Purpose of review
On the one hand, cardiac and aortic surgery is associated with a high rate of allogeneic blood transfusion. On the other hand, both bleeding and allogeneic blood transfusion is associated with increased morbidity, mortality, and hospital costs in cardiac and aortic surgery. This article reviews the current literature between 1995 and 2012 dealing with transfusion protocols in cardiovascular surgery. The 16 studies fitting these search criteria have evaluated the impact of the implementation of ROTEM/TEG based coagulation management algorithms on transfusion requirement and outcome in overall 8507 cardiovascular surgical patients.

Recent findings
The use of point-of-care (POC) transfusion and coagulation management algorithms based on viscoelastic tests such as thromboelastometry (ROTEM) and thrombelastography (TEG) in combination with POC platelet function tests such as whole blood impedance aggregometry (Multiplate) have been shown to be associated with reduced allogeneic blood transfusion requirements, reduced incidence of thrombotic/thromboembolic and transfusion-related adverse events, and improved outcomes in cardiac surgery.

Summary
Implementation of POC algorithms including a comprehensive bundle of POC diagnostics (thromboelastometry and whole blood impedance aggregometry) in combination with first-line therapy using immediately available specific coagulation factor concentrates (fibrinogen and prothrombin complex concentrate) and defining strict indications, calculated dosages, and clear sequences for each haemostatic intervention seems to be complex but most effective in reducing perioperative transfusion requirements and has been shown to be associated with a decreased incidence of thrombotic/thromboembolic events, transfusion-related adverse events, as well as with improved patients’ outcomes including 6-month mortality.

Keywords
goal-directed therapy, impedance aggregometry, point-of-care testing, thromboelastometry, transfusion-related adverse events

INTRODUCTION
Bleeding is an important issue in complex cardiac and aortic surgery and 15–20% of all blood products are transfused in this clinical setting worldwide [1]. However, transfusion practice between different hospitals show a high variation and more than 25% of allogeneic blood transfusions – in particular transfusion of fresh frozen plasma (FFP) and platelets – have been considered as inappropriate [2]. Nevertheless, the issue of inappropriate allogeneic blood transfusion did not change significantly during the last 20 years [3,4,5*].

BLEEDING AND TRANSFUSION AS INDEPENDENT RISK FACTORS FOR MORBIDITY AND MORTALITY IN CARDIOVASCULAR SURGERY
On the one hand, bleeding complications and mediastinal re-exploration are independently associated with worse outcomes in cardiovascular surgery. A retrospective analysis including 1188 adult patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) demonstrated that excessive postoperative haemorrhage was associated with an increased incidence of mediastinal re-exploration [odds ratio (OR) = 103.7; 95% confidence interval (CI) = 45.6–235.4; P < 0.0001], postoperative stroke

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KEY POINTS

- Bleeding and transfusion of allogeneic blood products have been shown to be independent risk factors for morbidity and mortality after cardiac surgery.
- Implementation of POC algorithms based on viscoelastic tests (thrombelastography or thromboelastometry) and platelet function analysis (whole blood impedance aggregometry) result in reduction of perioperative transfusion requirements.
- Implementation of POC algorithms (thromboelastometry and whole blood impedance aggregometry) in combination with calculated goal-directed haemostatic therapy (fibrinogen concentrate and prothrombin complex concentrate) using strict indications, calculated dosages, and clear sequences for each haemostatic intervention seems to be most effective in reduction of perioperative transfusion requirements and has been shown to be associated with a decreased incidence of thrombotic/thromboembolic events, transfusion-related adverse events, as well as with improved patients’ outcomes including 6-month mortality.

(OR = 3.3; 95% CI = 1.6–7.0; P = 0.0033), mechanical ventilation more than 24 h (OR = 3.4; 95% CI = 1.8–6.4; P = 0.0002), ICU stay more than 72 h (OR = 1.4; 95% CI = 1.2–3.2; P < 0.0001), and increased 30-day mortality (OR = 2.9; 95% CI = 2.9–3.0; P < 0.001) [6**]. Furthermore, excessive postoperative haemorrhage was associated with increased hospital costs (15 404 ± 8986 versus 8 499 ± 7 557 Euro; P < 0.001) [7].

On the contrary, there is overwhelming evidence that allogeneic blood transfusion itself is an independent risk factor for increased morbidity (acute lung injury, acute renal failure, thrombotic/thromboembolic events, stroke, nosocomial infections and sepsis), mortality, and hospital costs in patients undergoing cardiovascular surgery [8–10,11**,12–17,18*].

UNIVERSAL HAEMOSTATIC AGENTS: DO THEY EXIST?

During the last decades several attempts have been done to find a universal haemostatic agent capable to ensure haemostasis during and after cardiovascular surgery independent from the individual cause of bleeding. Almost all drugs studied in this context either failed to reduce bleeding and transfusion requirements if given as a prophylaxis or were associated with severe adverse events such as acute renal failure or thrombotic/thromboembolic events or even with increased mortality.

Antifibrinolytics

Antifibrinolytics have been shown to be effective in reducing bleeding and transfusion requirements in cardiac surgery. However, there are increasing concerns about safety particularly in patients with pre-existing thrombotic/thromboembolic events and renal insufficiency. Here, lysine analogues such as tranexamic acid and epsilon-aminocaproic acid seem to be more safe than aprotinin [19,20]. However, the optimal dose for lysine analogues in this setting has not yet been defined [21].

Fresh frozen plasma

Prophylactic administration of FFP failed to reduce bleeding and to correct coagulopathy in cardiac surgical and critically ill patients [5*,13–22–24,25*]. On the other hand, large FFP volumes (>15 ml per kg body weight) are necessary to achieve any haemostatic effect and on the other hand, these large FFP volumes are associated with a high incidence of transfusion-associated circulatory overload, acute lung injury, transfusion-related immunomodulation, nosocomial infections and sepsis [5*,13–17]. Therefore, the risk-benefit ratio of FFP transfusion seems not to be favourable in this clinical setting and an inappropriate use of FFP should be strictly avoided [5*,11**,13].

Recombinant factor VIIa

Administration of recombinant factor VIIa (rFVIIa) in patients who had undergone cardiac surgery and were bleeding resulted in decreased transfusion requirements but there were more critical serious adverse events including stroke in those patients randomized to receive rFVIIa [26]. These results are in line with a recently published meta-analysis including 4468 patients showing that patients treated with rFVIIa on an off-label basis had significantly more arterial thromboembolic events compared with patients that received placebo (5.5 versus 3.2%; P = 0.003), particularly among those patients who were 65 years of age or older (9.0 versus 3.8%; P = 0.003) [27]. Therefore, the uncritical and unspecific use of rFVIIa to stop bleeding in patients during and after cardiovascular surgery cannot be recommended.

PREDICTORS OF BLEEDING IN CARDIOVASCULAR SURGERY

Bleeding in cardiovascular surgery most often is multifactorial. Therefore, the problem cannot be solved by one single drug or haemostatic intervention. The bleeding risk can be influenced by
patients’ comorbidities and medications (in particular antiplatelet drugs and anticoagulants), kind of cardiovascular surgery (coronary artery bypass graft surgery versus complex cardiac surgery), CPB time, surgical technique, volume replacement therapy, and haemostatic management. The following factors have been shown to be predictive for bleeding in cardiovascular surgery:

1. Detected platelet dysfunction (rather than just a medical history of taking antiplatelet drugs). The effect of antiplatelet drugs on bleeding risk increases as follows: aspirin < ADP-receptor antagonists < GPIIbIIIa-receptor antagonists [28–32,33*,34*,35].

2. A low preoperative plasma fibrinogen concentration even if it is still within the normal range is an independent predictor of postoperative bleeding volume [36]. Again, a significant inverse correlation has been demonstrated between plasma fibrinogen concentration 2 h after cardiac surgery and postoperative blood loss [37]. Furthermore, reduced maximum clot firmness in FIBTEM (MCF < 8 mm) has been shown to be the best positive predictive value for a postoperative blood loss above 600 ml [35,38].

3. Elevated fibrin monomers or reduced preoperative or postoperative factor XIII activity [33*,37,39].

4. Reduced thrombin generation (due to oral anticoagulation with warfarin or other causes of vitamin K-dependent coagulation factor deficiencies (factor II, VII, IX and X) [40].

Furthermore, abnormal bleeding after cardiac surgery can be caused by residual heparin effects, protamine overdose, hyperfibrinolysis, (acquired) von Willebrand disease, and vascular diseases [41,42].

**ROUTINE LABORATORY TESTING VERSUS POINT-OF-CARE TESTING**

Routine laboratory testing (RLT) and point-of-care (POC) testing differ in turnaround time, test samples (platelet poor plasma versus whole blood) and assay methods (quantitative versus functional testing).

Whereas the turnaround time of RLT is too long (45–60 min) to be used to guide haemostatic therapy in severe perioperative bleeding the results of thromboelastometry (ROTEM) and whole blood impedance aggregometry (Multiplate) are available within 15–20 min [43*–46*,47]. Furthermore, they allow for timely detection of reduced clot firmness and hyperfibrinolysis, discrimination between fibrin polymerization disorders and platelet dysfunction, tissue factor expression on monocytes, as well as discrimination between residual heparin effects, protamine overdose and a deficiency of vitamin K-dependent coagulation factors [47,48*,49,50*]. Therefore, POC testing based on thromboelastometry and whole blood impedance aggregometry enable a calculated goal-directed therapy in bleeding patients. Furthermore, preinterventional FIBTEM A10 values facilitate a calculation of the required fibrinogen concentrate or cryoprecipitate dose to achieve a targeted FIBTEM A10 value in order to stop bleeding on time but to avoid any overtreatment and hypercoagulability at the same time [51,52,53**,54*,55,56*]. In addition, whole blood impedance aggregometry can be used to monitor the effects of antiplatelet drugs as well as of desmopressin and tranexamic acid on platelet function. This may allow for adjusting platelet function to a therapeutic window in order to stop bleeding on time but to avoid thromboembolic events at the same time [32,57,58].

**IMPACT OF TRANSFUSION PROTOCOLS ON PERIOPERATIVE BLEEDING, TRANSFUSION REQUIREMENTS, AND OUTCOME IN CARDIOVASCULAR SURGERY**

A PubMed search resulted in 16 studies dealing with transfusion protocols in cardiovascular surgery comparing POC-based algorithms versus algorithms based on routine laboratory testing and clinician discretion or standard of care. These studies are presented with their summary findings and major conclusions in Table 1. Most studies focused on differences in blood loss and transfusion requirements and some more recently published studies analyzed patient outcomes and hospital costs, too. Five studies are retrospective cohort studies (mainly before-and-after studies) [53**,59–62], three are prospective intervention versus retrospective control studies [51,52,63], and eight are randomized clinical trials (RCTs) [64–70,71**]. Overall, 8507 patients were included in these studies, most of them (7366 patients) in retrospective cohort studies before and after implementation of a POC-based transfusion protocol. Two hundred and eighty-five patients were included in prospective interventional versus retrospective control studies and 856 were included in RCTs.

Thrombelastography (TEG, Hemonetics Corp., Braintree, Massachusetts, USA) was used in eight studies [59,63–69] (published from 1995 to 2009). Here, three studies [64–66] focused on the use of heparinase-modified TEG enabling intraoperative
Table 1. Studies evaluating the impact of ROTEM/TEG based algorithms versus routine laboratory testing or routine clinical practice on transfusion requirements and outcomes in cardiac and aortic surgical patients (16 studies performed between 1995 and 2012 including overall 8507 patients)

<table>
<thead>
<tr>
<th>Author, journal, year</th>
<th>Study type</th>
<th>Patient population</th>
<th>Summary of findings and major conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiess BD, J Cardiothorac Vasc Anesth, 1995 [59]</td>
<td>RC; before and after institution of TEG-guided coagulation monitoring</td>
<td>1079 cardiac surgical patients</td>
<td>Significant lower incidence of overall transfusion during hospitalization (78.5 versus 86.3%) and in total transfusion in the operating room (57.9 versus 66.4%). Actual total median donor exposure was 8 versus 6 units. Mediastinal reexploration for haemorrhage was 5.7 versus 1.5%. Use of TEG monitoring before reexploration has decreased the costs and potential risk for patients undergoing CABG.</td>
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<tr>
<td>Shore-Lesserson L, Anesth Analg, 1999 [64]</td>
<td>RCT; TEG-guided transfusion algorithm (TEG with and without heparinase) versus RLT</td>
<td>105 complex cardiac surgical patients</td>
<td>TEG-guided algorithm resulted in fewer transfusions particularly in the postoperative period. The proportion of patients receiving FFP was 7.5% in the TEG group versus 30.8% in the control group (P = 0.002). Patients in the TEG group also received less volume of FFP (36 ± 142 versus 217 ± 463 ml; P &lt; 0.04). Patients receiving platelets were 13.2% in the TEG group versus 28.8% in the control group (P &lt; 0.05). The proportion of patients receiving PRBC (4.1 versus 59.6%; P = 0.06) and the volume of transfused PRBCs (545 ± 487 versus 475 ± 593 ml; P = 0.12) did not reach statistical significance. TEG-guided algorithm was found to be effective in reducing transfusion requirements in complex cardiac surgery.</td>
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<tr>
<td>Manikappa S, Ann Card Anaesth, 2001 [65]</td>
<td>RCT; heparinase-modified TEG versus RLT</td>
<td>150 patients undergoing CABGS with CPB</td>
<td>Consumption of whole blood, PRBCs and FFP was significantly less in the TEG group (P values 0.03, 0.05, 0.001, respectively). TEG helps in instituting appropriate blood and blood component therapy thereby avoiding unnecessary transfusion and associated risks. Accurate detection of coagulopathy is possible with heparinase pretreatment of the blood sample.</td>
</tr>
<tr>
<td>Royston D and von Kier S, Br J Anaesth, 2001 [66]</td>
<td>RCT; heparinase-modified TEG versus RLT</td>
<td>60 complex cardiac surgical patients</td>
<td>Incidence of blood component transfusion (FFP and/or platelets) during cardiac surgery was reduced significantly (16.7 versus 33.3%; P &lt; 0.05) as well as the amount of products used (5 FFP + 1 pool of platelets versus 16 FFP + 9 pool of platelets; P &lt; 0.05). Intraoperative monitoring of coagulation in the anticoagulated patient can be used to guide treatment.</td>
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<tr>
<td>Nuttall GA, Anesthesiology, 2001 [67]</td>
<td>RCT; POC algorithm guided treatment versus standard transfusion treatment</td>
<td>92 elective cardiac surgical patients with abnormal bleeding (92/836 = 11%)</td>
<td>Transfusion algorithm included TEG MA; platelet count, POC PT, POC aPTT and conventional fibrinogen measurements. The transfusion algorithm group received less FFP [0 (0–7) versus 3 (0–10); median (range); P = 0.0001] and platelet units [4 (0–12) versus 6 (0–18); P = 0.02]. The use of a POC algorithm guided transfusion algorithm in cardiac patients with abnormal bleeding after CPB reduced non-erythrocyte allogeneic transfusion in the OR.</td>
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<tr>
<td>Avidan MS, Br J Anaesth, 2004 [63]</td>
<td>PIS versus RC; POC-based algorithm versus RLT; retrospective case-control group based on clinician discretion</td>
<td>102 patients undergoing elective CABG with CPB (prospective); 108 patients in a retrospective control group (therapy based on clinician discretion)</td>
<td>POC-guided algorithm was based on Hepcon, TEG, and PFA-100 results. RLT-guided algorithm was based on the results of rapid available coronary artery testing (INR, aPTT, platelet count) and transfusion of haemostatic blood components was done only if specific criteria were met. All groups had similar median postoperative 24 h blood losses (POC group: 755 ml (606–975); RLT group: 850 ml (688–1093); CD group: 810 (550–1293); median (IQR); P = 0.03). The incidence of PRBCs, FFP and platelet transfusion was significantly higher in the retrospective CD group but there was no difference between the two algorithm-guided groups (POC versus RLT): PRBC: POC 68 versus RLT 69 versus CD 85%; P = 0.01; FFP: POC 4 versus RLT 0 versus CD 15%; P = 0.003; Platelets: POC 4 versus RLT 2 versus CD 13%; P = 0.02. Cardiac surgery services should use transfusion guidelines based on laboratory-guided algorithms, and the possible benefits of POC testing should be tested against this standard.</td>
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Table 1 (Continued)

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<th>Summary of findings and major conclusions</th>
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<tr>
<td>Anderson L, Transfus Med, 2006 [60]</td>
<td>RC; 6 months before and after introduction of a ROTEM-guided algorithm</td>
<td>990 cardiac surgical patients</td>
<td>After introduction of a ROTEM-guided coagulation management algorithm incidence of PRBC transfusion was decreased from 60 to 53%, FFP from 17 to 12% and platelets from 16 to 11%, respectively (P &lt; 0.05). Introduction of ROTEM has significantly decreased our use of PRBCs and blood products.</td>
</tr>
<tr>
<td>Spalding G, Eur J Cardiothorac Surg, 2007 [61]</td>
<td>RC; before and after implementation of bedside ROTEM analysis</td>
<td>1422 cardiac surgical patients (729 patients before and 693 after implementation)</td>
<td>After ROTEM implementation cumulative PRBC and platelets expenditure decreased by 25% and 50%, respectively. FFP expenditure remained unchanged. PCC and FXII were markedly reduced by 80% while rFVIIa was entirely omitted. Use of fibrinogen concentrate increased two-fold. The cumulative average monthly costs of all blood products and coagulation factor concentrates decreased from 126 000 Euro to 75 000 Euro. Average monthly costs for ROTEM were 1 580 Euro. Saved costs for blood and coagulation products clearly outweighed the expenses of ROTEM. Therefore, ROTEM-based coagulation management can be cost-effective.</td>
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<tr>
<td>Spalding G, Eur J Cardiothorac Surg, 2007 [61]</td>
<td>RCT; TEG-based algorithm versus clinician-and RLT-directed transfusion</td>
<td>224 patients undergoing elective CABG with CPB</td>
<td>There were no differences in transfused PRBCs (1 [0–1] versus 1 [1–2]; P = 0.599), blood loss (12 h mediastinal chest tube drainage: 480.5 ± 351 versus 591.4 ± 339.2 ml; P = 0.087), re-exploration for bleeding, and early clinical outcome between both groups. TEG group had significantly lower median (IQR) units of FFP [1 [1–1] versus [1–2]; P = 0.001] and platelets [1 [1–1] versus 1 [1–2]; P = 0.001] compared to the control group. Adopting such an algorithm into routine management may help to improve clinical outcome and reduce potential risks of transfusion-related complications and total costs after CABG.</td>
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<tr>
<td>Westbrook AJ, Heart Lung Circ, 2009 [69]</td>
<td>RCT; TEG-based algorithm versus physician’s choice based on RLT</td>
<td>69 cardiac surgical patients; pilot study</td>
<td>TEG-based management (including TEG Platelet Mapping) reduced total product usage (total of 37 versus 90 units of allogeneic blood products) by 58.8% in the study group but this was not statistically significant. This was associated with a statistically significant trend towards better short-term outcomes (blood loss, intubation time, ICU stay).</td>
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<td>Rahe-Meyer N, Br J Anaesth, 2009 [51]</td>
<td>PIS versus RC; FIBTEM-guided fibrinogen concentrate administration (six patients in prospective study group and 12 patients in retrospective controls)</td>
<td>57 patients undergoing elective aortic valve operations and ascending aorta replacement</td>
<td>In the prospective study group a first step with fibrinogen concentrate was added to the algorithm. FIBTEM-guided administration of 5.7 (0.7) g fibrinogen concentrate (targeted MCF in FIBTEM = 22 mm) established haemostasis, completely avoiding intraoperative transfusion of FFP and platelets. Transfusion of blood products after CPB and during the 24 h after surgical intervention was markedly lower in the study group (2.5 versus 16.4 units) as was 24 h perioperative transfusion (odds ratio 0.45; 95% confidence interval 0.2–0.9; P = 0.03) in multivariate logistic regression analysis.</td>
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<tr>
<td>Rahe-Meyer N, J Thorac Cardiovasc Surg, 2009 [52]</td>
<td>PIS versus RC; FIBTEM-guided fibrinogen concentrate administration (six patients in prospective study group and 12 patients in retrospective controls)</td>
<td>18 patients undergoing thoracoabdominal aortic aneurysm surgery</td>
<td>In the prospective study group a first step with fibrinogen concentrate was added to the algorithm. FIBTEM-guided administration of 7.8 ± 2.7 g fibrinogen concentrate (targeted MCF in FIBTEM = 22 mm) established haemostasis, completely avoiding intraoperative transfusion of FFP and platelets. Transfusion of blood products after CPB and during the 24 h after surgical intervention was markedly lower in the study group (2.5 versus 16.4 units) as was 24 h drainage volume (449 versus 1092 ml). Fibrinogen plasma levels and standard coagulation parameters were comparable between the two groups on the first postoperative day.</td>
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<tr>
<td>Girdauskas E, J Thorac Cardiovasc Surg, 2010 [70]</td>
<td>RCT; ROTEM-based algorithm versus routine transfusion practice based on clinical judgement and RCT</td>
<td>56 patients undergoing aortic surgery with hypothermic circulatory arrest</td>
<td>Protamine, tranexamic acid, FFP, platelets, PCC, and fibrinogen concentrate were used as homeostatic interventions in both groups. Transfusion of allogeneic blood was significantly reduced in the ROTEM group: 9 units (2–30) versus 16 units (9–23); median (IQR); P = 0.02. Most significant decrease was in the use of FFP: 3 units (0–12) versus 8 units (4–18); P = 0.005. ROTEM-guided algorithm significantly decreased the need for massive perioperative transfusion (odds ratio 0.45; 95% confidence interval 0.2–0.9; P = 0.03) in multivariate logistic regression analysis.</td>
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In a retrospective analysis of 3865 cardiac surgical patients, implementation of a coagulation management algorithm based on first-line therapy with specific coagulation factor concentrates (fibrinogen concentrate and PCC), combined with POC testing (ROTEM and Multiplate), was associated with decreased blood transfusion requirements (any allogeneic blood transfusion: 42.2 versus 52.5%; \( P < 0.0001 \); PRBC: 40.4 versus 49.7%; \( P < 0.0001 \); FFP: 1.1 versus 19.4%; \( P < 0.0001 \); platelets: 13.0 versus 10.1%; \( P = 0.0041 \)), decreased incidence of massive transfusion (1.26 versus 2.5%; \( P = 0.0057 \)) and decreased composite thrombotic/thromboembolic adverse events (1.77 versus 3.19%; \( P = 0.0115 \)). The incidence of fibrinogen concentrate (10.01% versus 3.73%; \( P < 0.0001 \)) and PCC administration (8.9 versus 4.42%; \( P < 0.0001 \)) increased. Overall costs for allogeneic blood products and coagulation factor concentrates per patient decreased by 6.5%, corresponding to a cost saving of about per year.

Administration of blood products and coagulation factor concentrates, incidence of massive transfusion, ventilation time, ICU stay, hospitalization, and 6-month mortality tended to be lower in the ROTEM group. Postoperative FFP transfusion (1.6 ± 2.2 versus 9.2 ± 6.6 units; \( P = 0.038 \)), composite postoperative bleeding and thrombotic/thromboembolic events (0 versus 80%; \( P = 0.048 \)), and resulting costs on transfusion and coagulation treatment (average cost-saving per case of 2757 Euro; \( P = 0.049 \)) were significantly reduced. MCF in FIBTEM was 19.6 mm (19–26 mm) in the ROTEM group at the end of surgery.

Power analysis based on the results of the RC of Görlinger K, Anesthesiology, 2011, revealed a sample size of at least 100 patients per group. After randomization of 50 patients to each group, a planned interim analysis revealed a significant decrease in erythrocyte transfusion rate (primary outcome parameter) in the POC group [3 units (2–6) versus 5 units (4–9); median (IQR); \( P < 0.001 \)]. Therefore, the study has to be terminated early according to the study protocol. The secondary outcome parameters of FFP [0 units (0–3) versus 5 units (3–8); \( P < 0.001 \)] and platelet transfusion rates [2 units (0–2) versus 2 units (0–5); \( P = 0.01 \)], postoperative mechanical ventilation time [316 min (230–513) versus 827 min (440–2835); \( P < 0.001 \)], length of ICU stay [21 h (18–31) versus 24 h (20–87); \( P = 0.019 \)], composite adverse events rate [ARF, sepsis, thrombotic complications, and allergic reaction] (8 versus 38%; \( P < 0.001 \)), costs of haemostatic therapy (average cost-saving per case of 1451 Euro), and 6-month mortality (4 versus 20%; \( P = 0.013 \)) were significantly lower in the POC group. In conclusion, POC coagulation testing reduced allogeneic blood transfusion and was associated with improved outcomes in coagulopathic patients undergoing complex cardiac surgery.
monitoring of coagulation already in the anticoagulated patient during CPB and its benefits in guiding haemostatic treatment. One further study [63] used Hepcon (Medtronic, Minneapolis, Minnesota, USA) and Platelet function Analyzer 100 (PFA-100, Siemens Healthcare Diagnostics GmbH, Eschborn, Germany) in addition to TEG, and another study [69] used TEG Platelet Mapping in addition to TEG. The other eight studies [51,52,53,54,60–62,70,71] (published from 2006 to 2012) used thromboelastometry (ROTEM, Tem International GmbH, Munich, Germany). Here, two studies [51,52] focused on FIBTEM-guided administration of fibrinogen concentrate in order to achieve prompt haemostasis in ascending or thoracoabdominal aortic surgery. Two recently published studies [53,71] used whole blood impedance aggregometry (Multiplate, Verum Diagnostica, Munich, Germany) in addition to ROTEM in their POC algorithm.

All 16 studies demonstrated a reduction in transfusion requirements in the POC group using viscoelastic tests (TEG or ROTEM). The effect size was dependent on the study population [simple coronary artery bypass graft (CABG) surgery or complex cardiac/aortic surgery], the average blood loss, the extent of POC diagnostics (TEG, ROTEM or ROTEM and Multiplate), and the availability of specific coagulation factor concentrates such as fibrinogen concentrate, four-factor prothrombin complex concentrate (PCC), and factor XIII concentrate for calculated goal-directed therapy. Only one study published by Avidan et al. [63] did not show an additional reduction in transfusion requirements for allogeneic blood products in the POC group (Hepcon, TEG and PFA-100) compared with the group with a transfusion protocol based on rapid available laboratory clotting tests and strict restriction of allogeneic blood transfusion to patients with abnormal bleeding. However, in both groups transfusion of FFP and platelets could almost completely be eliminated in contrast to a retrospective control group with transfusion based on clinician discretion. The low rate of FFP (0–4%) and platelet transfusion (2–4%) in both algorithm-based groups suggests that there were almost no coagulopathic patients included in this study dealing with patients undergoing elective CABG surgery. The average blood loss in all three groups was between 750 and 850 ml. Self-evident, POC testing did not result in further reduction of transfusion requirement in a nonbleeding and noncoagulopathic patient population when a restrictive transfusion protocol by itself was able to reduce transfusion requirements for FFP and platelets almost to zero. In a second study [69], a TEG-based protocol (including TEG Platelet Mapping) reduced total product usage by 58.8% but this difference did not achieve statistical significance in this pilot study. All other 14 studies demonstrated a significant reduction in transfusion requirements in the POC group. Here, in four studies the reduction in transfusion requirements was limited to FFP and platelets [64,66–68]. POC-diagnostic was most effective in patients undergoing complex cardiac or aortic surgery with detected abnormal bleeding [51,52,62,70,71]. On the one hand, reduction in transfusion requirements can be due to avoidance of inappropriate allogeneic blood transfusion. On the other hand, the efficacy can further be increased by more specific haemostatic interventions based on calculated goal-directed therapy. However, the latter is dependent on the availability of specific coagulation factor concentrates such as fibrinogen concentrate, PCC and FXIII concentrate. This may result in further significant reduction in transfusion requirement for FFP and platelets and by avoiding dilution of erythrocytes by high amounts of FFP also in further reduction in packed red blood cell transfusion.

In addition, seven studies reported a reduction in the incidence of mediastinal re-exploration [53,59,67,71], of massive transfusion [53,62,70,71] and a reduction in hospital costs [53,59,61,62,71]. None of the studies demonstrated increased hospital costs. Off-label use of rFVIIa – integrated in some algorithms as a rescue therapy if haemostatic therapy according to the algorithm failed – could almost completely be eliminated in five studies [53,61,62,70,71]. This was certainly important for cost savings in these studies and potentially also for reduction in the incidence of thrombotic/thromboembolic events.

Only the last four studies published between 2010 and 2012 by Girdauskas et al. [70], Görlinger et al. [53], Hanke et al. [62], and Weber et al. [71] demonstrated an improvement in patients’ outcome in the POC group. Most of these studies have not been included in the Cochrane analysis published in 2011 [72], as they were either not RCTs [53,62] or still ongoing at the time [71]. Therefore, this Cochrane analysis demonstrated a statistically significant effect of TEG or ROTEM-guided transfusion protocols on bleeding and transfusion requirements but failed to show any significant effect on patients’ outcomes. All these studies used a similar POC coagulation and transfusion management algorithm based on first-line goal-directed therapy with fibrinogen concentrate and PCC guided by ROTEM diagnostics first published by Görlinger et al. [47], two of them used whole blood impedance aggregometry (Multiplate), too [53,71]. Here, three studies demonstrated a reduction in thrombotic/thromboembolic events.
Furthermore, the RCT in coagulopathic patients undergoing complex cardiac surgery recently published by Weber et al. [71] showed a significant reduction in postoperative pulmonary dysfunction, postoperative ventilation time, stay at ICU, composite adverse events (acute renal failure, sepsis, thrombotic complications, and allergic reactions) (8 versus 38%; \( P < 0.001 \)) and 6-month mortality (4 versus 20%; \( P = 0.013 \)). As this single-centre study was not powered for mortality and safety the results have to be confirmed by adequately powered multicentre RCTs and huge prospective observational studies.

**PRINCIPLES OF POINT-OF-CARE-BASED GOAL-DIRECTED HAEMOSTATIC THERAPY**

The POC transfusion and coagulation management algorithms in the last four studies [53**,62,71**] seem to be most effective as these studies were performed in a patient population undergoing complex cardiac or aortic surgery, and the algorithms included a comprehensive bundle of POC diagnostics in combination with first-line therapy using immediately available specific coagulation factor concentrates such as fibrinogen concentrate, 4F-PCC, and FXIII concentrate. Furthermore, the POC algorithm was based on strict indications, calculated dosages, and clear sequences for each haemostatic intervention. In contrast to ‘horizontal algorithms’ (Fig. 1) as published by Shore-Lesserson et al. [64] and Bolliger et al. [73*], the sequence of haemostatic interventions is also explicitly defined in ‘vertical algorithms’ as published by Görlinger et al. [47,53**,74*] (Fig. 2). The latter are based on pathophysiological considerations first published by Görlinger [75] as the ‘pyramid of therapy in coagulopathic patients’ in 2006 (Fig. 3).

**Thromboelastometry (ROTEM)**

Larsen et al. [48*] demonstrated that the diagnostic performance and subsequent therapeutic consequences of thromboelastometry (ROTEM, Tem International GmbH, Munich, Germany) using a panel of specific reagents is superior to monanalysis with kaolin-activated viscoelastic tests. Simultaneous assessment of extrinsic (EXTEM,

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**FIGURE 1.** ‘Horizontal POC algorithm’ for coagulation and transfusion management in cardiovascular surgery based on thromboelastometry (ROTEM) and whole blood impedance aggregometry (Multiplate) in combination with goal-directed haemostatic therapy (original figure). The disadvantage of a ‘horizontal algorithm’ is that the sequence of haemostatic interventions is not explicitly defined in case of multifactorial coagulopathy which is common in perioperative severe bleeding. A10, amplitude of clot firmness 10 min after CT; AUC, area under the curve; CT, clotting time; EX, EXTEM; FIB, FIBTEM; HEP, HEPTEM; IN, INTEM; MCF, maximum clot firmness; ML, maximum lysis; POC, point-of-care; PCC, prothrombin complex concentrate.
Check and optimize preconditions before weaning from CPB:

- \( T_c > 36 \, ^\circ\text{C} \)
- \( \text{pH} > 7.2 \)
- \( C_a > 1 \text{mmol/l} \)
- \( Hb > 8 \text{g/dL} \)

**Drug history**

- **Yes**
  - **Yes**
    - **Reservation of platelet concentrates in the blood bank**
  - **No**
    - **Prophylaxis with tranexamic acid**
    - **Yes**
      - **2 g tranexamic acid**
      - \( (50-100 \text{ kg bw}) \)
      - **before CPB**
    - **No**
    - **CL\text{IB} < 85\%**
    - **Yes**
      - **Therapeutic intervention with 2 g tranexamic acid**
      - \( (50-100 \text{ kg bw}) \)
    - **No**
  - **No**
    - **Clopidogrel within the last 10 days?**
    - **Yes**
    - **Yes**
    - **Yes**
    - **Yes**
    - **No**
    - **No**
    - **No**
    - **No**
    - **Yes**
    - **No**
    - **No**

**Primary state of Multiplate:**

- **Yes**
  - **Reservation of platelet concentrates in the blood bank**
- **No**
  - **Consider fibrinogen substitution**
  - \( (50 \text{ mg/kg bw}) \)
  - **before protamine**

**ROTEM-analysis after declamping of the aorta**

- **Yes**
  - **Order platelet concentrates from the blood bank**
- **No**
  - **A10\text{EX} < 30 \text{ mm}**
    - **Yes**
      - **Order platelet concentrates from the blood bank**
    - **No**
  - **A10\text{FIB} > 6 \text{ mm}**

**FIGURE 2.** ‘Vertical POC algorithm’ for coagulation and transfusion management in cardiovascular surgery based on thromboelastometry (ROTEM) and whole blood impedance aggregometry (Multiplate) in combination with goal-directed haemostatic therapy (published in [53**]). Vertical algorithms seem to be more complex at the first view but have the advantage that the sequence of haemostatic interventions is explicitly defined in case of multifactorial coagulopathy, escalating therapeutic levels can be defined, and the algorithm can be entered at different time point of the operation. A10, amplitude of clot firmness 10 min after CT; ADP, ADP\text{test}; ASPI, ASPI\text{test}; AU, arbitrary unit; AUC, area under the curve;
FIGURE 2. (Continued)

Ca, ionized calcium; CLI, clot lysis index; COL, COLtest; CPB, cardiopulmonary bypass; CT, clotting time; DDAVP, desmopressin; EX, EXTEM; F VIII / vWF concentrate, factor VIII / von Willebrand factor concentrate; F XIII, factor XIII concentrate; FFP, fresh frozen plasma; FIB, FIBTEM; IN, INTEM; Hb, haemoglobin; HEP, HEPTEM; MCF, maximum clot firmness; PCC, prothrombin complex concentrate; PRBC, packed red blood cells; rFVIIa, activated recombinant factor VII; Tc, core temperature; TRAP, TRAPtest.
Tem International GmbH, Munich, Germany) and intrinsic (INTEM, Tem International GmbH, Munich, Germany) coagulation pathways, investigating fibrin polymerization (FIBTEM, Tem International GmbH, Munich, Germany) and the influence of heparin (HEPTEM, Tem International GmbH, Munich, Germany), direct thrombin inhibitors (ECATEM, Tem International GmbH, Munich, Germany) or fibrinolysis (APTEM, Tem International GmbH, Munich, Germany) provides more detailed and accurate diagnosis than using kaolin (TEG) alone, shortens the time for diagnosis, and helps to avoid administration of platelet concentrates when fibrinogen substitution would be more appropriate [48]. This may be in part responsible for the reduction in the incidence of thromboembolic events in the studies published by Görlinger et al. [53] and Weber et al. [71]. The use of reagents containing a heparin inhibitor (EXTEM, FIBTEM, and APTEM liquid test reagents) or heparinase (HEPTEM) allow for detection of haemostatic disorders already in the anticoagulated patient during CPB. FIBTEM results can be used to calculate the dosage of fibrinogen concentrate in order to achieve a targeted level of clot firmness (A10 or MCF) in FIBTEM [51,52,53,54,55]. Again, this may avoid any overtreatment, and therefore reduces the risk of thromboembolic events, too. Further details on thromboelastometry are described elsewhere [45,46,47,48,49,50,51,52,53,54,55,73,74,75].

**Whole blood impedance aggregometry (Multiplate)**

Platelet dysfunction due to antiplatelet drugs or CPB itself can be detected and the effect of desmopressin, tranexamic acid and platelet transfusion can be monitored timely by whole blood impedance aggregometry [29,47,53,57,58]. Multiplate results closely correlate with early stent thrombosis and mortality after implementation of drug-eluting stents, as well as with bleeding after stent implantation or cardiac surgery [28–32,33]. Therefore, whole blood impedance aggregometry ideally complements thromboelastometry in perioperative POC diagnostics.

**Specific coagulation factor concentrates for calculated goal-directed therapy**

Fibrinogen concentrate and PCC represent the main goal-directed haemostatic interventions in the POC algorithms used in the studies published by Girdauskas et al. [70], Görlinger et al. [53],

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**FIGURE 3.** Pyramid of therapy in coagulopathic patients. The sequence of haemostatic therapeutic interventions starts from the bottom of the pyramid and then continues to the top until haemostasis is achieved. Cai, ionized calcium; FFP, fresh frozen plasma; FVIII, coagulation factor VIII/von Willebrand factor concentrate; FXIII, coagulation factor XIII concentrate; Hb, haemoglobin; PCC, prothrombin complex concentrate; rFVIIa, activated recombinant factor VII; Tc, core temperature. Modified with permission from [75].
Hanke et al. [62], and Weber et al. [71**] demonstrating a significant reduction in transfusion requirements as well as an improvement in patients’ outcomes.

Fibrinogen concentrate
Fibrinogen plasma concentration and maximum clot firmness in FIBTEM have been shown to be good predictors for postoperative bleeding in cardiac surgery [36–38]. Furthermore, administration of fibrinogen concentrate has been shown to be effective and well tolerated to stop microvascular bleeding in cardiac and aortic surgery [51,52,53**,76]. Here, the required dosage of fibrinogen concentrate can be calculated based on the targeted increase in FIBTEM clot firmness (A10 or MCF) [51,52,53**,54**,55]. Further details on efficacy and safety of fibrinogen concentrate in the management of severe perioperative bleeding are summarized elsewhere [77**].

Prothrombin complex concentrate
PCC is administered in these POC algorithms in case of microvascular bleeding and thromboelastometric evidence of delayed coagulation initiation (EXTEM CT >90 s) due to a deficiency of vitamin K-dependent coagulation factors [53**,54**,71**]. In contrast to off-label use of rFVIIa, this seems not to be associated with an increased incidence of thrombotic/thromboembolic events if an overdose is strictly avoided [26,27,50**,53**,54**,71**]. However, more safety data are urgently needed. Further details on efficacy and safety of PCC in the management of severe perioperative bleeding are summarized elsewhere [78**,79,80].

CONCLUSION
Bleeding and transfusion is associated with worse outcome in cardiac surgery. Implementation of transfusion protocol with restrictive transfusion triggers has been shown to reduce perioperative transfusion requirements. Sixteen clinical studies including 8507 cardiac surgical patients demonstrated further reduction in perioperative transfusion requirements by POC coagulation management algorithms. Beyond that, some recently published studies using a POC algorithm based on thromboelastometry and whole blood impedance aggregometry in combination with goal-directed haemostatic therapy with fibrinogen concentrate and prothrombin complex concentrate showed improved patients’ outcomes, additionally. These results have to be confirmed by larger multicentre RCTs and prospective observational studies.

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Conflicts of interest
K.G. received honoraria for scientific lectures from CSL Behring GmbH, Marburg, Germany, Octapharma AG, Lachen, Switzerland, Tem International GmbH, Munich, Germany, and Verum Diagnostica GmbH, Munich, Germany.

REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 250).

This study raises important questions about the clinical benefit of much of current FFP usage.

The authors demonstrate the clinical relevance of excessive postoperative haemorrhage in cardiac surgery on morbidity and mortality.
This study suggests that blood or blood product transfusion during or after cardiac surgery is associated with increased short-term and long-term mortality.
Transect and transfusion


This study characterizes the increased hospital length of stay and cost associated with bleeding-related complications and/or transfusions occurring as a consequence of surgery, and supports implementation of blood-conservation strategies.


The authors report the impact of POC viscoelastic tests and platelet function analysis in patients undergoing mechanical circulatory support. Best Pract Res Clin Anaesthesiol 2011; 25:179–188.


The authors highlight the value of a standardized bleeding history and ADP-induced aggregation to identify patients undergoing cardiac surgery with an elevated bleeding risk and increased platelet transfusion requirements.


The authors demonstrate that a strategy based on preoperative platelet function testing to determine the timing of CABG in clopidogrel-treated patients reduced bleeding to the same amount observed in clopidogrel-naive patients.


The authors demonstrate that thromboelastometry offers faster turnaround times compared with routine laboratory testing, and therefore enables goal-directed haemostatic therapy.


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The authors demonstrate that hypercoagulability identified with viscoelastic tests is associated with a higher risk for a combination of thromboembolic complications and death after CABG surgery.


The authors describe algorithms for POC transfusion and coagulation management during liver transplantation. Anästh Intensivmed 2006; 47:145–159.

The authors review the principles and practice of POC viscoelastic tests performed with different activators and inhibitors in clinical coagulation and transfusion management.

The authors conclude that care should be taken to avoid excessive substitution with PCC, however, an accurate monitoring of patients' coagulation status may allow thrombotic risks to be reduced.

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