Point-of-Care Hemostatic Testing in Cardiac Surgery

A Stepped-Wedge Clustered Randomized Controlled Trial

BACKGROUND: Cardiac surgery is frequently complicated by coagulopathic bleeding that is difficult to optimally manage using standard hemostatic testing. We hypothesized that point-of-care hemostatic testing within the context of an integrated transfusion algorithm would improve the management of coagulopathy in cardiac surgery and thereby reduce blood transfusions.

METHODS: We conducted a pragmatic multicenter stepped-wedge cluster randomized controlled trial of a point-of-care–based transfusion algorithm in consecutive patients undergoing cardiac surgery with cardiopulmonary bypass at 12 hospitals from October 6, 2014, to May 1, 2015. Following a 1-month data collection at all participating hospitals, a transfusion algorithm incorporating point-of-care hemostatic testing was sequentially implemented at 2 hospitals at a time in 1-month intervals, with the implementation order randomly assigned. No other aspects of care were modified. The primary outcome was red blood cell transfusion from surgery to postoperative day 7. Other outcomes included transfusion of other blood products, major bleeding, and major complications. The analysis adjusted for secular time trends, within-hospital clustering, and patient-level risk factors. All outcomes and analyses were prespecified before study initiation.

RESULTS: Among the 7402 patients studied, 3555 underwent surgery during the control phase and 3847 during the intervention phase. Overall, 3329 (45.0%) received red blood cells, 1863 (25.2%) received platelets, 1645 (22.2%) received plasma, and 394 (5.3%) received cryoprecipitate. Major bleeding occurred in 1773 (24.1%) patients, and major complications occurred in 740 (10.2%) patients. The trial intervention reduced rates of red blood cell transfusion (adjusted relative risk, 0.91; 95% confidence interval, 0.85–0.98; P=0.02; number needed to treat, 24.7), platelet transfusion (relative risk, 0.77; 95% confidence interval, 0.68–0.87; P<0.001; number needed to treat, 16.7), and major bleeding (relative risk, 0.83; 95% confidence interval, 0.72–0.94; P=0.004; number needed to treat, 22.6), but had no effect on other blood product transfusions or major complications.

CONCLUSIONS: Implementation of point-of-care hemostatic testing within the context of an integrated transfusion algorithm reduces red blood cell transfusions, platelet transfusions, and major bleeding following cardiac surgery. Our findings support the broader adoption of point-of-care hemostatic testing into clinical practice.

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Keyvan Karkouti, MD
Jeannie Callum, MD
Duminda N. Wijeysundera, MD, PhD
Vivek Rao, MD, PhD
Mark Crowther, MD
Hilary P. Grocott, MD
Ruxandra Pinto, PhD
Damon C. Scales, MD, PhD
TACS Investigators

Correspondence to: Keyvan Karkouti, MD, Department of Anesthesia, Toronto General Hospital, 3EN, Toronto, ON, Canada M5G 2C4. E-mail keyvan.karkouti@uhn.ca

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Clinical Perspective

What Is New?

- Coagulopathic bleeding is a frequent complication of cardiac surgery that carries a heavy burden of illness.
- Point-of-care hemostatic tests offer certain advantages over conventional tests and are being increasingly used to guide therapy for patients undergoing cardiac surgery who are bleeding, but limited evidence exists supporting their effectiveness and safety in actual clinical practice.
- We therefore conducted a pragmatic multicenter stepped-wedge cluster randomized controlled trial of a point-of-care–based transfusion algorithm in 7402 consecutive patients undergoing cardiac surgery with cardiopulmonary bypass at 12 hospitals in Canada.

What Are the Clinical Implications?

- We found that implementation of point-of-care hemostatic testing within the context of a simple, integrated transfusion algorithm reduced red blood cell transfusions, platelet transfusions, and major bleeding following cardiac surgery.
- Our findings suggest that the use of point-of-care hemostatic testing improves the management of coagulopathy in cardiac surgery and support their broader adoption into clinical practice.

Cardiac surgery requiring cardiopulmonary bypass (CPB) is frequently complicated by coagulopathic bleeding.[1–3] As a result, a large proportion (≈20%) of patients develop major bleeding, which is a resource-intensive and clinically important complication that accounts for the majority (≈80%) of all blood transfusions in cardiac surgery and is associated with increased morbidity and mortality in patients undergoing cardiovascular procedures.[1,2,4–7] To reduce the burden of major bleeding in patients with cardiovascular disorders, therefore, optimal bleeding reduction strategies need to be identified and implemented.[8]

Guidelines aimed at improving the management of perioperative coagulopathic bleeding recommend the use of point-of-care (POC) hemostatic testing within the context of integrated transfusion algorithms.[1,9,10] Compared with standard hemostatic tests, POC tests have faster turnaround times and better ability to identify specific coagulation defects, thereby allowing for targeted and more rapid management of coagulopathic bleeding.[11–13] For these reasons, POC tests are being increasingly used to guide therapy in bleeding patients,[14] but evidence in support of their efficacy and safety is limited to nonrandomized studies without appropriate controls or small single-center randomized trials with high likelihood of bias.[15] Despite their widespread use, therefore, the utility of POC hemostatic testing as a bleeding reduction strategy in cardiac surgery (or other settings) has not been adequately assessed.

To determine whether POC hemostatic testing within the context of an integrated transfusion algorithm would reduce blood product transfusions and major bleeding following cardiac surgery across a network of hospitals, we conducted a pragmatic multicenter stepped-wedge cluster randomized controlled trial at 12 hospitals. Our hypothesis was that implementation of the algorithm would improve the management of coagulopathy and thereby reduce blood product transfusions.

METHODS

Hospitals and Participants

The trial was conducted from October 6, 2014 to May 1, 2015 at 12 Canadian hospitals. None of the sites used POC hemostatic testing for management of coagulopathy in cardiac surgery before the study. The trial included all patients who underwent cardiac surgery with CPB during the study period.

Study Design and Oversight

A pragmatic stepped-wedge cluster randomized controlled trial design was used to evaluate the intervention. Each hospital was randomly assigned to 1 of 6 groups (wedges), with each group consisting of 2 hospitals. The algorithm was sequentially implemented across the groups separated by 1-month intervals (steps) over a 7-month period, such that all hospitals received the intervention by the end of the study (Figure 1). Implementation order was determined randomly, stratified by cardiac surgery volumes to equalize the distribution of high- and low-volume hospitals in each group.

Research ethics board approval was obtained at the coordinating center (Toronto General Hospital, University Health Network) and all participating hospitals, all of which waived the need for informed consent from individual patients. The study was registered at Clinicaltrials.gov (NCT02200419). Patients or their surrogate decision makers were informed about the study and were provided with the option of not having their data used, but none chose to withdraw. Data were abstracted by trained personnel under the direction of each hospital's principal investigator and were entered into a Web-based database with built-in validity checks. A dedicated data manager assessed data quality throughout the study, and all queries were resolved by referring back to patients' medical records. Each site had access to their own data during the study, but only the data manager had access to the entire data set.

Intervention

The intervention involved the implementation of the transfusion algorithm (Figure 2) as standard-of-care for all patients who were having cardiac surgery with CPB. The POC assays included in the algorithm were ROTEM (Rotation Thromboelastometry; TEM International GmBH, Mississauga, ON) and PlateletWorks (Helena Laboratories, Beaumont, TX). ROTEM uses activated whole blood to rapidly measure the dynamics of clot formation. We used the EXTEM assay, which

Group 6 N=2 Hospitals	n=144	n=140	n=150	n=132	n=130	n=168	n=114
Group 5 N=2 Hospitals	n=192	n=197	n=227	n=214	n=211	n=258	n=203
Group 4 N=2 Hospitals	n=189	n=175	n=183	n=178	n=171	n=209	n=135
Group 3 N=2 Hospitals	n=136	n=121	n=122	n=136	n=115	n=146	n=135
Group 2 N=2 Hospitals	n=172	n=170	n=171	n=174	n=164	n=214	n=170
Group 1 N=2 Hospitals	n=204	n=220	n=216	n=220	n=214	n=250	n=212
Total (n=7402)	**n=1037**	**n=1023**	**n=1069**	**n=1054**	**n=1005**	**n=1245**	**n=969**
Period	**Baseline** Oct 1 2014– Nov 2 2014	**Step 1** Nov 3 2014 – Nov 30 2014	**Step 2** Dec 1 2014 – Jan 4 2015	**Step 3** Jan 5 2015 – Feb 1 2015	**Step 4** Feb 2 2015 – Mar 1 2015	**Step 5** Mar 2 2015 – Apr 5 2015	**Follow-up** Apr 6 2015 – May 1, 2015

Control Phase:

Intervention Phase:

Figure 1. Flow of hospitals and patients.
Each group (wedge) included 2 hospitals and each step lasted ≈1 month.

is a heparin-insensitive assay that uses tissue factor to activate the extrinsic pathway, to measure the clotting time (seconds) and the 10-minute estimate (A10; millimeters) of the maximum clot firmness (millimeters). Clotting time measures the time elapsed until initial fibrin formation,[16] and elevated clotting time suggests thrombin formation deficiency.[17,18] A10-EXTEM reflects platelet count and fibrinogen levels,[16,19] but cannot differentiate between thrombocytopenia and hypofibrinogenemia.[17] To detect hypofibrinogenemia, we used the FIBTEM assay, which contains cytochalasin D to inhibit platelet aggregation and thereby remove the contribution of platelets to the maximum clot firmness.[16] The A10-FIBTEM is highly correlated to the Clauss measure of fibrinogen and reliably detects hypofibrinogenemia during CPB when ≤8 mm.[19–21] ROTEM assays cannot detect disorders in primary hemostasis such as platelet adhesion defects (eg, von Willebrand factor deficiency) or platelet dysfunction caused by the conduct of CPB, because these defects are overwhelmed by the activators used in the assays.[16] We measured platelet function using the Plateletworks system, which estimates the number of functioning platelets by obtaining the number of platelets that fail to aggregate in the presence of collagen (ie, nonfunctioning platelets) relative to the total number of platelets in a whole-blood sample.[22] The threshold for recommending platelet therapy was based on the observed relationship between functional platelet count measured near the end of CPB and post-CPB bleeding.[23]

Other important features of the algorithm included an objective measure of blood loss to define a threshold that required therapy (60-g increase in surgical sponge weight over a 5-minute period),[24] the option to use allogeneic blood products or factor concentrates where indicated,[9,18,25] and a simple stepwise treatment approach targeting the 3 most important causes of coagulopathy in cardiac surgery: thrombocytopenia/platelet dysfunction, hypofibrinogenemia, and impaired thrombin generation.[25,26] The algorithm was evaluated in a single-center pilot study that found it to be feasible and potentially beneficial.[27] To avoid contamination, the center where the pilot study was conducted did not participate in this study and served solely as the coordinating center.

Because this was a pragmatic study, no other aspects of clinical care were modified and the use of blood conservation modalities (eg, antifibrinolytics, cell salvage) was not standardized and was left to the discretion of clinicians.

Before the initiation of the study, all anesthesia, surgery, and blood bank staff were educated about the details of the study. Within 1 month before algorithm initiation, clinical and research staff received on-site training for performing the assays, implementing the algorithm, and collecting the data. Following algorithm implementation, POC testing was to be conducted in all patients. In keeping with the pragmatic trial design, however, adherence to the algorithm was encouraged, but was not strictly enforced. Strict hemoglobin transfusion triggers for red blood cell transfusions were not specified by the algorithm. None of the hospitals used POC hemostatic testing for management of coagulopathy in cardiac surgery before the study, nor did any of them use preoperative autologous blood donation. In the preintervention phase, hospitals were instructed to continue their usual management of postcardiac surgery bleeding as per their institutional guidelines or standard of care.

Outcomes

The primary outcome was red blood cell transfusion occurring from the start of surgery to the end of postoperative day 7 (or hospital discharge if earlier). Secondary outcomes included other blood product transfusions and major bleeding during

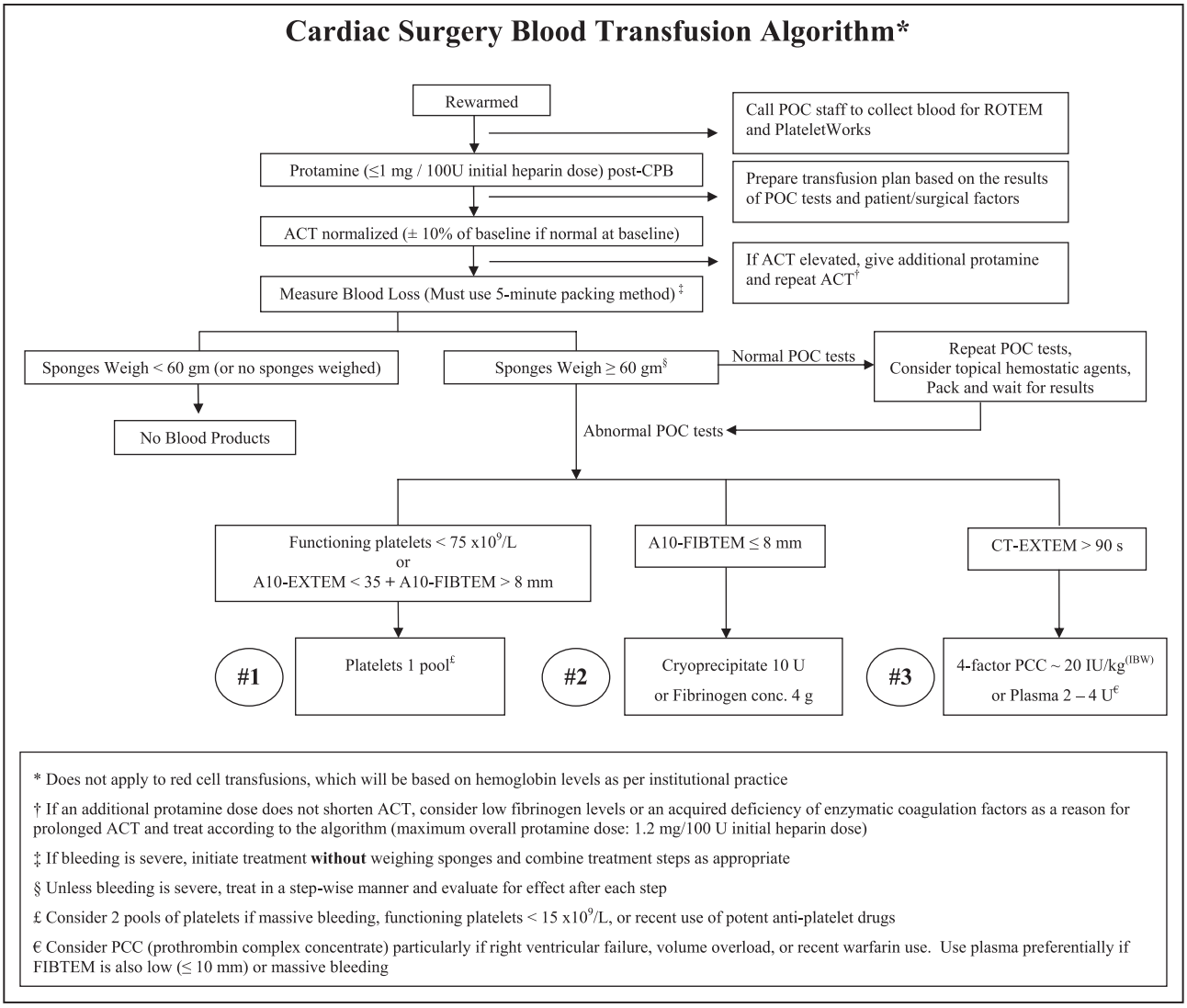

Figure 2. Transfusion algorithm.
Point-of-care (POC) tests consisted of ROTEM (Rotation Thromboelastometry; Tem International GmBH, Munich, Germany) and Plateletworks (Helena Laboratories, Beaumont, TX) systems. ROTEM measures included A10-EXTEM (clot amplitude at 10 minutes with the ROTEM extrinsic pathway assay: <35 mm implies impaired clot formation because of low fibrinogen levels or low platelet count); A10-FIBTEM (clot firmness amplitude at 10 minutes with ROTEM fibrinogen assay: ≤8 mm confirms low fibrinogen levels); and CT-EXTEM (clotting time with ROTEM extrinsic pathway assay: >90 s implies poor clot initiation possibly because of reduced coagulation factor levels or reduced thrombin generation). Functioning platelet count was obtained by the PlateletWorks assay. ACT indicates activated clotting time; CPB, cardiopulmonary bypass; IBW, ideal body weight.

the same follow-up period. Major bleeding was defined using the validated universal definition of bleeding in adult cardiac surgery (≥5 U of red blood cells, ≥5 U of plasma, chest tube drainage of ≥1000 mL within 24 hours of surgery, surgical reexploration, or administration of recombinant activated factor VII).[28,29] Other outcomes included units of blood products transfused, length of hospital stay, and in-hospital major complications. The latter was defined as the composite of in-hospital death, acute kidney injury (≥2-fold increase in creatinine or new renal replacement therapy),[30] sepsis, sternal infection, deep vein thrombosis, pulmonary embolism, myocardial infarction, and stroke. In-hospital follow-up for complications was censored at postoperative day 28.

Statistical Analysis

The primary analysis was intention to treat,[31] based on each hospital's randomly assigned date to convert from standard-of-care to POC-based hemostatic management, with the hospital being the unit of randomization and the individual patient being the unit of analysis. Patient characteristics before and after intervention were analyzed using the *t* test or Wilcoxon rank sum test for the continuous variables and χ^2 test for the categorical variables. For the primary outcome and secondary dichotomous outcomes, modified Poisson regression with sandwich estimator for standard errors was used to estimate the relative risk (RR) and we accounted for clustering by site

using fixed effects.[32–34] A time-dependent variable was used to denote the change in the intervention status as determined by the stepped-wedge randomization schedule. We included time (days) in the models to account for secular trends over time, because the failure to include such time effects can bias estimates of effect sizes.[34] Using the estimate from the model for RR and baseline rates of transfusion from our control rates data, we derived the number needed to treat and the corresponding 95% confidence intervals.

Negative binomial regression models that account for the overdispersion present in the data were used to analyze the number of different units transfused. Time to hospital discharge was analyzed using Cox proportional-hazards models with death censored, and the proportionality of hazards was examined by Schoenfeld residual plots. Both these 2 latter models took into account the clustering effect of patients within sites by including site as a fixed effect.

For the primary and all efficacy outcomes, we adjusted for the following prespecified confounders known to be associated with coagulopathic bleeding and transfusions[35–37]: sex; age (<70, 70 to <80, ≥80 years); body surface area (<1.5, 1.5–1.9, >1.9 m^2); preoperative hemoglobin concentration (≤10, 10 to <13, ≥13 g/dL); platelet count (≤100, 101–150, >150×10^9/L); international normalized ratio≥1.5; estimated glomerular filtration rate[38] (>90, >60–90, ≤60 mL/min or on dialysis); intra-aortic balloon pump; nonelective surgery; complex procedure (any procedure other than isolated coronary artery grafting, single-valve surgery, repair of atrial-septal defect, or myectomy); previous cardiac surgery; CPB duration (≤120, 121–179, ≥180 minutes); deep hypothermic circulatory arrest (0, 1–30, >30 minutes); cell salvage use; and tranexamic acid use.

The case-mix at each hospital was quantified by using multivariable logistic regression modeling with red blood cell transfusion as the outcome to calculate the adjusted (for all the covariates listed above) predicted probability of red blood cell transfusion for patients.

Analyses were conducted with (primary analysis) and without (sensitivity analysis) single imputation for missing covariates. We imputed missing continuous variables by using the means and missing discrete variables by using the modes of the corresponding variables. Sensitivity analyses also included modeling without adjusting for the prespecified risk factors for bleeding and a per-protocol analysis that used the actual protocol implementation date and excluded patients in the intervention phase in whom POC assays were not conducted. We also evaluated the differential effects of the intervention (by including the interaction term between the groups and the intervention) in each of the following subgroups: simple versus complex surgery and elective versus nonelective surgery.

The sample size estimate was based on a survey of individual hospital procedure volumes that suggested ≈7000 patients would undergo cardiac surgery with CPB during a 7-month study period, evenly divided between the control and intervention arms. The calculated power for this sample size was ≈90% to detect an 8% absolute difference in red blood cell transfusions, assuming a baseline rate of 50% and an intracluster correlation coefficient of 0.095 (derived from a previous multicenter study).[34,39] Data were analyzed using SAS version 9.3 (SAS Institute, Inc, Cary, NC). All tests were 2-sided with P≤0.05 denoting statistical significance. Drs Karkouti and Pinto had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

RESULTS

Participants and Hospitals

All hospitals completed the study and received the intervention according to the order specified by the stepped-wedge randomized allocation schedule; however, the initiation of the intervention was delayed by 1 to 10 days in 4 hospitals (online-only Data Supplement Table I). The study included all 7402 patients who underwent cardiac surgery with CPB at the 12 participating hospitals during the study period: 3555 of them during the control phase and 3847 during the intervention phase (Figure 1). No patient had POC assays conducted in the control phase, whereas the assays were conducted in 3411 (88.7%) patients in the intervention phase. A total of 421 (5.7%) patients had ≥1 missing variables; none were missing transfusion data. Patient characteristics were generally similar between the intervention and control phases, but surgical complexity and cell salvage use were higher in the intervention phase, whereas the use of topical hemostatic agents was higher in the control phase (Table 1). The adjusted predicted probability of red blood cell transfusion for patients in the control versus the intervention phase was only different in 1 of the 12 hospitals, but there was wide variability in predicted transfusion risk across hospitals (Figure 3).

Transfusions and Complications

Overall, red blood cell transfusion occurred in 3329 (45.0%), platelet transfusion in 1863 (25.2%), plasma transfusion in 1645 (22.2%), and cryoprecipitate in 394 (5.3%) patients. Factor concentrates were rarely used; only 61 (0.8%) patients received fibrinogen concentrate, 82 (1.1%) patients received prothrombin complex concentrate, and 56 (0.8%) patients received recombinant activated factor VII. Major bleeding occurred in 1773 (24.1%) patients, and 740 (10.2%) patients had ≥1 major complications. The outcomes at each hospital before and after the intervention are shown in Figure 4.

Effects of the Intervention

In most hospitals, the intervention was associated with variable decreases in crude rates of red blood cell transfusion, platelet transfusion, and major bleeding, but not plasma transfusions (Figure 4). After adjusting for hospital, secular time trends, and the prespecified risk factors for bleeding, the intervention significantly reduced the primary outcome of red blood cell transfusion rates (RR, 0.91; 95% confidence interval [CI], 0.85–0.98; P=0.02; number needed to treat, 24.7; 95% CI, 14.8–111.1).

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Table 1. Patient Characteristics, Clinical Status, and Surgical Parameters

Variable	Control (n=3555)	Intervention (n=3847)	*P* Value
Age, y, median (IQR)	67 (59–75)	67 (59–74)	0.03
Weight, kg, median (IQR)	83 (72–95)	81 (71–94)	0.004
Female, n (%)	904 (25.4)	951 (24.7)	0.48
Diabetes mellitus (I or II), n (%)	1204 (33.9)	1264 (32.9)	0.36
Hypertension, n (%)	2736 (77.0)	2962 (77.0)	0.98
Coronary artery disease, n (%)	2572 (72.4)	2817 (73.2)	0.40
Atrial fibrillation, n (%)	554 (15.6)	614 (16.0)	0.66
Stroke or TIA, n (%)	345 (9.7)	377 (9.8)	0.89
Peripheral vascular disease, n (%)	307 (8.6)	400 (10.4)	0.01
Deep vein thrombosis or pulmonary embolism, n (%)	87 (2.4)	108 (2.8)	0.33
Pulmonary disease, n (%)	451 (12.7)	460 (12.0)	0.34
Heparin-induced thrombocytopenia, n (%)	12 (0.34)	11 (0.29)	0.69
Hemoglobin, g/dL, median (IQR)	13.5 (12.2–14.5)	13.6 (12.3–14.7)	0.007
Platelet count, $\times 10^9$/L, median (IQR)	211 (175–254)	206 (171–248)	0.002
INR ≥1.5,* n/total n (%)	135/3451 (3.9)	175/3689 (4.7)	0.08
eGFR,† median (IQR)	79.2 (60.7–103.2)	83.0 (59.2–102.1)	0.26
Complex procedure,‡ n (%)	885 (24.9)	1055 (27.2)	0.01
Emergency surgery, n (%)	275 (7.8)	212 (5.6)	<0.001
Redo surgery, n (%)	250 (7.0)	198 (5.2)	0.001
Cardiopulmonary bypass, min, median (IQR)	98 (77–129)	100 (77–134)	0.08
Intra-aortic balloon pump, n (%)	98 (2.8)	144 (3.7)	0.02
Circulatory arrest, n (%)	108 (3.0)	151 (3.9)	0.04
Cell salvage, n (%)	633 (17.8)	923 (24.0)	<0.001
Tranexamic acid, n (%)	3357 (94.4)	3660 (95.1)	0.17
Topical hemostatic agent, n (%)	1276 (35.9)	829 (21.6)	<0.001

eGFR indicates estimated glomerular filtration rate; INR, international normalized ratio of prothrombin time; IQR, interquartile range; and TIA, transient ischemic attack.

* Total reflects number of patients with complete data for the variable.

† Estimated glomerular filtration rate (calculated by the Cockcroft-Gault method).[38]

‡ Any procedure other than isolated coronary artery grafting, single-valve surgery, repair of atrial-septal defect, or myectomy.

The intervention also reduced the rates of platelet transfusion (RR, 0.77; 95% CI, 0.68–0.87; *P*<0.001; number needed to treat, 16.7; 95% CI, 12.0–29.6) and major bleeding (RR, 0.83; 95% CI, 0.72–0.94; *P*=0.004; number needed to treat, 22.6; 95% CI, 13.7–64.1), but not the rates of plasma and cryoprecipitate transfusions (Table 2). Furthermore, the intervention resulted in a 13% (95% CI, –2 to 25%; *P*=0.08) per patient reduction in units of red blood cells transfused, a 24% (95% CI, 10%–36%; *P*=0.001) per patient reduction in doses of platelets transfused, but no change in units of plasma transfused (*P*=0.90). Overall, there was a 16% (95% CI, 1%–28%; *P*=0.04) reduction in units of allogeneic blood products transfused. The intervention did not affect complication rates (RR, 1.02; 95% CI, 0.81–1.28; *P*=0.87) or duration of hospitalization (hazard of being discharged with death censored=0.90; 95% CI, 0.72–1.13; *P*=0.38). The results were not materially different in the per-protocol analysis, when patients with missing covariates were excluded, or when models were constructed without adjustment for prespecified risk factors for bleeding (online-only Data Supplement Table II). There were no differential treatment effects in any of the prespecified subgroup analyses (tests for interaction *P*>0.1).

DISCUSSION

We conducted a pragmatic stepped-wedge cluster randomized controlled trial that included 7402 patients from 12 hospitals and found that the implementation of POC hemostatic testing as part of an integrated transfu-

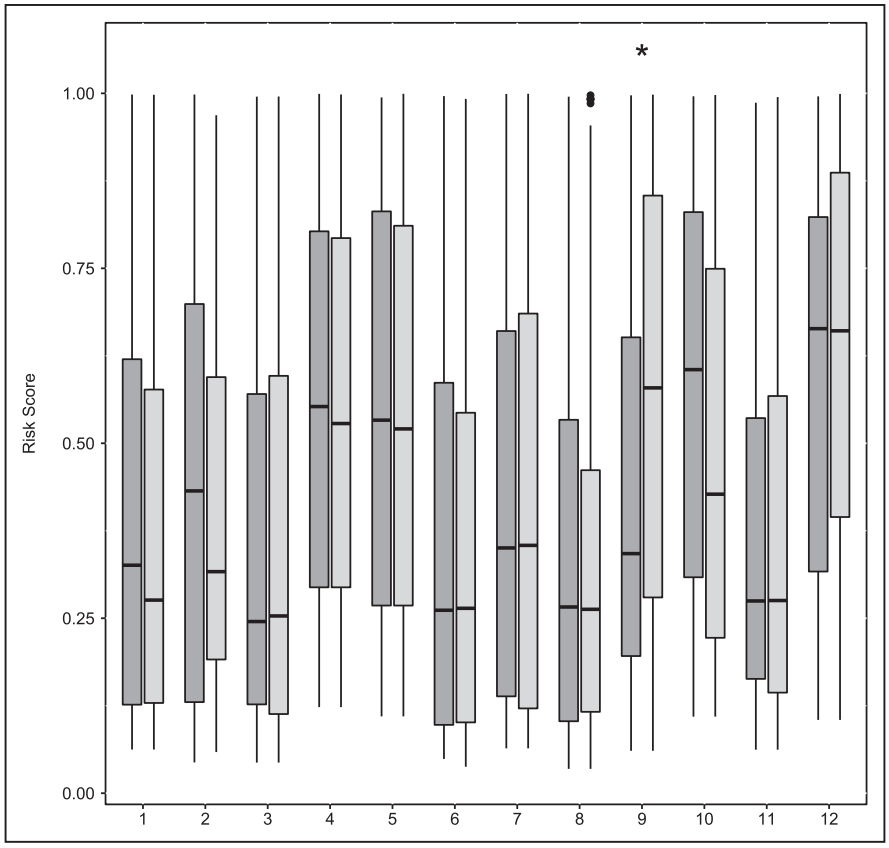

Figure 3. Box plots of the adjusted predicted probability of red blood cell transfusion for patients at each hospital to quantify the case-mix.

The x axis indicates participating hospitals; dark bars, preintervention phase; light bars, postintervention phase. Asterisk denotes $P<0.05$ for comparison of control versus intervention phase for hospital 9. The adjusted (for patient characteristics and site as fixed effect) predicted probabilities of red blood cell transfusion were not significantly different in the control versus the intervention phases for all other hospitals.

sion algorithm significantly reduced red blood cell transfusions, platelet transfusions, and major bleeding.

Previous research on the role of POC hemostatic testing for the management of coagulopathic bleeding is limited. A meta-analysis of 9 randomized trials found that the use of POC-based algorithms modestly reduced blood loss but had no effect on transfusions or major complications.[15] Notably, all the included trials were small (largest n = 224), single-center studies, and at high risk for bias.[15] A more recent review, which included an additional small (n=100) single-center randomized trial[40] and several cohort studies, found that implementation of POC-based algorithms was associated with reduced red blood cell (RR, 0.80; 95% CI, 0.77–0.84), platelet (RR, 0.57; 95% CI, 0.42–0.77), and plasma (RR, 0.34; 95% CI, 0.30–0.39) transfusions.[41]

The observed benefits in our trial were less pronounced than those detected in previous smaller, single-center studies. This is not surprising given that our trial was conducted across 12 hospitals with differing characteristics, patient case-mix, and resource allocation. Moreover, this was a pragmatic study that did not enforce a rigid treatment algorithm. Single-center studies have limited external generalizability and are predisposed to obtaining exaggerated effect sizes.[42] Thus, the results of our trial represent the most valid and generalizable estimates of the efficacy of transfusion algorithms that incorporate POC hemostatic testing.

We found that, for approximately every 20 to 30 patients enrolled, the intervention prevented 1 major bleeding episode with its associated need for transfusion of a variety of blood products. Although costs will vary, we estimate the cost of the testing materials used in this study to be ≈60 USD per patient, which compares favorably with other modalities that are routinely used in cardiac surgery. For example, cell salvage, which costs ≈200 USD for consumables per patient, seems to be only slightly more efficacious in reducing red blood cell transfusions (23% RR reduction, which is derived from methodologically poor studies that are prone to overestimation of treatment effect),[43] but it has no effect on major bleeding and may increase platelet and plasma transfusions.[44] Reducing platelet transfusions (23% RR reduction) was in fact the predominant effect of the in-

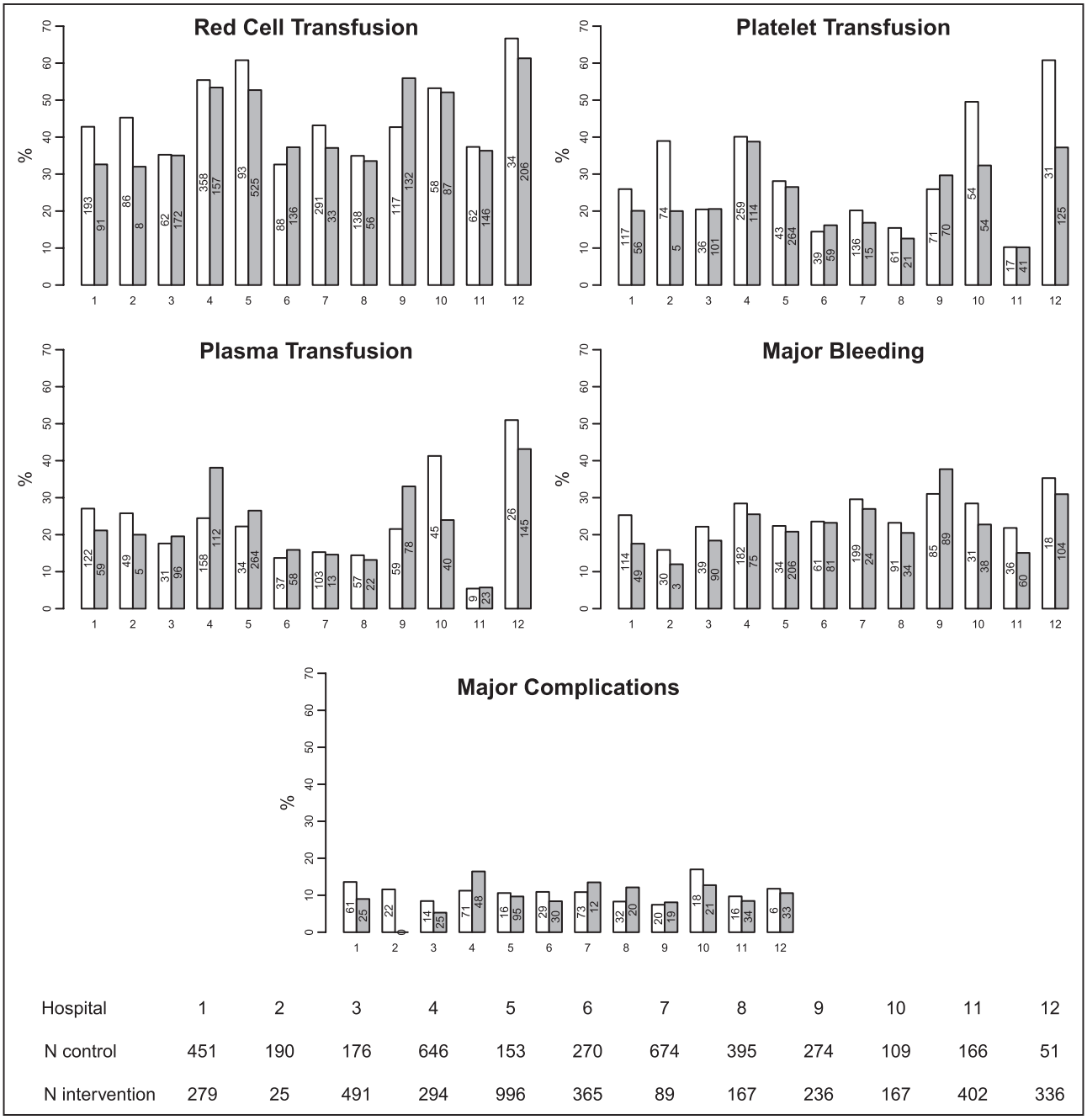

Figure 4. Unadjusted (crude) hospital-specific transfusion and major bleeding and complication rates.
The *x* axis indicates participating hospitals; white bars, preintervention phase; gray bars, postintervention phase. The individual bars depict numerators for each outcome by intervention phase (pre versus post) and by individual hospital. The total numbers of patients at each hospital are shown at the bottom. Hospitals are not presented in order of randomization.

tervention in this study. Because platelets have only a 5-day shelf-life, their inventory management is challenging and there are intermittent shortages (resulting in canceled surgeries) and high wastage rates.[32] Furthermore, the observed benefits in this trial were achieved using laboratory assays that are simple to perform, have short turnaround times, and have no likelihood of causing patient harm. Given the costs, limited availability, and both short- and long-term complications of transfusion and major bleeding,[1,2,4–7] our results suggest that our near-patient, POC-based testing strategy should be considered in all centers that regularly perform cardiac procedures.

Our study had several limitations. First, we did not allow for a transition period between the 2 phases of the study, and the last hospitals randomly assigned had only a 1-month exposure to the intervention. Thus, clinicians may not have had adequate time to become fully pro-

Table 2. Effects of the Intervention on Transfusions and Bleeding

Outcome	Relative Risk (95% Confidence Interval)	*P* Value
Red blood cell transfusions	0.91 (0.85–0.98)	0.02
Platelet transfusions	0.77 (0.68–0.87)	<0.001
Plasma transfusions	0.98 (0.86–1.12)	0.79
Cryoprecipitate or fibrinogen concentrate transfusions	1.26 (0.94–1.69)	0.11
Major bleeding*	0.83 (0.72–0.94)	0.004

*See text for definition

ficient with the POC assays and transfusion algorithm, which may have caused our trial to underestimate the treatment effect. Moreover, because this was a pragmatic study, we could not determine whether clinicians adhered to individual components of the algorithm or which aspects of the algorithm were primarily responsible for the observed effects. The implementation of an intervention in a stepped-wedge cluster randomized controlled trial can lead to biased estimates of effects if the before versus after analysis fails to consider variation in baseline patient characteristics across centers or changes over time that are unrelated to the intervention.[31] To overcome this limitation, we used multivariable regression modeling that controlled for these factors. Our intervention decreased rates of red blood cell and platelet transfusions, but did not decrease the use of other blood products that are frequently required, for example, plasma transfusions. We did not collect data on baseline anticoagulant use, and these medications could have impacted bleeding rates. However, standard practice at all sites was to discontinue the use of such drugs where possible, and our subgroup analysis based on urgency of surgery was consistent with our overall results.

In summary, we found that implementation of POC hemostatic testing within the context of a simple, integrated transfusion algorithm across 12 hospitals reduced red blood cell transfusions, platelet transfusions, and major bleeding following cardiac surgery. These findings suggest that the use of POC hemostatic testing improves the management of coagulopathy in cardiac surgery and support their broader adoption into clinical practice.

APPENDIX

The Transfusion Avoidance in Cardiac Surgery (TACS Research group) principal investigators at the participating hospitals were: B. Achen, MD, Department of Anesthesia, University Hospital, Edmonton, Alberta; S. Brar, MD, D. Morrison, MD, D. Wong, MD, Department of Anesthesia, Royal Columbian Hospital, New Westminster, BC; J. S. Bussières, MD, Department of Anesthesia, Institut Universitaire de Cardiologie et de Pneumologie de Québec, Quebec City, Quebec; J. Callum, MD, Transfusion Medicine, Sunnybrook Health Sciences Centre, Toronto, ON; T. de Waal, MD, Department of Anesthesia, Southlake Regional Health Centre, Newmarket, ON; H. Grocott, MD, Departments of Anesthesia & Perioperative Medicine and Surgery University of Manitoba, St. Boniface Hospital, Winnipeg, MB; C. Harle, MD, Department of Anesthesia, London Health Sciences Centre (LHSC), University Hospital, London, ON; E. de Médicis, MD, MSc, Department of Anesthesia, Sherbrooke Hopital Fleurimont (CHUS), Sherbrooke, Quebec; †C. McAdams, MD, Department of Anesthesia, Alberta Health Science Centre, Calgary, Alberta; S. Syed, MD, Department of Anesthesia, Hamilton Health Sciences Centre (HHSC), McMaster University, Hamilton, ON; D. Tran, MD, Department of Anesthesia, University of Ottawa Heart Institute, Ottawa, ON; T. Waters, MD, Department of Anesthesia, VCH Vancouver Coastal Health (UBC), Vancouver, BC.

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DISCLOSURES

None.

AFFILIATIONS

From Department of Anesthesia and Pain Management, Toronto General Hospital, University Health Network, University of Toronto, Canada (K.K.); Department of Laboratory Medicine and Pathobiology, Sunnybrook Health Sciences Centre, University of Toronto, Canada (J.C.); Department of Anesthesia and Pain Management, Toronto General Hospital, University Health Network, University of Toronto, and Li Ka Shing Knowledge Institute of St. Michael's Hospital, Canada (D.N.W.); Division of Cardiac Surgery, Department of Surgery, Toronto General Hospital, University Health Network, University of Toronto, Canada (V.R.); Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Canada (M.C.); Department

of Anesthesia and Perioperative Medicine, University of Manitoba, Winnipeg, Canada (H.P.G.); Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Canada (R.P.); Department of Critical Care Medicine, Sunnybrook Health Sciences Centre and Interdepartmental Division of Critical Care, University of Toronto, Canada (D.C.S.); and the Peter Munk Cardiac Centre, University Health Network, Toronto, Canada (K.K., D.N.W., V.R.).

FOOTNOTES

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Point-of-Care Hemostatic Testing in Cardiac Surgery: A Stepped-Wedge Clustered Randomized Controlled Trial

Keyvan Karkouti, Jeannie Callum, Duminda N. Wijeysundera, Vivek Rao, Mark Crowther, Hilary P. Grocott, Ruxandra Pinto, Damon C. Scales and TACS Investigators

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SUPPLEMENTAL MATERIAL

Table S1. Conversion from control to intervention schedule

Group	Hospital	Randomization Schedule	Actual Conversion
1	A	Nov 3 2014	Nov 3 2014
	B	Nov 3 2014	Nov 10 2014
2	A	Dec 1 2014	Dec 8 2014
	B	Dec 1 2014	Dec 1 2014
3	A	Jan 5 2015	Jan 15 2015
	B	Jan 5 2015	Jan 6 2015
4	A	Feb 2 2015	Feb 2 2015
	B	Feb 2 2015	Feb 2 2015
5	A	Mar 2 2015	Mar 2 2015
	B	Mar 2 2015	Mar 2 2015
6	A	Apr 6 2015	Apr 6 2015
	B	Apr 6 2015	Apr 6 2015

Table S2. Sensitivity analysis on the effects of the intervention on transfusions and major bleeding

	Per-Protocol Analysis† (n = 7055)		No imputation of missing variables (n = 6981)		No risk adjustment for a-priori-defined confounders‡ (n = 7402)	
Outcome	**Relative Risk (95% Confidence Interval)**	**P-value**	**Relative Risk (95% Confidence Interval)**	**P-value**	**Relative Risk (95% Confidence Interval)**	**P-value**
RBC transfusions	0.91 (0.84, 0.98)	0.01	0.91 (0.84, 0.98)	0.02	0.92 (0.85, 1.01)	0.06
Platelet transfusions	0.79 (0.70, 0.90)	<0.001	0.77 (0.68, 0.88)	<0.001	0.84 (0.73, 0.96)	0.008
Plasma transfusions	1.02 (0.89, 1.17)	0.73	0.98 (0.85, 1.12)	0.75	1.09 (0.94, 1.25)	0.26
Cryoprecipitate or fibrinogen concentrate transfusions	1.18 (0.88, 1.59)	0.26	1.30 (0.96, 1.75)	0.09	1.77 (1.01, 1.86)	0.04
Major bleeding*	0.84 (0.74, 0.97)	0.01	0.82 (0.72, 0.95)	0.006	0.90 (0.78, 1.03)	0.13

* See text for definition

† Using the actual site conversion dates and excluding patients who did not have point-of-care assessment in the intervention phase

‡ Controlling for clustering and secular time trends only