

Point-of-care coagulation testing in cardiac surgery: an updated narrative review

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Abstract: *Objective:* To summarize current literature and guidelines on the use of point-of-care coagulation tests (POCCT) in the treatment and prediction of perioperative bleeding during cardiac surgery and its impact on transfusion rate and patient outcome.

Background: Bleeding complications after cardiac surgery are common and can lead to postoperative anemia and allogeneic blood transfusions (ABT), they often require surgical re-exploration, prolong mechanical ventilation and ICU length of stay, increase health-care costs and can even cause death. Recent guidelines on patient blood management suggest that a timely diagnoses of underlying coagulation abnormalities is of paramount importance with the aim of only administering selectively those blood products or pro-hemostatic components that are actually needed and thereby reducing unnecessary ABT.

Discussion and conclusion: The cause of bleeding in the perioperative period during cardiac surgery is multifactorial. Preoperative antiplatelet or anticoagulant therapy can influence perioperative bleeding. The hemostatic changes induced by cardiopulmonary bypass can result in consumptive coagulopathy and hyperfibrinolysis. Therefore, finding the specific origin of the bleeding and the hemostatic derangement is of paramount importance. Conventional coagulation tests are not equipped to give this information in a timely manner in the setting of an acute bleeding. POCCTs have low predictive value for postoperative bleeding. However, evidence shows that individualized implementation of an algorithm with POCCTs can reduce ABT to the absolute essential, improve patient outcome and reduce health-care costs in the management of bleeding after cardiac surgery.

Keywords: Whole blood coagulation time' (Mesh); 'Cardiac surgical procedures' (Mesh); 'Point-of-care testing' (Mesh).

INTRODUCTION

Bleeding complications after cardiac surgery are common and can lead to postoperative anemia and allogeneic blood transfusions (ABT), they often require surgical re-exploration, prolong mechanical ventilation and ICU length of stay, increase health-care costs and can even cause death (1-3).

Incidences of excessive bleeding have been reported in up to 15% of patients undergoing cardiac surgical procedures leading to surgical re-exploration in 2 to 5% of patients (4-8). Approximately 15-20% of all blood products are used for complex cardiac surgery (2). The underlying etiology of those bleeding complications is a combination of surgical causes (i.e. inadequate surgical hemostasis at the end of surgery), pre-existing or acquired coagulation disorders and metabolic derangements (9). However, when emergency re-exploration is performed, only in a small portion of patients a surgical cause is found (5).

Coagulopathic bleeding after cardiac surgery often requires treatment by the administration of allogeneic blood products and pro-hemostatic components. Moreover, untreated coagulopathic bleeding can lead to further deterioration of the patient's hemostatic system, thereby worsening the coagulopathic status. Unfortunately, anemia and transfusion of allogeneic blood products including packed red blood cells (PRBCs), fresh frozen plasma and platelet concentrates have been identified as independent risk factors for worse patient outcome (10). Even transfusion of 1 or 2 units of PRBCs has been associated with increased morbidity and mortality in patients undergoing coronary artery bypass grafting (11-13). Risks associated with allogeneic blood transfusions are numerous and can grossly be subdivided into infectious (i.e. viral or bacterial contamination) and non-infectious adverse reactions (14-16). Nowadays, non-infectious complications are responsible for the majority of adverse events associated with transfusions in the developed countries with transfusion-related acute lung injury

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often being referred to as the most common cause of death related to transfusion worldwide (17-19). Moreover, multisystem organ failure, stroke, renal impairment, venous thromboembolism, increased hospital length of stay and ICU length of stay were all identified as independent transfusion risks in cardiac surgical patients (1, 2). In addition to ABT, the administration of pro-hemostatic components like prothrombin complex concentrate, recombinant factor VII and fibrinogen concentrate or cryoprecipitate has been associated with adverse thrombotic events and consequently its safety is still controversial (20, 21)

By the end of the nineties, scientists launched a concept named "Patient Blood Management" (PBM) which subsequently emerged worldwide with the aim of reducing ABT and thus improving patient outcomes (22). Blood management would become the standard of care and transfusion the alternative. This new way of thinking was driven by many reports of successful major surgery and even cardiac surgery in Jehovah's Witnesses patients together with the emergence of blood-borne diseases like hepatitis and acquired immune deficiency syndrome (AIDS) and further supported by the increasing numbers of reports on the adverse events of ABT (14). In fact, a paradigm shift took place from a product-centered approach to a patient-centered approach. Since then, many PBM programs have been evolved and nowadays PBM consists of three pillars, namely preoperative optimization of the patient's own red cell mass, the intraoperative minimization of surgical blood loss and finally the optimization of the patient's physiological tolerance of anemia. Of note, these measures might be most successful when being combined or used as bundles of care (23).

Recently, both European and American Societies published PBM-guidelines for adult and pediatric cardiac surgery (24-26). In the light of coagulopathic bleeding during and after cardiac surgery, guidelines suggest that a timely diagnosis of the underlying coagulation abnormality and subsequent intervention is of paramount importance with the aim of only administering selectively those blood products or pro-hemostatic components that are actually needed and thereby reducing unnecessary ABT. Without coagulation testing, blood products and hemostatic components are often administered empirically as "educated guesses" to prevent and/or treat severe perioperative bleeding and coagulopathy (27). These practices inevitably lead to under- or overdosing of procoagulants and a large amount of unnecessary transfusions,

which can expose the patient to circulatory overload, transfusion-related immunomodulation, nosocomial infections, sepsis and increase mortality (2, 28, 29). Point-of-care (POC) coagulation testing devices could be a crucial tool for early diagnosing coagulopathic bleeding and the administration of those specific components that are actually needed in the right dose for the right patient (28, 30-33). This translates in a reduction of adverse events and postoperative complications and therefore a reduction in health care cost after cardiac surgery (34).

In this review we will focus on the use of POC coagulation devices in cardiac surgery. We will summarize the etiology of coagulopathic bleeding after cardiopulmonary bypass, review the different commercially available POC devices and discuss their role in both the prediction and treatment of bleeding complications after cardiac surgery.

WHY DO PATIENTS BLEED AFTER CARDIAC SURGERY?

As mentioned before, the underlying etiology of bleeding complications after cardiac surgery is multifactorial and often related to coagulation disorders. Indeed, multiple factors might contribute to coagulopathic bleeding after cardiac operations including preoperative administration of anticoagulant drugs, incomplete heparin-reversal at the end of surgery, protamine overdosing and the specific hemostatic derangements that have arisen during cardiopulmonary bypass (CPB). Furthermore, also metabolic derangements like hypocalcemia, acidosis and hypothermia can significantly reduce the quality of clot formation (2, 5, 35-38)

Drugs affecting the hemostatic system

Patients scheduled for cardiac surgery are frequently treated preoperatively with drugs that interact with the hemostatic system. Antiplatelet therapy with acetylsalicylic acid and/or P2Y₁₂-inhibitors (clopidogrel, prasugrel or ticagrelor) is commonly used, especially in those patients undergoing coronary artery bypass grafting. Also, oral anticoagulants like vitamin-K-antagonists (warfarin or coumarin derivatives) or the newer direct oral anticoagulants (rivaroxaban, edoxaban, apixaban and dabigatran) are being used in a large number of patients (e.g. patients with atrial fibrillation or at risk for venous thromboembolism). Additionally, some patients are treated with low-molecular-weight heparin, unfractionated

heparin (UFH) or even bivalirudin preoperatively. When the discontinuation of dose drugs before the beginning of surgery is not adequately managed, patients may suffer from prolonged drug effect in the perioperative period contributing to an increased risk for coagulopathic bleeding after surgery. For each of dose drug classes, guidelines have suggested well-defined cessation times in order to significantly reduce unnecessary large amounts of perioperative blood losses and ABT (25, 39).

During cardiac surgical procedures high doses of UFH (typically loading doses of 300 to 500 U/kg supplemented by further bolus doses during the procedure) are traditionally administered to prevent thrombin generation and clot formation while on CPB (40). Even off-pump procedures require significant anticoagulation therapy with UFH although lower doses seem acceptable. After weaning from cardiopulmonary bypass, protamine sulfate is administered to antagonize heparin by dissociation from the antithrombin III-heparin complex. Ideally, the protamine dose should be titrated in such a way that all the residual heparin molecules become neutralized. However, when given in more than 1:1 dosing ratio with the initial heparin dose, it reduces platelet aggregation and enhances fibrinolysis. Even when given in a 1.3:1 dosing ratio it can impair thrombin regeneration and platelet aggregation (37, 38) and prolong the ACT (5). Therefore dosing protamine should not exceed the 1:1 ratio based on the initial heparin dose (38). Unfortunately, there is always the possibility of incomplete heparin antagonization and residual heparinization or heparin rebound is common after surgery.

When the administration of UFH in cardiac surgical patients is contraindicated due to known allergy for heparin or protamine or because the patient developed heparin-induced thrombocytopenia (HIT), the direct thrombin-inhibitor bivalirudin seems a valid alternative (41). However, its anticoagulant effect is prolonged up to about 40 minutes after discontinuation and no antidote exists for immediate reversal of its drug effect (41, 42)

Hemostatic effects of CPB

The etiology of postoperative bleeding after cardiac surgery is often complex and related to the hemostatic changes caused by CPB and cardiac surgery.

First of all, the major surgical trauma on itself induces platelet aggregation and the release of tissue factor. This activates the formation of a platelet plug

and the intrinsic and extrinsic coagulation pathways (36).

Secondly, the contact of whole blood with the tubing of the extracorporeal circuit induces a systemic inflammatory response with activation of procoagulant and anticoagulant factors which leads to thrombin generation and consumption of coagulation factors (5, 43, 44). The contact of fibrinogen with the non-endothelial surface activates and consumes platelets. Additionally, factor XIIIa is activated and starts the intrinsic pathway. Both pathways induce excessive thrombin generation which accelerates the consumption of coagulation factors and results in consumptive coagulopathy. To prevent this process, heparin is administered (36). It makes sure no immediate clotting arises as soon as the blood makes contact with the circuit. These inflammatory responses after contact activation with the non-endothelial surfaces will decrease when the surface becomes more biocompatible (44). The priming of the extracorporeal circuit with a crystalloid solution (40, 45) can result in a dilutional coagulopathy. Reducing priming volume from 1500ml to 1100ml can significantly reduce the need for ABT. These dilutional coagulopathic changes can be confirmed with rotational thromboelastometry (ROTEM) (29, 44).

Thirdly, CPB induced hyperfibrinolysis can diminish coagulation further. Initial activation of the intrinsic pathway forms active kallikrein that enhances the formation of bradykinin. When on cardiopulmonary bypass the pulmonary circulation is taken over by the bypass and bradykinin is not deactivated which leads to an accumulation. This enhances the formation of plasmin that breaks down the newly formed clot by cleaving the fibrinogen and fibrin. To prevent hyperfibrinolysis during cardiopulmonary bypass tranexamic acid or aprotinin can be administered (5, 36, 45). Tranexamic acid is a synthetic lysine analogue which inhibits plasmin and is recommended by guidelines to reduce ABT and reoperation for hemorrhage in cardiac patients (25). Aprotinin is a natural serine protease inhibitor and has been shown to be more effective in the reduction of blood loss during high risk cardiac surgery (46). However in the BART trial (47), it revealed a significantly higher mortality rate and subsequently aprotinin became no longer available in Europe. Afterwards, multiple RCT's proved aprotinin to be effective and Walkden and his colleagues performed a retrospective case-control study on more than 8000 patients (48) which revealed no causal relationship between the use of aprotinin and adverse events. A Cochrane review

on 252 RCTs (49) couldn't establish an increase in mortality, myocardial infarction, stroke or renal dysfunction either, which ultimately led to the reintroduction of aprotinin. Nowadays, the use is mainly considered off-label in high-risk surgeries.

SUMMARY OF AVAILABLE POINT-OF-CARE DEVICES

Viscoelastic tests

Thromboelastography

Thromboelastography (TEG®; Niles, IL, USA) is first described in 1948 by Hartert and determines clot stiffness during coagulation. Whole blood needs to be manually pipetted in a cup, which oscillates around a fixed, suspended pin. After clot formation is activated by a stimulant (tissue factor for rapidTEG or a contact-activator for kaolinTEG), the viscoelastic changes create an increasing torsion that is detected by an electromagnetic transducer (29,50). The effect of heparin can be counteracted by heparinase (HTEG) and with the functional fibrinogen test for TEG the interaction between fibrin and platelets can be withheld (Functional Fibrinogen). Results are given by a specific TEG output and their derived parameters (Table 1).

Thromboelastometry

Rotational thromboelastography (ROTEM®; Munich, Germany) is a modern modification of the TEG technology. In ROTEM the oscillation of a pin, in a fixed cup filled with whole blood, is optically detected by a charged coupled device (43,50). Coagulation activators, such as tissue factor for EXTEM and contact-activator for INTEM, are added to the cup. In HEPTEM heparinase is added and for FIBTEM cytochalasin D is added to the EXTEM test which inhibits the binding of fibrin to platelets. The test also results in specific shape recognition curves (Fig. 1). Although, they both offer the

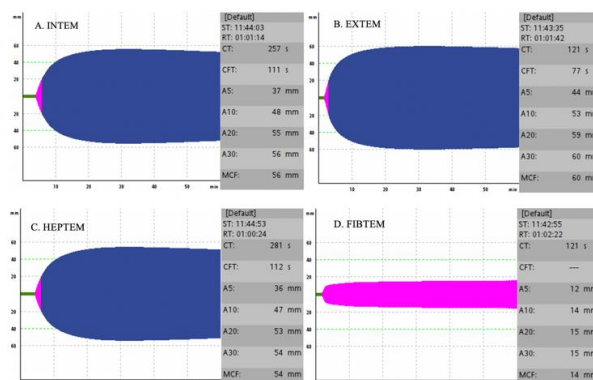
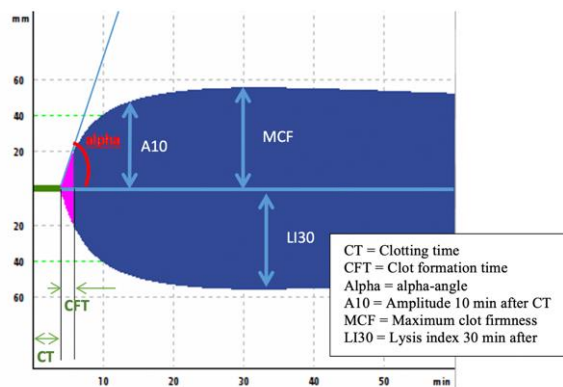


Fig. 1. — ROTEM: parameters and shape recognition curves A. INTEM (contact-activator); B. EXTEM (tissue factor); C. HEPTEM (heparinase); D. FIBTEM (cytochalasin D added to EXTEM).

same information on clot formation and firmness, the results of the two are not interchangeable(50). (Table 1).

Sonoclot Analyzer® (Sienco Inc, Arvada, CO, USA)

The Sonoclot Analyzer was first described in 1975 by von Kaulla as a device that measures the changing impedance to movement imposed by the developing clot on a small probe vibrating at an ultrasonic frequency in a coagulating blood sample (51). It has been described extensively (51), but briefly it detects the viscoelastic changes in viscosity

Table 1
 Comparison of viscoelastic test results

	ROTEM	TEG	Quantra
Contact activation	INTEM CT (s)	Kaolin R (min)	CT (s)
Neutralizing unfractionated heparin	HEPTEM CT (s)	Heparinase Kaolin R (min)	CTH
Tissue factor activation	EXTEM MCF (mm)	RapidTEG MA (min)	CS (hPa)
Block platelet contribution to clot formation	FIBTEM MCF (mm)	Functional Fibrinogen MA (mm)	Fibrinogen Contribution = FCS (hPa)
Block fibrinogen contribution to clot formation	/	/	Platelet Contribution = PCS (hPa)

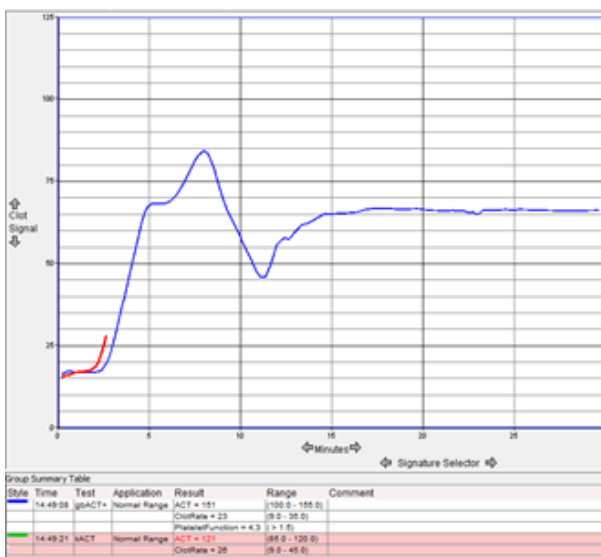


Fig. 2. — Sonoclot machine and signature.

of a whole blood sample after reagents have been added to initiate the clotting process (51-53). As the clot forms and the viscosity in the cup changes, a Sonoclot signature is plotted or quantitative results are given by ACT (Activated Clotting Time), Clot rate and Platelet function (54). (Fig. 2).

Activated Clotting Time device (ACT Plus® system, Medtronic, Minneapolis, MN, USA).

Activated clotting time or ACT can be measured separately via the whole blood coagulation test ACT. It is mostly used to detect therapeutic heparin effects during CPB. Although widely used, there is a poor correlation between measurement and heparin concentration when administered in low concentration (55). It is known to be more accurate before CPB and in higher heparin concentrations (5) (Fig. 3).



Fig. 3. — ACT.



Fig. 4. — Quantra® display.

Quantra® Hemostasis Analyzer (HemoSonics, LLC, Charlottesville, VA, USA)

Quantra Hemostasis Analyzer is a recently developed viscoelastic test that uses ultrasound to determine the formation of a clot in vitro. Strong correlations between results from Quantra® and ROTEM® tests could be confirmed (56,57). Ultrasonic waves are used to establish changes in resonance as the clot is formed. The use of ultrasound can be beneficial since there is no mechanical interaction with the clot formation (58). It uses a multi-channel cartridge that is automatically filled with whole blood from a citrated blood sample. It gives numeric results on a display, rather than the specific curves from TEG® or ROTEM® (57,59) (Fig. 4). The results are described as Clot Time (CT, seconds), Heparinase Clot Time (CTH, seconds), Clot Stiffness (CS, hectoPascals), and Fibrinogen Contribution (FCS, hPa). A more complete overview is given elsewhere (60) (Table 1).

Platelet function testing

Platelet function is severely affected during cardiopulmonary bypass. This because of changes in pH, platelet count due to consumptive coagulopathy, administered drugs, priming solutions and release of proinflammatory cytokines (61). Postoperative platelet count can be normal, however it can take up to 3 to 6 hours for platelet function to normalize after CPB (40). Here we give a short description of the available platelet function tests, however a more detailed comparative review is discussed elsewhere (62, 63).

The platelet function analyzer (i.e. PFA-100®) simulates primary hemostasis on small volumes of whole blood. When platelet plugs are formed in the capillary arteries, the blood flow is slowed down or stopped. The seconds needed for the flow to stop are described as closure time (CT). The CT can be prolonged by thrombocytopenia and shortened by the platelet activation during surgery, which can make the results of the test difficult to interpret in the perioperative setting (63, 64). In Multiplate®, platelets will adhere to the sensors after adding a stimulant to the whole blood and create a change in impedance of the electrodes. This change in impedance is described as 'Aggregation Units' or AU. Results are obtained as aggregation in AU, velocity (AU/min) and AUC (AU x min). It measures the platelet function in a physiological state with whole blood (63). ROTEM® Platelet works similarly (65). Results are given by A6 or amplitude at 6 minutes (Ohm), which describes how well platelets aggregate, by MS or maximum slope of the aggregation curve (Ohm/min), which describes how fast aggregation is initiated, and AUC or area under the curve (Ohm.min), which gives information on the overall platelet aggregation (65)

THE ROLE OF POINT-OF-CARE COAGULATION TESTS IN THE PERIOPERATIVE PERIOD OF CARDIAC SURGERY

The hemostatic management during cardiac surgery and cardiopulmonary bypass requires delicate monitoring. Routine coagulation tests, such as prothrombin time (PT) or activated partial thromboplastin time (aPTT) are solid tests, however insufficient and time-consuming (30-60 min) (2, 66) in the setting of an acute bleeding (43, 53, 66-69). Additionally, these coagulation tests have low predictive values for postoperative bleeding and transfusion needs. Only the preoperative determination of fibrinogen has a positive predictive value (PPV) of less than 20% and has shown to be

an independent predictor of postoperative bleeding and transfusion after cardiac surgery (25, 33, 70)

When perioperative or postoperative bleeding occurs, point-of-care coagulation tests (POCCT) can be very helpful in guiding therapeutical strategies and reducing the number of blood products that need to be transfused (71,72). In trauma patients and non-cardiac surgery patients the use of viscoelastic tests have shown to be beneficial in the treatment of bleeding (68, 73). Integrating ROTEM can increase the identification of acute traumatic coagulopathy with high sensitivity, however poor specificity (74). A large meta-analysis on the use of ROTEM in cardiac surgery could determine a number needed to threat of 9.4, which means that POC-guided transfusion in 10 patients can avoid transfusion in one patient (33).

The role of POCCT in the prediction of bleeding in cardiac surgery

Predictive factors for bleeding after cardiac surgery are platelet dysfunction, low preoperative fibrinogen concentration, reduced factor XIII activity, reduced thrombin generation, residual heparin effects, protamine overdoses or hyperfibrinolysis (2). Since a retrospective study (67) showed that thromboelastometry can be used to detect coagulation abnormalities prior to surgery, the possibility arose for preoperative POC coagulation analysis to predict postoperative bleeding. Evidence, however, shows that preoperative ROTEM or TEG analysis is not able to predict peri- and postoperative bleeding in cardiac surgery (75-77). Although a small retrospective analysis could find an association between preoperative CFT and MCF in ROTEM analysis and postoperative bleeding, possible explanation lies in the significant difference in preoperative platelet count between the two groups (67). In off-pump coronary bypass surgery retrospective analysis shows an association between abnormal ROTEM findings and an increased risk of perioperative bleeding (78).

The adenosine diphosphate (ADP) test of the Multiplate analyzer can be used to predict postoperative blood loss and the need for platelet transfusion in high-risk patients. Patients on thienopyridines undergoing cardiac surgery are at high risk for intra- and postoperative bleeding, in this group the ADP test can be helpful to predict the need for transfusion and postoperative bleeding (64). This has been confirmed by Ranucci and colleagues. They revealed an independent association between the ADP test and postoperative bleeding ($p = 0,007$)

and may possibly predict the postoperative need for transfusion of fresh frozen plasma and platelets (79). However, CPB and protamine have been described to have an inhibitory effect on the ADP test, which in turn can impair the predictive value of the test on perioperative bleeding. The suggestion is made to perform multiple activator tests and not only ADP to activate the coagulation to increase the predictive value of platelet function analyzers on bleeding during cardiac surgery (65).

The role of POCCT in the evaluation for perioperative coagulopathy

Point-of-care coagulation tests have a high negative predictive value (NPV) and a low PPV in determining coagulation abnormalities (65, 75, 76). The high NPV indicates that perioperative coagulopathy can be excluded as a reason for postoperative bleeding during cardiac surgery when POCCTs show no abnormalities. In that case the treatment plan is surgical reintervention and not ABT. A low PPV, on the other hand, indicates that in the presence of coagulation abnormalities postoperative bleeding doesn't automatically coincide. Nevertheless, when microvascular bleeding is accompanied by abnormalities in POCCT's, the bleeding may be due to hemostatic impairment and individualized substitution of coagulation factors should be administered (Table below) (79, 80).

More specifically, evidence shows that the post bypass alpha angle has as a high NPV of 82% and a PPV of 41% for excessive blood loss at 6 hours postoperatively (76). Clinical relevancy of the Quantra analyzer confirms a high negative predictive value for coagulation abnormalities and a low positive predictive value for postoperative bleeding (59). Other studies were not that conclusive. Lee and colleagues could find no predictive value of ROTEM in the prediction of chest drainage output (81). A systematic review by Corredor and colleagues found that TEG is poor in predicting postoperative bleeding, ROTEM has poor positive predictive values and for Sonoclot no correlation between the test results and postoperative blood loss could be found. Platelet mapping was only helpful in patients on aspirin and clopidogrel (82). Platelet

function analyzer can be helpful in the screening for patients with abnormalities of the primary hemostasis (63). ACT has a weak correlation with postoperative coagulopathy (4).

Implementation of POC tests in clinical practice, we can conclude these three situations (75, 76).

The role of POCCT within transfusion algorithms

Evidence shows that implementing an algorithm with restrictive transfusion triggers, which may be assisted with point-of-care coagulation tests, can reduce transfusion need (83) and improve patient outcome (2, 84). Görlinger and colleagues looked into studies that used transfusion protocols in cardiac surgery based on POCCT in comparison to conventional tests. Overall, they showed a reduction in transfusion needs in the POCCT group (2). A systematic review looked into the effect of viscoelastic tests (ROTEM, TEG and Sonoclot) on separate transfusion needs. Perioperative use of these tests could reduce the transfusion of red blood cells, fresh frozen plasma and platelets in a significant manner, as well as reduce perioperative bleeding and re-exploration (68). This could be confirmed by other studies (34, 85).

In 2017 elaborate guidelines in PBM during adult cardiac surgery became available after meticulous literature search by and discussion between task force members of the EACTS/EACTA (25). The introduction of POCCT's has led to the development of specific intraoperative algorithms to reduce blood transfusion in the management of perioperative bleeding. Several algorithms have been provided for the treatment of bleeding after cardiac surgery (2, 32, 63, 86). Görlinger and colleagues (63) described algorithms for POC-based coagulation management in cardiac surgery before and after weaning from cardiopulmonary bypass. They advise the use of vertical or horizontal algorithms in the treatment of perioperative bleeding. The use of vertical sequenced algorithm is recommended over the horizontal, since the vertical gives the benefit of gradually adjusting the treatment. Recently, the society of cardiovascular anesthesiologists have reviewed an improvement

Microvascular bleeding	Viscoelastic test	Evidence	Action
No	Impaired	Low PPV	No action required (No need for performing POC coagulation test)
Yes	Normal	High NPV	Surgical reintervention necessary
Yes	Impaired		Substitute coagulation factors or transfuse blood products according to ROTEM results

advisory with and without the implementation of POC devices in the management of perioperative bleeding in cardiac surgery patients (86). Every hospital with a cardiac surgery program should acquire their own protocols based on existing algorithms, dependent on available tests in their respective centers.

Notably, TEG may also be helpful in establishing tailored discontinuation time for antiplatelet therapy. A small retrospective study found that more than half of the patients could undergo surgery sooner. This way, it is possible to reduce the days of inadequate prophylaxis (87). Evidence summarized by Petricevic and colleagues could confirm the possibility of using TEG platelet mapping to reduce waiting times before surgery in patients taking clopidogrel. They also propose an perioperative algorithm using viscoelastic tests to guide perioperative management of bleeding for patients on antiplatelet therapy (88).

The impact of the use of POCCTs in transfusion algorithms on mortality has not yet been confirmed. Although a meta-analysis and Cochrane analysis could not confirm a reduction on mortality (32, 71, 89), a randomized controlled trial by Weber and colleagues could find a reduction in mortality. Hereby mentioning that their study was not powered to draw any conclusions on mortality (34).

SUMMARY

Since the cause of perioperative or postoperative bleeding in cardiac surgery patients is multifactorial, the treatment should be individualized and goal-directed to substitute the right components in the right patients (92). Although evidence shows that implementing an algorithm with restrictive transfusion triggers and point-of-care coagulation tests to guide transfusion can reduce ABT to the absolute essential, improve patient outcome and reduce health-care costs (32, 34, 68, 93) in the management of bleeding after cardiac surgery, routine use of POCCTs is not recommended (90). When perioperative blood loss is low, routine use of POCCT is not beneficial (91)

References

- Bolcato M., Russo M., Trentino K., Isbister J., Rodriguez D., Aprile A. 2020. Patient blood management: The best approach to transfusion medicine risk management. *Transfus Apher Sci.* 59(4):102779.
- Görlinger K., Dirkmann D., Hanke AA. 2013. Potential value of transfusion protocols in cardiac surgery. *Curr Opin Anaesthesiol.* 26(2):230-43.
- Ranucci M., Baryshnikova E., Castelvechio S., Pelissero G. 2013. Major bleeding, transfusions, and anemia: The deadly triad of cardiac surgery. *Ann Thorac Surg.* 96(2): 478-85.
- Hall TS., Sines JC., Spotnitz AJ. 2002. Hemorrhage Related Reexploration following Open Heart Surgery: The Impact of Pre-Operative and Post-Operative Coagulation Testing. *Vascular.* 10(2):146-53.
- Paparella D., Brister SJ., Buchanan MR. 2004. Coagulation disorders of cardiopulmonary bypass: A review. *Intensive Care Med.* 30(10):1873-81.
- Mehta RH., Sheng S., O'Brien SM., Grover FL., Gammie JS., Ferguson TB., et al. 2009. Reoperation for bleeding in patients undergoing coronary artery bypass surgery: Incidence, risk factors, time trends, and outcomes. *Circ Cardiovasc Qual Outcomes.* 2(6):583-90.
- Karthik S., Grayson AD., McCarron EE., Pullan DM., Desmond MJ. 2004. Reexploration for bleeding after coronary artery bypass surgery: Risk factors, outcomes, and the effect of time delay. *Ann Thorac Surg.* 78(2):527-34.
- Vivacqua A., Koch CG., Yousuf AM., Nowicki ER., Houghtaling PL., Blackstone EH., et al. 2011. Morbidity of bleeding after cardiac surgery: Is it blood transfusion, reoperation for bleeding, or both? *Ann Thorac Surg.* 91(6):1780-90.
- Ranucci M., Bozzetti G., Ditta A., Cotza M., Carboni G., Ballotta A. 2008. Surgical Reexploration After Cardiac Operations: Why a Worse Outcome? *Ann Thorac Surg.* 86(5):1557-62.
- Vlot EA., Verwijmeren L., Van De Garde EMW., Kloppenburg GTL., Van Dongen EPA., Noordzij PG. 2019. Intra-operative red blood cell transfusion and mortality after cardiac surgery. *BMC Anesthesiol.* 19(1):1-7.
- Bernard AC., Davenport DL., Chang PK., Vaughan TB., Zwischenberger JB. 2009. Intraoperative Transfusion of 1 U to 2 U Packed Red Blood Cells Is Associated with Increased 30-Day Mortality, Surgical-Site Infection, Pneumonia, and Sepsis in General Surgery Patients. *J Am Coll Surg.* 208(5):931-937.e2.
- Mazer CD., Whitlock RP., Fergusson DA., Hall J., Belley-Cote E., Connolly K., et al. 2017. Restrictive or liberal red-cell transfusion for cardiac surgery. *N Engl J Med.* 377(22):2133-44.
- Whitlock EL., Kim H., Auerbach AD. 2015. Harms associated with single unit perioperative transfusion: Retrospective population based analysis. *BMJ.* 350.
- Murphy GJ., Reeves BC., Rogers CA., Rizvi SIA., Culliford L., Angelini GD. 2007. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation.* 116(22):2544-52.
- Carson JL., Triulzi DJ., Ness PM. 2017. Indications for and Adverse Effects of Red-Cell Transfusion. *N Engl J Med.* 377(13):1261-72.
- Bolliger D., Buser A., Tanaka KA. 2019. Transfusion Requirements in Anesthesia and Intensive Care. *Curr Anesthesiol Rep.* 9(2):194-201.
- Gillis BM., Looney MR., Gropper MA. 2011. Reducing Non-Infectious Risks of Blood Transfusion. *Anesthesiology.* 115:635-49.
- McVey MJ., Kapur R., Cserti-Gazdewich C., Semple JW., Karkouti K., Kuebler WM. 2019. Transfusion-related Acute Lung Injury in the Perioperative Patient. *Anesthesiology.* 131(3):693-715.

19. Semple JW., Rebetz J., Kapur R. 2019. Transfusion-associated circulatory overload and transfusion-related acute lung injury. *Blood*. 133(17):1840-53.
20. Sørensen B., Spahn DR., Innerhofer P., Spannagl M., Rossaint R. 2011. Clinical review: Prothrombin complex concentrates - evaluation of safety and thrombogenicity. *Crit Care*. 15:201-9.
21. Kozek-Langenecker S., Sørensen B., Hess JR., Spahn DR. 2011. Clinical effectiveness of fresh frozen plasma compared with fibrinogen concentrate: A systematic review. *Crit Care*. 15(5):1-25.
22. Isbister J. 2005. Updates in Blood Conservation and Transfusion Alternatives. *J Aust Assoc Blood Conserv*. 2 (December):3-7.
23. Meybohm P., Richards T., Isbister J., Hofmann A., Shander A., Goodnough LT., et al. 2017. Patient Blood Management Bundles to Facilitate Implementation. *Transfus Med Rev*. 31(1):62-71.
24. Ferraris VA., Brown JR., Despotis GJ., Hammon JW., Reece TB., Saha SP., et al. 2011. 2011 Update To the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines. *Ann Thorac Surg*. 91(3):944-82.
25. Boer C., Meesters MI., Milojevic M., Benedetto U., Bolliger D., von Heymann C., et al. 2018. 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. *J Cardiothorac Vasc Anesth*. 32(1):88-120.
26. Faraoni D., Meier J., New H V., Van der Linden PJ., Hunt BJ. 2019. Patient Blood Management for Neonates and Children Undergoing Cardiac Surgery: 2019 NATA Guidelines. *J Cardiothorac Vasc Anesth*. 33(12):3249-63.
27. Fleming K., Redfern RE., March RL., Bobulski N., Kuehne M., Chen JT., et al. 2017. TEG-directed transfusion in complex cardiac surgery: Impact on blood product usage. *J Extra Corpor Technol*. 49(4):283-90.
28. Enriquez LJ., Shore-Lesserson L. 2009. Point-of-care coagulation testing and transfusion algorithms. *Br J Anaesth*. 103(SUPPL.1):i14-22.
29. Bolliger D., Tanaka KA. 2017. Point-of-Care Coagulation Testing in Cardiac Surgery. *Semin Thromb Hemost*. 43(4): 386-96.
30. Franchini M., Marano G., Veropalumbo E., Masiello F., Pati I., Candura F., et al. 2019. Patient Blood Management: A revolutionary approach to transfusion medicine. *Blood Transfus*. 17(3):191-5.
31. Bolliger D., Tanaka KA. 2013. Roles of thrombelastography and thromboelastometry for patient blood management in cardiac surgery. *Transfus Med Rev*. 27(4):213-20.
32. Kuiper GJAJM., van Egmond LT., Henskens YMC., Roekaerts PM., Maessen JG., ten Cate H., et al. 2019. Shifts of Transfusion Demand in Cardiac Surgery After Implementation of Rotational Thromboelastometry-Guided Transfusion Protocols: Analysis of the HEROES-CS (HEmostasis Registry of patiEntS in Cardiac Surgery) Observational, Prospective Open Cohort Datab. *J Cardiothorac Vasc Anesth*. 33(2):307-17.
33. Deppe AC., Weber C., Zimmermann J., Kuhn EW., Slotosch I., Liakopoulos OJ., et al. 2016. Point-of-care thromboelastography/thromboelastometry-based coagulation management in cardiac surgery: A meta-analysis of 8332 patients. *J Surg Res*. 203(2):424-33.
34. Weber CF., Görlinger K., Meininger D., Herrmann E., Bingold T., Moritz A. 2012. Point-of-care testing: A Prospective, Randomized Clinical Trial of Efficacy in Coagulopathic Cardiac Surgery Patients. *Anesthesiology*. 117(3):531-47.
35. De Robertis E., Kozek-Langenecker SA., Tufano R., Romano GM., Piazza O., Zito Marinosci G. 2015. Coagulopathy induced by acidosis, hypothermia and hypocalcaemia in severe bleeding. *Minerva Anestesiol*. 81(1):65-75.
36. Meesters MI., von Heymann C. 2019. Optimizing Perioperative Blood and Coagulation Management During Cardiac Surgery. *Anesthesiol Clin*. 37(4):713-28.
37. Mochizuki T., Olson PJ., Szlam F., Ramsay JG., Levy JH. 1998. Protamine reversal of heparin affects platelet aggregation and activated clotting time after cardiopulmonary bypass. *Anesth Analg*. 87(4):781-5.
38. Boer C., Meesters MI., Veerhoek D., Vonk ABA. 2018. Anticoagulant and side-effects of protamine in cardiac surgery: a narrative review. *Br J Anaesth*. 120(5):914-27.
39. Dunning J., Versteegh M., Fabbri A., Pavie A., Kolh P., Lockowandt U., et al. 2008. Guideline on antiplatelet and anticoagulation management in cardiac surgery. *Eur J Cardio-thorac Surg*. 34(1):73-92.
40. Fang ZA., Navaei AH., Hensch L., Hui SKR., Teruya J. 2020. Hemostatic Management of Extracorporeal Circuits including Cardiopulmonary Bypass and Extracorporeal Membrane Oxygenation. *Semin Thromb Hemost*. 46(1):62-72.
41. Koster A., Faraoni D., Levy JH. 2018. Argatroban and Bivalirudin for Perioperative Anticoagulation in Cardiac Surgery. *Anesthesiology*. 128(2):390-400.
42. McNair ED., Marcoux JA., Bally C., Gamble J., Thomson D. 2016. Bivalirudin as an adjunctive anticoagulant to heparin in the treatment of heparin resistance during cardiopulmonary bypass-assisted cardiac surgery. *Perfus (United Kingdom)*. 31(3):189-99.
43. Espinosa A., Stenseth R., Videm V., Pleym H. 2014. Comparison of three point-of-care testing devices to detect hemostatic changes in adult elective cardiac surgery: A prospective observational study. *BMC Anesthesiol*. 14(1): 1-7.
44. Warren OJ., Smith AJ., Alexiou C., Rogers PLB., Jawad N., Vincent C., et al. 2009. The Inflammatory Response to Cardiopulmonary Bypass: Part 1-Mechanisms of Pathogenesis. *J Cardiothorac Vasc Anesth*. 23(2):223-31.
45. Sniecinski RM., Chandler WL. 2011. Activation of the hemostatic system during cardiopulmonary bypass. *Anesth Analg*. 113(6):1319-33.
46. Deloge E., Amour J., Provenchère S., Rozec B., Scherrer B., Ouattara A. 2017. Aprotinin vs. Tranexamic acid in isolated coronary artery bypass surgery: A multicentre observational study. *Eur J Anaesthesiol*. 34(5):280-7.
47. Fergusson D., Hébert P., Mazer CD., Fremes S., MacAdams C., Murkin JM., et al. 2008. A Comparison of Aprotinin and Lysine Analogues in High-Risk Cardiac Surgery. *N Engl J Med*. 358(22):2319-31.
48. Walkden GJ., Verheyden V., Goudie R., Murphy GJ. 2013. Increased perioperative mortality following aprotinin withdrawal: A real-world analysis of blood management strategies in adult cardiac surgery. *Intensive Care Med*. 39(10):1808-17.
49. Henry DA., Carless PA., Moxey AJ., O'Connell D., Stokes BJ., McClelland B., et al. 2011. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews*.

50. Whiting D., DiNardo JA. 2014. TEG ROTEM: Technology and clinical applications. *Am J Hematol.* 89(2):228-32.
51. Hett DA., Walker D., Pilkington SN., Smith DC. 1995. Sonoclot analysis. *Br J Anaesth.* 75(6):771-6.
52. Tucci MA., Ganter MT., Hamiel CR., Klaghofer R., Zollinger A., Hofer CK. 2006. Platelet function monitoring with the Sonoclot analyzer after in vitro tirofiban and heparin administration. *J Thorac Cardiovasc Surg.* 131(6):1314-22.
53. Ganter MT., Hofer CK. 2008. Coagulation monitoring: Current techniques and clinical use of viscoelastic point-of-care coagulation devices. *Anesth Analg.* 106(5):1366-75.
54. Bischof DB., Ganter MT., Shore-Lesserson L., Hartnack S., Klaghofer R., Graves K., et al. 2015. Viscoelastic blood coagulation measurement with sonoclot predicts postoperative bleeding in cardiac surgery after heparin reversal. *J Cardiothorac Vasc Anesth.* 29(3):715-22.
55. Despotis GJ., Summerfield AL., Joist JH., Goodnough LT., Santoro SA., Spitznagel E., et al. 1994. Comparison of activated coagulation time and whole blood heparin measurements with laboratory plasma anti-Xa heparin concentration in patients having cardiac operations. *J Thorac Cardiovasc Surg.* 108(6):1076-82.
56. Baryshnikova E., Di Dedda U., Ranucci M. 2019. A Comparative Study of SEER Sonorheometry Versus Standard Coagulation Tests, Rotational Thromboelastometry, and Multiple Electrode Aggregometry in Cardiac Surgery. *J Cardiothorac Vasc Anesth.* 33(6):1590-8.
57. Groves DS., Welsby IJ., Naik BI., Tanaka K., Hauck JN., Greenberg CS., et al. 2020. Multicenter Evaluation of the Quantra QPlus System in Adult Patients Undergoing Major Surgical Procedures. *Anesth Analg.* 130(4):899-909.
58. Bolliger D., Kamber F., Mauermann E. 2021. Same Same but Different: Viscoelastic Hemostatic Assays in Cardiac Surgery. *J Cardiothorac Vasc Anesth.* 35(4):1037-9.
59. Zghaibe W., Scheuermann S., Munting K., Blaudszun G., Besser M., Ortmann E., et al. 2020. Clinical utility of the Quantra® point-of-care haemostasis analyser during urgent cardiac surgery. *Anaesthesia.* 75(3):366-73.
60. Ferrante EA., Blasler KR., Givens TB., Lloyd CA., Fisher TJ., Fischer TJ., et al. 2016. A novel device for the evaluation of hemostatic function in critical care settings. *Anesth Analg.* 123(6):1372-9.
61. Varghese SJ., Unni MK., Mukundan N., Rai R. 2005. Platelet functions in cardiopulmonary bypass surgery. *Med J Armed Forces India.* 61(4):316-21.
62. Paniccia R., Piora R., Liotta AA., Abbate R. 2015. Platelet Function tests: A Comparative Review. *Vasc Health Risk Manag.* 11:133-48.
63. Görlinger K., Jambor C., Hanke AA., Dirkmann D., Adamzik M., Hartmann M., et al. 2007. Perioperative coagulation management and control of platelet transfusion by point-of-care platelet function analysis. *Transfus Med Hemotherapy.* 34(6):396-411.
64. Koltai K., Kesmarky G., Feher G., Tibold A., Toth K. 2017. Platelet aggregometry testing: Molecular mechanisms, techniques and clinical implications. *Int J Mol Sci.* 18(8):1-21.
65. Petricevic M., Konosic S., Biocina B., Dirkmann D., White A., Mihaljevic MZ., et al. 2016. Bleeding risk assessment in patients undergoing elective cardiac surgery using ROTEM® platelet and Multiplate® impedance aggregometry. *Anaesthesia.* 71(6):636-47.
66. Ogawa S., Szlam F., Chen EP., Nishimura T., Kim H., Roback JD., et al. 2012. A comparative evaluation of rotation thromboelastometry and standard coagulation tests in hemodilution-induced coagulation changes after cardiac surgery. *Transfusion.* 52(1):14-22.
67. Gozdzik W., Adamik B., Wysoczanski G., Gozdzik A., Rachwalik M., Skalec T., et al. 2017. Preoperative thromboelastometry for the prediction of increased chest tube output in cardiac surgery. *Med (United States).* 96(30).
68. Whiting P., Al M., Westwood M., Ramos IC., Ryder S., Armstrong N., et al. 2015. Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: A systematic review and cost-effectiveness analysis. *Health Technol Assess (Rockv).* 19(58):1-228.
69. Lodewyckx C., Heinrichs J., Grocott HP., Karkouti K., Romund G., Arora RC., et al. 2018. Point-of-care viscoelastic hemostatic testing in cardiac surgery patients: a systematic review and meta-analysis. *Can J Anesth.* 65(12):1333-47.
70. Karlsson M., Ternström L., Hyllner M., Baghaei F., Nilsson S., Jeppsson A. 2008. Plasma fibrinogen level, bleeding, and transfusion after on-pump coronary artery bypass grafting surgery: A prospective observational study. *Transfusion.* 48(10):2152-8.
71. Wikkelsø A., Wetterslev J., Møller AM., Afshari A. 2016. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. *Cochrane Database Syst Rev.* (8):1465-858.
72. Veigas P V., Callum J., Rizoli S., Nascimento B., da Luz LT. 2016. A systematic review on the rotational thromboelastometry (ROTEM®) values for the diagnosis of coagulopathy, prediction and guidance of blood transfusion and prediction of mortality in trauma patients. *Scand J Trauma Resusc Emerg Med.* 24(1):1-14.
73. Stein P., Kaserer A., Sprengel K., Wanner GA., Seifert B., Theusinger OM., et al. 2017. Change of transfusion and treatment paradigm in major trauma patients. *Anaesthesia.* 72(11):1317-26.
74. Cohen J., Scorer T., Wright Z., Stewart IJ., Sosnov J., Pidcock H., et al. 2019. A prospective evaluation of thromboelastometry (ROTEM) to identify acute traumatic coagulopathy and predict massive transfusion in military trauma patients in Afghanistan. *Transfusion.* 59(S2):1601-7.
75. Davidson SJ., McGrowder D., Roughton M., Kelleher AA. 2008. Can ROTEM Thromboelastometry Predict Postoperative Bleeding After Cardiac Surgery? *J Cardiothorac Vasc Anesth.* 22(5):655-61.
76. Cammerer U., Dietrich W., Rampf T., Braun SL., Richter JA. 2003. The Predictive Value of Modified Computerized Thromboelastography and Platelet Function Analysis for Postoperative Blood Loss in Routine Cardiac Surgery. *Anesth Analg.* 96(1):51-7.
77. Sharma AD., Al-Achi A., Seccombe JF., Hummel R., Preston M., Behrend D. 2014. Does incorporation of thromboelastography improve bleeding prediction following adult cardiac surgery? *Blood Coagul Fibrinolysis.* 25(6):561-70.
78. Soh S., Kwak YL., Song JW., Yoo KJ., Kim HJ., Shim JK. 2017. Rotational Thromboelastometry Predicts Increased Bleeding After Off-Pump Coronary Bypass Surgery. *Ann Thorac Surg.* 104(4):1318-24.
79. Ranucci M., Baryshnikova E., Soro G., Ballotta A., De Benedetti D., Conti D. 2011. Multiple electrode whole-blood aggregometry and bleeding in cardiac surgery patients receiving thienopyridines. *Ann Thorac Surg.* 91(1):123-9.

80. Ranucci M., Colella D., Baryshnikova E., Di Dedda U. 2014. Effect of preoperative P2Y12 and thrombin platelet receptor inhibition on bleeding after cardiac surgery. *Br J Anaesth.* 113(6):970-6.
81. Lee GC., Kicza AM., Liu KY., Nyman CB., Kaufman RM., Body SC. 2012. Does rotational thromboelastometry (ROTEM) improve prediction of bleeding after cardiac surgery? *Anesth Analg.* 115(3):499-506.
82. Corredor C., Wasowicz M., Karkouti K., Sharma V. 2015. The role of point-of-care platelet function testing in predicting postoperative bleeding following cardiac surgery: A systematic review and meta-analysis. *Anaesthesia.* 70(6):715-31.
83. Karkouti K., McCluskey SA., Callum J., Freedman J., Selby R., Timoumi T., et al. 2015. Evaluation of a novel transfusion algorithm employing point-of-care coagulation assays in cardiac surgery: A retrospective cohort study with interrupted time-series analysis. *Anesthesiology.* 122(3): 560-70.
84. Engoren MC., Habib RH., Zacharias A., Schwann TA., Riordan CJ., Durham SJ. 2002. Effect of blood transfusion on long-term survival after cardiac operation. *Ann Thorac Surg.* 74(4):1180-6.
85. Mehaffey JH., Schubert SA., Gelvin MG., Charles EJ., Hawkins RB., Johnston LE., et al. 2017. A New Intraoperative Protocol for Reducing Perioperative Transfusions in Cardiac Surgery. *Ann Thorac Surg.* 104(1):176-81.
86. Raphael J., Mazer CD., Subramani S., Schroeder A., Abdalla M., Ferreira R., et al. 2019. Society of Cardiovascular Anesthesiologists Clinical Practice Improvement Advisory for Management of Perioperative Bleeding and Hemostasis in Cardiac Surgery Patients. *J Cardiothorac Vasc Anesth.* 33(11):2887-99.
87. Fleming K., Redfern R., Bobulski N., Naimy G., Kuehne M., Moront M. 2019. The Effect of Platelet Mapping on Length of Stay and Clinical Outcomes in a Cohort of Patients Undergoing Coronary Artery Bypass Grafting. *J Am Coll Cardiol.* 73(9):1394.
88. Petricevic M., Kopjar T., Biocina B., Milicic D., Kolic K., Boban M., et al. 2015. The Predictive Value of Platelet Function Point-of-Care Tests for Postoperative Blood Loss and Transfusion in Routine Cardiac Surgery: A Systematic Review. *Thorac Cardiovasc Surg.* 63(1):2-20.
89. Deppe AC., Weber C., Zimmermann J., Kuhn EW., Slottosch I., Liakopoulos OJ., et al. 2016. Point-of-care thromboelastography/thromboelastometry-based coagulation management in cardiac surgery: A meta-analysis of 8332 patients. *J Surg Res.* 203(2):424-33.
90. Serraino GF., Murphy GJ. 2017. Routine use of viscoelastic blood tests for diagnosis and treatment of coagulopathic bleeding in cardiac surgery: Updated systematic review and meta-analysis. *Br J Anaesth.* 118(6):823-33.
91. Lehmann F., Rau J., Malcolm B., Sander M., Heymann C Von., Moormann T., et al. 2019. Why does a point of care guided transfusion algorithm not improve blood loss and transfusion practice in patients undergoing high-risk cardiac surgery? A prospective randomized controlled pilot study. *BMC Anesthesiol.* 19:1-10.
92. Terwindt LE., Karlas AA., Eberl S., Wijnberge M., Driessen AHG., Veelo DP., et al. 2019. Patient blood management in the cardiac surgical setting: An updated overview. *Transfus Apher Sci.* 58(4):397-407.
93. Zbrozek A., Magee G. 2015. Cost of Bleeding in Trauma and Complex Cardiac Surgery. *Clin Ther.* 37(9):1966-74.