Curr Anesthesiol Rep (2017) 7:265–272
DOI 10.1007/s40140-017-0220-y

CARDIOVASCULAR ANESTHESIA (J FASSL, SECTION EDITOR)

Coagulation Management Strategies in Cardiac Surgery

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Published online: 27 June 2017

Abstract
Purpose of the Review Postoperative hemorrhage remains a clinically important problem after major cardiac surgery. This review focuses on the current evidence and emerging data relating to modern strategies in coagulation management in bleeding patients after cardiac surgery.
Recent Findings The use of standard laboratory coagulation tests including prothrombin time and activated partial thromboplastin time is limited by long turn-around time, and questionable sensitivity and specificity in major bleeding. Point-of-care coagulation testing including thromboelastometry and thromboelastography has been shown to reduce allogeneic blood product usage, and potentially morbidity. Perioperative coagulation therapy includes the transfusion of platelet concentrates or plasma products and the infusion of coagulation factor concentrates. However, threshold for intervention with these procoagulants are controversial, varying widely among institutions.
Summary Coagulopathy and bleeding after cardiac surgery are often multifactorial. A timely and proper hemostatic intervention guided by point-of-care coagulation testing might reduce complications secondary to hemodynamic instability, prolonged mechanical ventilation, and transfusion of large amounts of allogeneic blood products.

Keywords Cardiac surgery · Coagulopathy · Blood component transfusion · Coagulation management · Coagulation testing

This article is part of the Topical Collection on *Cardiovascular Anesthesia*

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Introduction

Approximately 5–15% of major cardiac surgical patients with cardiopulmonary bypass (CPB) suffer from postoperative hemorrhage [1–3]. Definitions of major hemorrhage and massive transfusion have been poorly standardized, but protracted postoperative bleeding commonly leads to anemia, increased use of blood products, pericardial tamponade, surgical re-exploration, organ failure, prolonged stay in the intensive care unit, and higher mortality [4, 5].

Etiology of bleeding after cardiac surgery is often obscured by multifactorial causes including inadequate surgical hemostasis, thrombocytopenia, platelet dysfunction, coagulation factor deficiency, fibrinolysis, heparin rebound, and metabolic derangements. While most of the early coagulopathic disorders might be contributed to CPB, intraoperative hemodilution, and consumption of coagulation factors, the untreated bleeding leads to furhter deterioration of the hemostatic system after surgery, thereby worsening the coagulopathic status of the patient. A timely hemostatic intervention reduces complications secondary to hemodynamic instability, mechanical ventilation, use of extracorporeal membrane oxygenation [5], and large amounts of allogeneic blood transfusion [6–9, 10•].

Transfusion of blood and blood products has been a crucial resuscitative measure in cardiac surgery for more than 60 years. Today, the majority of transfusion is selectively

administered as a component therapy including packed red blood cell (PRBC), platelets, plasma, and cryoprecipitate. In many European countries, the administration of coagulation factor concentrate has become standard therapy to manage postoperative bleeding [11].

However, it is crucial to determine the etiology of coagulopathic bleeding and the need for a specific component. To be most effective, a diagnostic procedure should be performed in a timely fashion, but standard laboratory coagulation tests usually take 30 to 90 min [12, 13]. Blood components are often administered empirically to prevent and/or treat severe coagulopathy when no point-of-care (POC) testing is available [9]. Although this approach can be life-saving in a patient with uncontrolled bleeding, imprecise selection and untimely dosing of hemostatic components may result in deleterious under- or over-dosing of procoagulants [14, 15].

It is estimated that 10 to 15% of the blood supply in the USA is consumed during or after cardiac surgery [16, 17]. Although the safety of blood products with regard to pathogen transmission risks has improved over the years, there are ongoing debates about non-infectious complications including storage lesions of PRBC, post-transfusion alloantibody formation, and transfusion-related acute lung injury (TRALI) [18–20]. There have been clinical efforts to minimize allogeneic blood product usage by utilizing a transfusion algorithm which incorporates point-of-care coagulation testing, and early uses of plasma-derived factor concentrates [3, 6, 7, 9, 21••].

This review focuses on the current evidence and emerging data relating to modern strategies in coagulation management in bleeding patients after cardiac surgery.

Coagulopathy After Cardiopulmonary Bypass

Coagulopathy after cardiac surgery is common, but its true incidence remains difficult to determine. It is highly variable depending on definition [22•], preexisting coagulopathy and medication, type of surgery, length of CPB, and surgical technique [23, 24]. However, postoperative coagulopathy and bleeding have major impact on morbidity and mortality [23] because of transfusion-related complications, surgical re-exploration, thromboembolic events, intubation time, and length of stay in the intensive care unit (ICU) [4, 25, 26]. In fact, excessive bleeding leads to surgical re-exploration in up to 50% of these patients [17, 23, 24, 27]. Surgical re-exploration has been associated with increased mortality and morbidity including bleeding, myocardial infarction, renal failure, and prolonged ventilator support [28].

Obvious surgical bleeding may be identified during re-exploration [27], but medical coagulopathy seems to be more common even in the case of re-exploration. Multiple factors as stated above in any combination might contribute to coagulopathy and increased bleeding after cardiac surgery [26], especially after prolonged CPB. It is usually impossible to exactly predict and determine the exact etiology and degree of the specific coagulation disorder without specific testing. Notably, changes in coagulation factor levels and platelet count are not linear to the degree of hemodilution [29]. Further, coagulopathy affects both the procoagulant and anticoagulant proteins, and the loss of procoagulant factors might be counter-balanced by reduced anticoagulants, e.g., antithrombin [29]. An individual case-specific evaluation is, therefore, crucial [29, 30]. The use of POC coagulation testing rather than conventional laboratory testing and the application of a proper transfusion algorithm has been recommended in the European guidelines for the treatment of massive postoperative bleeding to achieve a timely hemostatic intervention [31]. Such a strategy might reduce secondary complications due to massive postoperative bleeding [32]. However, trigger and target levels of coagulation factors in POC and laboratory testing for procoagulant intervention are still under debate [22•].

Perioperative Coagulation Testing

Conventional laboratory tests including prothrombin time (PT) and activated partial thromboplastin time (aPTT) have been used for a long time in the clinical setting. They might be especially useful as a screening tool for hereditary bleeding disorders, heparin anticoagulation, and control of vitamin K-dependent oral anticoagulants. However, a long turn-around time (30–45 min) and sensitivity to heparin during CPB make laboratory-based PT and aPTT impractical for guiding plasma transfusion in the case of serious bleeding immediately after CPB [15]. In addition, PT and aPTT do not reflect imbalances between procoagulant and anticoagulant factor activities or platelet function inhibition. In summary, there is a paucity of data supporting the use of PT/aPTT in predicting the multifactorial coagulopathy of perioperative patients [33, 34]. The use of a transfusion algorithm might partly compensate such limitations, and it has been effective in reducing blood usage in numerous studies in cardiac surgery [35].

Use of viscoelastic coagulation tests including thrombelastography (TEG®; Haemonetics, Niles, IL) and thromboelastometry (ROTEM®; TEM Innovations, Munich, Germany) has been reported to be better suited for coagulation testing in major surgery. ROTEM/TEG differs from conventional PT and aPTT testing in several aspects. First, they are primarily performed in the whole blood using citrated whole blood samples, and testing can be immediately started without plasma separation. Second, testing can be performed during CPB because a reagent containing a heparin neutralizer is available. Third, the key end point of viscoelastic testing is fibrin polymerization and platelet-fibrin interaction, which is not reflected in either PT or aPTT [36].

Key concepts and uses of TEG and ROTEM have been reviewed elsewhere [36, 37]. Briefly, ROTEM is performed using citrated whole blood sample (300 μl) which is placed in a plastic cup using an semi-automated pipette. The sample is recalcified with $CaCl_2$, 0.2 mmol l^{-1} (STARTEM; 20 μl), and activated with 20 μl of EXTEM (tissue factor, TF) or INTEM reagent (ellagic acid). Subsequently, the plastic pin is immersed in the blood. Once thrombin is generated in the blood, platelets are activated to express glycoprotein (GP) IIb/IIIa receptors, and fibrin is formed and polymerized. The interactions of GP IIb/IIIa receptors and polymerized fibrin increase the torque (viscoelasticity) between the cup and the rotating pin (at a 4.75° angle). The breakdown of fibrin strands by fibrinolysis decreases the torque. The change in torque is detected optically and is processed to trace clot formation and a possible clot breakdown.

The commonly used ROTEM variables include coagulation time (CT; seconds), clot formation time (CFT; seconds), α-angle (degrees), amplitude at 10 min after CT (A_{10}; millimeters), maximum clot firmness (MCF; millimeters), and maximum lysis (ML; maximal % decrease in clot firmness; Fig. 1). Several other tests are available in addition to EXTEM and INTEM for a specific diagnosis of coagulation problems. FIBTEM is a modified EXTEM test with cytochalasin D, which inhibits platelet cytoskeletal reorganization and, thus, fibrin(ogen) binding to platelet GP IIb/IIIa (Fig. 1a, b). By combining EXTEM and FIBTEM, the differential diagnosis of thrombocytopenia and/or hypofibrinogenemia is feasible within 20 min [38]. APTEM is also a modified EXTEM test, in which aprotinin inhibits plasmin in vitro if systemic fibrinolysis is present (Fig. 1d, e). HEPTEM contains a heparinase in addition to the INTEM reagent. It is used as a pair with INTEM for the diagnosis of systemic heparin activity (Fig. 1f) [39].

Technical principles of TEG are similar to ROTEM, but other reagents and parameters are used. For both systems, cartridge systems avoiding any pipetting have been recently introduced. They might allow for even shorter turn-around time, and a true point-of-care usage. Finally, the use of transfusion algorithm incorporating thromboelastometry in combination with factor concentrates has been shown to reduce allogeneic blood product usage in patients undergoing cardiac surgery with CPB [35]. In a randomized controlled study, the use of a POC-guided transfusion algorithm even reduced postoperative morbidity and mortality as compared to a standard regimen [9].

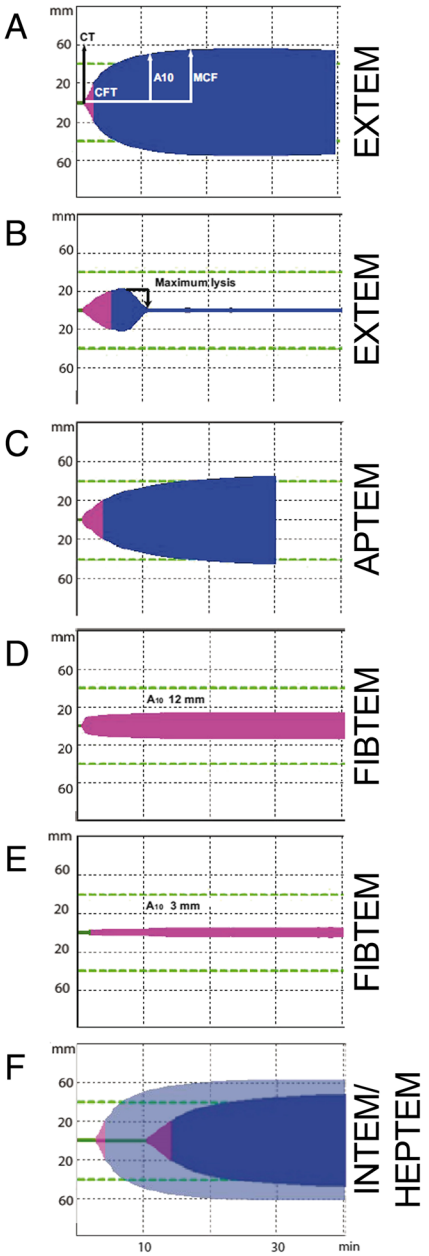

Fig. 1 Examples of ROTEM tracings. **a** Normal EXTEM; CT = clotting time (s), CFT = clot formation time (s), A_{10} = amplitude at 10 min after CT, MCF = maximum clot firmness. **b** Fibrinolysis demonstrated on EXTEM; maximum lysis >15% suggests profibrinolytic state. **c** Fibrinolysis resolved in vitro by aprotinin contained in APTEM. **d** FIBTEM indicates normal plasma fibrinogen (A_{10} 12 mm and MCF 15 mm). **e** Low plasma fibrinogen demonstrated by low A_{10} (3 mm) and MCF (4 mm) on FIBTEM. **f** Prolonged CT demonstrated on INTEM in the presence of heparin. The tracing is normalized on HEPTEM (transparent trace)

Perioperative Coagulation Therapy

1. *Platelet Transfusion*

Clinically relevant bleeding after CPB is frequently attributed to thrombocytopenia and/or platelet dysfunction due to CPB and/or to the intake of platelet function inhibitors. Both of them, thrombocytopenia and platelet dysfunction, are commonly used triggers for platelet transfusion [40]. However, there is no specific preoperative or postoperative threshold of platelet count that has been associated with increased bleeding. Typically, platelet transfusion occurs in perceived

bleeding tendency and post-CPB platelet count between 50×10^3 and 100×10^3 μl^{-1} [22•]. A simple transfusion algorithm using the cutoff value of 50×10^3 μl^{-1} rather than 100×10^3 μl^{-1} for coronary artery bypass grafting surgery (CABG) was effective in reducing the amount of transfused platelets without increasing postoperative bleeding or RBC transfusion [41]. However, no preoperative platelet inhibitors were used in this study.

Bleeding risk from aspirin monotherapy is most probably mitigated by the routine use of antifibrinolytic therapy in cardiac surgery [42]. In fact, the perioperative administration of tranexamic acid was able to reduce perioperative bleeding volume and transfusion of blood products in CABG patients with recent intake of aspirin [43••]. Similar findings were reported in patients with continued intake of clopidogrel before cardiac surgery [44]. These findings might also be interpreted as a general protective and blood-saving effect of tranexamic acid in cardiac surgery patients.

In the case of ongoing therapy with clopidogrel, preoperative assessment of residual responsiveness to adenosine 5′-diphosphate (ADP) seems reasonable because there is a relatively high incidence of clopidogrel non-responsiveness [45]. Marla et al. recently demonstrated that adjusting the preoperative waiting period between less than 1 and 5 days before CABG according to the residual platelet responsiveness is feasible without increasing bleeding in a prospective study of clopidogrel-treated patients (n = 86) and clopidogrel-naïve patients (n = 94). Twenty-four-hour chest tube drainage (median, 650 vs. 780 ml; P = 0.08), transfusion rates of PRBC (median, 2 units in both; P = 0.54), and 30-day mortality (one death in each group; P = 1.0) were similar between two groups [46]. For urgent procedures, a potential need for postoperative platelet transfusion can be assessed by preoperative testing for $P2Y_{12}$ inhibition [40]. However, routine testing of platelet ADP response is not yet recommended in cardiac surgical patients with preoperative $P2Y_{12}$ inhibitor therapy due to insufficient supporting data validated in large series and due to lack of well-defined threshold values limiting the reliability of the different platelet function tests.

Platelet transfusion is not always necessary to achieve adequate hemostasis in patients with dual treatment with aspirin and clopidogrel in contrast to treatment with a newer and more potent $P2Y_{12}$ inhibitor. Platelets are more extensively inhibited with prasugrel or ticagrelor as compared to clopidogrel [47]. Therefore, bleeding tendency and need for transfusion of blood products including platelets are significantly higher in patients undergoing cardiac surgery treated with prasugrel as compared to clopidogrel [48].

2. *Plasma Transfusion*

Transfusion of fresh frozen plasma (FFP) has been the standard to treat coagulation defects after CPB for many years. In fact, FFP is still the mainstay therapy at many cardiac centers in the USA and in the UK. Different plasma products are used including thawed plasma, plasma used within 24 h of collection, and others. In this review, we use the term "plasma" for all these products.

Use of plasma has recently been questioned due to only small incremental changes in coagulation factors despite liberal use of plasma. Coagulation factors (F) II, V, VII, and X are increased by median 10–16% after the transfusion of about 10 ml plasma kg^{-1}. To relevantly increase coagulation factor levels, large amounts of plasma transfusion are needed (about 30 ml kg^{-1} or about 10 bags of plasma in a 70-kg person) [49]. This might result in volume overload, especially in patients with limited cardiopulmonary reserve [50].

To avoid or reduce plasma transfusion and to relevantly increase coagulation factor concentrations, the use of coagulation factor concentrates has been suggested. In a recently published study, the administration of prothrombin complex concentrate (PCC) (n = 87), a lyophilized concentrate of FII, FVII, FIX, and FX, for acute warfarin reversal (INR 2.9), before surgery was more effective as compared to plasma transfusion [50]. Clinical impacts of a lower volume of PCC compared to plasma (mean, 89.7 vs. 819 ml) were evident in the shorter duration of therapy (20.9 vs. 141 min), the higher factor levels, and the lower incidence of fluid overload (3 vs. 13%; P = 0.048). Clinical experience and data in congenital and acquired bleeding management support the preferred use of factor concentrate over plasma when deficient factors are specifically known, and replacement factors are available as plasma-derived or recombinant freeze-dried protein(s) [11]. However, in massive hemorrhage and extensive factor deficiencies, plasma transfusion remains an important therapy as part of a massive transfusion protocol and as a means to replace FV and FXI as well as endogenous anticoagulants and fibrinolysis inhibitors [51, 52]. In addition, plasma products better preserve colloid osmotic pressure due to preservation of glycocalyx than crystalloids [53] with a potential positive impact on vascular integrity.

3. *Fibrinogen Concentrate and Cryoprecipitate*

Plasma fibrinogen is normally in the range of 2 to 4 g l^{-1}, but in relevant bleeding after cardiac surgery, its level might frequently be below 1.5 g l^{-1}. Despite not being fully elucidated, the threshold fibrinogen level for adequate hemostasis after CPB is reported to be ≥2 g l^{-1} (e.g., in the low normal range) [54, 55]. Emerging clinical data show some promise of further reducing plasma transfusion in cardiac surgery by primarily focusing on fibrinogen replacement [3, 6, 21••, 26]. Traditionally, plasma transfusion has been advocated for fibrinogen replacement. However, allogeneic plasma products contain fibrinogen at around 2 g l^{-1}, but post-transfusion fibrinogen levels achievable in a patient is only about 60% of

the original product level even after a massive plasma transfusion (i.e., 1 to 1.4 g l^{-1}) [56]. Therefore, fibrinogen-rich products such as cryoprecipitate or fibrinogen concentrates must be used for effective fibrinogen substitution in hypofibrinogenemia. Plasma-derived fibrinogen concentrate is treated with several pathogen reduction processes, and is free of ABO antibodies. However, cryoprecipitate is not treated with a pathogen reduction procedure, and thawing and blood type compatibility are prerequisite for transfusion.

Whereas several studies showed a relevant reduction of requirements of allogeneic products including platelets, FFP, and RBC after fibrinogen substitution in coagulopathic patients after cardiac surgery [3, 6, 21••, 26], more recent studies failed to show such an effect [57•, 58, 59]. The value of fibrinogen substitution in patients without hypofibrinogenemia or the prophylactic administration in patients without relevant bleeding seems highly questionable. Studies using cryoprecipitate for fibrinogen substitution are scarce. However, similar efficacy of fibrinogen concentrate (60 mg kg^{-1}) and cryoprecipitates (10 ml kg^{-1}) has been suggested [8, 60].

It seems important to diagnose hypofibrinogenemia in real time, and to promptly replace fibrinogen in the case of bleeding [10•]. Thromboelastometry has been used in several fibrinogen replacement studies in cardiac surgery [3, 6, 9, 21••, 58], and formulas for fibrinogen (in grams) based on FIBTEM (A_{10}, 10 min amplitude or MCF) have been suggested [3, 11, 58]. However, there seems not to be a universal FIBTEM-A_{10} or MCF threshold for fibrinogen replacement that is applicable to all types of patients and cardiac surgical procedures. FIBTEM values between 8 and 22 mm have been used. A recent post hoc analysis by Ranucci et al. showed that aiming for FIBTEM-MCF values >14 mm did not further reduce bleeding and transfusion of blood products [61••]. From a safety aspect, targeting for higher FIBTEM thresholds may result in overdosing of fibrinogen in some cases, in which bleeding is due to complex coagulopathy with deficiency of coagulation factors other than fibrinogen. A recent propensity score analysis on the adult cardiac surgical cases showed that the use of fibrinogen concentrate targeting fibrinogen level of 2 g l^{-1} (corresponding to a FIBTEM-A_{10} of about 10 mm) was not associated with increases in morality, major cardiac events, or thromboembolic events within 1 year compared to the cohort without fibrinogen replacement [62•].

4. *Other pro-hemostatic therapies*

Antifibrinolytic therapy is routinely used in cardiac surgery with CPB. Since the suspension of aprotinin, a direct plasmin inhibitor, in 2007, lysine analogues ε-aminocaproic acid (EACA) and tranexamic acid (TXA) are the two main antifibrinolytic agents. Despite that the suspension of aprotinin was ultimately reversed by the Health Canada and the European Medicines Agency in 2011 after it became evident that inappropriate data uses skewed the conclusion in the BART trial [63], aprotinin is no longer used as an antifibrinolytic in most countries including the USA. Antifibrinolytic therapy is effective in reducing bleeding and PRBC transfusion compared to the placebo in cardiac surgical patients on aspirin [43••]. However, in the case of severe hemodilution such as DHCA cases, antifibrinolytic therapy alone may not be sufficient to control bleeding, and multimodal hemostatic interventions to restore fibrin polymerization should be considered using viscoelastic testing. Lysine analogues are considered to be relatively safe interventions, and EACA and TXA are not associated with an allergic reaction after repeated exposures due to their low molecular weights (131 and 157 Da, respectively). Systemic thrombosis is uncommon with EACA or TXA, but their uses should not be cautioned in patients with a history of thrombosis, or disseminated intravascular coagulation. High doses or prolonged infusion of TXA has been associated with epileptogenic effects [43••]. This is presumably due to TXA crossing the blood-brain barrier and antagonizing GABA and glycine receptors [64].

Recombinant activated FVII (rFVIIa) is a synthetic coagulation factor concentrate that is indicated for the prevention and treatment of bleeding in patients with hemophilia with inhibitors. Hemostatic therapy using rFVIIa has become the mainstay bypassing therapy in hemophilia after it was shown to be effective with a relatively low risk of thrombosis [65]. Subsequently, rFVIIa has undergone a wide spread off-label use in the USA and elsewhere as a rescue hemostatic intervention in perioperative bleeding, especially after CPB [66]. Despite being highly effective in the treatment of refractory bleeding after cardiac surgery [67], the off-label use of rFVIIa has been associated with adverse thromboembolic events, especially in the arterial system [68]. Therefore, the off-label use of rFVIIa should be limited to hemophilia indications and as last-ditch therapy in refractory microvascular bleeding after open heart surgery [69].

The therapeutic substitution with factor XIII (10 to 50 IU kg^{-1}) after protamine administration to reduce postoperative bleeding was tested in three randomized controlled trials including a total of 527 patients [70–72]. None of these studies showed any beneficial effects of FXIII substitution regarding postoperative bleeding volumes and transfusion rates.

Specific Situations

1. *Platelet inhibitors*

There are an increasing number of patients presenting for semi-urgent and emergent cardiac surgery with intake of platelet inhibitors up to scheduled surgery. Whereas most cardiac surgeons are used to handle with aspirin-inhibited platelets, the more potent $P2Y_{12}$ inhibitors might still be a relevant problem. Especially the novel and more potent drugs as

prasugrel and ticagrelor have been associated with increased bleeding tendency, rate of surgical re-exploration, and the use of allogeneic blood products [48].

The use of antifibrinolytics might be sufficient in reducing bleeding in patients on aspirin, but platelet transfusions are frequently given to patients on $P2Y_{12}$ inhibitors. It is important to consider plasma half-lives of platelet inhibitors and their metabolites. Circulating residual $P2Y_{12}$ inhibitor activity might reduce therapeutic responses to platelet transfusion, and adding a wait time of 6–24 h would allow natural recovery of platelets from $P2Y_{12}$ inhibitors.

2. *Direct Oral Anticoagulants*

Direct oral anticoagulants (DOACs) are increasingly used as an alternative to warfarin for the prevention of stroke due to non-valvular atrial fibrillation, and for the prevention and treatment of deep venous thrombosis and pulmonary thromboembolism [73]. DOACs include the direct thrombin inhibitor dabigatran etexilate and the direct FXa inhibitors, rivaroxaban, apixaban, and edoxaban. Additional drugs will emerge on the market.

Recently, idarucizumab has been approved in the USA and many European countries for rapid reversal in patients receiving dabigatran. Idarucizumab is a humanized Fab fragment of murine monoclonal antibody, which rapidly binds to dabigatran, and neutralizes its anticoagulant effect. In a prospective cohort study including 90 patients with a serious bleeding or undergoing urgent surgical procedure, 5 g of intravenous idarucizumab completely effectively reversed the anticoagulant effect of dabigatran within minutes [74••].

For patients with direct Xa inhibitors, andexanet alfa, which is a recombinant factor Xa analogue lacking procoagulant activity, has been showed to effectively reverse their action. Andexanet alfa reversibly binds to an anti-Xa molecule with a half-life of about 1 h. In a prospective study including 67 patients, it reduced anti-Xa activity due to intake of direct Xa inhibitors by 80–90% [75••]. However, a continuous infusion for several hours might be necessary due to the short half-life of andexanet alfa.

Finally, aripazine (ciraparantag, PER977) is a synthetic small molecule (512 Da) which presumably reverses dabigatran and anti-Xa agents as well as heparin and low molecular weight heparin. This agent is still in phase I and II stages of clinical development.

Non-specific reversal agents including rFVIIa, PCC, and activated PCC (factor bypassing agent, FEIBA) are considered in the case of life-threatening bleeding induced by DOAC when specific antidotes are not available [76], but clinical evidence for their efficacy and dosing in DOAC reversal is lacking. However, the rapid reversal of an anticoagulant drug might be associated with increased risk of thromboembolic events in the target population which is usually aged and has an inherent high risk of complications due to coexisting diseases.

Conclusion

Coagulopathy and bleeding after cardiac surgery are often a multifactorial problem. Viscoelastic coagulation testing is a unique diagnostic modality focused on fibrin polymerization. Comprehensive coagulation testing during CPB and early intervention(s) targeting fibrin polymerization are more effective than conventional coagulation therapies with or without standard laboratory coagulating testing. With the exception of patients treated with oral anticoagulants, there is no data supporting preemptive (prophylactic) transfusions of plasma, platelets, or coagulation factors. Whole blood platelet function testing is also useful in guiding the management of patients on preoperative antiplatelet therapy.

Clinical trials should be focused on testing a combination of management strategies in the treatment of bleeding patients after cardiac surgery on effectiveness, adverse clinical outcomes, and costs in cardiac surgery.

Compliance with Ethical Standards

Conflict of Interest Daniel Bolliger and Kenichi A. Tanaka declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article includes only data from published studies with human or animal subjects which were performed in compliance with ethical standards.

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