Journal of Cardiothoracic and Vascular Anesthesia 33 (2019) 307–317

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Original Article

Shifts of Transfusion Demand in Cardiac Surgery After Implementation of Rotational Thromboelastometry–Guided Transfusion Protocols: Analysis of the HEROES-CS (HEmostasis Registry of patiEntS in Cardiac Surgery) Observational, Prospective Open Cohort Database

Gerhardus J.A.J.M. Kuiper, MD, PhD[*,†,1], Lieve T. van Egmond, MSc[‡], Yvonne M.C. Henskens, PhD[‡], Paul M. Roekaerts, MD, PhD[§], Jos G. Maessen, MD, PhD[¶], Hugo ten Cate, MD, PhD[‖,†], Wolfgang F. Buhre, MD, PhD[*], Marcus D. Lancé, MD, PhD[*]

[*]*Department of Anaesthesiology and Pain Treatment, Maastricht University Medical Center, Maastricht, the Netherlands*

[†]*Laboratory for Clinical Thrombosis and Haemostasis, Department of Internal Medicine, Cardiovascular Research Institute Maastricht, Maastricht University Medical Center, Maastricht, the Netherlands*

[‡]*Central Diagnostic Laboratory, Cluster for Haemostasis and Transfusion, Maastricht University Medical Center, Maastricht, the Netherlands*

[§]*Department of Intensive Care Medicine, Maastricht University Medical Center, Maastricht, the Netherlands*

[¶]*Department of Cardiothoracic Surgery, Maastricht University Medical Center, Maastricht, the Netherlands*

[‖]*Department of Internal Medicine, Maastricht University Medical Center, Maastricht, the Netherlands*

Objectives: Rotational thromboelastometry (ROTEM)-guided transfusion algorithms in cardiac surgery have been proven to be successful in reducing blood loss in randomized controlled trials. Using an institutional hemostasis registry of patients in cardiac surgery (HEROES-CS), the authors hypothesized that the use of ROTEM-guided transfusion algorithms would save blood products and overall costs in cardiac surgery in every day practice.

Design: Observational, prospective open cohort database.

Setting: Single-center academic hospital.

Participants: Cardiac surgery patients.

Interventions: Implementation of ROTEM-guided bleeding management.

Measurements and Main Results: A classical-guided algorithm and a ROTEM-guided algorithm were used for patient blood management in 2 cohorts. Primary outcome was the use and amount of blood products and hemostatic medication. Secondary outcomes were amount of rethoracotomies, length of stay, and 30-day mortality. Finally, costs and savings were calculated. The classical-guided cohort comprised 204 patients, and ROTEM-guided cohort comprised 151 patients. Baseline characteristics showed excellent similarities after propensity score matching of 202 patients. Blood loss was lower after ROTEM guidance ($p < 0.001$). Absolute risk reduction was 17% for red blood cells ($p = 0.024$), 12% for fresh frozen plasma ($p = 0.019$), and 4% for thrombocyte concentrates ($p = 0.582$). More tranexamic acid was given, but not more fibrinogen concentrate, while desmopressin was given less often. Hospital length of stay was reduced by an overall median of 2 and a mean of 4 days ($p < 0.001$). Mortality and rethoracotomy rates were not affected. Potential savings were about €4,800 ($5,630) per patient.

[1]*Address reprint requests to* Gerhardus J.A.J.M. Kuiper, MD, PhD, Department of Anesthesia and Pain Management, Toronto General Hospital, University Health Network, 200 Elizabeth St., EN3-434A, Toronto, ON M5G 2C4, Canada.

E-mail address: gerhardus.kuiper@one-mail.on.ca (G.J.A.J.M. Kuiper).

https://doi.org/10.1053/j.jvca.2018.08.203

Conclusions: Implementation of a ROTEM-guided transfusion algorithm in cardiac surgery patients reduced the use of blood products and hemostatic medication, hereby saving costs. Reductions in mortality and rethoracotomy rates could not be found.

Key Words: thromboelastometry; transfusion; algorithm; bleeding; cardiac surgery; mortality

TRANSFUSION OF blood components is basically a form of tissue allotransplantation. The safety of transfusion is of outmost concern because, despite strict protocols and surveillance in production and transfusion, adverse reactions still occur.[1] Transfusion-associated circulatory overload and transfusion-related fever are more common than death by a medical error.[2] One of the most common indications for transfusion of packed red blood cells, fresh frozen, plasma, and thrombocyte concentrates is significant blood loss resulting from trauma or major surgery.

Traditionally, the clinical decision for transfusion of blood products is based on algorithms and guidelines on the basis of classical blood tests. However, even before the publication of the 2013 guidelines on the management of severe perioperative bleeding by the European Society of Anaesthesiology,[3] a shift from using traditional laboratory tests to whole blood viscoelastic tests was noticeable. In a landmark single-center, retrospective cohort study by Görlinger et al., it was shown that rotational thromboelastometry (ROTEM)–guided transfusion was implemented successfully for patients undergoing cardiovascular surgery, which led to reduced blood transfusion requirements and decreased thrombotic or thromboembolic adverse events.[4] The main clinical advantage of ROTEM-guided transfusion algorithms is that treatment can be initiated earlier compared with that using traditional laboratory tests.[5] In addition, ROTEM-guided algorithms reduce the amount of transfusion and are associated with decreased mortality by allowing for the management of blood loss in a goal-directed approach.[6,7]

Prospective studies of the implications of ROTEM implementation on transfusion needs and costs in cardiac surgery are scarce. Haas et al. published a systematic review, of which only 4 studies had a prospective design.[8] Of these 4 prospective studies, one was reported on 100 pediatric patients and the 3 other studies were randomized controlled trials in 100, 56, and 61 patients, respectively. Since the publication of the Haas et al. article, several other publications have been published,[9] but no large prospective cohort studies investigating the daily routine before and after implementation of ROTEM-guided transfusion algorithms have been published.

The authors' hemostasis registry of patients in cardiac surgery (HEROES-CS) addressed changes in outcomes of surgery before and after ROTEM implementation for guiding transfusion. The present study was designed to gather all relevant information on preoperative, intraoperative, and postoperative variables of cardiac surgery patients that could explain transfusion demand of allogeneic blood products and other procoagulant medication in a single-center design. From the resulting database, the authors extracted patient and procedure characteristics and calculated transfusion needs, adverse bleeding events, and eventually potential costs or savings associated with the implementation of ROTEM diagnostics.

Based on previous studies, the authors' hypothesis was that ROTEM-guided transfusion algorithms would reduce transfusion needs of allogeneic blood products, possibly increase the use of prohemostatic medication, and potentially reduce adverse bleeding events. Overall, the authors expected that ROTEM implementation would produce significant cost savings in cardiac surgery patients.

Materials and Methods

Study Setting and Ethics

The HEROES-CS database was established for this prospective, observational study of patients undergoing cardiac surgery. Patient, surgical, laboratory, and transfusion characteristics were collected during 2 consecutive periods of 3 months in a single tertiary university hospital. All data acquisition was performed by study investigators who were not directly involved in patient management. About 1,000 cardiac surgeries are performed yearly in the authors' hospital.[10] In the first period of the study, prospective data were collected from patients who underwent surgery from October 10, 2011, to January 13, 2012. The second study period included patients who underwent surgery from February 25, 2014, up to July 8, 2014, and included a 1-month break of enrollments in April 2014 because of leave of the data acquisitor. These 2 study periods were choosen at random, allowing for enough time between them for clinicians to establish familiarity with ROTEM diagnostics. Follow-up was 30 days from the day of surgery or until discharge from the hospital. If a patient was discharged within 30 days of follow-up, a control visit was made by telephone, which is standard practice in the authors' hospital. The control visit is done merely for gaining information about current functional status (eg, revalidation, mortality) and patient satisfaction about their stay in the hospital. This study was approved by the local medical ethics committee, and the need for patient consent was waived.

Population and Surgical Procedures

All patients undergoing cardiac surgery in the respective periods formed part of the study cohort. Patient data were collected prospectively if surgery took place during regular operating hours. Data of surgeries performed outside of regular

operating hours were collected retrospectively the day after the procedure. There were no exclusion criteria for this study.

Antithrombotic and antiplatelet medications were withheld or bridged in all elective cases, except for acetylsalicylic acid, which was continued. On arrival to the operating room, standard monitoring was applied. Large-bore intravenous access and an arterial catheter was placed for all patients. Induction of anesthesia was performed according to hospital protocol. After intubation, a central venous catheter was placed, preferably in the right internal jugular vein. Maintenance was performed using continuous total intravenous anesthesia with propofol and an opioid. Activated clotting times (ACTs) were analyzed using a point-of-care (POC) device, and 2 g of tranexamic acid (TXA) was administered before initiation of the extracorporeal circulation (ECC), if applicable. Heparin was administered in a dose of 300 IU/kg of body weight (Heparin Leo; Leo Pharmaceutical Products BV, Weesp, the Netherlands) for a goal ACT >400 seconds before ECC initiation. Hematocrit was maintained >23 % (which equals about 7 g/dL hemoglobin)[11] during ECC under normothermic conditions. Heparin was reversed with protamine (Valeant Pharmaceuticals, Eschborn, Germany) in a 1:1 ratio of the loading dose. An extra protamine dose could be given if the ACT was >10% of the baseline value. Intraoperative bleeding was managed with a team approach (ie, anesthesiologist, cardiac surgeon, and perfusionist) using the basic principles from the algorithms presented in Figs. 1 and 2. Intraoperatively, ACT analysis was preferred over HEPTEM because of the turnaround time. Timing of chest closure in relationship to the coagulation state was a team decision, with the cardiac surgeon having the final call. Chest closure was performed by the cardiac surgeon or under supervision of the cardiac surgeon. At the end of surgery, all patients were transferred to the intensive care unit (ICU) sedated and intubated. On arrival to the ICU, transfusion algorithms were initiated immediately. In nonbleeding patients, 100 mg of acetylsalicylic acid was given intravenously 6 hours after ICU arrival, if indicated.

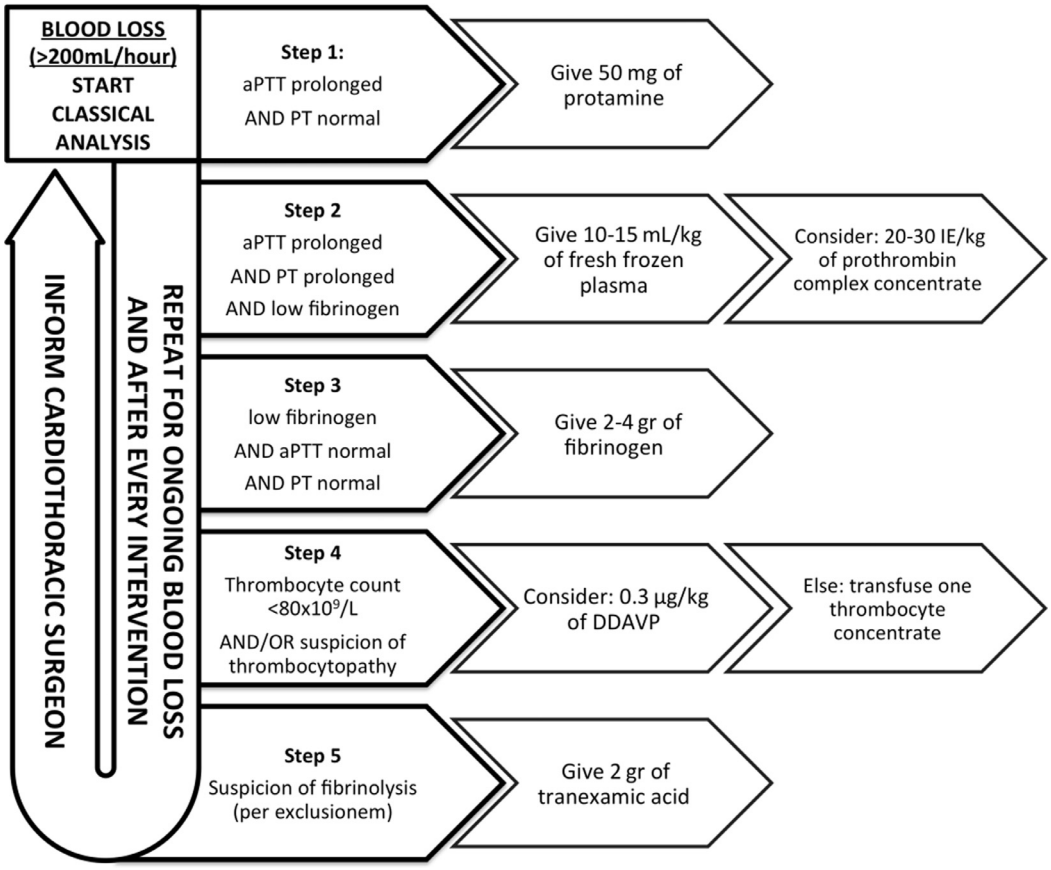

Fig. 1. Classical-guided transfusion algorithm for postoperative blood loss >200 mL per hour. In the first step, residual heparin is assessed using activated partial thromboplastin time, and if evident, protamine is given as an antidote. The second step is used to detect deficiencies in circulating coagulation proteins, as evidenced by prolonged clotting times on activated partial thromboplastin time and prothrombin time and by low fibrinogen. If deficiencies are detected, fresh frozen plasma is recommend; prothrombin complex concentrate can be given as an alternative in cases of normal fibrinogen levels or with fibrinogen concentrate. In the third step the amount of fibrinogen is investigated. In isolated hypofibrinogenemia, fibrinogen is given as a concentrate. In the fourth step the contribution of the thrombocytes for coagulation is determined. To improve thrombocyte function, first 1-desamino-8-D-arginine vasopressin can be considered. If 1-desamino-8-D-arginine vasopressin is not given, thrombocyte transfusion should be initatied. In the last and fifth step tranexamic acid can be given for high suspicion of fibrinolysis if all previous steps are negative. After each investigation or if blood loss is ongoing, the aforementioned step(s) needs to be reevaluated with the primary conditions for adequate hemostasis (no anemia, no acidosis, no hypothermia, and no hypocalcemia). Any blood loss >200 mL in the first hour and afterward needs to be conveyed to the cardiac surgeon on duty. aPTT, activated partial thromboplastin time; DDAVP, 1-desamino-8-D-arginine vasopressin; PT, prthrombin time.

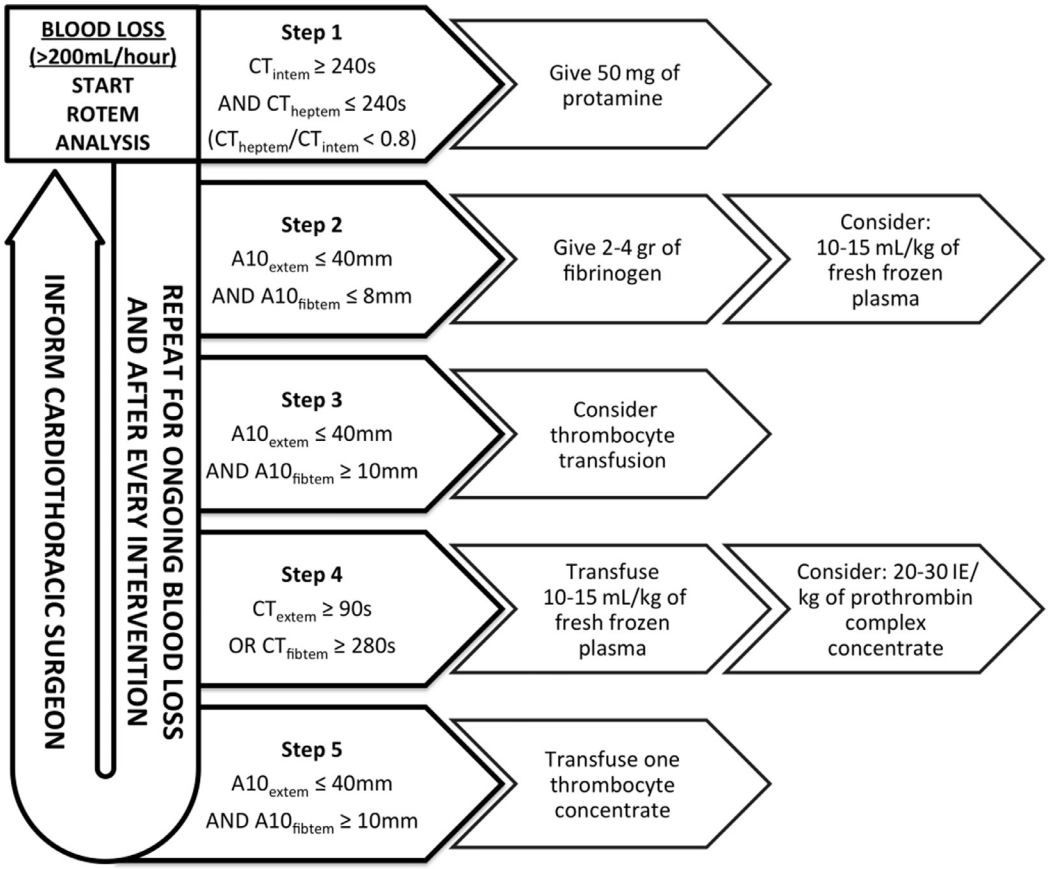

Fig. 2. ROTEM-guided transfusion algorithm for postoperative blood loss >200 mL per hour. In the first step, residual heparin is assessed, and if evident, protamine is given as an antidote. In the second step the amount of fibrinogen is investigated. If it is too low, fibrinogen is given as concentrate; fresh frozen plasma can be used as an alternative. In the third step the contribution of the thrombocytes for the coagulation profile is determined and if deemed too low, thrombocyte transfusion can be considered. The fourth step is used to detect deficiencies in circulating coagulation proteins given as prolonged clotting times in EXTEM and FIBTEM. If a prolonged clotting time is detected on either measurement, transfusion of fresh frozen plasma is recommended; prothrombin complex concentrate can be given as an alternative. In the last and fifth step, transfusion of one thrombocyte concentrate is recommended when the thrombocyte contribution to hemostasis is too low. After each intervention or if blood loss is ongoing the aforementioned step(s) needs to be reevaluated with the primary conditions for adequate hemostasis (no anemia, no acidosis, no hypothermia, and no hypocalcemia). Any blood loss >200 mL in the first hour and afterwards needs to be conveyed to the cardiac surgeon on duty. A10, amplitude at 10 minutes; CT, clotting time.

Transfusion Algorithms

Patients in the first cohort were treated according to standard laboratory results on the discretion of the attending clinicians (see Fig 1). During surgery and on arrival to the ICU, all patients were treated for hypothermia (<35˚C), anemia (hematocrit <23 %), acidosis (pH <7.25), and hypocalcemia (below normal) first (primary conditions for adequate hemostasis). The following measurements were taken for all patients: pH, temperature, calcium level, hematocrit, thrombocyte counts, fibrinogen level, prothrombin time (PT) as internal normalized ratio (INR), and activated partial thromboplastin time (aPTT). Bleeding accompanied by a hematocrit level <23 % was used as a red blood cell transfusion trigger. Platelet concentrates were administered if thrombocyte counts decreased to <80 ($\times 10^9$/L) or bleeding was believed to be due to platelet dysfunction. 1-Desamino-8-D-arginine vasopressin (DDAVP) could be given for suspected platelet dysfunction with adequate thrombocyte counts. Prolonged PT or INR or low fibrinogen levels were used as a trigger for fresh frozen plasma transfusion. Prothrombin complex concentrate could be given in cases of prolonged PT and INR in normovolemic patients (eg, for vitamin K antagonist [VKA] reversal or for acquired [non-VKA] coagulopathy after ECC). Low fibrinogen could be treated with fibrinogen concentrate (FC) when PT or INR was normal. Protamine was given for prolonged aPTTs if a residual heparin effect was suspected.

Patients in the second cohort were transfused on the basis of thromboelastometry-based transfusion algorithms (see Fig 2). Again, during surgery and on arrival to the ICU, all patients were treated for hypothermia (<35 ˚C), anemia (hematocrit <23 %), acidosis (pH <7.25), and hypocalcemia (below normal) first (primary conditions for adequate hemostasis). ROTEM analysis could be performed during surgery if determined necessary by the operating team of surgeons, anaesthesiologists, and

perfusionists. ROTEM analysis was done for every patient in the ICU, using the following guidelines:

- First, the primary conditions of adequate hemostasis in each patient were optimized.
- If no bleeding was observed from the chest tubes (ie, no bleeding >100 mL in the first hour), no additional treatment was required.
- If drainage was 100 to 200 mL in the first hour, 2 g of TXA was administered with 50 mg of protamine (if evidence for circulating heparin was present on ROTEM analysis in step 1 of Fig 2). DDAVP, 0.3 μm/kg, was administered if there was high suspicion of (acquired) von Willebrand disease or a suspected platelet dysfunction.
- If drainage was >200 mL in the first hour or when there was continued bleeding in subsequent hours, the ROTEM algorithm was restarted (see Fig 2).

Laboratory Measurements

ACT measurements were performed on a POC basis (Hemotec ACT II Automated Coagulation Timer; Medtronic Inc, Minneapolis MN) in the operating room using native whole blood. Arterial blood gas sampling also was performed on a POC basis (GEM Premier 3000; Instrumentation Laboratory, Lexington MA) in heparinized tubes for pH and calcium.

All other blood samples drawn perioperatively from patients were sent to the central diagnostic laboratory via a pneumatic tube system. ROTEM results were made available to view in real time using a secure connection between the ROTEM devices and computers in the operating room and ICU. After finalizing the ROTEM analysis, all results were transferred to the electronic patient management system for later review. Blood for ROTEM, aPTT, PT, and fibrinogen analysis was drawn in 3.2% citrate tubes (BD Vacutainer; Becton Dickinson, Breda, the Netherlands). For the thrombocyte count, blood was drawn in K2-EDTA tubes (BD Vacutainer).

Thrombocyte count, hematocrit, and hemoglobin measurements were performed using a Sysmex XE-5000 analyzer (Sysmex Corporation, Kobe, Japan). Fibrinogen levels were determined using a Sysmex CA-7000 analyzer (Sysmex) after centrifugation for 10 minutes at 2,000 g using the Clauss method.[12]

Thromboelastometry analysis was performed using a ROTEM-delta device (TEM International GmbH, Munich, Germany) following standard protocols. Analyzed ROTEM parameters were clotting time, amplitude at 10 minutes, and maximal clot formation. These parameters were performed in EXTEM, INTEM, FIBTEM, and HEPTEM standard assays. In the EXTEM and FIBTEM assays, coagulation is activated extrinsically with the use of tissue factor. In the FIBTEM assay a platelet inhibitor (cytochalasin D) is added for a qualitative assessment of fibrinogen only. The INTEM and HEPTEM assays are activated via the intrinsic pathway. In the HEPTEM assay, heparinase is added to eliminate any possible heparin effect on the sample.

End Point Definitions

The perioperative end points—the amount of blood loss (mL/patient) during surgery (calculated by losses from the ECC machine and weighing of swabs) and in the ICU (from chest tubes)—were recorded as primary outcomes. Secondary outcomes were as follows: the total amount of administered packed red cells, fresh frozen plasma, and thrombocyte concentrates (U/patient), which was cross-checked with the author's hospital transfusion database and the amount of prohemostatic medication given during and after the surgery—DDAVP (μg/patient); human FC (g/patient) (Haemocomplettan P; CSL Behring, Breda, NL); recombinant activated factor VII (mg/patient) (NovoSeven; Novo Nordisk Inc, Alphen aan den Rijn, NL); protamine sulphate (mg/patient); prothrombin complex concentrate (IU/patient) (Cofact; Sanquin Plasma Products BV, Amsterdam, The Netherlands); calcium gluconate (mmol/patient); and TXA (mg/patient). Tertiary outcomes were as follows: length of stay (LOS) in days in the ICU and hospital. In addition, the amount and percentage of patients needing a rethoracotomy, the number of laboratory results acquired for coagulation management per patient, and 30-day mortality were evaluated.

Predictive Variables

The following preoperative variables were considered for end point prediction and subgroup analysis: sex; age, weight; height; body surface area; logistic EuroSCORE[13] (low mortality risk: EuroSCORE <3, medium mortality risk: EuroSCORE ≥3 but <6, high mortality risk: EuroSCORE ≥6); elective versus emergency surgery; type of surgery (ie, coronary artery bypass grafting [CABG] surgery, aortic valve surgery, combined CABG/aortic valve surgery); antiplatelet medication use (eg, Cyclooxygenase 1 (COX1) [ie, acetylsalicylic acid], P2Y12 [eg, clopidogrel], and GPIIbIIIa blockers); bridged VKA use; direct oral anticoagulant use; hematocrit level; thrombocyte count; INR; kidney function (estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation[14]); and blood group.

The following intraoperative variables were acquired for end point prediction: length of surgical procedure, duration on ECC, duration of cross-clamping, hematocrit level, thrombocyte count, and temperature on arrival to the ICU.

Potential Costs and Savings

Costs of the transfusion of blood components, prohemostatic medication, laboratory assessments of coagulation, and tertiary end points (rethoracotomy resulting from bleeding cause and ICU and non-ICU hospital LOC) were calculated. Costs were adopted from the Dutch Healthcare Authority (Nederlandse Zorgautoriteit), which is appointed by the Dutch government for controlling the tariffs in the Dutch health care system.

Table 1
Baseline Characteristics

	Unmatched Full Cohorts			Propensity-Score Matched Cohort Paitents		
	Classical-Guided Transfusion (n = 204)	ROTEM-Guided Transfusion (n = 151)	p Value	Classical-Guided Transfusion (n = 101)	ROTEM-Guided Transfusion (n = 101)	p Value
Demographics						
Male sex (%)	140 (68.6)	113 (74.8)	0.236	73 (72.3)	71 (70.3)	0.877
Age, y (IQR)	69 (61-75)	68 (59-75)	0.275	70 (60-74)	68 (61-75)	0.479
Weight, kg (IQR)	80.0 (72.0-90.0)	80.0 (70.0-93.4)	0.804	78 (70-89)	78 (68-90)	0.988
Height, cm (IQR)	172 (166-178)	172 (166-178)	0.843	171 (166-176)	171 (165-177)	0.938
BSA, m^2 (IQR)	1.95 (1.81-2.10)	1.96 (1.81-2.14)	0.962	1.93 (1.80-2.06)	1.93 (1.77-2.10)	0.067
Antiplatelet and atnicoagulant medication						
No medication (%)	29 (14.2)	26 (17.2)	0.461	12 (11.9)	14 (13.9)	0.834
Antiplatelet medication only (%)	123 (60.3)	97 (64.2)	0.507	66 (65.3)	68 (67.3)	0.882
Acetylsalicylic acid only (%)	104 (84.6)	83 (85.6)	0.852	51 (77.3)	58 (85.3)	0.272
Clopidogrel only (%)	1 (0.8)	0. (0.0)	1.000	1 (1.5)	0 (0.0)	0.493
Dual antiplatelet medication (%)	18 (14.6)	14 (14.4)	1.000	14 (21.2)	10 (14.7)	0.373
Bridged VKA only (%)	41 (20.1)	22 (14.6)	0.207	16 (5.8)	15 (14.9)	0.839
Therapeutic LMWH only (%)	2 (1.0)	0 (0.0)	0.510	1 (1.0)	0 (0.0)	0.493
DOAC only (%)	0 (0.0)	2 (1.3)	0.180	0 (0.0)	2 (2.0)	0.496
Combined medication use (%)	9 (4.4)	4 (2.6)	0.569	6 (5.9)	2 (2.0)	0.162
Clinical and laboratory characteristics						
Hematocrit, L/L (IQR)	0.42 (0.39-0.44)	0.41 (0.38-0.43)	0.004	0.41 (0.38-0.43)	0.41 (0.38-0.43)	0.780
Thrombocyte count, $\times 10^9$/L (IQR)*	231 (186-278)	243 (206-274)	0.224	243 9190-281)	243 (206-274)	0.467
INR, s/s (IQR)†	1.03 (0.99-1.07)	0.98 (0.95-1.03)	< 0.001	1.02 (0.99-1.06)	0.98 (0.96-1.04)	0.003
Blood group 0/A/B/AB (%)	89/96/15/4 (43.6/47.1/7.4/2.0)	65/73/10/3 (43.0/48.3/6.6/2.0)	0.991	37/52/10/2 (36.6/51.5/9.9/2.0)	43/45/10/3 (42.6/44.6/9.9/3.0)	0.764
MDRD-eGFR, mL/min/1.73m^2 (IQR)‡	74.6 (60.3-89.5)	69.9 (58.7-85.6)	0.064	72.9 (57.7-88.6)	74.5 (62.4-91.3)	0.449
Elective surgery (%)	190 (93.1)	142 (94.0)	0.829	93 (92.1)	95 (94.1)	0.783
Type of surgery						
Isolated CABG surgery (%)	96 (47.1)	73 (48.3)	0.830	53 (52.5)	49 (48.5)	0.673
Off-pump CABG surgery (%)	3 (3.1)	4 (5.5)	0.464	0 (0.0)	0 (0.0)	1.000
Isolated AVR surgery (%)	44 (21.6)	29 (19.2)	0.599	24 (23.8)	19 (18.8)	0.492
TAVI procedure (%)	20 (45.5)	10 (34.5)	0.467	11 (45.8)	7 (36.8)	0.756
Combined CABG/AVR surgery (%)	42 (20.6)	26 (17.2)	0.496	6 (5.9)	11 (10.9)	0.311
Other procedures (%)	22 (10.8)	23 (15.2)	0.259	18 (17.8)	22 (21.8)	0.597
Logistic EuroSCORE (IQR)	4.49 (2.27-8.81)	3.93 (2.15-8.33)	0.542	4.39 (1.90-10.65)	3.67 (2.18-7.99)	0.640
Low mortality risk group (%)	43 (21.1)	33 (21.9)	0.896	25 (24.8)	23 (22.8)	0.869
Medium mortality risk group (%)	85 (41.7)	65 (43.0)	0.828	36 (35.6)	44 (43.6)	0.314
High mortality risk group (%)	76 (37.3)	53 (35.1)	0.738	40 (39.6)	34 (33.7)	0.465

Abbreviatons: AVR, aortic valve replacement; BSA, body surface area; CABG, coronary artery bypass grafting; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; IQR, interquartile range; LMWH, low molecular weight heparin; MDRD, Modification of Diet in Renal Disease equation; TAVI, transcatheter aortic valve implantation; VKA, vitamin K antagonist.

* n = 200 for classical-guided and n = 148 for ROTEM-guided transfusion groups.

† n = 195 for classical-guided and n = 142 for ROTEM-guided transfusion groups.

‡ n = 204 for classical-guided and n = 146 for ROTEM-guided transfusion groups.

Statistical Analysis

Categorical data are presented as number and percentage, and interval data are presented as median and interquartile range or mean [minimum-maximum]. Normally distributed data were analyzed using the 2-tailed unpaired Student *t* test. Continuous variables with skewed distribution were analyzed using Mann-Whitney U testing and dichotomous variables by means of Fisher exact test. Propensity score matching was performed in a 1:1 manner by using a multivariable logistic regression model with cohort group as the dependent variable and the baseline characteristics from Table 1 as independent variables. Subgroup analysis was performed on the unmatched data set. The following 2 subgroups were defined—the type of surgery subgroup, which yielded the largest number of patients, and the subgroup with the largest consumption of blood products. A p value < 0.05 was considered to be significant. All data analyses were done using SPSS, Version 23 (IBM Corp, Armonk NY). Graphs were constructed using GraphPad Prism (GraphPad Prism, Version 5.0a for Windows; GraphPad Software, San Diego CA).

Results

Complete Analysis of All Patients

Three hundred fifty-five patients were enrolled in the study, of whom 204 were included in the conventional-guided transfusion group and 151 in the ROTEM-guided group. Baseline characteristics (see Table 1) were not different between the

Table 2
Intraoperative and Postoperative Variables

	Classical-Guided Transfusion (n = 101)	ROTEM-Guided Transfusion (n = 101)	p Value
Intraoperative variables			
Length of surgery, min (IQR)	180 (140-225)	202 (163-278)	0.002
ECC time, min (IQR)	85 (64-112)	93 (65-140)	0.109
Cross-clamping time, min (IQR)	60 (42-78)	67 (47-93)	0.040
ACT post ECC, % of baseline (IQR)	95 (87-103)	102 (91-114)	0.015
Postoperative variables			
Hematocrit, L/L (IQR)	0.29 (0.27-0.31)	0.29 (0.26-0.33)	0.513
Platelet count, $\times 10^9$/L (IQR)	116 (91-147)	151 (126-182)	< 0.001
Fibrinogen level, g/L (IQR)	1.8 (1.5-2.3)	1.9 (1.6-2.4)	0.226
Temperature on arrival to ICU,˚C (IQR)	36.3 (35.9-36.7)	36.1 (35.8-36.4)	0.006

NOTE. Results are median (IQR).
Abbreviations: ACT, activated clotting time; ECC, extracorporeal circulation; ICU; intensive care unit; IQR, interquartile range.

2 groups, except for minimal differences in hematocrit (42 % v 41 % or 0.42 *v* 0.41 L/L; p = 0.004) and INR (1.03 *v* 0.98; p < 0.001), which were both lower in the ROTEM-group. On the basis of propensity score matching, the study consisted of 202 matched patients (see Table 1). INR remained significantly different between the 2 groups. The majority of patients were men (72.3% *v* 70.3%, respectively). A small portion (11.9% *v* 13.9%) had no antiplatelet or anticoagulant medication before cardiac surgery, whereas most patients had only antiplatelet medication (65.3% *v* 67.3%), of which the largest proportion used solely acetylsalicylic acid. A small percentage of patients underwent emergency cardiac surgery (7.9% *v* 5.9%), and half the patients underwent an isolated CABG surgery procedure. Isolated aortic valve replacement surgery was performed in about 20% of the patients, making it the second largest subgroup. Logistic EuroSCORE did not differ between the 2 groups (p = 0.640) at a median of 4.39 for the classical-guided group versus 3.67 for the ROTEM-guided group. The proportions of low-, medium-, and high-risk mortality according to EuroSCORE were evenly distributed in both algorithm groups.

Intraoperative and postoperative variables are presented in Table 2. The main findings were that patients in the ROTEM-guided transfusion group had 20 minutes longer length of surgery, were on ECC approximately 10 minutes longer, and had 5 minutes longer of aortic cross-clamping. On the other hand, the ACT post-ECC was higher and closer to 100% of baseline in the ROTEM-guided group. Hematocrit and fibrinogen levels on arrival to the ICU were not significantly different between the 2 groups. However, the thrombocyte count was significantly higher in the ROTEM-guided group, whereas temperature was significantly lower.

Primary outcome parameters demonstrated multiple differences between the 2 cohorts (Table 3). Overall, ROTEM guidance of transfusion was associated with less blood loss on the day of surgery (890 *v* 565 mL; p < 0.001 [both a decline intraoperatively and postoperatively]) and less transfusion of red blood cell concentrates (55% *v* 39%) and fresh frozen plasma (19% *v* 7%) but not of thrombocyte concentrates. Of the prohemostatic medications, reductions in DDAVP and calcium gluconate were observed, whereas the use of TXA increased significantly in patients for whom the ROTEM-guided algorithm was used. There was no increase in the number of patients who received fibrinogen. No prothrombin complex concentrate was given to any of the patients during either period. For the tertiary end points, a tendency toward a reduction in the percentage of rethoracotomies (17.8% *v* 10.9%), mean ICU LOS (3 *v* 2 d), and a 30-day survival rate (96.0% *v* 93.1%) was observed after ROTEM implementation. However, none of these differences was statistically significant. Hospital LOS was reduced by a mean of 4 days after ROTEM implementation (p < 0.001). Of 6 (classical) and 10 (ROTEM) patients, it could not be determined whether they still were alive after 30 days because no call was answered for the control visit by telephone (p = 0.436). Finally, potential savings (based on the mean difference per patient) was more than 4,800 Euro (5630 USD) per patient after implementation of ROTEM-guided transfusion protocols (Table 4).

Isolated CABG Surgery Subgroup

Similarly, an analysis of the isolated CABG surgery group was made, which was the largest subgroup with the most standardized surgical procedures (Supplement Tables S1 to S4). In this isolated CABG subgroup, potential savings resulting from ROTEM implementation were approximately 4,500 Euro (5,278 USD) per patient.

High EuroSCORE Subgroup

In order to determine whether the adoption of the new ROTEM-guided transfusion protocol influenced outcome parameters, another subgroup of patients was examined, mainly those who are prone to high consumption of blood products. Multivariate analysis with the preoperative variables as predictors for the total consumption of blood products (total number of red blood cell, fresh frozen plasma, and thrombocyte concentrate transfusion combined) showed that EuroSCORE would correlate with transfusion the best ($\beta = 0.297$; p < 0.001; [$r^2 = 0.090$, F ratio 32.2]; p < 0.001). In Fig 3 the distribution among the 3 EuroSCORE groups (low, medium, and high) and their protocol subdivision are shown for each blood product. Patients with higher EuroSCOREs were prone

Table 3
Primary and Secondary End Points

	Classical-Guided Transfusion (n = 101)	ROTEM-Guided Transfusion (n = 101)	p Value
Primary end points			
Estimated blood loss day 1, mL (IQR)	890 (570-1,300)	565 (352-810)	< 0.001
Intraoperative, mL (IQR)	150 (50-215)	183 (100-305)	0.016
Postoperative, mL (IQR)	700 (460-1,100)	320 (230-550)	< 0.001
1st h mL (IQR)	80 (50-120)	50 (20-90)	0.003
2nd h, mL (IQR)	80 (40-120)	50 (20-90)	0.002
Cell saver autologous return, mL (IQR)	442 (319-572)	370 (250-590)	0.055
Allogeneic transfusion products*			
Patients who received RBC (%)	56 (55.4)	39 (38.6)	0.024
On day of surgery, U	0 (0-2); 1.8 [0-19]	0 (0-1); 0.6 [0-8]	0.003
Intraoperative, U	0 (0-1); 0.8 [0-15]	0 (0-0); 0.4 [0-8]	0.248
Patients who received FFP (%)	19 (18.8)	7 (6.9)	0.019
On day of surgery, U	0 (0-0); 0.8 [0-14]	0 (0-0); 0.3 [0-6]	0.031
Intraoperative, U	0 (0-0); 0.4 [0-9]	0 (0-0); 0.2 [0-6]	0.244
Patients who received TC (%)	20 (19.8)	16 (15.8)	0.582
On day of surgery, U	0 (0-0); 0.3 [0-6]	0 (0-0); 0.3 [0-3]	0.676
Intraoperative, U	0 (0-0); 0.2 [0-3]	0 (0-0); 0.2 [0-3]	0.455
Secondary end points: prohemostatic medication*			
Patients who received TXA (%)	88 (87.1)	97 (96.0)	0.040
On day of surgery, g	3 (3-3); 2.9 [0-6]	3 (3-3); 2.8 [0-5]	0.248
Intraoperative, g	3 (3-3); 2.6 [0-5]	3 (3-3); 2.8 [0-5]	0.455
Patients who received PTM (%)	95 (94.1)	94 (93.1)	1.000
On day of surgery, mg	250 (250-300); 251 [0-700]	250 (200-300); 240 [0-500]	0.361
Intraoperative, mg	250 (250-300); 251 [0-700]	250 (200-300); 240 [0-500]	0.369
Patients who received DDAVP (%)	17 (16.8)	0 (0.0)	< 0.001
On day of surgery, μg	0 (0-0); 4.3 [0-30]	0 (0-0); 0 [0-0]	< 0.001
Intraoperative, μg	0 (0-0); 0.3 [0-30]	0 (0-0); 0 [0-0]	0.317
Patients who received FC (%)	9 (8.9)	17 (16.8)	0.140
On day of surgery, g	0 (0-0); 0.3 [0-8]	0 (0-0); 0.4 [0-4]	0.109
Intraoperative,- g	0 (0-0); 0.1 [0-8]	0 (0-0); 0.4 [0-4]	0.005
Patients who received rFVIIa (%)	1 (1.0)	0 (0.0)	1.000
On day of surgery, mg	0 (0-0); 0.1 [0-6]	0 (0-0); 0 [0-0]	0.317
Intraoperative, mg	0 (0-0); 0 [0-0]	0 (0-0); 0 [0-0]	1.000
Patients who received CG (%)	19 (18.8)	7 (6.9)	0.019
On day of surgery, mmol	0 (0-0); 1.3 [0-27.6]	0 (0-0); 0.2 [0-9.2]	0.001
Intraoperative, mmol	0 (0-0); 0.9 [0-20.7]	0 90-0); 0.1 [0-6-9]	0.001
Tertiary end points*			
Rethoracotomy (%)	18 (17.8)	11 (10.9)	0.228
Due to bleeding (%)†	12 (66.7)	7 (63.6)	1.000
ICU length of stay, d	1 (1-2); 3 [0-65]	1 (1-1); 2 [0-19]	0.202
Hospital length of stay, d	9 (7-16); 13 [0-81]	7 (6-9); 9 [1-50]	< 0.001
30-d mortality (%)	4 (4.0)	7 (6.9)	0.537
Lost to follow-up (%)	6 (5.9)	10 (9.9)	0.436

Abbreviations: CG, calcium gluconate; DDAVP, 1-desamino-8-D-arginine vasopressin; FC, fibrinogen concentrate; FFP, fresh frozen plasma; ICU, intensive care unit; PTM, protamine; RBC, red blood cell; rFVIIa, recombinant activated factor VII; TC, thrombocyte concentrate; TXA, tranexamic acid.

* Results are median (interquartile range [IQR]); mean [min-max].

† Composite end point of rethoracotomy for tamponade, thorax drain bleeding, or mixed reasons.

to more transfusion of red blood cells, fresh frozen plasma, and thrombocyte concentrates. This was evident for both subgroups according to transfusion algorithm. The high EuroSCORE group thus was chosen for a more in-depth examination (Supplement Tables S5-S8). For the high EuroSCORE subgroup, ROTEM implementation could save more than €2,300 ($2,697) per patient.

Discussion

The main consequence of the introduction of a ROTEM-guided transfusion protocol for cardiac surgery bleeding management was a significant reduction of blood loss perioperatively and a lesser need for transfusion of allogeneic red blood cells and fresh frozen plasma in the authors' hospital. On the other hand, an increase in the use of TXA, but not of FC, was observed as a more condensed alternative source of fibrinogen compared with fresh frozen plasma. The mean intraoperative fibrinogen use was 0.3 g greater in the ROTEM group. ICU laboratory results showed no difference of fibrinogen levels. Possibly, fibrinogen could have resulted in diminished blood loss, while it was being consumed doing so. On the other hand, the effect of the increase in TXA on decreased blood loss and decreased allogeneic blood transfusion is hard

Table 4
Estimation of Costs and Potential Savings Owing to Implementation of a ROTEM-Guided Algorithm

Costs – Euro (USD) per patient*	Classical-guided transfusion	ROTEM-guided transfusion	Potential savings
Allogeneic transfusion products - total			624.66 (732.74)
Red blood cell concentrate	589.40 (691.38)	282.07 (330.87)	307.33 (360.50)
Fresh frozen plasma	221.52 (259.85)	51.69 (60.63)	169.83 (199.21)
Thrombocyte concentrate	269.56 (316.20)	122.06 (143.18)	147.49 (173.01)
Prohaemostatic medication - total			5.98 (7.01)
Tranexamic acid	19.27 (22.60)	17.54 (20.57)	1.73 (2.03)
Protamine	9.02 (10.58)	8.83 (10.36)	0.19 (0.22)
DDAVP	8.81 (10.33)	0.00 (0.00)	8.81 (10.33)
Fibrinogen concentrate	174.10 (204.22)	179.08 (210.06)	-4.98 (-5.84)
Activated recombinant factor VII	0.05 (0.06)	0.00 (0.00)	0.05 (0.06)
Calcium gluconate	0.29 (0.34)	0.10 (0.12)	0.19 (0.22)
Laboratory tests - total			-56.70 (-66.51)
ROTEM	26.56 (31.16)	95.53 (112.06)	-68.97 (-80.90)
Activated partial thromboplastin time	8.75 (10.26)	5.80 (6.80)	2.95 (3.46)
Prothrombin time as INR	3.72 (4.36)	1.34 (1.57)	2.38 (2.79)
Fibrinogen level	14.35 (16.83)	11.35 (13.31)	3.00 (3.52)
Thrombocyte count	18.85 (22.11)	14.91 (17.49)	3.94 (4.62)
Tertiary endpoints - total			4259.87 (4,996.91)
Rethoracotomy for bleeding cause†	933.92 (1,095.51)	544.79 (639.05)	389.13 (456.46)
ICU length of stay	7071.28 (8,294.75)	3861.14 (4,529.19)	3210.14 (3,765.56)
Non ICU hospital length of stay	3052.41 (3,580.54)	2391.82 (2,805.65)	660.60 (774.90)
Grand total			4833.81 (5,670.16)

Abbreviations: DDAVP, 1-desamino-8-D-arginine vasopressin; ICU,intensive care unit; INR, international normalized ratio.
* Based of means of each cohort and the current NZa tariffs
† Composite endpoint of rethoracotomy for tamponade, thorax drain bleeding, or mixed reasons

to determine. TXA is a potent drug, and hyperfibrinolysis is difficult to diagnose with ROTEM because it is only apparent in overt hyperfibrinolysis. In a similar postcardiac surgery population, even the use of in vitro recombinant tissue plasminogen activator could not induce fibrinolysis in the ROTEM assays of patients using TXA.[15]

Meanwhile, the use of DDAVP and activated recombinant factor VII decreased to nearly none, and the use of thrombocyte concentrates appeared to be unchanged. Furthermore, tertiary end points appeared to be unaffected by the introduction of a ROTEM-guided algorithm, except for shorter median and mean hospital LOS. However, because the costs of the tertiary end points outweigh those of the transfusion products, prohemostatic medications, and the laboratory tests, potential cost saving could be substantial at an estimated €4.8 million ($5.6 million) per year for the authors' hospital with about 1,000 procedures annually. The authors are aware that costs and savings will fluctuate among countries because of the varying prices and restrictions of transfusion products and prohemostatic medication, therefore this estimation best applies to European and Dutch institutions.

Although the 2 groups were observed 2 years apart, baseline characteristics did not differ. The only difference was seen in hematocrit level and INR, which were both lower in the ROTEM-guided group. The authors believe that the clinical importance of this significant difference is negligible because neither would necessitate an intervention. Despite this finding, propensity score matching was performed, resulting in 2 groups of 101 patients each. Important differences seem to be apparent during and after the surgery, and this is unlikely to be the result of changes in surgical technique. In the propensity analysis, no off-pump CABG precedures were performed and perfusion techniques were unchanged. The intraoperative and postoperative variables in the ROTEM-guided group suggest a greater risk of bleeding compared with the classical-guided group; longer operating times, longer ECC times, and longer cross-clamping times are risk factors for the occurrence of bleeding and the use of blood products thereafter.[16-19] On the contrary, the higher thrombocyte counts on arrival to the ICU would be more advantageous for the ROTEM-guided group. However, high thrombocyte counts do not indicate adequate thrombocyte function. Overall, baseline characteristics did not indicate a difference between the 2 groups in potential transfusion need, but in the end, less transfusion products were administered to the ROTEM group despite patients in that cohort having a greater risk for transfusion on the basis of intraoperative variables. The reduction in red blood cell transfusion was about 17%, which is an adequate decrease for daily practice.

In the present study, the number of rethoracotomies resulting from bleeding decreased (11.8% in the classical group *v* 6.9% in the ROTEM group; $p = 0.335$) to the level reported in the literature.[19-21] In the Dutch DECS trial, reexploration because of bleeding occurred in 6.8% of patients.[20] This amount was even lower (5.7%) in the group without preemptive dexamethasone, which has been the common practice in the authors' hospital. Reexploration resulting from bleeding was observed in 3.6% of patients in one other study for which prolonged ECC time (especially >150 min) was demonstrated to be a risk factor for bleeding.[21] Another study showed a

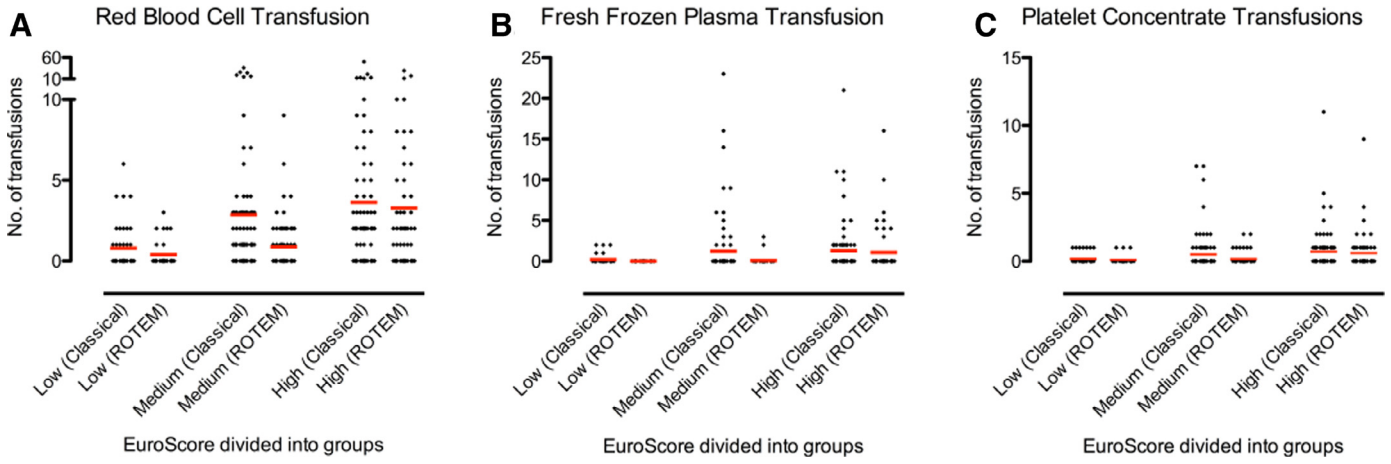

Fig. 3. Distribution of blood product use among EuroSCORE groups and their protocol subdivisions. The amount of transfusions each patient (*black diamonds*) received for the 3 blood products is shown. Each transfusion product was subdivided by the EuroSCORE of each patient in the following 3 classes: low mortality risk (EuroSCORE <3), medium mortality risk (EuroSCORE ≥3 but <6), and high mortality risk (EuroSCORE ≥6). Lastly the graphs were split between the 2 cohorts (classical-guided versus ROTEM-guided algorithm). The *red bars* represent the mean number of transfusions for all patients in their respective lane.

similar percentage (3.6%) for reexplorations for bleeding post-surgery.[19] Those authors found that prolonged ECC and cross-clamping times resulted in more coagulopathic bleeding. In the present study the ROTEM-guided transfusion group had longer ECC and cross-clamping times compared with the classical-guided transfusion group, which did not result in more rethoracotomies because of bleeding. Coagulopathic bleeding might be diagnosed and managed more efficiently using ROTEM results, such that normal coagulation profiles in bleeding patients would necessitate surgical intervention.

Consequent monitoring of hemostasis results in earlier interventions with the use of transfusion, medication, or surgical means. ROTEM-guided treatment of perioperative bleeding can be initiated up to 25 minutes sooner than when using traditional laboratory tests.[5] As a consequence, less blood is shed and less dilutional coagulopathy might occur because of the continued infusion of crystalloids or colloids in a bleeding patient while waiting for test results.

Mortality data were compared with a previous report of cardiac procedures performed from 2007 to 2010 in the Netherlands.[10] The present study's 30-day mortality rate of 5.4% (11 of 202 patients in the propensity score matched group) was greater than the reported 3.0% in the study by Siregar et al.[10] The calculated EuroSCORE in the present study predicts lower mortality rates but appears to reflect national figures; the median logistic EuroSCORE in the database of the Netherlands Association for Cardio-Thoracic Surgery was 4.0, whereas in the present study's HEROES-CS database the median logistic EuroSCORE was 4.39 in the classical group and 3.67 in the ROTEM group. Other distributions of patient and clinical characteristics in the present study are in line with the national results—about 70% male sex, average age between 65 and 70 years old, half the patients needed isolated CABG surgery, and only 5% of surgeries were emergency procedures. Mean hospital LOS was 8.7 days (or 12.4 d when the extended LOS in the referring hospital was included) in the national database. The present study demonstrates that mean LOS was reduced after implementation of ROTEM-guided transfusion algorithms from 13 days to 9 days. This all leads to the authors' conclusion that the HEROES-CS database is still a good representative subset of cardiac surgery practice in the Netherlands.

The present study's subgroup analysis of isolated CABG surgery showed lower EuroSCOREs (2.85 in 2011 and 2.65 in 2014 for each transfusion group) compared with national figures (averages were 4.9 in 2011 and 4.7 in 2014 for isolated CABG surgery).[22] In the present study's high-risk mortality subgroup (EuroSCORE ≥6), which is more prone to the need for transfusion, ROTEM guidance resulted in less blood loss and use of cell saver return of autologous blood. TXA and FC were given more in the ROTEM group, whereas allogeneic blood products were distributed evenly between the 2 groups. This is reflected in the potential cost savings, which were lower for high-risk cardiac surgery when ROTEM-guided transfusion protocols were implemented compared with the isolated CABG surgery subgroup. Cost-effectiveness was maintained because there is shorter hospital LOS in this subgroup of typically large consumers of transfusion products.

One of the variables that could have introduced bias and explained the effect of these new ROTEM-guided protocols is that clinicians need to become familiar with the protocols. Classical-guided transfusion algorithms are well known and do not require rechecking of the protocol each time bleeding occurs. New protocols and guidelines, however, must be learned and may be consulted more frequently, which would improve adherence and therefore could explain the study's positive findings. Using ROTEM as a blueprint, patient blood management attitude was changed at the authors' institution and this required an investment in time, money, and personnel. Also, information bias might have occurred in both groups because of missing data after discharge from the authors' hospital to the referral hospital. Thirty-day control telephone call follow-ups were made for all patients,

but information was not retrieved from all of them. This could mean that some patients may have died, but this is unclear. In these cases, patients were lost to follow-up. However, of all control visits performed, no new patient had been reported by the spouse as experiencing death after discharge. Missing data on transfusions after discharge are present because control visits did not include questions about transfusions. However, asking patients about not-yet-recorded transfusions might have introduced recall bias.

In conclusion, ROTEM-guided transfusion algorithms reduced transfusion needs of allogeneic blood products, increased the use of prohemostatic medications, and reduced adverse bleeding events. Overall, ROTEM implementation has the potential to save costs in cardiac surgery. To achieve this, a hospital's attitude toward patient blood management using ROTEM needs to be changed radically and requires time and expense, which is not represented is this study.

Acknowledgements

The authors acknowledge all who participated in acquiring data for this study.

Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1053/j.jvca.2018.08.203.

References

1 Bolton-Maggs PH, Cohen H. Serious Hazards of Transfusion (SHOT) haemovigilance and progress is improving transfusion safety. Br J Haematol 2013;163:303–14.
2 Carson JL, Grossman BJ, Kleinman S, et al. Red blood cell transfusion: A clinical practice guideline from the AABB*. Ann Intern Med 2012;157:49–58.
3 Kozek-Langenecker SA, Afshari A, Albaladejo P, et al. Management of severe perioperative bleeding: Guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol 2013;30:270–382.
4 Görlinger K, Dirkmann D, Hanke AA, et al. First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: A retrospective, single-center cohort study. Anesthesiology 2011;115:1179–91.
5 Olde Engberink RH, Kuiper GJ, Wetzels RJ, et al. Rapid and correct prediction of thrombocytopenia and hypofibrinogenemia with rotational thromboelastometry in cardiac surgery. J Cardiothorac Vasc Anesth 2014;28:210–6.
6 Wikkelsø A, Wetterslev J, Møller AM, et al. Thromboelastography (TEG) or rotational thromboelastometry (ROTEM) to monitor haemostatic treatment in bleeding patients: A systematic review with meta-analysis and trial sequential analysis. Anaesthesia 2017;72:519–31.
7 Whiting P, Al M, Westwood M, et al. Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: A systematic review and cost-effectiveness analysis. Health Technol Assess 2015;19:1–228;v-vi.
8 Haas T, Görlinger K, Grassetto A, et al. Thromboelastometry for guiding bleeding management of the critically ill patient: A systematic review of the literature. Minerva Anestesiol 2014;80:1320–35.
9 Nakayama Y, Nakajima Y, Tanaka KA, et al. Thromboelastometry-guided intraoperative haemostatic management reduces bleeding and red cell transfusion after paediatric cardiac surgery. Br J Anaesth 2015;114:91–102.
10 Siregar S, Groenwold RH, Versteegh MI, et al. Data resource profile: Adult cardiac surgery database of the Netherlands Association for Cardio-Thoracic Surgery. Int J Epidemiol 2013;42:142–9.
11 Society of Thoracic Surgeons Blood Conservation Guideline Task ForceFerraris VA, Brown JR, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg 2011;91:944–82.
12 Clauss A. Rapid physiological coagulation method in determination of fibrinogen. Acta Haematol 1957;17:237–46.
13 Roques F, Michel P, Goldstone AR, et al. The logistic EuroSCORE. Eur Heart J 2003;24:881–2.
14 Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–70.
15 Kuiper GJ, Kleinegris MC, van Oerle R, et al. Validation of a modified thromboelastometry approach to detect changes in fibrinolytic activity. Thromb J 2016;14:1.
16 Surgenor SD, Kramer RS, Olmstead EM, et al. The association of perioperative red blood cell transfusions and decreased long-term survival after cardiac surgery. Anesth Analg 2009;108:1741–6.
17 Salis S, Mazzanti VV, Merli G, et al. Cardiopulmonary bypass duration is an independent predictor of morbidity and mortality after cardiac surgery. J Cardiothorac Vasc Anesth 2008;22:814–22.
18 Nissinen J, Biancari F, Wistbacka JO, et al. Safe time limits of aortic cross-clamping and cardiopulmonary bypass in adult cardiac surgery. Perfusion 2009;24:297–305.
19 Hall TS, Sines JC, Spotnitz AJ. Hemorrhage related reexploration following open heart surgery: The impact of pre-operative and post-operative coagulation testing. Cardiovasc Surg 2002;10:146–53.
20 van Osch D, Dieleman JM, Nathoe HM, et al. Intraoperative high-dose dexamethasone in cardiac surgery and the risk of rethoracotomy. Ann Thorac Surg 2015;100:2237–42.
21 Dacey LJ, Munoz JJ, Baribeau YR, et al. Reexploration for hemorrhage following coronary artery bypass grafting: Incidence and risk factors. Northern New England Cardiovascular Disease Study Group. Arch Surg 1998;133:442–7.
22 Mortality in The Netherlands after heart surgery in the period 2007-2015. Available at http://www.nvtnet.nl/index.asp?page_id=126. Accessed December 21, 2017.