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

Klaus Görlinger, Dr. med,* Daniel Dirkmann, Dr. med,† Alexander A. Hanke, Dr. med,† Markus Kamler, PD Dr. med,‡ Eva Kottenberg, PD Dr. med,* Matthias Thielmann, PD Dr. med,‡ Heinz Jakob, Prof. Dr. med,§ Jürgen Peters, Prof. Dr. med‖

ABSTRACT

Introduction: Blood transfusion is associated with increased morbidity and mortality. We developed and implemented an algorithm for coagulation management in cardiovascular surgery based on first-line administration of coagulation factor concentrates combined with point-of-care thromboelastometry/impedance aggregometry.

Methods: In a retrospective cohort study including 3,865 patients, we analyzed the incidence of intraoperative allogeneic blood transfusions (primary endpoints) before and after algorithm implementation.

Results: Following algorithm implementation, the incidence of any allogeneic blood transfusion (52.5 *vs.* 42.2%; $P < 0.0001$), packed red blood cells (49.7 *vs.* 40.4%; $P < 0.0001$), and fresh frozen plasma (19.4 *vs.* 1.1%; $P < 0.0001$) decreased, whereas platelet transfusion increased (10.1 *vs.* 13.0%; $P = 0.0041$). Yearly transfusion of packed red blood cells (3,276 *vs.* 2,959 units; $P < 0.0001$) and fresh frozen plasma (1986 *vs.* 102 units; $P < 0.0001$) decreased, as did the median number of packed red blood cells and fresh frozen plasma per patient. The incidence of fibrinogen concentrate (3.73 *vs.* 10.01%; $P < 0.0001$) and prothrombin complex concentrate administration (4.42 *vs.* 8.9%; $P < 0.0001$) increased, as did their amount administered per year (179 *vs.* 702 g; $P = 0.0008$ and 162×10^3 U *vs.* 388×10^3 U; $P = 0.0184$, respectively). Despite a switch from aprotinin to tranexamic acid, an increase in use of dual antiplatelet therapy (2.7 *vs.* 13.7%; $P < 0.0001$), patients' age, proportion of females, emergency cases, and more complex surgery, the incidence of massive transfusion [(≥10 units packed red blood cells), (2.5 *vs.* 1.26%; $P = 0.0057$)] and unplanned reexploration (4.19 *vs.* 2.24%; $P = 0.0007$) decreased. Composite thrombotic/thromboembolic events (3.19 *vs.* 1.77%; $P = 0.0115$) decreased, but in-hospital mortality did not change (5.24 *vs.* 5.22%; $P = 0.98$).

Conclusions: First-line administration of coagulation factor concentrates combined with point-of-care testing was associated with decreased incidence of blood transfusion and thrombotic/thromboembolic events.

What We Already Know about This Topic

- Transfusion of allogeneic blood products is associated with increased morbidity and mortality in cardiac surgical patients

What This Article Tells Us That Is New

- In a retrospective analysis of cardiac surgical patients, implementation of a coagulation management algorithm based on first-line therapy with specific coagulation factor concentrates, combined with point-of-care testing, was associated with decreased blood transfusion requirements and decreased thrombotic/thromboembolic adverse events

* Senior Staff Anesthesiologist, † Staff Anesthesiologist, Klinik für Anästhesiologie und Intensivmedizin, Universitätsklinikum Essen, Essen, Germany. ‡ Senior Staff Cardiovascular Surgeon, Klinik für Thorax- und Kardiovaskuläre Chirurgie, Universitätsklinikum Essen. § Professor of Thoracic and Cardiovascular Surgery, Universität Duisburg-Essen, and Chairman, Klinik für Thorax-und Kardiovaskuläre Chirurgie, Universitätsklinikum Essen, Essen, Germany. ‖ Professor of Anesthesiology and Intensive Care Therapy, Universität Duisburg-Essen, and Chairman, Klinik für Anästhesiologie und Intensivmedizin, Universitätsklinikum Essen.

Received from the Klinik für Anästhesiologie und Intensivmedizin, Universitätsklinikum Essen, Universität Duisburg-Essen, Essen, Germany. Submitted for publication Sept. 12, 2010. Accepted for publication July 28, 2011. Support was provided solely from institutional and/or departmental sources. The authors acknowledge the following potential conflicts of interest: Dr. Görlinger received fees and honoraria from CSL Behring GmbH, Marburg, Germany, and TEM International GmbH, Munich, Germany, for consulting and scientific lectures. Drs. Dirkmann and Hanke received honoraria for scientific lectures from CSL Behring GmbH. Drs. Görlinger and Dirkmann contributed equally to this manuscript.

Address correspondence to Dr. Görlinger: Klinik für Anästhesiologie und Intensivmedizin, Universitätsklinikum Essen, Hufelandstraße 55, D-45122 Essen, Germany. klaus@goerlinger.net. Anesthesiology 2011; 115:1179–91

TRANFUSION of packed red blood cells (PRBC), fresh frozen plasma (FFP), cryoprecipitate, and platelet concentrates is strongly associated with increased morbidity and mortality in cardiovascular surgery, patients with myocardial infarction, and critically ill patients.[1–3] This includes transfusion-related acute lung injury, transfusion-associated circulatory overload, ischemic postoperative morbidity, and sepsis.[3–13] Furthermore, blood transfusion is associated with prolonged hospital stay as well as increased hospital costs.[3]

Smaller studies suggest that implementation of point-of-care (POC) coagulation tests coupled to algorithm-based management decreases transfusion requirements in cardiac surgery.[14–18] However, these studies vary widely with respect to the scope of POC measurements performed, availability and use of coagulation factor concentrates, and by consideration of either the intraoperative or postoperative period.

Based on a 5-yr experience in POC-supported coagulation management in liver transplantation[19–20] we developed and implemented an algorithm including POC-supported coagulation management in cardiovascular surgery, based on first-line therapy with specific coagulation factor concentrates, such as fibrinogen concentrate and prothrombin complex concentrate (PCC), combined with point-of-care thromboelastometry and impedance aggregometry.[21] To assess the impact of this approach on transfusion requirements, we compared transfusion rates before and after implementation of this new practice pattern.

Materials and Methods

In this retrospective, single-center, cohort study, we assessed all patients who underwent surgery at our institution's cardiovascular department before (2004) and after (2009) implementation and refinement of POC-supported coagulation management and first-line therapy with specific coagulation factors (fig. 1). The study was approved by the local ethics committee.

Measurements

Demographic data, incidence of preoperative anticoagulant medication, frequency and type of surgery, cardiopulmonary bypass (CPB) time, and aortic cross-clamp time were analyzed. The incidence of any intraoperative allogeneic blood transfusion, the incidence of transfusion of PRBC, FFP, platelet concentrates, and the incidence of massive transfusion (≥10 units of PRBC intraoperatively transfused) were defined as primary endpoints. As secondary endpoints, the transfusion requirements for PRBC, FFP, platelet concentrates, the incidence of unplanned surgical reexploration within 48 h of primary surgery, and the incidence of and requirements for fibrinogen concentrate, PCC, antithrombin concentrate (AT), factor XIII concentrate (FXIII), and activated recombinant factor VII (rFVIIa) were analyzed. In addition, electronic physician reports (1,441 in 2004 and 1,582 in 2009) were analyzed for venous thrombosis, pulmonary embolism, other arterial embolism, stroke, and coronary bypass graft occlusion detected by postoperative coronary angiography. Postoperative coronary angiography was performed in case of a troponin I concentration greater than 30 ng/ml within 12 h after surgery, persistent angina pectoris, persistent new ST-segment elevation, or severe cardiac arrhythmia with hemodynamic instability. Furthermore, the incidence of postoperative renal replacement therapy and in-hospital mortality were analyzed.

Calculation of costs was based on the price for blood products and coagulation factor concentrates in 2009: 1 U PRBC, 85 euros; 1 U FFP, 65 euros; 1 pooled platelet concentrate, 250 euros; 1g fibrinogen concentrate, 288 euros; 500 U PCC, 126 euros; 500 U AT, 44 euros; 1,250 U FXIII, 527 euros; and 4,8 mg rFVIIa, 3,203 euros.

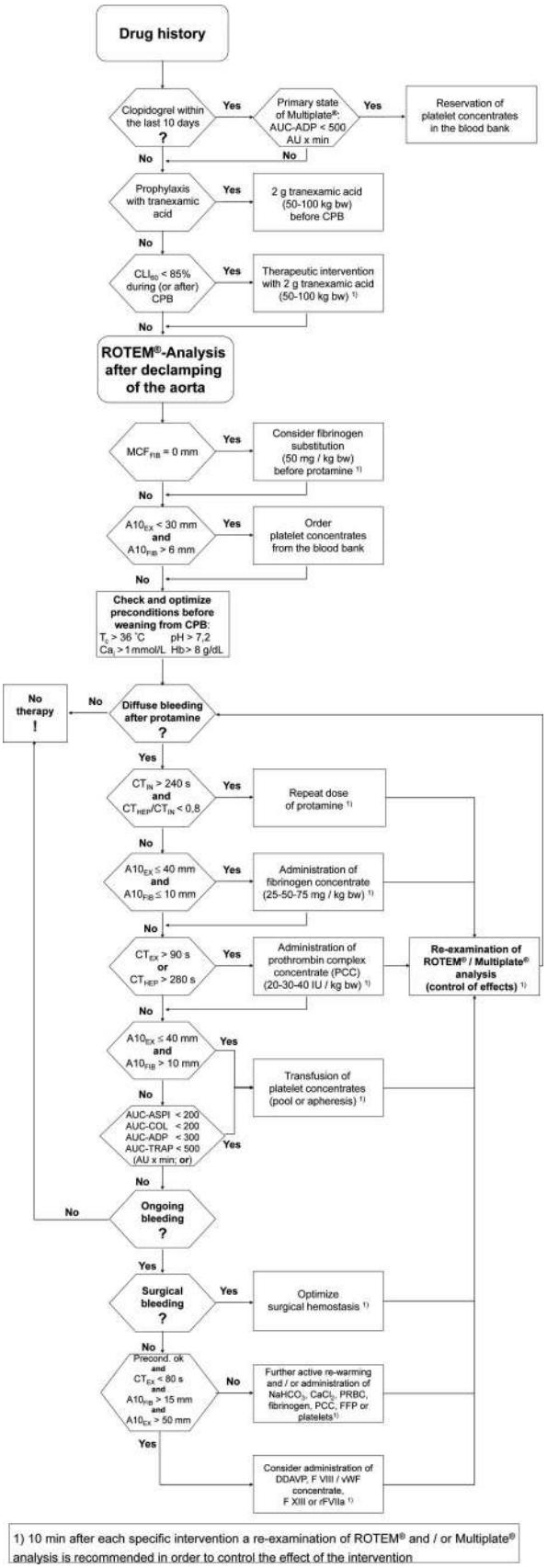
Cardiopulmonary Bypass Circuit Characteristics

Cardiopulmonary bypass components and technique did not change during the study period. An open, phosphorylcholine-coated circuit (model Essen; Sorin Group Deutschland GmbH, Munich, Germany) was used in all patients, with a phosphorylcholine-coated membrane oxygenator and cardiotomy reservoir (Dideco Avant® D903; Dideco-Stöckert, Munich, Germany), driven by a nonpulsatile roller pump (Stöckert SIII; Stöckert Instruments, Munich, Germany) with a mean flow of 2.4 L/min/m^2. Mean arterial pressure was adjusted to 50 to 60 mmHg by phenylephrine or norepinephrine, if required. Furthermore, a heparin-coated arterial blood filter (Affinity® CB351 with Carmeda®; Medtronic Europe S.A., Tolochenaz, Switzerland) and a prebypass filter (Pall Pre-Bypass Plus® 0.2 μm; Pall GmbH, Dreieich, Germany) was used. The circuit was primed with 1,030 ml Ringer's lactate, 445 ml gelatin polysuccinat (Gelafundin 4%; B. Braun, Melsungen, Germany), 90 ml mannitol, 20%, and 35 ml sodium bicarbonate, 8.4%. Shed blood suction and left heart venting were performed with two separated roller pumps, and the cardiotomy reservoir's blood was retransfused. A cell saver (Cell Saver 5+; Hemonetics GmbH, Munich, Germany) was used only in cases of clinically relevant bleeding after weaning from CPB.

POC Methods

Activated Clotting Time. Monitoring of anticoagulation by heparin was performed using activated clotting time (ACT+ test, Hemochron Jr. Signature Whole Blood Coagulation System; International Technidyne Corp., Edison, NJ). This test is activated by silicium, kaolin, and phospholipids; is insensitive to aprotinin; and shows a linear correlation with heparin concentration over a range from 1 to 6 units heparin/ml. Single-use cuvettes for POC prothrombin time/international normalized ratio measurements were also available, and were used occasionally after implementation of POC-supported management in patients with suspected deficiency of vitamin K-dependent coagulation factors.[22]

Thromboelastometry. As the mainstay method of our POC-supported coagulation management we used thromboelastometry (ROTEM®; Tem International GmbH, Munich, Germany), a refinement of thromboelastography first de-



scribed by Hartert.[23] Thromboelastometry is much less sensitive to movement artifact compared with the classic thromboelastography system, enabling its mobile use in the operating room. It provides four independent measuring channels and assays with different activators and additives are commercially available to detect and differentiate specific hemostatic defects such as hyperfibrinolysis, heparin and protamine effects, hypofibrinogenemia and fibrin polymerization disorders, coagulation factor deficiencies, and thrombocytopenia. Extrinsically activated tests (EXTEM®, FIBTEM®, and APTEM®) are activated by tissue factor and contain a heparin inhibitor, which neutralizes heparin effects in a concentration of up to 5 U of unfractionated heparin/ml. Therefore, these tests can already be performed during cardiopulmonary bypass so as to detect hyperfibrinolysis or to predict bleeding problems even before heparin reversal by protamine. EXTEM® assay can serve as a screening test sensitive to deficiencies of vitamin K-dependent coagulation factors, fibrinogen, factor XIII, and platelets. In the FIBTEM® assay, any contribution of platelets to clot firmness is eliminated by cytochalasin D, a potent inhibitor of actin polymerization, an essential part of the platelets' cytoskeleton-mediated contractility apparatus. FIBTEM® allows detection of fibrinogen deficiency or fibrin polymerization disorders, *e.g.*, induced by infused colloids or by factor XIII deficiency. The APTEM® assay contains the antifibrinolytic drug aprotinin, thus assisting in defining the potential effects of administrating antifibrinolytic drugs. Together with the other assays, APTEM® enables an estimation whether an antifibrinolytic therapy alone may normalize coagulation or whether additional measures are required, *e.g.*, administration of fibrinogen or platelets.

The INTEM® and HEPTEM® assays are intrinsically activated by ellagic acid. The HEPTEM® assay in addition contains heparinase to eliminate any heparin effect. A shortening of the clotting time (CT) in the HEPTEM® compared with the INTEM® assay specifically confirms the presence of unneutralized heparin.

Fig. 1. Algorithm for point-of-care-supported coagulation management in cardiovascular surgery used in 2009. Thromboelastometric variables were clot lysis index, clotting time, maximum clot firmness, and amplitude of clot firmness 10 min after clotting time; assays were EXTEM®, FIBTEM®, INTEM®, and HEPTEM®. Multiple electrode aggregometry variables were area under the curve and arbitrary unit; assays were ASPItest®, COLtest®, ADPtest®, and TRAPtest®. A10 = amplitude of clot firmness 10 min after clotting time, ASPI = ASPItest®, ADP = ADPtest®, AU = arbitrary unit, AUC = area under the curve, Ca_i = ionized calcium, CLI = clot lysis index, COL = COLtest®, CPB = cardiopulmonary bypass, CT = clotting time, DDAVP = desmopressin, FFP = fresh frozen plasma, F VIII/vWF concentrate = factor VIII/von Willebrand factor concentrate, F XIII = factor XIII concentrate, MCF = maximum clot firmness, PCC = prothrombin complex concentrate, PRBC = packed red blood cells, rFVIIa = activated recombinant factor VII, T_C = core temperature, TRAP = TRAPtest®.

For interpretation of thromboelastometric assays we used the following variables as part of our POC-supported coagulation management algorithm (fig. 1): CT is the time from adding the start reagent to the citrated blood sample until the clot starts to form (clot firmness of 2 mm). Prolongation of CT may be a result of coagulation factor deficiencies or anticoagulants such as heparin, dependent on the test used. Maximum clot firmness (MCF) represents the greatest amplitude of the thromboelastometric trace and reflects the "strength" of the clot. A low MCF is indicative of decreased platelet concentration and/or function, decreased fibrinogen concentration and/or fibrin polymerization disorders, or low activity of factor XIII. A mechanically weak clot represents a severe bleeding risk.[24] In order to shorten the time to treat, we replaced in our algorithm MCF by the amplitude of clot firmness after 10 min (A10). A10 correlates well with MCF but allows for a 10- to 15-min shorter decision time for therapeutic interventions.[20] Clot lysis index 60 represents the percentage of clot firmness in relation to the MCF remaining at 60 min after CT. Clot lysis index 60 values less than 85% are indicative of systemic hyperfibrinolyis. Like other methods, thrombelastometry has limitations, because assays are not sensitive to the effects of von Willebrand factor deficiency or antiplatelet drugs such as aspirin, clopidogrel, or prasugrel. Only platelet dysfunctions which affect platelet activation *via* thrombin receptors and supratherapeutic doses of glycoprotein IIb/IIIa receptor antagonists will influence ROTEM® results. Further details about thromboelastometry are described elsewhere.[19,21,25]

Whole Blood Impedance Aggregometry. Platelet aggregation was measured by impedance aggregometry, also called multiple electrode aggregometry (MEA) (Multiplate®; Verum Diagnostica GmbH, Munich, Germany). Platelet dysfunction mediated by antiplatelet drugs like aspirin, nonsteroidal antiinflammatory drugs, platelet P2Y12 receptor antagonists, glycoprotein IIb/IIIa receptor antagonists, or by CPB itself can be detected by whole blood impedance.[21,25–26] MEA results closely correlate both with early stent thrombosis and mortality after implantation of drug-eluting coronary stents, as well as with bleeding complications after stent implantation or cardiac surgery.[27–30] Therefore, MEA complements thromboelastometry in perioperative POC coagulation diagnostics. In MEA, the increase in impedance is measured over a period of 6 min after stimulation of platelets by arachidonic acid (ASPItest®), collagen (COLtest®), adenosine diphosphate (ADPtest®), or thrombin receptor activating peptide 6 (TRAPtest®). The area under the curve (AUC) is used as the main variable for platelet aggregation and is expressed in AU × min, or arbitrary units × minute.

Interventions and Protocols before and after Implementation of the POC-supported Coagulation Management Algorithm

Antifibrinolytics. Following withdrawal of aprotinin, we switched our previous routine of prophylactic low-dose administration of antifibrinolytic drugs from aprotinin to tranexamic acid. In 2004, aprotinin had been infused intravenously in a dosage of 2.5×10^6 kallikrein inhibitor units (10^6 kallikrein inhibitor units before CPB, 10^6 kallikrein inhibitor units contained in the priming solution, and 500×10^3 kallikrein inhibitor units following termination of CPB). In 2009, tranexamic acid was routinely infused with an intravenous dosage of 2 g (patients with 50–100 kg body weight) before CPB. No further continuous infusion was given and a second intravenous dose of 1 to 2 g was administered only with prolonged duration of CPB or if hyperfibrinolysis was detected by thromboelastometry. In patients with preexisting thromboembolic events or severe renal dysfunction, tranexamic acid was given only following detection of hyperfibrinolysis.

Heparin/Protamine Management. Four-hundred U heparin per kg body weight were administered intravenously before CPB to achieve an ACT of more than 400 s. Additional injections of 50–100 U heparin per kg body weight were given as needed. If the target ACT was not obtained despite repeated heparin administrations, 500–1,000 U of AT were infused. After weaning from CPB, 3 mg protamine per kg body weight were administered (Protamin ME 1000 I.E./ml; MEDA Pharma, Bad Homburg, Germany; 10 mg protamine hydrochloride corresponded to 1,000 heparin antidote units). Further protamine injections of up to an overall dose of 4 mg per kg body weight were given, if necessary. After implementation of POC thromboelastometry, additional protamine injections were only made if the CT in the INTEM® assay was unduly prolonged (more than 240 s) and the CT was at least 20% shorter in the HEPTEM® assay.

Preconditions of Hemostasis. Before weaning from CPB, body temperature (urinary bladder) exceeded 36°C, and pH and ionized calcium concentration were normalized.

Packed Red Blood Cells. PRBC were transfused to maintain a hemoglobin concentration between 8 and 10 g/dL in due consideration of physiologic transfusion triggers such as tachycardia, hypotension, signs of ischemia in the electrocardiogram, lactic acidosis, and the dynamics of bleeding, according to the German guidelines for therapy with blood components and plasma derivatives at the discretion of the responsible anesthesiologist. This transfusion trigger did not change over the study period.

Fresh Frozen Plasma. Before implementation of the POC-supported coagulation management, FFP was transfused in case of ongoing diffuse bleeding following ACT-confirmed heparin reversal and suspected coagulation factor deficiency. After implementation of POC-supported coagulation management, FFP was transfused if CT in EXTEM® (more than 90 s) or HEPTEM® (more than 280 s) tests was prolonged, especially if CT prolongation did not respond to administration of PCC.

Platelet Concentrates. Before implementation of the POC-supported coagulation management, platelets were transfused as pooled (4–6 donors; $2.4–3.6 \times 10^{11}$ platelets per unit) or apheresis (single donor; $2–3 \times 10^{11}$ platelets per unit) platelet concentrates in case of clinically relevant diffuse bleeding and the presence of a low platelet concentration

(less than 100,000/μL) and/or suspected platelet dysfunction.[31] Following implementation of the POC management algorithm, platelet transfusion was performed in case of clinically relevant diffuse bleeding after heparin reversal and decreased clot firmness in the EXTEM® assay (A10 $\leq$ 40 mm) combined with a normal clot firmness in the FIBTEM® assay (A10 $>$ 10 mm) or with decreased platelet aggregation, as revealed by MEA (AUC-ASPItest® $<$ 200 AU x min; AUC-COLtest® $<$ 200; AUC-ADPtest® $<$ 300; or AUC-TRAPtest® $<$ 500).

Fibrinogen Concentrate. Before implementation of the POC-supported coagulation management, fibrinogen concentrate (Hemocomplettan®P; CSL Behring GmbH, Marburg, Germany) was used if diffuse bleeding did not stop following FFP and platelet transfusion, and if hypofibrinogenemia was suspected or definitely detected by conventional laboratory tests (Clauss method or derived fibrinogen assay). Following implementation of the POC management algorithm fibrinogen concentrate was administered as a first-line therapy in case of clinically relevant diffuse bleeding after heparin reversal and reduced clot firmness in both the EXTEM® (A10 $\leq$ 40 mm) and FIBTEM® assays (A10 $\leq$ 10 mm). Usually, 25 mg fibrinogen concentrate per kg body weight were administered in order to increase A10 in FIBTEM® by 4 mm, 37.5 mg per kg to increase A10 in FIBTEM® by 6 mm, 50 mg per kg to increase A10 in FIBTEM® by 8 mm, and 75 mg per kg to increase A10 in FIBTEM® by 12 mm.[19] If the bleeding still continued, further fibrinogen concentrate was administered for a target of an A10 $>$ 15 mm in the FIBTEM® and an A10 $>$ 50 mm in the EXTEM® assays. Fibrinogen concentrate is approved in Germany since 1985 for hereditary hypo-, dys-, and afibrinogenemia, and acquired hypofibrinogenemia, while cryoprecipitate is not in use.

Prothrombin Complex Concentrate. Before implementation of the POC-supported coagulation management, PCC (Beriplex®P/N; CSL Behring GmbH, or Octaplex®; Octapharma GmbH, Lagenfeld, Germany) was used if diffuse bleeding did not stop following FFP and platelet transfusion and deficiency of vitamin K-dependent coagulation factors was suspected (*e.g.*, because of pretreatment with oral anticoagulants) or when detected by conventional laboratory tests (prothrombin time/international normalized ratio). Following implementation of the POC algorithm, PCC was only administered in case of clinically relevant diffuse bleeding after heparin reversal in the absence of or after an already-treated fibrinogen deficiency and a prolonged CT in the EXTEM® (more than 90 s) or HEPTEM® (more than 280 s) assays. Usually, 20–25 U PCC per kg body weight were administered if CT in EXTEM® was longer than 90 s and 35–40 U PCC was administered if CT in EXTEM® was longer than 100 s in the presence of severe bleeding.[19] In case of ongoing diffuse bleeding, further PCC administration (20–25 U per kg) was considered if the CT in the EXTEM® assay did not decrease below 80 s. In contrast to the three-factor PCCs approved in the United States, four-factor PCCs used in Europe (such as Beriplex® and Octaplex®) contain balanced amounts of the coagulation factors II, VII, IX, and X, as well as protein C and S.[32–33] PCC is approved in Germany since 1996 for the prophylaxis and therapy of bleeding in patients with hereditary and acquired deficiency of vitamin K-dependent coagulation factors.

Antithrombin Concentrate. Before implementation of the POC-supported coagulation management, AT (Kybernin®P; CSL Behring GmbH, or Atenativ®; Octapharma GmbH) was used in patients who did not achieve an ACT more than 400 s after two additional injections of 50–100 U of heparin per kg body weight and almost routinely in patients receiving PCC administration. After implementation of the POC-supported coagulation management, a fixed combination of PCC and AT was abolished and AT was only used when target ACT values were not achieved by heparin alone.

Further Therapeutic Options. In case of ongoing diffuse bleeding despite optimization of preconditions of hemostasis, surgical hemostasis, and conventional hemostatic therapy, administration of DDAVP (Minirin® parentera; Ferring GmbH, Kiel, Germany), coagulation factor VIII/von Willebrand factor concentrate (Hemate®P; CSL Behring GmbH), FXIII (Fibrogammin®P; CSL Behring GmbH), or rFVIIa (NovoSeven®; Novo Nordisk A/S, Bagsværd, Denmark) could be considered. Later, these drugs were part of the implemented algorithm.

Principles of the POC-supported Coagulation Management Algorithm. POC testing and hemostatic therapy were only done in patients at high risk for bleeding or with clinically relevant diffuse bleeding after heparin reversal with protamine. According to our POC-supported coagulation management algorithm, hemostatic therapy was performed with the following prioritization, if indicated by POC measurements: 1. Optimization of hemostatic preconditions, 2. Reversal of residual heparin effects with protamine, 3. Fibrinogen substitution, 4. PCC administration, 5. FFP transfusion, 6. Platelet transfusion, 7. Factor XIII, and 8. rFVIIa administration as a rescue therapy. The specific treatment criteria are presented in figure 1. Further details of the principles of our POC-supported coagulation management have been described previously.[19,21]

Statistics

Data are presented as means ($\pm$SD), medians (25th/75th percentile), numbers, and percentages, as appropriate. Statistical calculations were performed with GraphPad Prism® Version 4.02 for Windows (GraphPad Software Inc., San Diego, CA). Normally distributed data (Kolmogorov–Smirnov test) were analyzed by the Student two-tailed *t* test for unpaired samples. Data which were not normally distributed were analyzed by the Mann–Whitney U-test. For analysis of frequencies, the X^2-test was performed. In all tests, an *a priori* α-error $P < 0.05$ was considered statistically significant.

To strengthen the evidence that differences in primary outcomes were not based on preexisting trends, we also compared the incidence of allogeneic blood transfusion in the

Table 1. Patient Demographics and Surgical Characteristics

	Before Implementation of Point-of-care-supported Coagulation Management (2004)	After Implementation of Point-of-care-supported Coagulation Management (2009)	*P* Value
Age (years)	64.4 ± 12.7	66.4 ± 12.9	<0.0001
Male/Female (n, %)	1,224/494 (71.2/28.8%)	1,441/706 (67.1/32.9%)	0.0065
ASA physical classification	3 [3/3]	3 [3/3]	0.2020
Phenprocumon (Marcumar) (n, %)	110/1,441 (7.6%)	217/1,582 (9.7%)	0.0410
Dual antiplatelet therapy (aspirin + Clopidogrel) (n, %)	39/1,441 (2.7%)	217/1,582 (13.7%)	<0.0001
Glycoprotein IIb/IIIa receptor inhibitors (Abciximab, Eptifibatide or Tirofiban) (n, %)	1/1,441 (0.07%)	1/1,582 (0.06%)	0.9470
Elective/emergency surgery (n, %)	1,589/129 (92.5/7.5%)	1,922/225 (89.5/10.5%)	0.0018
Annual cardiovascular surgeries in relation to total cardiovascular surgeries during 2004 to 2009 (n, %)	1,718/11,112	2,147/11,112	<0.0001
Coronary artery bypass graft surgery (n, %)	896/1,718 (52.2%)	832/2,147 (43.4%)	<0.0001
Aortic valve surgery, with or without ascending aortic replacement (n, %)	277/1,718 (16.1%)	383/2,147 (17.8%)	0.1722
Mitral valve surgery (n, %)	130/1,718 (7.6%)	132/2,147 (8.9%)	0.0931
Tricuspid valve surgery (n, %)	28/1,718 (1.6%)	40/2,147 (1.9%)	0.6708
Complex cardiac surgery (n, %)	143/1,718 (8.3%)	238/2,147 (11.1%)	0.005
Transplant surgery (heart or bilateral lung transplant) (n, %)	35/1,718 (2.0%)	33/2,147 (1.5%)	0.2927
Aortic surgery (Aortic dissections, type A and B, thoracic aortic aneurysms) (n, %)	43/1,718 (2.5%)	52/2,147 (2.4%)	0.9546
CPB time (min)	118 [95.5/149]	115 [89/151]	0.0183
Aortic cross-clamp time (min)	78 [61/96.5]	74 [56/96]	0.0049

Data are presented as numbers (%), means ± SD, or medians (25th/75th percentile).

ASA = American Society of Anesthesiologists; complex cardiac surgery = combined coronary artery bypass graft surgery and valve surgery or multi-valve surgery; CPB = cardiopulmonary bypass.

first and the second half of the year (2004) before implementation of POC-supported coagulation management.

For binary outcome variables, we calculated relative risks and 95% CI. The relative risks gives the number of times more likely (relative risks more than 1) or less likely (relative risks less than 1) an event is likely to happen in the cohort after implementation of the POC algorithm (2009) compared with the cohort before (2004).

Results

Between 2004 and 2009, 11,112 patients underwent surgery in our cardiovascular department. The patients' demographics and surgical characteristics of the assessed cohorts are summarized in table 1. Since initiation of POC measurements in 2005, 9,394 patients underwent surgery until 2009, and 13,160 thromboelastometric and 5,970 MEA measurements were performed during this period. Of note, POC measurements were only performed in patients at high risk for bleeding or in those with signs of clinically relevant diffuse bleeding after heparin reversal with protamine, with an average of eight ROTEM® and six MEA measurements in these patients, respectively. Thus, thromboelastometry was performed in approximately 17.5% and MEA in 10.6% of patients.

As depicted in table 1, the number of patients undergoing surgery increased (approx. 25%), as did their mean age, the proportion of female patients, patients on oral anticoagulants or with dual antiplatelet therapy, and emergency cases. Furthermore, part of coronary artery bypass graft surgery was replaced by a larger number of cases involving complex cardiac surgery (*e.g.*, combined coronary artery bypass graft and valve surgery or multivalve surgery). CPB and aortic cross-clamp times decreased by 3 and 4 min, respectively.

Within the year before implementation of POC-supported coagulation management (2004), the incidence of transfusion of any allogeneic blood product and PRBC markedly increased (49.3 *vs.* 55.8%; $P = 0.0064$ and 45.4% *vs.* 54.1%; $P = 0.0004$, respectively) from the first to the second half of the year. In the same period, the incidence of platelet transfusion moderately increased (8.7 *vs.* 11.5%; $P = 0.0485$) and the incidence of FFP transfusion slightly decreased (21.3 *vs.* 17.4%; $P = 0.0385$), whereas the incidence of massive transfusion did not change (2.31 *vs.* 2.7%; $P = 0.5994$). Thus, there was no prevailing trend in 2004 that should have biased data derived in 2009.

Despite the above-mentioned shift in the surgical spectrum and the trend to a higher incidence of allogeneic

Table 2. Primary and Secondary Binary Endpoints: Transfusion and Outcome

	Before Implementation of Point-of-care-supported Coagulation Management (2004)	After Implementation of Point-of-care-supported Coagulation Management (2009)	*P* Value	Relative Risk of Cohort 2009 Compared with Cohort 2004
Primary binary endpoints: Incidence of transfusion				
Any allogeneic blood product transfusion (n, %)	902/1,718 (52.5%)	906/2,147 (42.2%)	<0.0001	0.804 (0.752–0.859)
PRBC transfusion (n, %)	854/1,718 (49.7%)	868/2,147 (40.4%)	<0.0001	0.813 (0.758–0.872)
FFP transfusion (n, %)	333/1,718 (19.4%)	24/2,147 (1.1%)	<0.0001	0.058 (0.038–0.087)
Platelet transfusion (n, %)	173/1,718 (10.1%)	280/2,147 (13%)	0.0041	1.295 (1.083–1.548)
Massive transfusion (≥10 units of PRBC) (n, %)	43/1,718 (2.50%)	27/2,147 (1.26%)	0.0057	0.502 (0.312–0.81)
Secondary binary endpoints: Factor concentrates, adverse events, and mortality				
Fibrinogen concentrate administration (n, %)	64/1,718 (3.73%)	215/2,147 (10.01%)	<0.0001	2.688 (2.048–3.528)
PCC administration (n, %)	76/1,718 (4.42%)	191/2,147 (8.9%)	<0.0001	2.011 (1.553–2.603)
AT administration (n, %)	148/1,718 (8.61%)	170/2,147 (7.92%)	0.4689	0.919 (0.744–1.135)
FXIII administration (n, %)	10/1,718 (0.58%)	0/2,147 (0%)	0.0013	0
rFVIIa administration (n, %)	1/1,718 (0.06%)	0/2,147 (0%)	0.9111	0
Reexploration rate (unscheduled within 48 h) (n, %)	72/1,718 (4.19%)	48/2,147 (2.24%)	0.0007	0.533 (0.372–0.764)
Venous thrombosis (n, %)	14/1,441 (0.97%)	9/1,582 (0.57%)	0.2032	0.586 (0.254–1.349)
Pulmonary embolism (n, %)	5/1,441 (0.35%)	1/1,582 (0.57%)	0.08	0.182 (0.021–1.558)
Other arterial embolism (n, %)	3/1,441 (0.35%)	2/1,582 (0.13%)	0.5806	0.607 (0.102–3.629)
Stroke (n, %)	12/1,441 (0.83%)	7/1,582 (0.44%)	0.1751	0.531 (0.21–1.346)
Coronary bypass graft occlusion (n, %)	12/1,441 (0.83%)	9/1,582 (0.57%)	0.3830	0.683 (0.289–1.617)
Composite thrombotic/ thromboembolic adverse events (n, %)	46/1,441 (3.19%)	28/1,582 (1.77%)	0.0115	0.554 (0.348–0.882)
Renal replacement therapy (n, %)	122/1,441 (8.47%)	127/1,582 (8.03%)	0.6614	0.948 (0.747–1.203)
In-hospital mortality (n, %)	90/1,718 (5.24%)	112/2,147 (5.22%)	0.9756	0.996 (0.760–1.305)

Data are presented as numbers (%), relative risk (95% CI of relative risk).

AT = antithrombin concentrate; FFP = fresh frozen plasma; FXIII = factor XIII concentrate; PCC = prothrombin complex concentrate; platelet = platelet concentrate; PRBC = packed red blood cells; rFVIIa = recombinant activated factor VII.

blood transfusion within 2004, the incidence of intraoperative transfusion (table 2 and fig. 2A) as well as transfusion requirements (fig. 2B) significantly decreased after implementation of POC-supported coagulation management. Specifically, the incidence of transfusion of any allogeneic blood product (52.5 *vs.* 42.2%; $P < 0.0001$), of PRBC (49.7 *vs.* 40.4%; $P < 0.0001$), and in particular of FFP (19.4 *vs.* 1.1%; $P < 0.0001$) markedly decreased, whereas the incidence of platelet transfusion significantly increased, albeit moderately (10.1 *vs.* 13.0%; $P = 0.0041$). Furthermore, the overall amount of transfusion requirements decreased (fig. 2B), as did the median number (25th/75th percentile) of transfused units per patient of PRBC (3,276 *vs.* 2,959 units per year and 0 U per patient [0/3] *vs.* 0 U per patient [0/2]; $P < 0.0001$) and of FFP (1,986 *vs.* 102 units per year and 0 U per patient [0/0] *vs.* 0 U per patient [0/0]; $P < 0.0001$). In contrast, the increase in the overall (fig. 2B) and the median number of transfused units of platelets per patient (336 *vs.* 581 units per year and 0 U per patient [0/0] *vs.* 0 U per patient [0/0]; $P = 0.085$, respectively) did not attain statistical significance.

Furthermore, the median of transfused units of PRBC in transfused patients also decreased significantly, whereas the median of transfused units of platelet concentrates in transfused patients increased significantly (table 3). However, the median of transfused units of FFP in transfused patients did not change (table 3).

Data describing the use of specific coagulation factor concentrates in the two cohorts are presented in table 2 and figure 3A and B. The incidence of administration both of fibrinogen concentrate (3.73 *vs.* 10.01%; $P < 0.0001$) and of PCC (4.42 *vs.* 8.9%; $P < 0.0001$) increased substantially, whereas the incidence of therapy with factor XIII concentrate (0.58 *vs.* zero; $P = 0.0013$) decreased. The incidence of therapy with AT concentrate did not change and only a single patient received therapy with rFVIIa in 2004, whereas no case of off-label use of rFVIIa was observed after implementation of the algo-

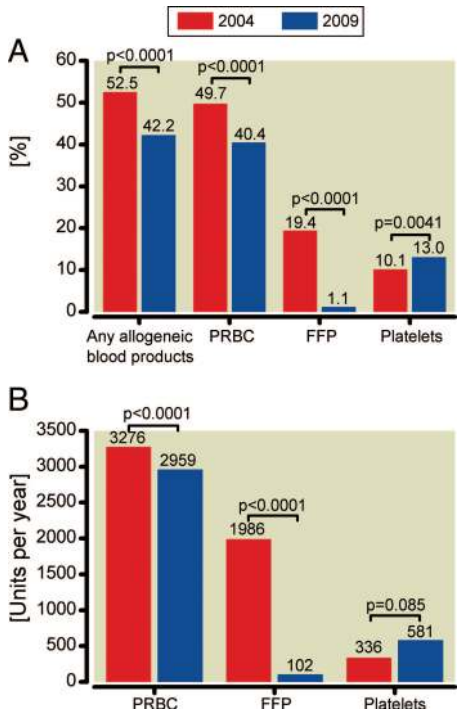


Fig. 2. Incidence of intraoperative transfusion of allogenic blood products (*A*) and total intraoperative transfusion requirements per year (*B*) in patients undergoing surgery in the cardiovascular department before (2004) and after (2009) implementation of the point-of-care-supported coagulation management algorithm. FFP = fresh frozen plasma, platelets = pooled or apheresis platelet concentrates, PRBC = packed red blood cells.

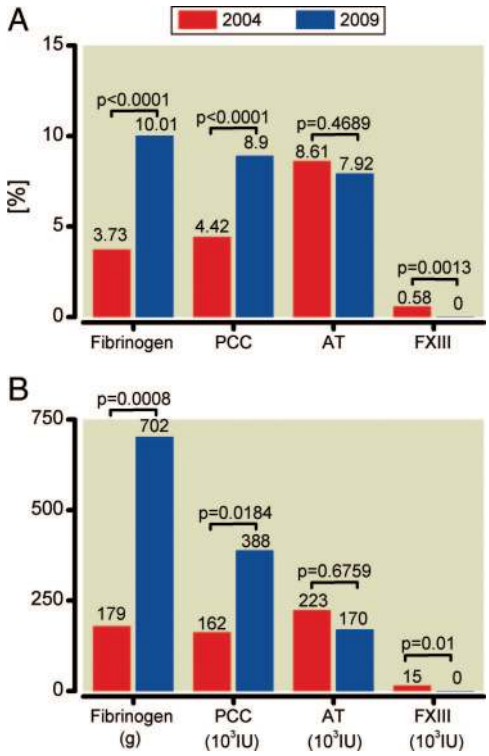


Fig. 3. Incidence of intraoperative therapy with coagulation factor concentrates (*A*) and total intraoperative requirements per year for coagulation factor concentrates (*B*) in all patients undergoing surgery in the cardiovascular department before (2004) and after (2009) implementation of the point-of-care supported coagulation management algorithm. AT = antithrombin concentrate, fibrinogen = fibrinogen concentrate, FXIII = factor XIII concentrate, IU = international unit, PCC = prothrombin complex concentrate.

rithm. The overall (fig. 3B) and the median requirements for fibrinogen concentrate (179 g *vs.* 702 g per year and 0 g [0/0] *vs.* 0 g [0/0]; $P = 0.0008$) and for PCC (162×10^3 U *vs.* 388×10^3 and 0 U [0/0] *vs.* 0 U [0/0]; $P = 0.0184$) also increased significantly. On the other hand, the overall (fig. 3B) and median requirements for factor XIII concentrate (15×10^3 IU *vs.* 0 U and 0 U [0/0] *vs.* 0 U [0/0]; $P = 0.01$) decreased significantly, whereas the administered amount (fig. 3B) of AT concentrate and its median use (223×10^3 U *vs.* 170×10^3 U and 0 U [0/0] *vs.* 0 [0/0]; $P = 0.6759$) did not change. In contrast, the median dose of AT concentrate in treated patients (table 4) decreased significantly. The median dose of fibrinogen concentrate and of PCC in treated patients did not change.

The incidence of massive transfusion (≥ 10 units of PRBC transfused intraoperatively) (2.5 *vs.* 1.26%; $P =$

Table 3. Transfusion Requirements in Transfused Patients before and after Implementation of the Point-of-care-supported Coagulation Management Algorithm

	Before Implementation of Point-of-care-supported Coagulation Management (2004)	After Implementation of Point-of-care-supported Coagulation Management (2009)	*P* Value
PRBCs transfused (units/transfused patients; median [25^{th}/75^{th} percentile])	3,276/854; 3 (2/4)	2,959/868; 2 (2/4)	0.0049
FFP transfused (units/transfused patients; median [25^{th}/75^{th} percentile])	1,986/333; 4 (4/6)	102/24; 4 (2/5)	0.1325
Platelets transfused (units/transfused patients; median [25^{th}/75^{th} percentile])	336/173; 2 (1/2)	581/280; 2 (2/2)	0.0019

Data are presented as numbers (transfused units per year/transfused patients per year) and median (25th/75th percentile).
FFP = fresh frozen plasma; platelets = pooled or apheresis platelet concentrates; PRBC = packed red blood cells.

Table 4. Administration of Coagulation Factor Concentrates in Treated Patients before and after Implementation of the Point-of-care Coagulation Management Algorithm

	Before Implementation of Point-of-care-supported Coagulation Management (2004)	After Implementation of Point-of-care-supported Coagulation Management (2009)	*P* Value
Fibrinogen administered (g/treated patients; median [25th/75th percentile])	179/64; 2 (2/3)	702/215; 3 (2/4)	0.0528
PCC administered (10^3 U/treated patients; median [25th/75th percentile])	162/76; 2 (1.5/3)	388/191; 2 (1.5/2.5)	0.352
AT administered (10^3 U/treated patients; median [25th/75th percentile])	223/148; 1 (1/2)	170/172; 1 (1/1)	0.0001
FXIII administered (10^3 U/treated patients; median [25th/75th percentile])	15/10; 1.25 (1.25/1.25)	No treated patient	—
rFVIIa administered (mg/treated patients; median [25th/75th percentile])	4.8/1; 4.8 (4.8/4.8)	No treated patient	—

Data are presented as numbers (administered coagulation factor concentrates per year/treated patients per year) and median (25th/75th percentile).

AT = antithrombin concentrate; FXIII = factor XIII concentrate; U = international unit; PCC = prothrombin complex concentrate; rFVIIa = activated recombinant factor VII.

0.0057) and of reexploration (4.19 *vs.* 2.24%; $P = 0.0007$) also decreased significantly (table 2 and fig. 4).

The incidence of composite thrombotic/thromboembolic adverse events decreased (3.19 *vs.* 1.77%; $P = 0.0115$), whereas the incidence of renal replacement therapy did not change (table 2). In hospital-mortality also did not change (5.24 *vs.* 5.22%; $P = 0.98$), despite a significant increase in the patients' age, proportion of females, emergency cases, and of complex cardiac surgery. Considering these latter variables predicted an increase in mortality by 0.65% in the 2009 cohort compared with the 2004 cohort, according to the formulae of the logistic EuroSCORE.[34–35]

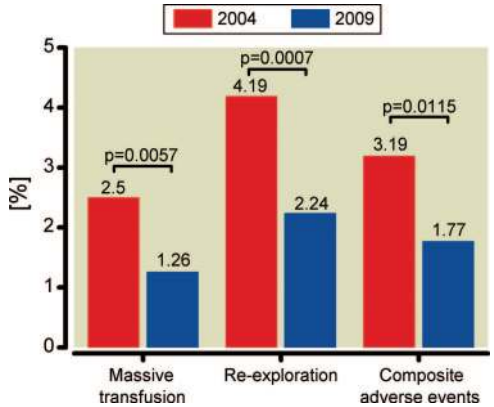


Fig. 4. Incidence of intraoperative massive transfusion (≥10 units of packed red blood cells), unplanned reexploration surgery within 48 h following initial surgery, and composite thrombotic/thromboembolic adverse events (venous thrombosis, pulmonary embolism, other arterial embolism, stroke, and coronary bypass graft occlusion) in patients undergoing cardiovascular surgery before (2004) and after (2009) implementation of a point-of-care-supported coagulation management algorithm.

Overall costs for allogeneic blood products and coagulation factor concentrates per patient decreased by 6.5%, corresponding to a cost-saving of about 50,000 euros per year (table 5).

Discussion

The data of this retrospective, cohort study including 3,865 cardiovascular patients demonstrate that implementation of a coagulation management algorithm based on first-line therapy with specific coagulation factor concentrates combined with POC testing was associated with significantly and substantially decreased allogeneic blood transfusion incidence (primary endpoints) and requirements, as well as with decreased incidence of thrombotic/thromboembolic adverse events.

This was not a randomized prospective trial with and without the use of specific coagulation factor concentrates or POC testing; instead, it involved a complex change in practice patterns. Nevertheless, the decrease in transfusion incidence and requirements in a more complex patient population supports a beneficial effect of the use of POC testing and the first-line therapy with coagulation factor concentrates, guided by the implemented coagulation management algorithm.[34–38] Furthermore, this observation was made despite aprotinin being replaced by tranexamic acid between the two study periods. This might be clinically relevant, since in a recent Cochrane Database analysis, data from head-to-head trials suggested an advantage of aprotinin over the lysine analogues tranexamic acid and ε aminocaproic acid in terms of decreased perioperative blood loss and decreased receipt of allogeneic blood transfusion.[39] However, these head-to-head comparisons showed a lower risk of death with lysine analogues when compared with aprotinin.

We consider an important element of our approach that we preferentially use hemostatic tests (thromboelastometry

Table 5. Costs for Transfusion and Coagulation Therapy

	Before Implementation of Point-of-care-supported Coagulation Management (2004)	After Implementation of Point-of-care-supported Coagulation Management (2009)	Difference (%)
Mean costs for allogeneic blood products	286.12	187.89	−34.3%
Mean costs for coagulation factor concentrates	71.67	146.66	104.6%
Mean overall costs for allogeneic blood products and coagulation factor concentrates	357.79	334.56	−6.5%

Data are presented as mean costs per patient in euros.

and MEA), whose results are available within 10–15 min after blood sampling. In contrast, results of thrombelastography® (TEG®; Hemonetics Corp., Braintree, MA) and TEG Platelet Mapping® are available after 30–40 min.[40–41] Furthermore, in a recent multicenter study, the median turnaround time for conventional coagulation tests has been shown to be 88 min. with a range from 29 to 235 min.[42] Hence, based on this approach, the clinician can make therapeutic decisions earlier than by using other technologies. In addition, the use of complementary assays with different activators and additives enables a more precise specification of the hemostatic disorder prevailing. However, implementation of our POC-supported coagulation management algorithm did not only change our diagnostic approach to the management of bleeding. Rather the timely availability of thromboelastometric and MEA results also enables an early and specific first-line therapy with fibrinogen concentrate and PCC (nonallogeneic blood products) with a "bleed-to-treat" time of 15–20 min. Thus, timely POC testing combined with early-targeted treatment with specific coagulation factor concentrates should be implemented together for ideal use.

The authors are aware that this kind of coagulation management is not standard practice in the United States. The standard practice in the United States resembles much more our coagulation management in 2004 with first-line therapy with FFP and/or platelets. However, first-line therapy with fibrinogen concentrate and/or PCC supplanted the use of FFP in our study, an approach also suggested by Spalding *et al.*[17] and Schöchl *et al.*[43] This is likely to be a main mechanism in decreasing the incidence and overall amount of FFP transfusion by about 95%.

The rationale for the use of fibrinogen concentrate and PCC can be summarized as follows: Fibrinogen is the coagulation factor that decreases first and below a critical concentration during massive hemorrhage, and fibrinogen concentration has been shown to best predict perioperative bleeding in cardiac surgery.[24,36,44–47] Furthermore, fibrinogen concentrate has been shown to be effective in decreasing blood loss and transfusion requirements in cardiac surgery without an increased incidence of thromboembolic events.[48–50]

In addition, activity of coagulation factors II, VII, and X decreases significantly within 2 to 24 h after cardiac surgery, whereas factor VIII activity increases to 125% and 193% when compared with baseline at the respective times.[46] Since PCC does not contain factor VIII and FFP does, decreased thrombin generation can be restored more specifically by PCC administration without the need for factor VIII administration, both for reversal of oral anticoagulants and in most settings of severe hemorrhage.[32,33,43,44,51–57] Furthermore, the incidence of thromboembolic events after calculated administration of well balanced four-factor PCCs seems to be very low.[58] Here, calculation of the required PCC dosage can be based on the Quick value, international normalized ratio, or CT in EXTEM®.[19,21,55,57]

We are also aware that our approach using fibrinogen concentrate and/or four-factor PCCs as an early, first-line therapy differs from clinical practice in the United States, particularly because only three-factor PCCs are approved in the United States and neither is approved by the Food and Drug Administration for this indication. Fibrinogen concentrate was approved by the Food and Drug Administration in 2009 only for hereditary fibrinogen deficiency.

Notably, early, quantitatively calculated, first-line therapy with fibrinogen concentrate and/or PCCs along with POC-guided management was not only associated with a decreased incidence of allogeneic blood transfusion, but also with a decreased incidence of composite thrombotic/thromboembolic adverse events. However, our data need confirmation by prospective randomized trials.

Compared with other studies[14–18] implementing various POC-supported coagulation management algorithms, the observed decrease in transfusion requirement is considerably greater, particularly with respect to FFP transfusion. Whereas Shore-Lesserson *et al.*,[14] Ak *et al.*,[15] and Anderson *et al.*[16] reported a decrease in the incidence of FFP transfusion from a baseline of 17–28% to 7.5–17% after a change in their coagulation management, we started with an incidence of FFP transfusion of 19.4% and were able to decrease this to 1.1% after implementation of our coagulation management algorithm, which was modified following our experience in liver transplant surgery.[19–21] These quantitatively different results may also be due to the following aspects. In contrast to Anderson *et al.*,[16] we started the use of our POC-supported coagulation management already during surgery and did not wait until the patients' admission to the intensive care unit. Furthermore, we used a combination of thromboelastometry

and MEA for POC measurements so as to assess platelet function. In fact, only Westbrook *et al.*[18] used a method for platelet function analysis, Platelet Mapping®, in addition to thromboelastography. The inclusion of MEA in our POC-supported algorithm allowed for timely and specific detection of platelet dysfunction. Thus, although the incidence of dual antiplatelet therapy increased fivefold from 2.7% to 13.7%, the incidence of platelet transfusion increased only from 10.1% to 13.0%. This is noteworthy, since in our study transfusion requirements for PRBC decreased, whereas transfusion requirements for PRBC increased in most studies dealing with perioperative bleeding in patients with dual antiplatelet therapy.[59] In addition, the replacement of aprotinin by tranexamic acid would have been expected to be associated with increased transfusion requirements.[39]

There are several limitations of our study. First, our study is retrospective and reflects only the experience of a single center. Second, we cannot clearly define the impact different parts of our POC-supported coagulation management strategy have in contributing to the decreased transfusion requirements observed. On the one hand, several authors have noted that even the implementation of any transfusion algorithm alone can result in decreased transfusion requirements, presumably by resulting in more educated physicians.[60–62] On the other hand, the results of our study suggest that an algorithm based on POC testing for overall coagulation and platelet function in combination with a first-line therapy with coagulation factor concentrates, rather than allogeneic blood products, is associated with a distinct decrease in transfusion requirements and a decrease in thrombotic/thromboembolic adverse events, as well. These results have to be confirmed by prospective randomized trials.

Furthermore, there are several potential confounders unaccounted for in our study, such as potential improvement of surgical techniques or training, as well as improved clinical competence in hemostasis management of the anesthesiologists. With regard to surgery, there was no obvious change in surgical techniques or in the qualification of the teams involved. Accordingly, CPB and aortic cross-clamp times decreased by only 3 min and 4 min, respectively. It is unlikely that this change can explain the decrease in transfusion requirements and adverse events observed.

Furthermore, the decreased incidence of allogeneic blood transfusion after implementation of POC-supported coagulation management cannot be explained by an preexisting trend of decreased blood transfusion requirements, because within the year before implementation the incidence of transfusion of any allogeneic blood product and PRBC markedly increased.

In conclusion, implementation of a coagulation management algorithm based on early, first-line therapy with fibrinogen concentrate and/or PCCs combined with POC testing using thromboelastometry and impedance aggregometry was associated with a marked decrease in the incidence of allogeneic blood transfusion and of transfusion requirements when compared with temporal controls. This was despite a patient population that was sicker and more likely to bleed. Furthermore, the incidence of massive transfusion, reexploration, and of thrombotic/thromboembolic adverse events also decreased.

References

1. Marik PE, Corwin HL: Efficacy of red blood cell transfusion in the critically ill: A systematic review of the literature. Crit Care Med 2008; 36:2667–74
2. Aronson D, Dann EJ, Bonstein L, Blich M, Kapeliovich M, Beyar R, Markiewicz W, Hammerman H: Impact of red blood cell transfusion on clinical outcomes in patients with acute myocardial infarction. Am J Cardiol 2008; 102:115–9
3. Murphy GJ, Reeves BC, Rogers CA, Rizvi SI, Culliford L, Angelini GD: Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation 2007; 116:2544–52
4. Banbury MK, Brizzio ME, Rajeswaran J, Lytle BW, Blackstone EH: Transfusion increases the risk of postoperative infection after cardiovascular surgery. J Am Coll Surg 2006; 202:131–8
5. Dara SI, Rana R, Afessa B, Moore SB, Gajic O: Fresh frozen plasma transfusion in critically ill medical patients with coagulopathy. Crit Care Med 2005; 33:2667–71
6. Khan H, Belsher J, Yilmaz M, Afessa B, Winters JL, Moore SB, Hubmayr RD, Gajic O: Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. Chest 2007; 131:1308–14
7. Pereboom IT, de Boer MT, Haagsma EB, Hendriks HG, Lisman T, Porte RJ: Platelet transfusion during liver transplantation is associated with increased postoperative mortality due to acute lung injury. Anesth Analg 2009; 108:1083–91
8. Renaudier P, Rebibo D, Waller C, Schlanger S, Vo Mai MP, Ounnoughene N, Breton P, Cheze S, Girard A, Hauser L, Legras JF, Saillol A, Willaert B, Caldani C: Pulmonary complications of transfusion (TACO-TRALI). Transfus Clin Biol 2009; 16:218–32
9. Sarani B, Dunkman WJ, Dean L, Sonnad S, Rohrbach J, Gracias VH: Transfusion of fresh frozen plasma in critically ill surgical patients is associated with an increased risk of infection. Crit Care Med 2008; 36:1114–8
10. Shanwell A, Andersson TM, Rostgaard K, Edgren G, Hjalgrim H, Norda R, Melbye M, Nydrén O, Reilly M: Post-transfusion mortality among recipients of ABO-compatible but non-identical plasma. Vox Sang 2009; 96:316–23
11. Sørensen B, Bevan D: A critical evaluation of cryoprecipitate for replacement of fibrinogen. Br J Haematol 2010; 149:834–43
12. Spiess BD, Royston D, Levy JH, Fitch J, Dietrich W, Body S, Murkin J, Nadel A: Platelet transfusions during coronary artery bypass graft surgery are associated with serious adverse outcomes. Transfusion 2004; 44:1143–8
13. Stanworth SJ: The evidence-based use of FFP and cryoprecipitate for abnormalities of coagulation tests and clinical coagulopathy. Hematology Am Soc Hematol Educ Program 2007; 179–86
14. Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin MA: Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. Anesth Analg 1999; 88:312–9
15. Ak K, Isbir CS, Tetik S, Atalan N, Tekeli A, Aljodi M, Civelek A, Arsan S: Thromboelastography-based transfusion algorithm reduces blood product use after elective CABG: A prospective randomized study. J Card Surg 2009; 24:404–10
16. Anderson L, Quasim I, Soutar R, Steven M, Macfie A, Korte W: An audit of red cell and blood product use after the institution of thromboelastometry in a cardiac intensive care unit. Transfus Med 2006; 1:31–9
17. Spalding GJ, Hartrumpf M, Sierig T, Oesberg N, Kirschke CG, Albes JM: Cost reduction of perioperative coagulation man-

agement in cardiac surgery: Value of "bedside" thrombelastography (ROTEM). Eur J Cardiothorac Surg 2007; 31:1052–7

18. Westbrook AJ, Olsen J, Bailey M, Bates J, Scully M, Salamonsen RF: Protocol based on thromboelastograph (TEG) outperforms physician preference using laboratory coagulation tests to guide blood replacement during and after cardiac surgery: A pilot study. Heart Lung Circ 2009; 18:277–88
19. Görlinger K: Coagulation management during liver transplantation. Hämostaseologie 2006; 26(3 Suppl 1):S64–76
20. Goerlinger K, Dirkmann D, Hanke A, Dusse F, Hartmann M: ROTEM®-based algorithm for point-of-care coagulation management in visceral surgery and liver transplantation: Experience of eight years and 829 LTX. Liver Tranplant 2008; 14(Suppl 1):S203–4
21. Görlinger K, Jambor C, Hanke AA, Dirkmann D, Adamzik M, Hartmann M, Rahe-Meyer N: Perioperative coagulation management and control of platelet transfusion by point-of-care platelet function analysis. Transfus Med Hemother 2007; 34:396–411
22. Herbstreit F, Winter EM, Peters J, Hartmann M: Monitoring of haemostasis in liver transplantation: Comparison of laboratory based and point of care tests. Anaesthesia 2010; 65:44–9
23. Hartert H: Blutgerinnungsstudien mit der Thrombelastographie, einem neuen Untersuchungsverfahren. Klin Wochenschr 1948; 26:577–83
24. Reinhöfer M, Brauer M, Franke U, Barz D, Marx G, Lösche W: The value of rotation thromboelastometry to monitor disturbed perioperative haemostasis and bleeding risk in patients with cardiopulmonary bypass. Blood Coagul Fibrinolysis 2008; 19:212–9
25. Kozek-Langenecker SA: Perioperative coagulation monitoring. Best Pract Res Clin Anaesthesiol 2010; 24:27–40
26. Velik-Salchner C, Maier S, Innerhofer P, Kolbitsch C, Streif W, Mittermayr M, Praxmarer M, Fries D: An assessment of cardiopulmonary bypass-induced changes in platelet function using whole blood and classical light transmission aggregometry: The results of a pilot study. Anesth Analg 2009; 108:1747–54
27. Ferreiro JL, Sibbing D, Angiolillo DJ: Platelet function testing and risk of bleeding complications. Thromb Haemost 2010; 103:1128–35
28. Rahe-Meyer N, Winterhalter M, Boden A, Froemke C, Piepenbrock S, Calatzis A, Solomon C: Platelet concentrates transfusion in cardiac surgery and platelet function assessment by multiple electrode aggregometry. Acta Anaesthesiol Scand 2009; 53:168–75
29. Sibbing D, Braun S, Morath T, Mehilli J, Vogt W, Schömig A, Kastrati A, von Beckerath N: Platelet reactivity after clopidogrel treatment assessed with point-of-care analysis and early drug-eluting stent thrombosis. J Am Coll Cardiol 2009; 53:849–56
30. Solomon C, Hartmann J, Osthaus A, Schöchl H, Raymondos K, Koppert W, Rahe-Meyer N: Platelet concentrates transfusion in cardiac surgery in relation to preoperative point-of-care assessment of platelet adhesion and aggregation. Platelets 2010; 21:221–8
31. Greinacher A, Kiefel V, Klüter H, Kroll H, Pötzsch B, Riess H: Recommendations for platelet transfusion by the Joint Thrombocyte Working Party of the German Societies of Transfusion Medicine and Immunohaematology (DGTI), Thrombosis and Haemostasis Research (GTH), and Haematology and Oncology (DGHO). Transfus Med Hemother 2006; 33:528–43
32. Holland L, Warkentin TE, Refaai M, Crowther MA, Johnston MA, Sarode R: Suboptimal effect of a three-factor prothrombin complex concentrate (Profilnine-SD) in correcting supratherapeutic international normalized ratio due to warfarin overdose. Transfusion 2009; 49:1171–7
33. Kalina U, Bickhard H, Schulte S: Biochemical comparison of seven commercially available prothrombin complex concentrates. Int J Clin Pract 2008; 62:1614–22
34. Nashef SAM, Roques F, Hammill BG, Peterson ED, Michel P, Grover FL, Wyse RKH, Ferguson TB: Validation of European system for cardiac operative risk evaluation (EuroSCORE) in North American cardiac surgery. Eur J Cardiothor Surg 2002; 22:101–5
35. Roques F, Michel P, Goldstone AR, Nashef SAM: The locistic EuroSCORE. Eur Heart J 2003; 24:1–2
36. Karlsson M, Ternström L, Hyllner M, Baghaei F, Nilsson S, Jeppsson A: Plasma fibrinogen level, bleeding, and transfusion after on-pump coronary artery bypass grafting surgery: A prospective observational study. Transfusion 2008; 48:2152–8
37. Shehata N, Naglie G, Alghamdi AA, Callum J, Mazer CD, Hebert P, Streiner D, Wilson K: Risk factors for red cell transfusion in adults undergoing coronary artery bypass surgery: A systematic review. Vox Sang 2007; 93:1–11
38. van Straten AH, Kats S, Bekker MW, Verstappen F, ter Woorst JF, van Zundert AJ, Soliman Hamad MA: Risk factors for red blood cell transfusion after coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2010; 24:413–7
39. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, Ker K: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2011; (3):CD001886
40. Jeger V, Zimmermann H, Exadaktylos AK: Can RapidTEG accelerate the search for coagulopathies in the patient with multiple injuries? J Trauma 2009; 66:1253–7
41. Scharbert G, Auer A, Kozek-Langenecker S: Evaluation of the Platelet Mapping Assay on rotational thromboelastometry ROTEM. Platelets 2009; 20:125–30
42. Toulon P, Ozier Y, Ankri A, Fléron MH, Leroux G, Samama CM: Point-of-care *versus* central laboratory coagulation testing during haemorrhagic surgery. A multicenter study. Thromb Haemost 2009; 101:394–401
43. Schöchl H, Nienaber U, Hofer G, Voelckel W, Jambor C, Scharbert G, Kozek-Langenecker S, Solomon C: Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. Crit Care 2010; 14:R55
44. Bolliger D, Görlinger K, Tanaka KA: Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. ANESTHESIOLOGY 2010; 113:1205–19
45. Fenger-Eriksen C, Ingerslev J, Sørensen B: Fibrinogen concentrate–a potential universal hemostatic agent. Expert Opin Biol Ther 2009; 9:1325–33
46. Ternström L, Radulovic V, Karlsson M, Baghaei F, Hyllner M, Bylock A, Hansson KM, Jeppsson A: Plasma activity of individual coagulation factors, hemodilution and blood loss after cardiac surgery: A prospective observational study. Thromb Res 2010; 126:e128–33
47. Ucar HI, Oc M, Tok M, Dogan OF, Oc B, Aydin A, Farsak B, Guvener M, Yorgancioglu AC, Dogan R, Demircin M, Pasaoglu I: Preoperative fibrinogen levels as a predictor of postoperative bleeding after open heart surgery. Heart Surg Forum 2007; 10:E392–6
48. Karlsson M, Ternström L, Hyllner M, Baghaei F, Flinck A, Skrtic S, Jeppsson A: Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. Thromb Haemost 2009; 102:137–44
49. Rahe-Meyer N, Pichlmaier M, Haverich A, Solomon C, Winterhalter M, Piepenbrock S, Tanaka KA: Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: A pilot study. Br J Anaesth 2009; 102:785–92
50. Rahe-Meyer N, Solomon C, Winterhalter M, Piepenbrock S, Tanaka K, Haverich A, Pichlmaier M: Thromboelastometry-

guided administration of fibrinogen concentrate for the treatment of excessive intraoperative bleeding in thoracoabdominal aortic aneurysm surgery. J Thorac Cardiovasc Surg 2009; 138:694–702

51. Bruce D, Nokes TJ: Prothrombin complex concentrate (Beriplex P/N) in severe bleeding: Experience in a large tertiary hospital. Crit Care 2008; 12:R105
52. Lorenz R, Kienast J, Otto U, Egger K, Kiehl M, Schreiter D, Kwasny H, Haertel S, Barthels M: Efficacy and safety of a prothrombin complex concentrate with two virus-inactivation steps in patients with severe liver damage. Eur J Gastroenterol Hepatol 2003; 15:15–20
53. Lorenz R, Kienast J, Otto U, Kiehl M, Schreiter D, Haertel S, Barthels M: Successful emergency reversal of phenprocoumon anticoagulation with prothrombin complex concentrate: A prospective clinical study. Blood Coagul Fibrinolysis 2007; 18:565–70
54. Pabinger-Fasching I: Warfarin-reversal: Results of a phase III study with pasteurised, nanofiltrated prothrombin complex concentrate. Thromb Res 2008; 122(Suppl 2):S19–22
55. Scherer R, Gille A, Erhard J, Paar D, Kox WJ: The effect of substitution with AT III- and PPSB-concentrates in patients with terminal liver insufficiency. Anaesthesist 1994; 43: 178–82
56. Schick KS, Fertmann JM, Jauch KW, Hoffmann JN: Prothrombin complex concentrate in surgical patients: Retrospective evaluation of vitamin K antagonist reversal and treatment of severe bleeding. Crit Care 2009; 13:R191
57. Vigué B, Ract C, Tremey B, Engrand N, Leblanc PE, Decaux A, Martin L, Benhamou D: Ultra-rapid management of oral anticoagulant therapy-related surgical intracranial hemorrhage. Intensive Care Med 2007; 33:721–5
58. Hanke AA, Rodewald L, Joch C, Görlinger K: Efficacy and long-term safety of a pasteurised nanofiltrated prothrombin complex concentrate (Beriplex P/N). J Thromb Haemost 2009; 7(Suppl 2):863
59. Levy JH, Tanaka KA: The anticoagulated patient: Strategies for effective blood loss management. Surgery 2007; 142(4 Suppl):S71–7
60. Despotis G, Avidan M, Eby C: Prediction and management of bleeding in cardiac surgery. J Thromb Haemost 2009; 7(Suppl 1):111–7
61. Enriquez LJ, Shore-Lesserson L: Point-of-care coagulation testing and transfusion algorithms. Br J Anaesth 2009; 103(Suppl 1):i14–22
62. Nuttall GA, Oliver WC, Santrach PJ, Bryant S, Dearani JA, Schaff HV, Ereth MH: Efficacy of a simple intraoperative transfusion algorithm for nonerythrocyte component utilization after cardiopulmonary bypass. ANESTHESIOLOGY 2001; 94: 773–81