	0 (0)
Pericardial thrombus intraoperatively	1 (0.2)	1 (0.2)
New-onset atrial fibrillation [*]	46 (9.1)	33 (6.5)
Mediastinitis [*]	0 (0)	1 (0.2)
Respiratory infection [*]	5 (1.0)	4 (0.8)
Prolonged duration of mechanical ventilation (> 24 h) [*]	10 (2.0)	15 (2.9)

Data are expressed as n (%).

Abbreviations: ACT, activated clotting time; CPB, cardiopulmonary bypass; CVA, cerebrovascular accident; ICU, intensive care unit; TIA, transient ischemic attack.

^{*} During ICU stay or in first 24 hours postoperative.

statistically significant differences in postoperative blood loss and hemoglobin levels, the absolute differences were apparently too small to warrant significantly more administration of transfusion products and might therefore not be clinically relevant. No differences were found for other individual secondary parameters, although the total percentage of patients receiving either PRBC, platelets, or thrombocytes was higher in the ACT ≥ 480 seconds group ($p = 0.045$). This study was not powered to find differences in the occurrence of thromboembolic events, but the results do not show important differences between the two ACT groups.

In recent decades, most RCTs comparing different target ACT values have primarily explored the efficacy of a lower ACT value in conjunction with a coated CPB circuit versus a higher ACT value with an uncoated system or another type of coating,^{23–27} thus making it difficult to determine the impact of the lower ACT value on its own. Only a few studies compared different ACT targets while using similar CPB systems and conduct in both study arms. The targets used in these studies differed from the targets in the current study. In three studies including CABG patients with sample sizes between 30 and 63 patients and ACT targets between 300 and 600 seconds, no differences in blood loss or transfusion requirements were found.^{16–18} Only in the study by Braatz et al. comparing an ACT of 480 seconds with an ACT of 680 seconds including 29 CABG patients was a difference in postoperative blood loss found.²⁸ However, the authors note that excessive blood loss in one patient in the higher ACT group, qualified as a surgical bleeding and requiring re-exploration, might have been a confounding factor. Transfusion requirements were not reported. In a larger study by Nutall et al., surgical procedures other than CABG and redo operations were also included;¹⁹ 178 patients were randomized to target an ACT of 480 or 600 seconds. No differences in blood loss and blood product transfusion were found. Lower transfusion requirements when maintaining a lower ACT target were only found in two studies by Von Segesser et al. and Aldea et al.^{13,14} The lower ACT targets (180 and 250 seconds, respectively) were compared with their standard ACT target (480 and 450 seconds, respectively). Von Segesser et al., however, recommend higher ACT values during prolonged periods of low flow. In the study by Aldea et al., the lower rate of transfusion was not accompanied by a lower amount of postoperative blood loss. This study is the only one that showed a significant difference in the occurrence of adverse events. In the higher ACT group, more thromboembolic events occurred (1, 0.8% v 6, 5.0%). The other studies either did not report or did not find significant differences.

A target ACT of ≥ 400 seconds was compared with a target ACT of ≥ 480 seconds, which is the range of ACT values currently used in the Netherlands during CPB when using conventional bypass systems. The patients in the higher ACT group received, on average, a 35% larger heparin dose compared with patients in the lower ACT group. A broader range of target ACT values might have resulted in larger differences in outcomes, but the participating hospitals were hesitant to target ACT values below 400 seconds with lower doses of heparin.

Optimizing patient blood management to reduce blood loss and transfusion requirements requires a multidisciplinary approach and involves many aspects.¹⁰ Managing appropriate heparin dosing is one of them. This study, however, shows that the influence of the variation in ACT targets (≥ 400 v ≥ 480 seconds) and related heparin dose, as used in many centers nowadays, is limited. The small difference in postoperative blood loss and hemoglobin value that was found in this study did not lead to differences in PRBC transfusion. The total transfusion of blood products was less in the lower ACT group, although the difference in transfusion rate of individual products was not significant between groups. It appears that the range of ACT targets, from 400 to 480 seconds, is safe and comparable in terms of patient outcome. It is questionable whether further reducing ACT values may lead to important reductions in transfusion requirements, given the small differences found in this study, while safety might be compromised at some point. Other adjustable factors such as the continued use of preoperative antithrombotic medication, the ratio of protamine to heparin, and preoperative Hb value, might be of greater impact when striving to improve patient blood management.

This study has several limitations. The first limitation concerns the number of patients. At the interim analysis, the initial anticipated event rate of 40% PRBC transfusion was adjusted to 19.4%, reflecting the mean PRBC transfusion rate at that point during the study. The necessary number of patients was adjusted from 736 to 505 patients per group. The power for the primary outcome measure was unchanged, but the study was not powered to detect differences in the occurrence of thromboembolic events and other adverse events. As a consequence, only descriptive statistics were reported for adverse events. For the 1,015 patients in the AST population for whom adverse events are reported, no remarkable differences between groups were observed. The occurrence of thromboembolic events at different levels of anticoagulation might be the subject of future studies. Second, perfusionists and cardio-anesthesiologists were not blinded to group randomization for practical reasons. Third, the transfusion strategy followed the recommendations of the European Task Force on Patient Blood Management for Adult Cardiac Surgery.¹⁰ These recommendations do not prescribe strict cutoff values, which leads to differences in transfusion strategy between hospitals and leaves room for interpretation by the treating physician. In general, PRBC transfusion has become increasingly restrictive in the participating hospitals over the last decade. The focus has become more on balancing the patient's oxygen demand and consumption rather than maintaining a specific hemoglobin level, which is in line with European task force recommendations. The need for thrombocytes and plasma transfusion is mainly determined by clinical signs of bleeding in combination with viscoelastic testing. As a fourth limitation, the number of patients per hospital was equally divided per treatment group using block-randomization per hospital. However, differences will exist regarding the conduct of CPB, continued use of preoperative antithrombotic medication, conduct of anesthesia, and surgical procedures between the hospitals participating in this study.

Finally, in this study, the Hemochron Signature whole blood microcoagulation system was used for ACT measurement. It is well known that interdevice differences exist between types of ACT devices due to, among other influences, differences in analyzing methodology and the type of coagulation activator used.²⁹ Therefore, the outcomes for the ACT targets of ≥ 400 and ≥ 480 seconds, as used in this study, should be interpreted with care when using another type of ACT device.

Conclusion

This study showed that a target ACT of ≥ 400 seconds is equivalent to a target ACT of ≥ 480 seconds in terms of intraoperative and postoperative PRBC transfusion rates in the modern cardiac surgery setting with biocompatible coated CPB. Postoperative blood loss was slightly, though significantly, higher at an ACT target of ≥ 480 seconds, but did not lead to differences in transfusion requirements. The rate of occurrence of thromboembolic events was similar in both groups. The authors conclude that the range of ACT targets, from 400 to 480 seconds, is comparable in terms of patient outcomes after undergoing cardiac surgery with CPB.

Declaration of competing interest

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CRedit authorship contribution statement

Karin A.M. Gorter: Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Marco C. Stehouwer:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Roel de Vroege:** Writing – review & editing, Investigation, Funding acquisition, Data curation, Conceptualization. **Dannique Zuthof:** Writing – review & editing, Investigation, Data curation. **Michael I. Meesters:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Peter G. Noordzij:** Writing – review & editing, Conceptualization. **Ed D. Niesten:** Writing – review & editing, Investigation. **Willem J.L. Suyker:** Writing – review & editing, Supervision, Conceptualization.

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Supplementary materials

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References

- Edmunds LH Jr, Colman RW. Thrombin during cardiopulmonary bypass. *Ann Thorac Surg* 2006;82:2315–22. <https://doi.org/10.1016/j.athoracsur.2006.06.072>.
- Despotis GJ, Avidan MS, Hogque CW Jr. Mechanisms and attenuation of hemostatic activation during extracorporeal circulation. *Ann Thorac Surg* 2001;72:1821–31. [https://doi.org/10.1016/s0003-4975\(01\)03211-8](https://doi.org/10.1016/s0003-4975(01)03211-8).
- Yavari M, Becker RC. Anticoagulant therapy during cardiopulmonary bypass. *J Thromb Thrombolysis* 2008;26:218–28. <https://doi.org/10.1007/s11239-008-0280-4>.
- Hyde JA, Chinn JA, Graham TR. Platelets and cardiopulmonary bypass. *Perfusion* 1998;13:389–407. <https://doi.org/10.1177/026765919801300603>.
- Mochizuki T, Olson PJ, Szlam F, et al. Protamine reversal of heparin affects platelet aggregation and activated clotting time after cardiopulmonary bypass. *Anesth Analg* 1998;87:781–5. <https://doi.org/10.1097/0000539-199810000-00008.b>.
- Griffin MJ, Rinder HM, Smith BR, et al. The effects of heparin, protamine, and heparin/protamine reversal on platelet function under conditions of arterial shear stress. *Anesth Analg* 2001;93:20–7. <https://doi.org/10.1097/0000539-200107000-00005>.
- Nielsen V. Protamine enhances fibrinolysis by decreasing cloth strength: Role of tissue factor-initiated thrombin generation. *Ann Thorac Surg* 2006;81:1720–7. <https://doi.org/10.1016/j.athoracsur.2005.12.027>.
- Karkouti K, Wijesundera DN, Yau TN, et al. The independent association of massive blood loss with mortality in cardiac surgery. *Transfusion* 2004;44:1453–62. <https://doi.org/10.1111/j.1537-2995.2004.04144.x>.
- Cuenca JS, Diz PG, Sampedro FG, et al. Method to calculate the protamine dose necessary for reversal of heparin as a function of activated clotting time in patients undergoing cardiac surgery. *J Extra Corpor Technol* 2013;45:235–41.
- Boer C, Meesters MI, Milojevic M, et al. 2017 EACTS/EACTA guidelines on patient blood management for adult cardiac surgery. *J Cardiothorac Vasc Anesth* 2018;32:88–120. <https://doi.org/10.1053/j.jvca.2017.06.026>.
- Bull BS, Huse WM, Brauer FS, et al. Heparin therapy during extracorporeal circulation: II. *J Thorac Cardiovasc Surg* 1975;69:685–91.
- Young JA, Kisker CT, Doty DB. Adequate anticoagulation during cardiopulmonary bypass determined by activated clotting time and the appearance of fibrin monomer. *Ann Thorac Surg* 1978;26:232–40. [https://doi.org/10.1016/s0003-4975\(10\)63676-4](https://doi.org/10.1016/s0003-4975(10)63676-4).
- Von Segesser LK, Weiss BM, Pasic M, et al. Risk and benefit of low systemic heparinization during open heart operations. *Ann Thorac Surg* 1994;58:391–7. [https://doi.org/10.1016/0003-4975\(94\)92213-6](https://doi.org/10.1016/0003-4975(94)92213-6).
- Aldea GS, O'Gara P, Shapira OM, et al. Effect of anticoagulation protocol on outcome in patients undergoing CABG with heparin-bonded cardiopulmonary bypass circuits. *Ann Thorac Surg* 1998;65:425–33. [https://doi.org/10.1016/s0003-4975\(97\)01347-7](https://doi.org/10.1016/s0003-4975(97)01347-7).
- Raner G, Hu Y, Trowbridge C, et al. Comparison of blood concentration and weight-based heparin and protamine dosing strategies for cardiopulmonary bypass: A systematic review and meta-analysis. *Cureus* 2024;16. <https://doi.org/10.7759/cureus.54144>.
- Lax M, Pesonen E, Hiippala S, et al. Heparin dose and point-of-care measurements of hemostasis in cardiac surgery—Results of a randomized controlled trial. *J Cardiothorac Vasc Anesth* 2020;34:2362–8. <https://doi.org/10.1053/j.jvca.2019.12.050>.
- Johnell M, Elgue G, Larsson R, et al. Coagulation, fibrinolysis, and cell activation in patients and shed mediastinal blood during coronary artery bypass grafting with a new heparin-coated surface. *J Thorac Cardiovasc Surg* 2002;124:321–32. <https://doi.org/10.1067/mtc.2002.122551>.

- 18 Ranucci M, Cazzaniga A, Soro G, et al. The antithrombin III-saving effect of reduced systemic heparinization and heparin-coated circuits. *J Cardiothorac Vasc Anesth* 2002;16:316–20. <https://doi.org/10.1053/jcan.2002.124140>.
- 19 Nuttall GA, Smith MM, Smith BB, et al. A blinded randomized trial comparing standard activated clotting time heparin management to high target active clotting time and individualized Hepcon HMS heparin management in cardiopulmonary bypass cardiac surgical patients. *Ann Thorac Cardiovasc Surg* 2022;28:204–13. <https://doi.org/10.5761/atcs.0a.21-00222>.
- 20 Piaggio G, Elbourne DR, Evans SJW, et al. Reporting of noninferiority and equivalence randomized trials. Extension of the CONSORT 2010 statement 2012;308:2594–604. <https://doi.org/10.1001/jama.2012.87802>.
- 21 Meybohm P, Bein B, Brosteanu O, et al. A multicenter trial of remote ischemic preconditioning for heart surgery. *N Engl J Med* 2015;373:1397–407. <https://doi.org/10.1056/NEJMoa1413579>.
- 22 Ahn E, Kang H. Intention to treat versus as treated versus per protocol approaches to analysis. *Korean J Anesthesiol* 2023;76:531–9. <https://doi.org/10.4097/kja.23278>.
- 23 Karlsson M, Hannuksela M, Appelblad M, et al. Cardiopulmonary bypass and dual antiplatelet therapy: A strategy to minimise transfusions and blood loss. *Perfusion* 2020;35:236–45. <https://doi.org/10.1177/0267659119867005>.
- 24 Aldea GS, Dourounian M, O’Gara P, et al. Heparin-bonded circuits with a reduced anticoagulation protocol in primary CABG: A prospective, randomized study. *Ann Thorac Surg* 1996;62:410–7.
- 25 Ovrum E, Holen EA, Tangen G, et al. Completely heparinized cardiopulmonary bypass and reduced systemic heparin: Clinical and hemostatic effects. *Ann Thorac Surg* 1995;60:365–71. [https://doi.org/10.1016/0003-4975\(95\)00366-s](https://doi.org/10.1016/0003-4975(95)00366-s).
- 26 Kuitunen AH, Heikkilä LJ, Salmenperä MT. Cardiopulmonary bypass with heparin-coated circuits and reduced systemic anticoagulation. *Ann Thorac Surg* 1997;63:438–44. [https://doi.org/10.1016/s0003-4975\(96\)01099-5](https://doi.org/10.1016/s0003-4975(96)01099-5).
- 27 Sáenz A, Larrañaga G, Alvarez L, et al. Heparin-coated circuit in coronary surgery. A clinical study. *Eur J Cardiothorac Surg* 1996;10:48–53.
- 28 Braatz E, Sesartic V, Liska J. Will high-dose heparin affect blood loss and inflammatory response in patients undergoing cardiopulmonary bypass? *Perfusion* 2021;36:63–9. <https://doi.org/10.1177/0267659120924917>.
- 29 Li H, Serrick C, Rao V, et al. A comparative analysis of four activated clotting time measurement devices in cardiac surgery with cardiopulmonary bypass. *Perfusion* 2021;36:610–9. <https://doi.org/10.1177/0267659120949351>.