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The Predictive Value of Platelet Function point-of-care Tests for Postoperative Blood Loss and Transfusion in Routine Cardiac Surgery: a systematic review

ABSTRACT

Excessive bleeding after cardiopulmonary bypass (CPB) operations remains to be a persistent problem and weak platelet function certainly contributes to bleeding diathesis. Antiplatelet therapy (APT) is an integral component of perioperative management in patients undergoing cardiac surgery procedures, both with and without use of CPB. In addition to individual variability in platelet function, different preoperative APT administration/discontinuation management further affects platelet function which in turn may reflect bleeding tendency. However, the impact of drug induced platelet inhibition on early postoperative bleeding extent, however, remains difficult to predict. Herein, we reviewed the available evidence on the association between platelet function testing values and the extent of bleeding and transfusion requirements in early perioperative period. Currently, the association between platelet function measured by *ex vivo* assay and the occurrence of bleeding events remains uncertain. The intent of this review is to provide comprehensive literature insight into published evidence investigating the possibility of platelet function tests to predict bleeding extent as well as transfusion requirements in cardiac surgery patients.

INTRODUCTION

Bleeding extent as well as transfusion of allogeneic blood products certainly affect outcome following cardiac surgery procedures. Up to 10% of patients undergoing cardiac surgery experience excessive postoperative hemorrhage[1]. Christensen et al investigated the relationship between postoperative hemorrhage and clinical outcome following cardiac surgical procedures [2]. Patients that experienced excessive postoperative bleeding had higher 30-day mortality and other adverse outcomes such as stroke, reexploration, intensive care unit stay and mechanical ventilation[2]. Those findings are in line with results reported by Dixon et al [3]. Authors undertook a multivariate logistic regression analysis of the risk factors associated with mortality in 2599 consecutive patients undergoing cardiac surgery [3]. With aim to consider the possibility that chest tube drainage (CTD) may in itself be harmful, the risk factors examined included the volume of CTD at 24 hours[3]. CTD was the strongest independent predictor of mortality ($p<0.001$) [3]. Although results reported by Dixon et al [3] have numerous implications for surgical practice, the question how to predict and prevent excessive CTD, remains challenging. The meticulous hemostatic surgical technique is mandatory [4], however sometimes is insufficient to achieve adequate hemostasis, probably due to coagulopathic component of bleeding.

Platelet function plays important role in pathogenesis of hemostatic disorder and consequent bleeding diathesis in cardiac surgery patients. Platelet function may be considered as a continuous variable that expresses widespread range among individuals. Widespread range of platelet activity among individuals arises from different factors such as: 1) widespread interindividual variability in inherent platelet activity , 2) widespread variability in platelet inhibitory response to antiplatelet therapy (APT) and 3) individual ability to recover platelet function after APT cessation, which is also influenced by timing of discontinuation and type of drug used. There is evidence that heritable factors play a major

role in determining platelet aggregation[5] and such a variability in platelet aggregation may in some degree explain proclivity towards bleeding as well as ischemic events. In addition to heritable factors, platelet function is dominantly influenced by APT. Patients experiencing the therapeutic effects of APT and requiring cardiac surgery are at risk for adverse bleeding events and transfusion requirements. Patients receiving APT have different degrees of platelet inhibition. Widespread variability in platelet responses to the most commonly prescribed antiplatelet drugs such as acetylsalicylic acid (ASA) and clopidogrel (CLO) have been established by various platelet function assays [6]. The bleeding risk has recently become accentuated by the widely prevalent dual antiplatelet therapy with ASA and CLO. Despite the current guidelines, many centers continue with APT up to day of surgery, disregarding the recommendations for a drug free interval before surgery. For example, data from 2858 acute coronary syndrome patients in the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse Outcomes with Early implementation of the ACC/AHA Guidelines) Initiative demonstrated that 87% of CLO treated patients underwent CABG $\leq$ 5 days after treatment with a consequently increased blood transfusion requirement [7]. Notably, 5-15% of patients with an acute coronary syndrome require an urgent cardiac operation with recently administered antiplatelet drugs [7].

The considerable heterogeneity in platelet inhibitory response to APT makes it difficult to safely use arbitrary interval for drug discontinuation prior to surgery without incurring excessive thrombotic or bleeding risks with premature versus too late discontinuation. Therefore, an individual approach in preoperative assessment of the bleeding risks is warranted. Bedside suitable platelet function testing could play an important role in the prediction and prevention of excessive bleeding after CPB. Notably, conventional coagulation tests have been shown to be unreliable in predicting postoperative bleeding [8,9]. Platelet function testing presents a kind of phenotyping approach that provides quantification

of platelet function by summarizing the effects of all previously mentioned covariates that influence platelet activity. Theoretically, platelet function tests could guide clinical decision making in patients on APT. Evaluating the efficiency of platelet inhibition in the preoperative settings offers to identify patients in whom excessive bleeding is likely and often preventable [10]. Velik-Salchner et al[10] showed that bedside suitable platelet function test was capable to discriminate patients according to preoperative APT exposure [10] as well as to detect CPB induced changes in platelet aggregation[10,11].

Hemostatic disorders became more apparent with perioperative use of novel antithrombotic drugs such as prasugrel and ticagrelor. Prasugrel, third generation thienopyridine achieves more rapid and greater platelet inhibition than clopidogrel and is substantially associated with higher rates of major and minor bleeding in cardiac surgery patients[12,13]. Ticagrelor, novel, nonthienopyridine antiplatelet drug achieves more pronounced inhibition of platelet function than clopidogrel [12]. More potent antiplatelets to which patients are more often exposed in close proximity to surgery require prudent hemostatic management. Despite the fact that novel antithrombotic drugs achieve greater inhibition of platelet aggregation with a lower rate of non-responders [14], it is obvious that antiplatelet drugs act in a wide range of inhibition. Such variability may occur during the initiation of therapy, steady-state administration as well as after discontinuation of treatment with variable interval needed to achieve recovery after drug discontinuation. Consequently, platelet function testing seems reasonable. Use of platelet function testing may help improve hemostatic management by stratification of patients according to different levels of platelet inhibition, thus different risks of excessive bleeding due to platelet dysfunction. In this way it would be possible to determine “safe window” of platelet inhibition that would permit safe surgery in regard to bleeding risk. In certain proportion of patients APT could be discontinued even before the recommended waiting period and in this way it could be possible to minimize

both bleeding and ischemic events occurrence. Cangrelor, a reversible intravenous P2Y12 inhibitor has a fast onset of action and very short half-life [15] which allows for precise temporal programming of platelet inhibition and has recently been used for bridging APT in patients scheduled for cardiac surgery[16]. Short-acting (eptifibatide and tirofiban) and long-acting (abciximab) GPIIB/IIIA inhibitors cause profound platelet inhibition. Since some patients on GPIIB/IIIA inhibitors require emergent surgery, particular attention should be paid to patients on long acting agents such as abciximab. New anticoagulation agents such as factor Xa inhibitor rivaroxaban and apixaban and direct thrombin inhibitor such as dabigatran may further amplify hemostatic disorder in cardiac surgery patients. There is some evidence that point-of-care devices are not suitable for assessment of hemostatic disturbances caused with factor Xa inhibitor administration[17]. However, further elaboration on this issue goes far beyond the scope of this review article.

In this article, we reviewed available evidence on the utility of platelet function testing in assessment of excessive bleeding as well as transfusion requirements in patients undergoing cardiac surgery. The intent of this review is to provide comprehensive insight into published evidence investigating whether platelet function tests are capable to predict excessive bleeding and transfusion requirements in cardiac surgery patients by matching quantified platelet function with evaluated endpoints such as bleeding extent and transfusion requirements.

METHODS

PUBMED and MEDLINE were searched using predefined search terms such as “platelet function testing” , “bleeding cardiac surgery” and “transfusion cardiac surgery” using Boolean logic operators [AND] and [OR]. Abstracts were evaluated, and relevant full-text articles were obtained. In addition to, reference lists of selected publications were analyzed for additional linking studies. Articles that addressed the relation between platelet function testing and bleeding outcomes as well as transfusion requirements in cardiac surgery patients were included in review. During literature review we aimed to plot platelet function testing against different endpoints. Excessive bleeding was defined as proposed by authors in respective manuscripts. Different authors proposed different ways to define excessive bleeding. Excessive bleeding as an endpoint was mainly defined in respect to extent of CTD in certain amount of time. Different amounts of CTD revealed in different timeframes were used and patients were defined as excessive bleeders if their CTD exceeded predefined cutoff value for excessive bleeding. The other important endpoint was “transfusion requirements”. Through searched literature we observed transfusion requirements for different procoagulant blood components transfusion. Although transfusion requirements for platelet concentrate would have clear rationale, we decided to assess for all procoagulant blood components transfusion requirements. In non-interventional studies where attending anesthesiologists and surgeons are unaware of platelet function testing results and where decision to transfuse procoagulant blood components relies either on institutional algorithm or solely on the clinical judgment, weak platelet function may cause wet field which in turn may be treated with different types of procoagulant blood components , depending on the institutional algorithm or preference of clinicians blinded to platelet function results.

Therapeutic approach to surgically or coagulopathically-induced bleeding is quite different. Bedside assessment of blood hemostatic properties has several advantages over conventional coagulation testing. First of all, turnaround time from sampling blood to obtaining results is often crucial. Although point-of-care tests show more variation and lower precision, the focus should be on the accuracy sufficient to make appropriate clinical decisions timely. Despite the fact that standard coagulation testing is focused more on accuracy than on turnaround time [18] conventional coagulation testing failed to predict postoperative bleeding in cardiac surgery patients [8,9]. In addition to, conventional laboratory tests are unable to decompose multifactorial pathogenesis of hemostatic disorder as described by Paparella et al [19].

Thromboelastograph (TEG) has been used in hospital laboratories since its development by Hartert in 1944 at Heidelberg University. Spiess et al published the first study evaluating the relationship between TEG and bleeding extent after cardiac surgery [8]. In small study cohort (38 patients) TEG was predictor of postoperative hemorrhage[8]. However, platelet function was only indirectly assessed since modified TEG with platelet function mapping was not available. Nowadays, two most commonly employed point-of-care devices for assessment of viscoelastic blood properties are thromboelastograph (TEG, Haemoscope Corporation, Niles, IL, USA) and the ROTEM thromboelastometer (TEM International GmbH, Munich, Germany). Differences as well as similarities between thromboelastography and thromboelastometry systems should be briefly elaborated. Both systems measure viscoelastic properties of blood clot by employing a vertical pin held in the blood sample, contained within a cup[20]. Technical aspects of differences between two systems as well as advantages and disadvantages of one system over the other are published by Jackson et al in “head to head” comparison[20]. Although these two devices share the very

similar concept, divergent results on similar samples were reported by Nielsen et al[21]. Of more importance, in particular in this review article, should be noted that only TEG provides platelet function mapping by adding specific platelet function agonists that allow for quantification of platelet function through different pathways. In addition to TEG Platelet Mapping, various bedside suitable , point-of-care platelet function tests have been increasingly used. Nowadays, several devices are available. Detailed description of mostly used current platelet function testing devices has been already published[22].

ASSOCIATION BETWEEN PLATELET FUNCTION TESTS FINDINGS AND BLEEDING OUTCOMES AND TRANSFUSION REQUIREMENTS

Conflicting data have been published regarding ability of point-of-care platelet function assays to predict bleeding extent as well as transfusion requirement after cardiac surgery.

Poston et al investigated the predictive value of platelet function testing in assessment of bleeding and thrombotic events after off-pump coronary artery surgery (CABG) [23]. Two point-of-care platelet function devices were used: (1) TEG assay using arachidonic acid agonist (Thrombelastograph Platelet Mapping (Haemoscope Corporation, Niles, Ill), and (2) Whole blood aggregometry (WBA) (model592A, Chronolog, Havertown, Pennsylvania). Intraoperative amount of bleeding significantly correlated with the decrease in platelet function as assessed by WBA ($r=0.42$, $p<0.05$), but not TEG (p=ns). The same TEG device failed to significantly correlate with 24 hour CTD in study by Carrol et al [24]. It should be noted that patients on APT were excluded from the study a priorily[24] thus making the cohort to be of low bleeding risk in terms of platelet dyfunction. The role of platelet function testing in group of patients not exposed to APT seems to be questionable. The fact is that platelet function testing may be of the greatest benefits in patients who are exposed to APT.

Contrary to, Preisman et al reported TEG parameter using adenosine diphosphate (ADP) agonist to significantly predict bleeding extent [25] with a sensitivity of 78% and specificity of 84%. Comparison between patients with normal and abnormal TEG ADP test revealed larger amount of 24-h CTD in group of patients with abnormal TEG ADP test[25]. In addition to, the same TEG parameter significantly correlated with transfusion of platelet concentrate (Spearman's rho= -0.75, p=0.02). Kwak et al introduced an idea about timing of surgery according to TEG platelet mapping results for patients with CLO administered in proximity to surgery[26]. Patients were divided into three groups according to tertiles of distribution of the percentage of platelet inhibitory response to CLO therapy [26]. Patients in the third tertile (the most pronounced platelet inhibition) had a significantly greater amount of postoperative CTD [26]. Significantly more patients in the third tertile required packed red blood cells and fresh frozen plasma transfusion with higher number of units transfused than those patients with higher residual platelet reactivity following APT administration[26]. ROC analysis revealed optimal cutoff value for postoperative transfusion requirement as 70% platelet inhibitory response to CLO [26]. Accentuated platelet inhibitory response to CLO , but not discontinuation date and preoperative drug free interval, remained independent risk factor for transfusion requirements[26]. Weitzel et al conducted prospective observational study using TEG platelet mapping with adenosine-diphosphate (ADP) , arachidonic acid (AA) and collagen (COL) as agonists [27]. TEG platelet mapping assay with collagen as activator (MAcollagen) was found to be the only parameter significantly lower in high bleeding groups in both pre- and post-CPB setting. Furthermore, pre- and post-CPB MAcollagen significantly correlated with 24 hour CTD extent while only pre-CPB MAaa (Pearson correlation coefficient (r) -0.324, p=0.041) correlated with 24 hour CTD [27]. Although MAadp did not correlate significantly, it is worthwhile to mention that recent preoperative CLO exposure was exclusion criterion which in turn may raise the question whether the obtained results would be

different in lower range of MAadp values expected in patients exposed to CLO preoperatively. Mahla et al conducted the first prospective interventional study of a platelet function measurement based strategy to reduce bleeding and waiting time in CLO treated patients undergoing CABG (TARGET-CABG study)[28]. Platelet function testing was performed using TEG with ADP agonist [28]. Patients receiving CLO were divided into three groups according to platelet function test results and the surgery timing was adjusted for each group according to platelet reactivity as follows : MA-ADP >50 mm – surgery within 1 day , MA-ADP 35-50 mm – surgery within 3-5 days and surgery after 5 days following CLO discontinuation if MA-ADP was below 35 mm. All three subgroups along with CLO naive patients were comparable for the primary (CTD at 24 hours) and secondary endpoints (total number of transfused red blood cells) [28]. Such a strategy allowed for approximately 50% reduction in waiting time than recommended in the current guidelines [29,30] suggesting the fact that uniform waiting period for discontinuation of antiplatelet drugs[29,30] as suggested in guidelines may be actually obsolete.

With specific aim to evaluate whether Hemostatus – platelet activating factor clotting time (PACT, Hemostatus, Medtronic, Inc, Parker, CO) device findings correlate with postoperative blood loss, Despotis et al[31] conducted prospective observational study[31]. In cohort group of 150 patients undergoing cardiac surgery requiring CPB, PACT significantly (r=-0.85) correlated with 4 hours CTD [31]. Authors concluded that PACT may be useful tool for prediction of excessive bleeding [31]. Although using the same device in similar research and clinical setting, the study of Ereth et al [32] showed substantially opposite results to those published by Despotis et al[31]. PACT values obtained after protamine administration correlated weakly with 4 hours CTD (r=-0.30, p=0.014). However, the correlations between postprotamine PACT values and 24 hour CTD as well as with transfusion requirements were not significant [32]. PACT had comparable results to routine laboratory coagulation tests in

prediction of excessive hemorrhage and authors didn't support its use in regular clinical practice. Furthermore, Ereth et al[33] conducted another prospective study that duplicated study settings of Despotis et al[31] with aim to determine the relation between PACT performed within one hour following intensive care unit arrival and blood loss[33]. Again, PACT values didn't correlate with blood loss [33] whilst prothrombin time (PT) strongly correlated with CTD ($p<0.0001$) [33]. Notably, only PT correlated with transfusion of platelets and fresh frozen plasma [33]. However, this particular correlation should be interpreted with caution since attending physicians were unaware of only PACT results, but authors did not describe specific hemostatic protocol. Thus, those correlations are expected if procoagulant blood products administration was targeted after PT values.

Dietrich et al conducted prospective study with aim to investigate the relationship between platelet function tests (four different methods: TEG, modification of impedance aggregometry, PFA-100 ® and platelet function PAF test) and postoperative bleeding extent in cardiac surgery patients[34]. Postoperative CTD could not be predicted by platelet function tests performed preoperatively[34]. However, this findings should be interpreted cautiously since the study enrolled a total of 16 consecutive patients, thus probably being underpowered.[34]. Wahba et al conducted prospective comparative study enrolling 40 patients scheduled for elective cardiac surgery. PFA-100 ® and Hepcon HMS were compared in assessment of bleeding prediction to each other and with conventional lab and operative data[35]. Preoperative PFA-100 ® closing time significantly correlated to total blood loss ($r=0.41$, $p=0.022$). Contrary to, preoperative Hepcon ® HMS data failed to correlate with postoperative blood loss ($r=0.18$, $p=0.37$)[35]. Although PFA-100® was found to significantly correlate to CTD , authors considered study to be negative since the correlation of blood loss with PFA-100 ® was not greater than with the results of conventional and simple coagulation tests such as platelet count, D-dimers or duration of CPB[35]. Using PFA-

100 ® device Slaughter et al conducted prospective study on 58 adults undergoing primary elective CABG[36]. Collagen/ADP closure time, measured both pre-operatively and 15 min after protamine administration failed to correlate with either 6 or 12 hours CTD. Collagen/ADP closure time at 15 minutes after protamine administration did not significantly differ between patients transfused or not transfused with platelet concentrate [36]. In detecting "bleeders", PFA–100® was found to have positive and negative predictive values of 18% and 98% [36]. Those results direct authors to conclude that PFA-100® may be useful in identifying patients unlikely to benefit from platelet transfusion , therefore help to avoid unnecessary platelet transfusion [36]. Forestier et al compared PFA-100® and Hemostatus point-of-care platelet function tests in study cohort divided into two groups with respect to excessive bleeding presence following arrival to intensive care unit[37]. Patients were not exposed to APT at least for 7 days prior to surgery, and additionally were excluded from study if diffuse bleeding occurred without identified surgical source of bleeding after protamine administration[37]. Platelet function tests were performed following arrival to ICU, either when excessive hemorrhage was diagnosed or after 3 hours following arrival to ICU[37]. There were no significant differences in Hemostatus and PFA-100® parameter values between "bleeders" and "non-bleeders" [37]. In addition to, both Hemostatus and PFA-100® parameter values did not correlate with amount of CTD [37]. Based on observed overall lack of correlation between platelet function tests and CTD, authors suggested that these platelet function assays should not be routinely used in cardiac surgical patients[37]. However, they presumed that these tests would be more efficient for patients considered to be at higher risk of bleeding[37]. Fattorutto et al conducted prospective study with aim to evaluate if PFA-100® predicts postoperative blood loss[38]. PFA-100® failed to predict postoperative bleeding[38]. Several issues has to be discussed in this paper by Fattorutto et al[38]. Study recruited 70 patients with normal coagulation function and platelet count in

whom APT had been withdrawn for at least 5 days before surgery. It is obvious that study was performed in non-bleeding patients group since mean total CTD was 495±301 mL and the incidence of excessive CTD was found to be only 6%. Therefore, one may expect that almost every test must fail to predict excessive bleeding in patients that are not bleeding excessively. Cammerer et al conducted prospective study enrolling 255 patients with aim to evaluate weather modified rotational thromboelastometry (ROTEG™) and platelet function analyzer PFA-100® were predictive of postoperative blood loss [39]. ROTEG™ and PFA-100® tests performed after CPB were significantly different between patient groups divided with the respect to the presence of excessive postoperative blood loss [39]. In contrast to, preoperative ROTEG™ findings failed to predict postoperative blood loss [39]. Noteworthy, abnormal bleeding was defined in two ways [39], and the definition of excessive bleeding influenced the ability of PFA-100® to distinguish patients according to bleeding diathesis [39]. While preoperative PFA-100® showed significant differences between patient groups divided according to extent of 750 mL of 6 hrs postoperative bleeding, the differences were not present if patients were divided according to study protocol data (upper quartile of blood loss in respective cohort group)[39]. Finally, reported high negative predictive values suggest the role of point-of-care tests in bleeding prediction and decision making process by identifying patients who will tend to not bleed caused by hemostatic disorder , which direct management of possible bleeding to surgical treatment[39].

Gerrah et al investigated the possibility of bleeding prediction using cone and plate(let) analyzer (CPA , Impact-R , DiaMed, Cressier/Morat, Switzerland) in cardiac surgery patients[40]. The major advantage of CPA over the rest of platelet function analyzers is the fact that CPA measures platelet function as well as the interaction between platelets and von Willebrand factor (vWF). Patients with pathologic values of CPA parameters had both the higher incidence of excessive postoperative bleeding (> 965 mL , 44% vs. 0%), as well as

higher amount of blood loss (908 +/- 322 mL vs. 337 +/- 78 mL) indicating preoperative platelet function as assessed with CPA as an independent risk factor determining adverse bleeding events [40].

Solomon et al [41] used two point-of-care platelet function analyzers (Multiple electrode aggregometry, Multiplate (MEA), Verum Diagnostica GmbH and Dynabyte Informationssysteme GmbH, Munich, Germany); and cone and plate (let) analyzer (CPA) – Impact R (DiaMed, Cressier/Morat, Switzerland)) with aim to investigate which test is superior in preoperative assessment of platelet concentrate transfusion. MEA was found to be more useful in predicting patients prone to intraoperative platelet concentrate transfusion [41]. Rahe-Meyer et al provided valuable contribution to evaluation of relationship between MEA results and bleeding extent as well as platelet concentrates transfusion[42]. MEA findings were divided into tertiles of value distribution [42]. There were no significant differences between the low and the high tertile of MEA tests with respect to 24-h drainage volume [42]. Pre-operative MEA ADP and COL tests were predictive of platelet concentrate transfusion[42]. Authors concluded that platelet function assay offers the possibility of an early estimation of the risk of transfusion [42]. In our opinion, this contribution was very valuable since prediction of platelet concentrate transfusion allows for timely hemostatic intervention. In this study, attending clinicians were blinded for platelet function tests results, however, platelet concentrate administration was a first line therapy in patients considered for hemostatic interventions with known recent exposure to APT. However, the question whether the application of MEA may reduce the amount of platelet concentrate transfusion by targeted administration remained uncertain [42]. Reece et al [43] conducted study with aim to determine whether platelet function disorder as assessed by MEA would predict excessive bleeding and blood transfusion. The study conducted in prospective, clinician blinded fashion enrolled 44 patients. Although CTD was measured hourly for 12 hours and until chest tube

removal, authors did not report correlations between CTD extent and platelet function test values [43]. MEA showed significant differences between transfused and non-transfused patients during chest closure , ADP test (18 U vs 29 U; p=0.01) and TRAP test (65U vs 88U, p=0.01), respectively [43]. Moreover, authors performed ROC[44] analysis with aim to detect the cut-of value of MEA tests that suggest transfusion requirements [43]. Measured ROC area under curve areas were small (0.691 for TRAP test and 0.674 for ADP test) which consequently results in weak prediction models of ROC analysis [43]. Threshold effect for transfusion outcome was 100 U (TRAP test) and 31 U (ADP test) with specificity values 1 for both tests, but low sensitivity values of 0.333 and 0.267, respectively [43]. However, high specificity for observed cut-of values allows for determination of patients who will probably be free of transfusion [43]. Another study investigating association between MEA and postoperative bleeding and platelet transfusion was conducted by Ranucci et al [45]. A total number of 87 patients with preoperatively administered thienopyridines were retrospectively analyzed [45]. ROC analysis was performed and ADP test value of 31 AUC was predictive of excessive bleeding with a sensitivity of 72% and a specificity of 66% [45]. High negative predictive value of 92% suggested the possible role of platelet function test in decision making algorithm by directing hemostatic management towards surgical hemostasis in cases of normal platelet function test values. Authors described positive relationship between ADP test and platelet transfusion, however this should be interpreted cautiously since the study was retrospective and ADP test value less than 40 AUC[45] influenced hemostatic management in respective study cohort. Petricevic et al investigated the possibility of excessive bleeding prediction using MEA in 211 patients following CABG [46]. MEA was performed preoperatively using ASA sensitive (ASPI test) and thienopyridines sensitive (ADP test) platelet function tests[46]. Both ASPI (p=0.014) and ADP (p=0.003) tests correlated significantly with 24 h CTD [46] and ROC analysis found ASPI test value of <20 AUC , as

well as ADP test value of <73 AUC to be bleeder determinants[46]. The same research group conducted another prospective study recruiting 148 patients who required elective cardiac surgery[47]. In this study, use of MEA was supplemented with rotational thromboelastometry (ROTEM) and tests were performed simultaneously in three perioperative time points. The important finding of this study was that the strongest correlations between MEA and ROTEM were observed at third time point of blood sampling (after protamine administration)[47]. Thus, not only preexisting platelet function (influenced by inherent activity and/or APT) , but platelet function altered by CPB and surgical trauma itself , may more precisely reflect bleeding tendency[47]. Weber et al conducted, to our best knowledge, the only one prospective, randomized clinical trial evaluating the efficacy of point-of-care devices in coagulopathic cardiac surgery patients[48]. Two hemostatic transfusion managements were compared: control group was managed using transfusion algorithm based on conventional laboratory findings, while transfusion management in interventional group was directed according to findings of two point-of-care devices (TEM and MEA) [48]. Study was terminated earlier because the planned interim analysis of the primary outcome (the number of units of packed red blood cells administered in the first postoperative 24 hrs) revealed significant group differences favoring interventional group[48]. In addition to, patients in the conventional group lost more blood in early postoperative phase [48]. We may conclude that point-of-care directed transfusion management resulted with targeted and reduced amount of allogeneic products transfused followed by lower extent of postoperative bleeding. Recently, Schimmer et al [49] published retrospective study[49] with aim to find out whether platelet function tests results reflected postoperative bleeding extent or transfusion requirements[49]. Put briefly, decreased preoperative MEA platelet function test values were associated with increase in postoperative blood transfusion requirements[49]. Neither of MEA tests performed preoperatively correlated with postoperative bleeding extent [49]. Di Dedda et al

published retrospective analysis of prospectively collected data[50] with aim to assess the platelet inhibitory response to thienopyridines, to assess the dynamics of platelet function after thienopiridines cessation and finally to evaluate the relationship between platelet function test values and bleeding and transfusion outcomes[50]. Using repetitive measurements of MEA ADP test , authors have found that patients with adequate preoperative platelet inhibitory effect revealed with thienopyridines have the mean ADP test increase of 12 U/day following drug discontinuation[50]. Those data are very valuable since authors described platelet recovery dynamics following thienopyridines discontinuation[50]. The same research group (SCORE research group) previously defined cut-off value of ADP test 31 AUC to delineate excessive bleeding tendency after cardiac surgical procedures[45]. Therefore, known cut-of value of 31 AUC, together with expected daily recovery dynamics of 12 AUC per day, allows for tailored preoperative management of thienopyridines discontinuation. On the other hand, if patient on thienopiridines treatment has value of ADP test above cut-of, it seems reasonable to proceed with surgery without thienopiridines free interval of 5 days as proposed by guidelines[29]. Considering bleeding outcomes, the last ADP test value prior to surgery was significantly associated with postoperative bleeding ($p=0.002$) [29]. Finally authors concluded that platelet function testing immediately prior to surgery is determinant of postoperative bleeding and requirement for platelet concentrates transfusions[50]. Since the study was retrospective analysis of prospectively collected data, results (especially for platelet concentrate transfusion in thienopyridines responsive patients subgroup) should be interpreted cautiously because ADP test value was a part of decision making process thus creating bias[29].

Alstrom et al investigated platelet function in patients undergoing CABG with recent preoperative ASA and CLO exposure (within 3 days)[51] using flow cytometry including VASP phosphorylation and two bedside suitable point-of-care analyzers, VerifyNow System

(Accumetrics, San Diego, Calif) and the TEG Platelet Mapping device[51]. The authors sough to evaluate whether preoperatively performed assessment of platelet function could predict the risk of bleeding and transfusion requirements following cardiac surgical procedures [51]. VerifyNowP2Y12 was the only platelet function assay that showed significant correlations with total blood loss (Spearman's Rho 0.29, p=0.03) and the total number of red blood cell transfusions (r=0.43, p<0.01). Notably, none of the above mentioned assays predicted transfusion of platelet concentrate and fresh frozen plasma [51]. Interestingly, TEG PlateletMapping-MAADP test revealed Spearman's Rho of only 0.01 in correlation with total blood loss[51] which was substantially opposite than findings reported by Presiman et al[25] who found the same device to be of clinical usefulness in prediction of postoperative bleeding[25]. Very recent study by Rosengart et al[52] evaluated the ability of platelet function testing to identify CABG patients at increased risk for bleeding and transfusion outcomes[52]. Study enrolled patients who underwent isolated CABG with documented preoperative CLO administration[52]. Preoperative platelet function was assayed within 24 hours of surgery by measuring P2Y12 receptor blockade with the VerifyNow system (Accumetrics, San Diego, Calif). Patients were divided according to presence of higher platelet reactivity units (PRU) (≥237 PRU) or lower platelet reactivity (<236 PRU). Lower PRU subgroup was more likely to bleed excessively (OR 1.99; 95% CI, 1.02-3.88, p=0.04; c-index 0.584) and to be transfused with procoagulant blood components (OR, 2.33; 95% CI, 1.2-4.54; p=0.01; c-index, 0.603). In addition to, authors performed exploratory analysis in which patients were divided into three groups according to PRU value distribution (high (>290 PRU), intermediate (200-290 PRU) and low (<200 PRU). Odds of having excessive CTD and procoagulant blood component increased significantly as an incremental function of exploratory patients grouping according to PRU value distribution (OR, 2.26; p<0.001). Authors concluded that the risks of bleeding and transfusion outcomes can be easily

predicted using point-of-care platelet function testing[52] although results should be interpreted cautiously due to retrospective study design.

DISCUSSION

Bleeding in cardiac surgery is multicausal, and several factors such as comorbidities, preoperative medications, surgical technique and perioperative hemostatic management as well as the complexity of surgical procedure influence the extent of postoperative blood loss.

Thus, it seems that due to multicausality in pathogenesis of excessive bleeding following cardiac surgery, attempts to create a universal hemostatic agent will certainly fail.

Several platelet function assays are available, and paucity of data exists regarding its clinical utility, but different assays and different study designs hamper the meaningful comparisons. Generally, platelet function testing cutoffs used among different centers are derived from manufacturers, on the clinical leaders' opinion or are based on the retrospective/prospective studies conducted in respective centers in order to delineate clinical outcomes (bleeding, transfusion and adverse clinical outcomes). However, there is shortage of generally applicable cutoffs that could be reproduced and implemented by worldwide centers. This shortage arises from the lack of prospective multicentric trials that would firstly define the cutoffs for bleeding events, transfusion requirements as well as for ischemic events.

Put briefly, to be clinically useful, a platelet function assay must fulfill several criteria: 1) the platelet function test should be validated in large number of specific patient groups. Stratification of patients according to the respective risks should be feasible, and if possible, platelet function assays should provide "safety window" range of values that should be targeted when deciding on preoperative APT administration and/or discontinuation, 2) the assay should be bedside suitable, user friendly and should have as short as possible "turnaround time" (time from blood sampling to obtaining results) in order to provide timely detection of risk for bleeding and subsequent risk of transfusion which would in turn allow for timely hemostatic interventions. Such an approach requires studies to be conducted in

prospective fashion to determine whether the platelet function test can identify patients at risk for a particular adverse outcome (excessive bleeding , excessive allogeneic blood products transfusion requirements, adverse ischemic events) using ROC curve[44] analysis.

When assessing the role of platelet function tests for prediction of bleeding and transfusion outcomes some methodological considerations should be addressed. Different study designs were used in different investigations with aim to evaluate association between platelet function test results and bleeding extent and transfusion requirements.

Prospective observational studies are capable to provide the most accurate cutoffs with sensitivity and specificity that are best possible in clinical settings. Experimental study setting is not ethically acceptable. For example, although prospective studies using platelet function tests should be “clinician blinded”, patients receive hemostatic therapy according to regular clinical protocols and procoagulant blood components administration certainly attenuate correlations coefficient between measured platelet function test values and observed bleeding extent. Secondly, cutoffs that are defined in prospective observational studies using ROC analyses should be tested through prospective randomized studies to assess the safety, efficacy and cost-effectiveness of customized approaches based on platelet function testing results. Generally, various platelet function testing provide a high negative predictive values[39] which in turn may allow for (1) a reduction in the number of days that patients with a preoperatively administered dual APT are off antiplatelet agents, as suggested by the current guidelines[29,30] and for (2) reduction of procoagulant components transfusion rate. Such an approach would lead to determination of the optimal safe period from discontinuation of APT to surgery for the individual patient and would minimize unnecessary transfusions. Again, such a tailored approach should be evaluated through prospective randomized clinical outcome evaluating trials.

As previously mentioned, prospective studies are the most suitable for assessment of bleeding risks and transfusion requirements. However, there are several retrospective studies addressing same issue[45,49,50,52]. The major drawback of retrospective studies is the fact that evaluated platelet function testing was used in clinical decision making process. Although such studies have often high number of patients from databases, it is obvious that observed associations are in certain degree distorted by the fact that platelet function tests were used in clinical decision making process, thus probably creating bias in estimations of relationship between test results and both bleeding extent and transfusion requirements.

When discontinuing preoperative APT, one should be aware that some proportion of those patients is resistant to APT (have high degree of residual platelet reactivity despite appropriate treatment). Our working group recently found 31.3% of patients to be ASA resistant preoperatively[53]. Therefore, ASA discontinuation in this subgroup of patients may lead to further increase of platelet reactivity and pose patients to proclivity to ischemic events. In addition to, resistance to CLO therapy , increasingly administered antiplatelet drug in preoperative phase may be present in range between 25% -60%[54]. Therefore, use of point-of-care platelet function analyzers may prevent not only bleeding events but also ischemic events by detecting those patients who experience high on-treatment platelet reactivity who might benefit from late or no APT discontinuation. Too early APT discontinuation may lead to onset of platelet hyperactivity [55,56] and subsequently cause adverse ischemic events in preoperative phase. Finally, use of platelet function analyzers may provide dual benefit in terms of prevention of both bleeding and ischemic events.

Literature review revealed both positive and negative studies regarding association between platelet function analyzer findings and both bleeding outcomes and transfusion requirements. Heterogeneity of devices and variability in study settings hampers evidence and makes it somehow hard to pool the findings and make strong conclusions. Firstly, there is

no generally accepted definition of excessive bleeding and observed definitions vary widely across literature (Table 1). Standardized definition of excessive bleeding is necessitating. We propose measurement of CTD in first 24 hours and the extent of CTD should be divided by patient's weight. Patients should be characterized as bleeders if their 24 h CTD (ml/kg) exceeds 75th percentile of distribution in predefined sample of patients. Such a definition makes the most reliable correlation, and is not distorted to different anthropometric measures, perfusionistic, surgical and anesthetic techniques. Such an approach dichotomizes bleeding outcome. The alternative approach would be to correlate platelet function test findings with CTD as expressed in form of continuous variable. Any significant correlations should further be tested for accuracy via ROC analysis[44]. In this way it would be possible to reach the best sensitivity/specificity ratio as well as positive and negative predictive values. Drawbacks of the CTD quantification were briefly discussed by Ti et al[9]. One should be aware that blood loss measured as CTD consists of a mixture of fluids, including actual blood loss, serous drainage and fluid left in the pleural cavities. Furthermore, bleeding is consisted of two types depending on the origin of bleeding: (1) bleeding due to hemostatic disorder including platelet dysfunction and (2) bleeding due to surgical issues.

Treatment options of hemorrhage in cardiac surgery are continuously evolving. Recently, Gorlinger et al provided comprehensive insight into this issue[57]. It is however obvious that appropriate hemostatic management in cardiac surgery patients should be consisted of bundle of protective strategies to prevent and treat excessive bleeding such as:

1) Preoperative bleeding risk stratification , based mainly on detection of patients who have weak platelet function thus proclivity to excessive bleeding. This part is largely elaborated in present review article.

2) Intraoperative transfusion management based on point-of-care hemostatic tests. There is evidence for efficacy of such a transfusion management based on tests for assessments of viscoelastic blood properties (ROTEM) and platelet function tests[48]. Different treatment modalities are available depending on possibilities of each cardiac surgery center. We propose algorithm for perioperative hemostatic management that we use at our center (Figure 1.). Such an algorithm provides a concept that may be applied generally and adjusted to different point-of-care hemostatic tests as well as different hemostatic treatment modalities available.

3) Surgical measures to achieve meticulous hemostasis

Bleeding due to surgical issues should not be underestimated for two reasons: (1) it certainly affects the extent of CTD which was found to be independently associated with adverse outcomes after cardiac surgery[2,3] , and (2) more than 70% of patients undergoing re-exploration for excessive bleeding have had bleeding vessel identified (surgical cause of bleeding)[4]. Surgeon performance may contribute significantly to such a complication. Biancari et al hypothesized that individual surgeons performance may contribute significantly to bleeding outcome [4]. Retrospective study on 2001 patients reported re-exploration for bleeding rate of 5.3% [4]. Of more importance rates of re-exploration varied between 1.4% and 11.7% ($p<0.0001$) according to different surgeons performing hemostasis [4]. Furthermore, variable of individual surgeon was found to be independent predictor for re-exploration for excessive bleeding, as well as for CTD of $\geq$ 1600 mL [4]. Kim et al demonstrated that individual surgeon was found to be strongest factor associated with transfusion outcome in patients undergoing CABG with recent CLO exposure[58]. Therefore, meticulous surgical technique must be cornerstone on appropriate hemostatic management since individual surgeon's skills may be important as much as the preoperative APT discontinuation management based on platelet function testing. Moreover, Loor et al [59]

developed and implemented a formal operative checklist to reduce technical reasons for postoperative bleeding[59]. Easily performed hemostasis checklist based on the most common sites of bleeding was developed[59]. Implementation of such bleeding checklist resulted in increased number of cases operated on between consecutive reoperations[59]. Therefore, in order to optimize bleeding outcomes, meticulous surgical technique along with checklist for bleeding should be inextricably included to perioperative APT administration management targeted after platelet function testing.

In conclusion, appropriate perioperative hemostatic management should inevitably include bedside suitable point-of-care devices and hemostatic management should be based on goal-directed hemostatic therapy, so called “theranostic approach” [45,48,57,60-62]. Such an approach may reduce the rate of reexploration for bleeding from up to 75% [4] to 20% [48] , as recently described by Weber et al through prospective randomized trial [48]. Point-of-care guided hemostatic algorithm may reduce the rate of reexplorations due to hemostatic disorder and direct reexploration surgery dominantly to surgical cause of bleeding. The reduction of unnecessary as well as inefficient surgical reexplorations rate certainly may improve clinical outcome. There are a large number of studies dealing with prediction and prevention of excessive bleeding in cardiac surgery patients. Platelet function analyzers should definitely be included in modern hemostatic management with aim to frame safety therapeutic window (between bleeding and ischemic events). We suggest use of platelet function testing in perioperative setting of cardiac surgery patients. However, when using such devices, one should be aware of platelet function testing limitations in estimating risk for excessive bleeding and transfusion requirements. Such devices may not always provide accurate prediction of bleeding which can be easily explained by the fact that bleeding is consisted of both surgical bleeding and bleeding due to hemostatic disorder of which platelet function is only one part. In process of decision making based on point-of-care hemostatic tests one

should account with the possibility of excessive bleeding despite normal values of hemostatic tests. The reason for such a phenomenon may be the fact surgical hemostasis is not always as good as it should be, in particular in teaching hospitals. Meticulous surgical hemostasis must be performed in order to exclude surgical cause of bleeding. Procoagulant blood component administration should be targeted after both platelet function assay results and TEM/TEG results. Antifibrinolytics as well as DDAVP should be considered in cases where weak platelet function or high fibrinolysis index is detected using point-of-care devices. Multicausality in hemostatic disorders requires multidisciplinary and comprehensive approach in treatment. "One size fits for all" approach in hemostatic management seems to be obsolete, and shift towards personalized approach using bedside suitable point-of-care devices in bleeding and transfusion requirements optimization is certainly required.

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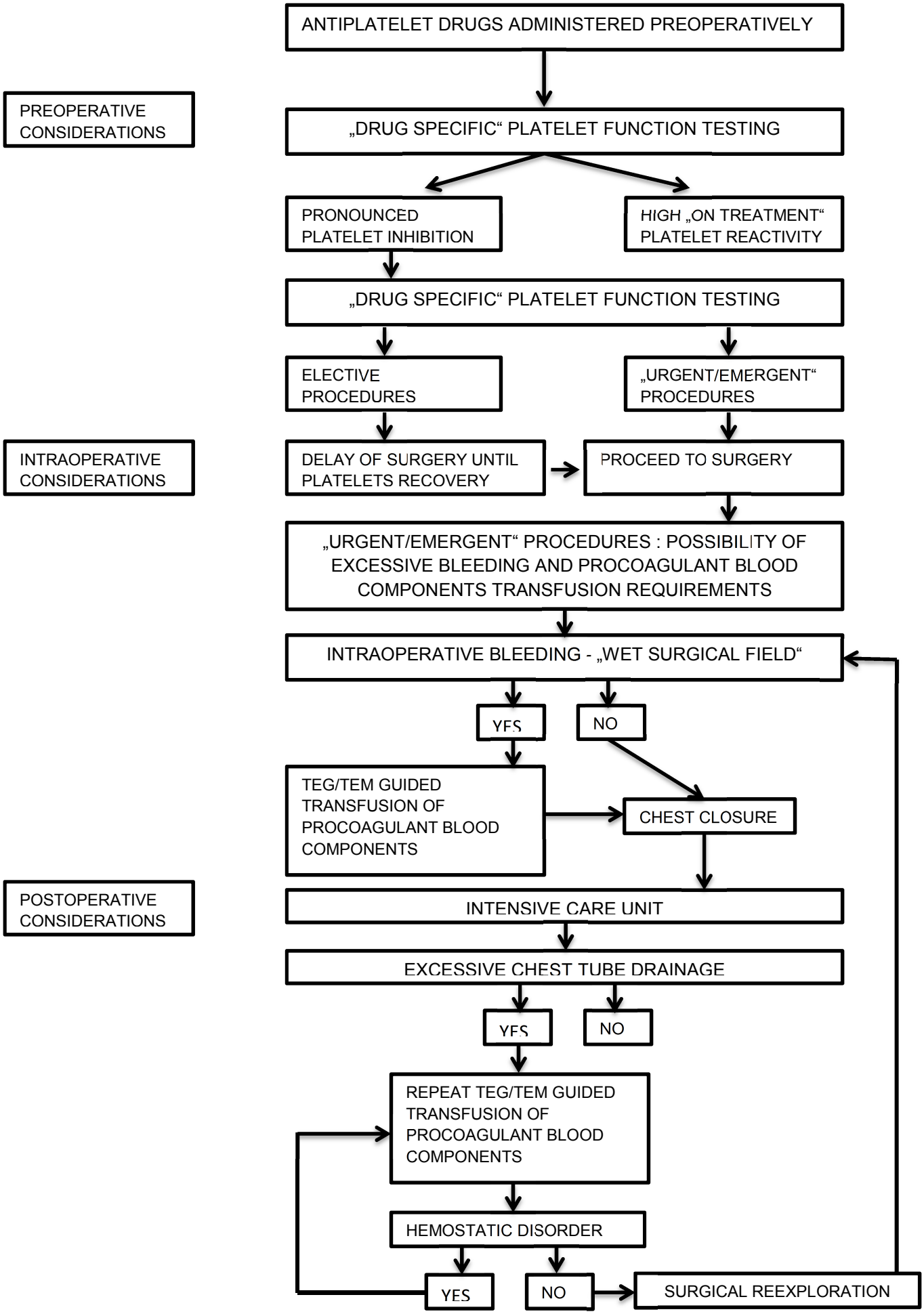
Figure Legends:

Figure 1. Perioperative hemostatic management algorithm (TEG/TEM: thromboelastography/thromboelastometry)


PREOPERATIVE CONSIDERATIONS
ANTIPLATELET DRUGS ADMINISTERED PREOPERATIVELY
„DRUG SPECIFIC“ PLATELET FUNCTION TESTING
PRONOUNCED PLATELET INHIBITION
HIGH „ON TREATMENT“ PLATELET REACTIVITY
„DRUG SPECIFIC“ PLATELET FUNCTION TESTING
ELECTIVE PROCEDURES
„URGENT/EMERGENT“ PROCEDURES
INTRAOPERATIVE CONSIDERATIONS
DELAY OF SURGERY UNTIL PLATELETS RECOVERY
PROCEED TO SURGERY
„URGENT/EMERGENT“ PROCEDURES : POSSIBILITY OF EXCESSIVE BLEEDING AND PROCOAGULANT BLOOD COMPONENTS TRANSFUSION REQUIREMENTS
INTRAOPERATIVE BLEEDING - „WET SURGICAL FIELD“
YES
NO
TEG/TEM GUIDED TRANSFUSION OF PROCOAGULANT BLOOD COMPONENTS
CHEST CLOSURE
POSTOPERATIVE CONSIDERATIONS
INTENSIVE CARE UNIT
EXCESSIVE CHEST TUBE DRAINAGE
YES
NO
REPEAT TEG/TEM GUIDED TRANSFUSION OF PROCOAGULANT BLOOD COMPONENTS
HEMOSTATIC DISORDER
YES
NO
SURGICAL REEXPLORATION

AUTHOR YEAR	TYPE OF STUDY	ANTITHROMBOTIC MEDICATIONS MANAGEMENT	PLATELET FUNCTION TEST RESULTS USED TO GUIDE HEMOSTATIC MANAGEMENT	STUDY COHORT	PLATELET FUNCTION TEST	TIMING OF PLATELET FUNCTION TESTING	DEFINITION AND/OR INCIDENCE OF EXCESSIVE BLEEDING	BLEEDING OUTCOME	TRANSFUSION REQUIREMENTS
Lennon et al, 2004	Prospective observational study	patients who had received clopidogrel within week before surgery were excluded ; patients had taken aspirin up to a variable interval before surgery	no	50 CABG and valve surgery patients	Plateletworks (Helena Laboratories, Beaumont, TX)	before the commencement of anesthesia and on completion of surgery	not reported	Correlations with CTD were non-significant both pre- (r=0.07, p=0.58) and post-operatively (r=0.14, p=0.34)	not reported
Despotis et al, 1996	Prospective observational study	aspirin 67 patients ; heparin 42 patients ; warfarin 9 patients (within 1 week before surgery)	no	150 patients undergoing cardiac surgery	Platelet-activated clotting test (PACT) (Hemostatus ® ; Medtronic, Inc., Parker, CO)	1) baseline (before anesthesia induction) ; 2) CPB (shortly before discontinuation of CPB) ; 3) post CPB (after heparin/protamine neutralization) ; 4) after arrival in the ICU	excessive microvascular bleeding was defined as diffuse bleeding from the surgical site without an identifiable surgical source	Excessive blood loss was successfully predicted (Significant correlations with CTD).	not reported

Ereth et al, 1997	Prospective observational study	not reported	no	200 patients undergoing cardiac surgery	PACT (Hemostatus ® ; Medtronic, Inc., Parker, CO)	1) after induction of anesthesia ; 2) 40 min after initiation of cardiopulmonary bypass ; 3) 20-40 min after protamine administration	more than 200 mL/h (or 100 mL/h) of CTD in the first 4 hours in the ICU		No correlation between transfusion requirements and post-protamine PACT values
					Thromboelastography (TEG, Haemoscope Corp., Glenview, IL)			The postprotamine TEG MA also correlated with the 4 hour CTD (r=-0.32, p=0.003)	not reported
Ereth et al, 1998	Prospective observational study	not reported	no	100 patients undergoing cardiac surgery	PACT (Hemostatus ® ; Medtronic, Inc., Parker, CO)	within 1 h after patient's arrival to the ICU	The two disease states of bleeding after CPB were determined by > an average of 100 ml/h and 200 ml/h CTD in the first 4 h in the ICU	None of PACT values correlated with CTD	not reported
Wahba et al, 1998	Prospective observational study	patients on APT less than 10 days prior to surgery were excluded	no	40 patients undergoing cardiac surgery	PFA - 100 ® (DADE Diagnostika, Unterschleissheim, Germany)	1) during anesthesia before institution of CPB and 2) at completion of surgery	not reported ; CTD presented as a continuous variable	Preoperative PFA-100 ® closing time significantly correlated with CTD (r=0.41, p=0.022).	not reported
					PACT (Hepcon/Hemostatus ™ , Medtronic, Dusseldorf, Germany)			Hepcon HMS did not correlate with CTD (r=0.18, p=0.37)	
Dietrich et al, 1998	Prospective observational study	patients had not received aspirin for at least 10 days	no	16 patients undergoing CABG	PFA - 100 ® ; Dade, Miami, FL, USA	1) after intubation ; 2) 15 min after heparin/protamine	not reported ; CTD presented as a continuous	Only TEG-MA performed postoperatively	not reported

					Impedance aggregometry (Chronolog, Havertown, PA, USA) TEG - Thromboelastograph D (Hellige , Freiburg , Germany) Platelet function-PAF test (PFT, Medtronic, Parker, CO, USA)	reversal ; 3) three hours following admission to ICU	variable	correlated significantly with CTD	
Slaughter et al, 2001	Prospective observational study	preoperative treatment with platelet glycoprotein receptor inhibitors, but not aspirin was considered as exclusion criteria	no	58 patients undergoing CABG	PFA - 100 ® (Dade-Behring Inc., Miami, FL, USA)	1) preoperatively ; 2) 5 min after heparin administration ; 3) 5 min after initiation of CPB ; 4) 15 min after protamine administration	cumulative 6h CTD exceeding 646 ml/6h	Non-significant correlations were detected between PFA - 100 ® and CTD.	Non-significant differences in collagen/ADP closure times (15 min after protamine administration) between patients transfused and not transfused with PC
Forestier et al, 2002	Prospective observational study	patients who had taken APT within 7 days of the surgery, and those on heparin or anticoagulant therapy were excluded	no	45 patients undergoing cardiac surgery	PFA - 100 ® (Dade-Behring Inc., Miami, FL, USA) PACT (Hepcon/Hemostatus ™ , Medtronic, Rueil-Malmaison, France)	1) on arrival in the ICU for all patients ; 2) when excessive bleeding was diagnosed or after 3 h in the ICU	CTD >1ml/kg/h for at least 1 h during the first 6 h after surgery	Platelet function testing devices failed to correlate with CTD	not reported

					PAP-4 aggregometer; (BIO/DATA Corporation , Paris, France)				
Fattorutto et al, 2003	Prospective observational study	APT withdrawn for at least five days before surgery	no	70 patients undergoing cardiac surgery	PFA - 100 ® (Dade-Behring Inc., Miami, FL, USA)	1) before CPB ; 2) after protamine-induced heparin neutralization	excessive CTD was defined as > 200 ml for two successive hours	The pre-CPB CECT measurement correlated weakly with first- and second-hour CTD (r=0.32, p=0.01 and r=0.34, p=0.01, respectively)	not reported
Cammerer et al, 2003	Prospective observational study	41% patients received aspirin within 5 days before surgery ; 6% received ticlopidine/clopidogrel until surgery ; 6% received coumadine until surgery	no	255 patients undergoing cardiac surgery	PFA-100 ™ (Dade Behring, Schwalbach, Germany) Thromboelastography - ROTEG ™ (Pentapharm, Munich, Germany)	1) directly after the induction of anesthesia ; 2) during CPB after rewarming ; 3) 15 min after protamine administration	Abnormal bleeding: 1) CTD 750 ml/6h; 2) CTD exceeding 75th percentile (500 ml/6h postoperatively)	Solely the measurements after CPB showed significantly different values of both ROTEG and PFA between patients divided with respect to excessive CTD presence	not reported
Poston et al, 2005	Prospective observational study	preoperative aspirin was continued through the date of surgery	no	76 patients undergoing off-pump CABG	TEG (Haemoscope Corporation, Niles, IL, USA)	1) prior to skin incision ; 2) Immediately after skin closure	24h CTD >800 mL	Perioperative decline in platelet function as assessed by WBA correlated with intraoperative blood loss (R=0.42, p<0.05), Perioperative decline in TEG-MA significantly	not reported

					Whole blood aggregometry (Chronolog , Havertown, Pennsylvania)			correlated with 24 hour hemoglobin loss (r=0.45, p<0.05)	
Carrol et al, 2006	Prospective observational study	patients on APT were excluded	no	75 patients	TEG (Haemoscope Corporation, Niles, IL, USA)	1) before heparin administration ; 2) 15 minutes after heparin reversal with protamine ; 3) one hour post operation	Bleeding assessment by observer agreement: not bleeding, oozing or excessive bleeding	None of platelet function test parameters significantly correlated with bleeding	not reported
Preisman et al, 2010	Prospective observational study	57 patients were exposed to aspirin ; 34 patients were exposed to clopidogrel preoperatively	no	59 patients undergoing CABG	TEG (Haemoscope Corporation, Niles, IL, USA) platelet mapping with determination of the tensile strength of the platelet-fibrin clot induced by ADP (MAadp) or arachidonic acid (MAaa)	prior to induction of anesthesia	cluster analysis revealed two groups of patients with respect to bleeding tendency. CTD was significantly higher in bleeding group (1216 ± 310 mL vs. 576±105mL)	MAadp parameter was the only TEG parameter that significantly predicted bleeding tendency (p=0.004).	Significant correlation existed between the use of PC and MAadp in patients with bleeding tendency (Rho=-0.75, p=0.02)

Kwak et al, 2010	Prospective observational study	patients were preoperatively exposed to aspirin and clopidogrel	no	100 patients undergoing off-pump CABG	TEG (Haemoscope Corporation, Niles, IL, USA) platelet mapping (MAadp)	immediately before the induction of anesthesia	>200 mL/h in two consecutive hours	Patients with the most pronounced platelet inhibition percentage had a significantly greater amount of post-operative CTD	Patients with the most pronounced platelet inhibition were more frequently transfused with PRBSs and FFP. ROC analysis defined cutoff value for transfusion requirements (70% platelet inhibitory response to clopidogrel)
Weitzel et al, 2012	Prospective observational study	Patients on aspirin were included but exposure to clopidogrel was exclusion criterion	not for platelet mapping, but standard TEG was used as a target for transfusion administration	40 patients undergoing cardiac surgery	TEG (Haemoscope Corp, Niles, IL, USA) , platelet mapping (MAcollagen, MAadp and MAaa)	pre- and post-CPB	>1000mL/24h CTD	pre- and post-CPB Macollagen and pre-Maaa showed significant correlation with 24-h CTD	not reported
Mahla et al, 2012	Prospective interventional, single center, unblinded study	patients with background aspirin with/without clopidogrel treatment	Yes (timing of surgery in clopidogrel treated patients was tailored after TEG MA results)	180 patients undergoing elective CABG	TEG (Haemonetics Corporation Braintree, MA) platelet mapping (MAadp and MAaa)	preoperative period	not reported	There was no difference in CTD between clopidogrel-treated and clopidogrel-naive patients	No differences in the total amount of PRBCs transfused to clopidogrel-treated patients as compared with clopidogrel-naive patients (p=0.540)

Gerrah et al, 2006	Prospective observational study	2 (6%) patients were exposed to aspirin preoperatively	no	32 patients undergoing cardiac surgery	Cone and Plate(let) Analyzer, CPA, Impact-R (Diamed, Cressier/Morat, Switzerland)	1) during induction of anesthesia ; 2) immediately after sternotomy ; 3) 10 min after heparin injection ; 4) 10 and 30 min after establishment of CPB ; 5) after discontinuation of CPB ; 6) 10 min after protamine injection ; 7) at the end of the operation	severe blood loss > 965 mL of CTD	According to multivariate analysis postoperative bleeding was found to be significantly and linearly dependent of the preoperative platelet function by average size and surface coverage (p=0.003 and 0.001, respectively).	No difference was found between the percentage of patients who received transfusions and preoperative CPA parameters

Rahe-Meyer et al, 2009	Prospective observational study	aspirin discontinued for more than 4 days in 55 patients and clopidogrel discontinued for at least one week before surgery in 58 patients	no	60 patients undergoing cardiac surgery	Multiplate ® , Dynabyte Medical , Munich , Germany	1) before induction of anesthesia and 2) at the end of operation	not reported	No significant differences between the low and the high tertile of platelet function were noted with respect to 24-hour CTD	Patients with Multiplate results within lower tertile received significantly more PC transfusion (Preoperative tests: p=0.006 for the ADP test and p=0.03 for the COL test ; Postoperative tests: p=0.028 for the ADP test).
Solomon et al, 2010	Prospective observational study	5 (10%) of patients exposed to aspirin within 3 days of surgery	no	50 consecutive CABG and AVS patients	Multiplate ®, Dynabyte Medical , Munich , Germany	before induction of the anesthesia	not reported	not reported	Multiplate ASPI, ADP and COL test significantly correlated with PC transfused intraoperatively
					Cone and Plate(let) Analyzer , CPA , Impact-R , Diamed, Cressier/Morat, Switzerland				CPA parameters did not correlate significantly with transfusion parameters
Reece et al, 2011	Prospective observational study	7/44 patients exposed to aspirin ; 1/44 to clopidogrel and 4/44 to aspirin and clopidogrel within 6 days before surgery	no	44 patients undergoing CABG	Multiplate ® , Dynabyte Medical , Munich , Germany (ASPI test , ADP test , TRAP test)	1) induction of anesthesia ; 2) 20 min on cardiac bypass ; 3) chest closure ; 4) ICU arrival	not reported	not reported	ADP (18 U vs. 29 U; p=0.01) and TRAP (65 U vs. 88 U; p=0.01) tests performed during chest closure were significantly lower in transfused patients

Ranucci et al, 2011	Retrospective analysis of prospectively collected data	patients were exposed to clopidogrel within 7 days of surgery	yes	87 patients undergoing cardiac surgery	Multiplate ® , Dynabyte Medical , Munich , Germany (ADP test , TRAP test)	preoperatively	≥800 ml/12 hours CTD	ADP test was independently associated with postoperative bleeding (Regression coefficient -0.47, p=0.007). ROC analysis revealed ADP test cut-off 31 AUC to delineate excessive bleeding.	Patients with ADP test AUC lower than 31 U had significantly higher rate of PC transfusion (p=0.044)
Petricevic et al, 2012	Prospective observational study	patients were exposed to aspirin and/or clopidogrel	no	211 CABG patients	Multiplate ® , Dynabyte Medical , Munich , Germany	preoperatively	24 hour CTD ≥ 11.33 ml/kg	Significant correlations between the ASPI test and ADP test with 24 h CTD were found. ROC delineated ASPI < 20 AUC and ADP<73 AUC as a "bleeder" determinant	ASPI , but not ADP test was significantly lower in a group of patients transfused with PRBC
Webber et al, 2012	Prospective, randomized parallel-group single center study	preoperative APT, including aspirin, was ceased at least 6 days before surgery	yes	100 patients undergoing cardiac surgery	Multiplate ®, Dynabyte Medical , Munich , Germany (ASPI test ,ADP test , TRAP test) ROTEM ®, Tem International, Munich , Germany	intraoperatively	not reported	Patients in the conventional group lost more blood after admission to the ICU. However, there was no difference in reexploration rate.	Compared with the conventional group, patients in the POC group were transfused less often with PC, FFP, rVIIa

Schimmer et al, 2012	Retrospective observational clinical study	Patients were exposed to APT	yes	223 adult cardiac surgical patients	Multiplate ®, Dynabyte Medical , Munich , Germany (ADP test , ASPI test, TRAP test)	1) beginning of anesthesia ; 2) 30 min upon arrival on the ICU	not reported	Pathological values of ASPI, ADP and TRAP test values did not reflect higher postoperative CTD.	ADP test value <534AU*min was associated with more PCs transfusion. TRAP test value <941 Au*min was associated with more RBC transfusion (p=0.02) and PC transfusion (p=0.02).
Petricevic et al, 2013	Prospective observational study	patients were exposed to aspirin and/or clopidogrel preoperatively	no	148 patients (elective cardiac surgery)	Multiplate ®, Dynabyte Medical, Munich, Germany ROTEM ®, Tem International, Munich, Germany	1) preoperatively; 2) during CPB ; 3) after protamine administration	24 hour CTD ≥ 12.46 ml/kg	ASPI , ADP , TRAP test significantly correlated to 24 hour CTD All TEM tests significantly correlated to 24 hour CTD	not reported
Di Dedda et al, 2013	Retrospective analysis of prospectively collected data	aspirin was not discontinued before surgery ; clopidogrel was discontinued within 7 days before surgery	yes	344 patients undergoing cardiac operations	Multiplate ®, Dynabyte Medical, Munich, Germany	preoperatively	not reported	The last ADP test before the operation was significantly associated (p=0.002) with postoperative CTD.	The last ADP test before the operation was significantly associated (p=0.001) with postoperative PC transfusions
Alstrom et al, 2009	Prospective observational study	aspirin was continued until surgery ; clopidogrel was ceased within three days before surgery	no	60 patients undergoing CABG	VerifyNow P2Y12 test and Aspirin test (Accumetrics, San Diego, CA)	1) before anesthesia ; 2) after protamine	not reported	VerifyNow significantly correlated to CTD (r=0.29 , p=0.03)	VerifyNow significantly correlated with a total number of PRBCs transfusions (r=0.43, p<0.01)

					TEG 5000 Hemostasis Analyzer and PlateletMapping (Haemoscope Corporation, Niles, Illinois, USA) MAaa and MAadp parameters used.			no significant correlations were observed for TEG 5000 (r=0.01, p=0.98)	no significant correlations were observed for TEG 5000 (r=0.05, p=0.69)
Rosengart et al, 2013	Retrospective analysis of prospectively collected data	54% of patients received clopidogrel preoperatively; 70% of patients received aspirin preoperatively	yes	276 patients undergoing CABG	VerifyNow P2Y12 test (Accumetrics, San Diego, CA)	preoperatively	12 hours CTD > 437 mL	Multivariate analysis showed that CTD alone was not significantly different between the higher- and lower-PRU groups (p=0.09).	Multivariate analysis revealed patients with lower PRU to require procoagulant components transufsion (OR, 2.82; 95% CI, 1.39-5.73; p=0.0004; c-index, 0.642)

Table 1.

Summary of the studies evaluating the relationship between platelet function test findings and bleeding as well as transfusion outcomes.

List of abbreviations: ADP: Adenosine diphosphate induced aggregation; APT: Antiplatelet therapy; ASPI: Arachidonic acid induced aggregation; AUC: Area under the curve; AVS: Aortic valve surgery; CABG: Coronary artery bypass graft; CECT: Collagen/epinephrine closure time; CI: Confidence interval; COL: Collagen; CPA: Cone and platelet analyzer; CPB: Cardiopulmonary bypass; CTD: Chest tube drainage; FFP: Fresh frozen plasma; ICU: Intensive care unit; MA: Maximal amplitude; MAaa: platelet-fibrin clot tensile strength induced by archidonic acid; MAadp: platelet-fibrin clot tensile strength induced by ADP; OR: Odds ratio; PACT: Platelet-activated clotting test; PC: Platelet concentration; PFA: Platelet function analysis; POC: Point of care; PRBC: Packed red

blood cells; PRU: Platelet reactivity units; rVIIa: Recombinant factor VIIa; ROC: Receiver operating characteristic; TEG: Thromboelastography; TRAP: Thrombin receptor activating peptides induced aggregation; U: Units.