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

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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. 11.1%; 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 × 10⁸ vs. 388 × 10⁸ 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
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 cardiovascular 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 transplantation19–20 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/m². 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+; Hemotec 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-
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. Extrinsicly 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 APTEM®. 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, Ca²⁺ = ionized calcium, CLI = clot lysis index, COL = COLtest®, CPB = cardiopulmonary bypass, CT = clotting time, DDAPV = 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, rFVIIIa = activated recombinant factor VII, TC = core temperature, TRAP = TRAPtest®.

1) 10 min after each specific intervention a re-examination of ROTEM® and/or Multiplate® analysis is recommended in order to control the effect of the intervention.
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 hyperfibrinolysis. 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 with 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 × 10^6 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 × 10^11 platelets per unit) or apheresis (single donor; 2–3 × 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. 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 ≤ 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-APSitest < 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 ≤ 40 mm) and FIBTEM® assays (A10 ≤ 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. 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. 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. 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 (±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 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 X²-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...
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 give 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 marked 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 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 1. Patient Demographics and Surgical Characteristics

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<tr>
<td>Age (years)</td>
<td>64.4 ± 12.7</td>
<td>64.4 ± 12.9</td>
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<tr>
<td>Male/Female (n, %)</td>
<td>1,224/494 (71.2/28.8%)</td>
<td>1,441/706 (67.1/32.9%)</td>
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<tr>
<td>ASA physical classification 3</td>
<td>3 [3/3]</td>
<td>3 [3/3]</td>
</tr>
<tr>
<td>Phenprocumon (Marcumar) (n, %)</td>
<td>110/1,441 (7.6%)</td>
<td>217/1,582 (9.7%)</td>
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<tr>
<td>Dual antiplatelet therapy (aspirin + Clopidogrel) (n, %)</td>
<td>39/1,441 (2.7%)</td>
<td>217/1,582 (13.7%)</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa receptor inhibitors (Abciximab, Eptifibatide or Tirofiban) (n, %)</td>
<td>1/1,441 (0.07%)</td>
<td>1/1,582 (0.06%)</td>
</tr>
<tr>
<td>Elective/emergency surgery (n, %)</td>
<td>1,589/129 (92.5/7.5%)</td>
<td>1,922/225 (89.5/10.5%)</td>
</tr>
<tr>
<td>Annual cardiovascular surgeries in relation to total cardiovascular surgeries during 2004 to 2009 (n, %)</td>
<td>1,718/11,112 2,147/11,112</td>
<td>1,718/11,112 2,147/11,112</td>
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<tr>
<td>Coronary artery bypass graft surgery (n, %)</td>
<td>896/1,718 (52.2%)</td>
<td>832/2,147 (43.4%)</td>
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<td>Aortic valve surgery, with or without ascending aortic replacement (n, %)</td>
<td>277/1,718 (16.1%)</td>
<td>383/2,147 (17.8%)</td>
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<tr>
<td>Mitral valve surgery (n, %)</td>
<td>130/1,718 (7.6%)</td>
<td>132/2,147 (6.9%)</td>
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<td>Tricuspid valve surgery (n, %)</td>
<td>28/1,718 (1.6%)</td>
<td>40/2,147 (1.9%)</td>
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<tr>
<td>Complex cardiac surgery (n, %)</td>
<td>143/1,718 (8.3%)</td>
<td>238/2,147 (11.1%)</td>
</tr>
<tr>
<td>Transplant surgery (heart or bilateral lung transplant) (n, %)</td>
<td>35/1,718 (2.0%)</td>
<td>33/2,147 (1.5%)</td>
</tr>
<tr>
<td>Aortic surgery (Aortic dissections, type A and B, thoracic aortic aneurysms) (n, %)</td>
<td>43/1,718 (2.5%)</td>
<td>52/2,147 (2.4%)</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>118 [95.5/149]</td>
<td>115 [89/151]</td>
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<tr>
<td>Aortic cross-clamp time (min)</td>
<td>78 [61/96.5]</td>
<td>74 [56/96]</td>
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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.
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Table 2. Primary and Secondary Binary Endpoints: Transfusion and Outcome

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<tr>
<td>Any allogeneic blood product transfusion (n, %)</td>
<td>902/1,718 (52.5%)</td>
<td>906/2,147 (42.2%)</td>
<td>&lt;0.0001 0.804 (0.752–0.859)</td>
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<tr>
<td>PRBC transfusion (n, %)</td>
<td>854/1,718 (49.7%)</td>
<td>868/2,147 (40.4%)</td>
<td>&lt;0.0001 0.813 (0.758–0.872)</td>
</tr>
<tr>
<td>FFP transfusion (n, %)</td>
<td>333/1,718 (19.4%)</td>
<td>24/2,147 (1.1%)</td>
<td>&lt;0.0001 0.058 (0.038–0.087)</td>
</tr>
<tr>
<td>Platelet transfusion (n, %)</td>
<td>173/1,718 (10.1%)</td>
<td>280/2,147 (13%)</td>
<td>0.0041 1.295 (1.083–1.548)</td>
</tr>
<tr>
<td>Massive transfusion (≥10 units of PRBC) (n, %)</td>
<td>43/1,718 (2.50%)</td>
<td>27/2,147 (1.26%)</td>
<td>0.0057 0.502 (0.312–0.81)</td>
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| 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 (0.07%)                                                            | 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. 11.1%; 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-
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 \( \times 10^3 \) U vs. 388 \( \times 10^3 \) U 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 \( \times 10^3 \) 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 \( \times 10^3 \) U vs. 170 \( \times 10^3 \) U and 0 U [0/0] vs. 0 U [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 (\( \geq 10 \) 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

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<tr>
<td>PRBCs transfused (units/transfused patients; median [25th/75th percentile])</td>
<td>3,276/854; 3 (2/4)</td>
<td>2,959/868; 2 (2/4)</td>
<td>0.0049</td>
</tr>
<tr>
<td>FFP transfused (units/transfused patients; median [25th/75th percentile])</td>
<td>1,986/333; 4 (4/6)</td>
<td>102/24; 4 (2/5)</td>
<td>0.1325</td>
</tr>
<tr>
<td>Platelets transfused (units/transfused patients; median [25th/75th percentile])</td>
<td>336/173; 2 (1/2)</td>
<td>581/280; 2 (2/2)</td>
<td>0.0019</td>
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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.
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

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 \( \text{H9255} \)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 4. Administration of Coagulation Factor Concentrates in Treated Patients before and after Implementation of the Point-of-care Coagulation Management Algorithm

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<tr>
<td>Fibrinogen administered (g/treated patients; median 25th/75th percentile)</td>
<td>179/64; 2 (2/3)</td>
<td>702/215; 3 (2/4)</td>
<td>0.0528</td>
</tr>
<tr>
<td>PCC administered (10³ U/treated patients; median 25th/75th percentile)</td>
<td>162/76; 2 (1.5/3)</td>
<td>388/191; 2 (1.5/2.5)</td>
<td>0.352</td>
</tr>
<tr>
<td>AT administered (10³ U/treated patients; median 25th/75th percentile)</td>
<td>223/148; 1 (1/2)</td>
<td>170/172; 1 (1/1)</td>
<td>0.0001</td>
</tr>
<tr>
<td>FXIII administered (10³ U/treated patients; median 25th/75th percentile)</td>
<td>15/10; 1.25 (1.25/1.25)</td>
<td>No treated patient</td>
<td>—</td>
</tr>
<tr>
<td>rFVIIa administered (mg/treated patients; median 25th/75th percentile)</td>
<td>4.8/1; 4.8 (4.8/4.8)</td>
<td>No treated patient</td>
<td>—</td>
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Data are presented as numbers (administered coagulation factor concentrates per year/treated patients per year) and median (25th/75th percentile).

\( \text{AT} = \) antithrombin concentrate; \( \text{FXIII} = \) factor XIII concentrate; \( \text{U} = \) international unit; \( \text{PCC} = \) prothrombin complex concentrate; \( \text{rFVIIa} = \) activated recombinant factor VII.

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**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.
loss and transfusion requirements in cardiac surgery without fibrinogen concentrate has been shown to be effective in decreasing blood transfusion by about 95%.24,36,44–47 Furthermore, fibrinogen concentration has been shown to best predict perioperative bleeding during massive hemorrhage, and fibrinogen concentration factor that decreases first and below a critical concentration, PCC can be summarized as follows: Fibrinogen is the coagulation mechanism in decreasing the incidence and overall amount of FFP transfusion.41 Wherever fibrinogen concentrate and/or PCC supplanted the use of FFP and/or platelets. However, 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.14 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 concentration has been shown to be effective in decreasing blood loss and transfusion requirements in cardiac surgery without an increased incidence of thromboembolic events.28–50 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 studies14–18 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

### Table 5. Costs for Transfusion and Coagulation Therapy

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<tr>
<td>Mean costs for allogeneic blood products</td>
<td>286.12</td>
<td>187.89</td>
<td>−34.3%</td>
</tr>
<tr>
<td>Mean costs for coagulation factor concentrates</td>
<td>71.67</td>
<td>146.66</td>
<td>104.6%</td>
</tr>
<tr>
<td>Mean overall costs for allogeneic blood products and coagulation factor concentrates</td>
<td>357.79</td>
<td>334.56</td>
<td>−6.5%</td>
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Data are presented as mean costs per patient in euros.
and MEA for POC measurements so as to assess platelet function. In fact, only Westbrook et al. 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. In addition, the replacement of aprotinin by tranexamic acid would have been expected to be associated with increased transfusion requirements.

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. 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.

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