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Platelet Function Testing for Cardiac Surgery Patients on Antiplatelet Therapy: The Extreme Variability of Point-Of-Care Tests

Beatrice O. Ondondo

Cardiff Metropolitan University, Llandaff Campus, 200 Western Ave, Cardiff CF5 2YB.
*Corresponding author E-mail: Beatrice.Ondondo@wales.nhs.uk

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Platelets play a pivotal role in coagulation, and both quantitative and qualitative platelet defects can lead to major bleeding during and after surgery. Moreover, patients with cardiac disease are often on antiplatelet therapies as part of routine management, which predisposes to increased risk of perioperative bleeding due to inhibited platelet function. In some cases, antiplatelet therapy is interrupted briefly before scheduled cardiac surgery in order to reduce the risk of haemorrhage; however, this can increase the risk of perioperative thrombosis if not monitored carefully. Furthermore, individual patients respond differently to antiplatelet therapy. Therefore, point-of-care tests that determine platelet function could provide improved, personalised evidence-based treatment and management of such high-risk cardiac patients. This article reviewed various methods and devices used for testing platelet function at point-of-care in cardiac patients on antiplatelet therapy who were undergoing cardiac surgery. The consensus is that point-of-care testing of platelet function can offer three main advantages for the timely management of preoperative and perioperative coagulation in cardiac surgery patients who are on antiplatelet therapy: 1.) Assessing the effectiveness of antiplatelet therapy to quickly identify patients with resistance, who have increased risk of pre- and perioperative thrombotic events. 2.) Assessing platelet function recovery following treatment withdrawal to determine optimal timings for cardiac surgery, in order to avoid excessive haemorrhage, and reduce waiting times and hospitalisation costs for patients scheduled for cardiac surgery. 3.) Efficient use of transfusion blood products. However, an important finding of this review is that there exists extreme variability and a lack of correlation among the various point-of-care platelet function testing assays. Furthermore, the assays show inconsistencies in predicting blood loss, or adverse thrombotic and haemorrhagic events in cardiac patients on antiplatelet therapy and those undergoing surgery. It is imperative that point-of-care platelet function tests accurately predict the risks of bleeding and thrombosis in order to be clinically relevant in the preoperative, perioperative and long-term post-operative care and management of cardiac surgery patients on antiplatelet therapy. The extreme variability of these tests, coupled with inconsistencies in predicting adverse events do not support the high costs of large-scale implementation.

Keywords: Platelet function testing; Platelet function assays; Point of care testing; Antiplatelet therapy; Cardiac disease; Cardiac surgery; Thrombosis; Haemorrhage.

The demand for blood transfusion products is higher for cardiac disease patients undergoing cardiac surgery[1-3], particularly those on antiplatelet therapy. Platelets are important in the maintenance of blood clotting to prevent excessive bleeding. Both qualitative (thrombocytopathy) and quantitative (thrombocytopenia) platelet disorders can prevent or reduce effective clotting[4-7],

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which can cause massive blood loss, leading to haemorrhagic shock and acute anaemia during surgery, trauma or obstetrical events. Excessive bleeding frequently occurs in individuals with underlying clotting disorders, including platelet disorders.

Although platelets are important for blood clotting, excessive platelet activity (or high platelet reactivity following withdrawal of antiplatelet therapy) can cause severe and life-threatening thromboembolic events including venous thromboelism (deep vein thrombosis (DVT) and pulmonary embolism (PE)) [8] in high-risk cardiac patients. In particular, cardiac patients with acute coronary syndromes (ACS) often present with platelet aggregation and thrombus formation[9]. To prevent thromboembolic events in such high-risk patients, thromboprophylaxis (antiplatelet and anticoagulant drugs) is administered as part of routine care and management. However, these drugs (which slow the coagulation process and disrupt platelet function through a number of mechanisms) may also prevent effective blood clotting during cardiac surgery and in the perioperative recovery period, as well as in emergency trauma for cardiac patients on thromboprophylaxis. In such scenarios, transfusion of blood products becomes necessary in order to compensate for lost blood and clotting factors, and to prevent acute anaemia. However, besides cost implications, blood product transfusion comes with the risk of complications such as alloimmunisation and dilutional thrombocytopenia and hypocalcaemia[10] . Thus, in cases where cardiac surgery is not urgent, antiplatelet therapy can be withdrawn temporarily to allow platelet function recovery before surgery is undertaken. Although this can reduce blood loss and subsequently, the need for transfusion, it however poses an increased risk of blood clots during the pre- and perioperative period when the patients are not on antiplatelet treatment. Therefore, platelet function has to be monitored carefully and constantly in these patients using point-of-care devices, which offer the advantage of shorter turnaround times compared to centralised laboratory testing.

Assessing the preoperative functional quality of platelets in patients scheduled for cardiac surgery (particularly those on antiplatelet drugs) is important to help predict the risk of haemorrhage and thrombosis. If performed directly at the point-of-care, preoperative platelet function tests can inform urgent decisions for transfusion of patients undergoing cardiac surgery, while postoperative platelet function testing can help to monitor patient recovery and mitigate severe adverse events. Meeting these objectives requires point-of-care assays that not only accurately and reliably assess platelet function, but must also provide results within a short time. By enabling critical decisions to be made relatively quickly, point-of-care platelet function testing has in some cases achieved significant reduction in the risk of severe bleeding and complications of disseminated intravascular coagulation during cardiac surgery in patients on indefinite anti-platelet therapy[11-16]. In addition to improved clinical outcomes for cardiac surgery patients, some studies have shown that point-of-care platelet function testing has significantly reduced both the numbers of transfusions, and the amount of transfusion products (red cell concentrates, fresh frozen plasma or platelet units) used, thus saving costs[12].

This article reviewed the use of various point-of-care platelet function assays in cardiac patients on antiplatelet therapy to identify assays that can accurately predict adverse events and blood product requirements during cardiac surgery. Such assays could be implemented on a large-scale for the timely care and management of cardiac patients on antiplatelet therapy, particularly during cardiac surgery.

Platelet function testing at point-of-care: Why is it important?

Point-of-care testing (POCT) refers to the diagnostic, monitoring or screening tests performed near the patient by a healthcare professional outside the traditional centralised accredited laboratory. Results are obtained within a short time, and the rapid turnaround time enables immediate diagnosis and treatment. POCT is therefore particularly useful for assessing the conditions of critically ill patients in need of urgent medical intervention, as the rapid tests help to inform quick decisions on their treatment and monitoring, hence improving clinical outcomes[17-20]. Platelet function tests are useful in the diagnosis and management of patients with bleeding disorders, including those with inherited and acquired platelet function disorders. However, since platelets are also implicated in

thrombosis, platelet function tests are also widely used in monitoring the efficacy of antiplatelet drug therapy in patients requiring blood thinning and disruption of platelet aggregation to prevent thrombosis. Platelet function tests could therefore be instrumental in point-of-care settings to predict the likelihood of adverse haemorrhagic events in high-risk patients, as well as predicting the risk of thrombosis in patients with arterial thrombotic diseases. Considering the rise in aging population, majority of which is at increased risk of thrombo-embolic events, and therefore requiring indefinite antiplatelet therapy, platelet function testing at point-of-care could provide accelerated diagnosis and treatment or prevention of cardiovascular events in this population.

Although a number of platelet function tests are available (such as bleeding time, light transmission (optical) platelet aggregometry, whole blood impedance aggregometry, flow cytometry, measurement of platelet release and platelet micro-particles), most of them are labour intensive, time-consuming and require special equipment and expertise in specialised laboratories. Portable and easy-to-use platelet function testing devices can provide timely care and management of patients at risk of excessive bleeding or thrombosis during surgery, trauma and other emergencies[21, 22].

Point-of-care platelet function testing in cardiovascular disease and cardiac surgery

Cardiac surgery is associated with numerous complications that increase blood loss, and often requires immediate transfusion of RBCs, plasma or platelets. Moreover, due to an increased risk of thromboembolic events, cardiac disease patients such as those with ACS and coronary heart disease (CHD) are given long-term dual antiplatelet therapy for the secondary prevention of cardiovascular thrombotic events, and other complications associated with percutaneous coronary interventions (PCI) and coronary artery bypass graft (CABG) [23, 24]. Patients who have undergone PCI to fit coronary stents often use aspirin and clopidogrel (or other combinations of antiplatelet drugs) to reduce the risk of stent thrombosis[24].

Undoubtedly, a combination of platelet dysfunction (due to dual antiplatelet therapy), lower platelet counts due to haemodilution and the depletion of clotting factors during surgery can increase significantly the risk of postsurgical bleeding in these groups of cardiac patients[23, 25]. It is therefore important that when cardiac patients on antiplatelet therapy require surgery or related interventions, their platelet function be assessed accurately at the point-of-care in order to prevent the risk of excessive bleeding or risk of thrombosis during recovery[11-13]. Thus, point-of-care testing for platelet function is necessary for the preoperative assessment of cardiovascular patients with complications requiring intensive care and cardiac surgery, but more so, for those who are on antiplatelet drug therapy in order to manage effectively their treatment during and after surgery[14, 26-28].

Several studies already indicate that platelet function testing at point-of-care predicts the risk of bleeding and thrombosis in patients undergoing PCI or CABG[11, 15, 29-32]. Moreover, point-of-care testing for platelet function may help to reduce blood loss and minimise blood product transfusions during cardiac surgery[12, 26, 33, 34]. Platelet function testing at point-of-care is also instrumental in monitoring the effectiveness of antiplatelet therapy in these patients, in order to assess the need and clinical benefit for switching to more potent platelet inhibitors in patients who show resistance to their ongoing regimens (treatment failure)[35]. This is important because treatment failure is known to cause ischemic events including stent thrombosis, strokes, myocardial infarction and cardiovascular death.

Point-of-Care tests for evaluating platelet function

Point-of-care methods for assessing platelet function include PFA-100 (Platelet Function Analyzer), MEA (Multiple Electrode Aggregometry), PlateletWorks, VerifyNow, Impact Cone and Platelet analyzer, TEG/ ROTEM (Thromboelastography & Rotational Thromboelastometry) and TEG PlateletMapping[27, 28, 36-42]. These methods have been used in a broad range of clinical settings and their role in the management of cardiac patients on anti-platelet therapy and those undergoing cardiac surgery is discussed below:

PFA-100 system (Platelet Function Analyzer)

PFA-100 is a whole blood point-of-care assay that assesses platelet function based on adhesion and aggregation under high shear

conditions. It measures closure time i.e. time taken for a platelet plug to form and occlude blood flow through apertures on a collagen-coated membrane infused with ADP or epinephrine. It has the main advantage of measuring platelet adhesion and aggregation under high shear conditions, which simulates the *in vivo* primary haemostatic mechanisms. It is also fully automated, easy-to-use, quick, and gives reproducible results. Furthermore, the use of commercially available cartridges provides consistency across various settings.

As early as the year 2000, the PFA-100 assay enabled the identification of prolonged closure time in patients with valvular heart disease[43], which was linked to increased risk of intra-operative bleeding, thus predicting the need for blood products. However, a study of 146 patients undergoing primary CABG used PFA-100 to predict whether increased bleeding risk was linked to either preoperative or postoperative platelet dysfunction but did not find any correlation[44]. Furthermore, a separate study assessing PFA-100 and Hemostatus POCT tests for platelet function in patients with and without excessive bleeding after cardiac surgery with cardiopulmonary bypass (CPB) found that although excessive bleeding was associated with both abnormal closure time (CT) and activated clotting time (ACT), there was no dramatic decrease in platelet aggregation[45]. Although this study cast doubt on the efficacy of platelet function testing for routine use after cardiac surgery, it nonetheless confirmed its usefulness in the management of patients with increased risk of post-bypass bleeding[45].

Subsequently, PFA-100 correctly identified patients at risk of excessive bleeding following CPB[46]. A study assessing the impact of decisions influenced by PFA-100 in the reduction of blood loss and blood component use after routine coronary artery surgery with CPB found that, although decisions based on PFA-100 results did not reduce blood loss, they effectively reduced transfusions of RBCs and other blood components after routine cardiac surgery[33]. Another study found PFA-100 to provide high specificity for adequate platelet function in patients undergoing CABG, and suggested that not only was the assay important in identifying postoperative platelet hyper-reactivity associated with myocardial lesion, but it might also be useful in accurately gauging the need for platelet concentrates and therefore guiding platelet transfusions[47]. Indeed, PFA-100 successfully identified CPBG patients who were unlikely to benefit from platelet transfusions[48, 49]; hence, could be instrumental in preventing the unnecessary use of platelet concentrates.

PFA-100 was effective in pre-operatively identifying aspirin hyper-responsive coronary artery disease (CAD) patients and informing the decisions as to whether or not to discontinue aspirin therapy during surgery[50]. Furthermore, when used to measure residual platelet reactivity in cardiac patients treated pre-operatively with aspirin, PFA-100 accurately predicted recurrent cardiovascular events in patients undergoing CABG[51]. These studies demonstrated the clinical utility of PFA-100 as a point-of-care platelet function test in the management and care of CAB patients. Measuring aspirin resistance in a 5-year follow-up cohort by PFA-100 revealed a positive correlation of hospitalized cardiovascular events with aspirin resistance[52], confirming the link between aspirin resistance and cardiovascular complications. Other studies suggest that PFA-100 with Collagen/Epinephrine is a more useful point-of-care platelet function test for risk stratification in ACS because of its high sensitivity to functional alterations of von Willebrand factor (VWF), in addition to its wide application in identifying patients with high platelet reactivity[53].

Pre-operative platelet function testing by PFA-100 in 660 patients undergoing CABG surgery, and 421 patients undergoing single aortic valve replacement (AVR) revealed that platelet dysfunction was more significantly higher in AVR[54], suggesting that AVR patients have an increased risk of haemorrhage. PFA-100 also accurately identified prolonged closure times in patients undergoing AVR[55], thus predicting the need for intraoperative transfusion and contributing to improved management of high-risk AVR patients. It also predicted the value of platelet function in the management and prevention of intra- and post-operative blood loss during cardiac surgery[49, 56]. Furthermore, as it measures platelet function in a high shear environment, it remains the assay of choice in studying valvular heart disease, a condition only detected under conditions of high shear stress.

VerifyNow system

VerifyNow is a fully automated platelet aggregation assay that measures change in light transmission over time through an anticoagulated whole blood sample. It measures platelet aggregation based on the agglutination of fibrinogen-coated beads following activation of platelets by an agonist[57], and has been shown to give results that are similar to those obtained using aggregometry[58]. Agglutination of fibrinogen-coated beads results in increased light transmission, and the greater the platelet activation and aggregation, the greater the light transmission through the sample. Cartridges are available for various agonists: arachidonic acid (aspirin assay), ADP/PGE_1 (P2Y12 assay), TRAP (IIb/IIIb assay), hence allowing measurement of different aspects of platelet function.

VerifyNow is widely used in point-of-care settings (such as emergency cardiac surgery) to monitor antiplatelet therapy. It was used successfully to monitor antiGPIIb/IIIa therapy in patients with coronary artery disease[57, 59], aspirin and clopidogrel therapy in patients undergoing PCI[60], and in predicting peri- and post-operative bleeding in patients on antiplatelet therapy. The assay also established a correlation between preoperative platelet inhibition and surgical blood loss or transfusion requirements in 60 patients on dual anti-platelet therapy awaiting CABG[61]. Furthermore, a recent study confirmed VerifyNow as an effective point-of-care test to assess platelet function recovery before initiation of CABG after clopidogrel withdrawal[62]. This resulted in reduced waiting times, but without any risk of increased haemorrhage[62].

VerifyNow robustly detects the effects of aspirin[63], and may be useful in emergency cardiac surgery to identify pre-operatively hyper- or hypo-responsiveness to aspirin that could cause severe events. Postoperative aspirin unresponsiveness as measured by VerifyNow was found to result in thrombosis after cardiac surgery in paediatric patients with congenital heart disease[64], suggesting that the assay can be used at point-of-care to monitor aspirin therapy and improve the management of these patients. Furthermore, in a study of 222 patients undergoing PCI, VerifyNow confirmed that hypo-responsiveness to clopidogrel caused a 6-fold increased risk of major adverse cardiovascular events (MACE)[65], thus highlighting its clinical utility in identifying PCI patients with a higher risk for events such as strokes, myocardial infarction (MI) and cardiac death. VerifyNow was also used to determine on-treatment platelet reactivity and identify thrombotic events in patients with stent thrombosis[66], and separately to detect impaired responsiveness to clopidogrel after coronary stent implantation in diabetic patients[67]. Moreover, a study by Mangiacapra used VerifyNow to evaluate the influence of platelet reactivity after clopidogrel on myonecrosis in 250 patients undergoing PCI, and found a correlation between platelet reactivity and an increased risk of myonecrosis[68].

The Verify Pre-Op TIMI 45 study highlighted the clinical utility of VerifyNow assay in predicting bleeding during CABG in patients treated with clopidogrel[15]. Moreover, VerifyNow was used to demonstrate that platelet aggregation recovered more quickly following clopidogrel withdrawal (within 5 days, as opposed to the recommended 7-14 days), suggesting that the assay could be instrumental in determining the optimal timing of clopidogrel discontinuation before elective cardiac surgery, without increasing the risk of postoperative bleeding[69], thus saving costs. Although VerifyNow does not allow for assessment of platelet function under conditions of shear, the assay remains useful in monitoring of antiplatelet therapy in heart conditions that are not influenced by shear stress, and has been effectively used in large clinical trials such as GRAVITAS[70], TRIGGER-PCI [71], GENERATIONS[72], ARCTIC[73] and ANTARCTIC[35].

Platelet Works system

PlateletWorks is a rapid, whole blood point-of-care assay that measures platelet numbers before and after aggregation, upon activation with an agonist[74]. Aggregated platelets are excluded based on their larger size, thus resulting in a null or near-zero platelet count in individuals with normal platelet function. Drug-induced inhibition of platelet aggregation is then determined by calculating percentage inhibition of platelet aggregation in the presence of antiplatelet drugs such as aspirin and clopidogrel. PlateletWorks is useful during cardiac surgery to determine residual platelet activity and for monitoring antiplatelet therapy.

PlateletWorks has demonstrated clinical utility as a point-of-care test for monitoring platelet response to a range of antiplatelet agents including aspirin and clopidogrel[74]. This is important in acute-care settings such as during PCI and CPBG surgeries, which are commonly associated with thrombosis and haemorrhage, respectively. Clinical utility of PlateletWorks was further demonstrated in a study of 50 CABG patients on clopidogrel therapy, which found that platelet aggregation correlated significantly with postoperative chest drainage volume and that poor platelet aggregation resulted in increased usage of transfusion products in the post-operative period[13]. This study highlighted the usefulness of PlateletWorks as a point-of-care assay for platelet function testing in predicting the risk of excessive bleeding.

PlateletWorks also identified patients at risk of adverse cardiac events and increased bleeding following stent implantation in 1069 patients on clopidogrel who were undergoing elective PCI with stent implantation (the POPULAR study)[75]. This is crucial for guiding the timing of surgery and treatment of bleeding in patients undergoing CABG. Furthermore, compared to TEG, PlateletWorks was found to be a more reliable predictor of blood product use and chest tube drainage in patients undergoing CPB[76]. Recent studies using PlateletWorks identified increased risk of myocardial infarction and re-hospitalization following coronary angiography, and uncovered a correlation between point-of-care platelet function testing and bleeding[77,78]. However, an earlier prospective observational study of 50 patients undergoing elective cardiac surgery for CABG or cardiac valve replacement (CVR) compared PlateletWorks with turbidimetric platelet aggregometry for assessing aspirin-related platelet dysfunction and found that PlateletWorks was not reliable for detecting aspirin-related platelet defects in cardiac surgery patients[79]. If confirmed, this might limit the use of PlateletWorks as a point-of-care platelet function test for cardiac surgery patients, because a majority of these patients are usually on aspirin, in combination with a second antiplatelet drug. Further studies need to investigate the utility of PlateletWorks in CABG and CVR patients treated with aspirin.

MEA (Multiple Electrode Platelet Aggregometry)

MEA measures platelet aggregation using whole blood and generates results in a very short time. It operates on the principle of impedance platelet aggregometry, and uses an aggregometer known as Multiplate analyzer[80]. The Multiplate analyzer has five electrodes, which offers the advantage of measuring five parameters of platelet function simultaneously. Platelet agonists activate and aggregate whole blood causing increased electrical impedance between the wires of the electrodes, and the resulting impedance is measured over time.

In point-of-care settings, MEA has also proved to be important in pre-operative identification of patients with high risk of blood loss, and in the management of severe postoperative bleeding. A prospective, randomized, controlled trial investigating the impact of point-of-care preoperative platelet function testing on blood product usage in CABG surgery using MEA and TEG PlateletMapping found that platelet function testing led to a significant reduction in all blood product transfusions[81]. This also highlighted the importance of preoperative point-of-care platelet function testing in cost saving by reducing the numbers of transfusions. Pre-operative use of MEA to monitor platelet inhibition by dual aspirin and clopidogrel therapy at point-of-care effectively detected platelet inhibition in patients undergoing elective CABG surgery, and as expected found that the need for postoperative transfusion was higher in patients on dual antiplatelet therapy[82]. This study used postoperative blood loss and need for transfusion as the measures of clinical outcome.

A prospective observational study of more than 200 patients undergoing isolated CABG showed that MEA could predict the likelihood of excessive postoperative bleeding and identify patients at risk[83]. Similarly, a separate study evaluated the prediction of excessive bleeding after elective cardiac surgery in 148 patients by MEA and TEM, and showed that both methods accurately predicted excessive post-operative bleeding[84]. Furthermore, low aggregometry, measured using MEA accurately identified cardiac surgery patients with a significantly higher need for platelet concentrate transfusions [85], indicating that MEA could be used in point-of-care platelet function testing to help in the planning and management of pre- and perioperative platelet concentrate transfusions. Similar findings were observed

in patients undergoing aortocoronary bypass or aortic valve surgery[86], where MEA predicted the risk for stent thrombosis based on platelet hyper-reactivity[87]. MEA also preoperatively identified CABG patients with resistance to aspirin[88]. As resistance to aspirin is associated with major adverse ischemic events following CABG, MEA could be a useful point-of-care platelet function assay to guide the dosing of aspirin or addition of clopidogrel to the treatment and care plans of CABG patients experiencing aspirin resistance. These studies not only highlight the potential of MEA in identifying patients likely to require postoperative transfusion, but also demonstrate that MEA could be instrumental in informing the timely initiation of haemostatic interventions and blood component therapies to prevent excessive postoperative blood loss.

On the contrary, a prospective study investigating perioperative platelet aggregation in children with chronic heart disease by MEA found that blood loss was higher despite a good platelet aggregation response, suggesting that MEA was unsuitable for predicting increased perioperative blood loss[89], at least in children. Moreover, a pilot study investigating platelet function changes in paediatric cardiac operations and their relationship with postoperative bleeding using MEA did not find any association with postoperative bleeding[90]. These studies suggests that the clinical utility of MEA in children and paediatric cardiac patients undergoing cardiac surgery needs to be evaluated, as the assay requirements might differ significantly between adults and children. These findings provide enough ground to push for all devices for point-of-care platelet function testing to be optimised for use on both adult and paediatric patients.

TEG/ROTEM (viscoelastic methods)

These methods provide the continuous measurement and display of the viscoelastic properties of a whole blood sample from the initial phase of fibrin formation to clot retraction and ultimately fibrinolysis. They have the advantage of visually monitoring and quantifying blood coagulation, including the propagation, stabilization and dissolution phases of clot formation under low shear conditions. Clotting is accelerated using activators such as kaolin and tissue factor, and impedance is measured. Usually, impedance increases as clot strength increases. As these assays measure the rate and quality of clot formation, they are useful in the prediction of surgical bleeding, determination of the need for blood products and in the monitoring of anti-platelet drugs. However, even though the TEG/ ROTEM assays are widely used in point-of-care assessment of coagulation during cardiac surgery where they have significantly improved clinical outcomes, and cut costs by reducing overall consumption of blood products[20, 81], they have not been used extensively for evaluating platelet function in cardiac patients undergoing cardiac surgery. Therefore, their clinical utility in this field remains unknown. Further clinical research should assess TEG/ROTEM platelet function assays such as Rotem Platelet®[91], and evaluate their clinical utility in cardiac surgery and in cardiac patients on dual antiplatelet therapy.

TEG Platelet Mapping Assay and Cone and PlateLet Analyzer

TEG Platelet Mapping Assay measures platelet inhibition relative to the patient's baseline viscoelastic profile, and provides results as percentage platelet aggregation. The IMPACT Cone and PlateLet Analyzer uses an automatic and computerized system that evaluates *in vitro* primary haemostasis to assess platelet function[92, 93]. In the Cone and PlateLet assay, platelets are activated *in vitro* by an agonist, and both their aggregation and adhesion to a polystyrene-covered plate under conditions of shear stress are measured. These assays have been used to assess platelet function and monitor antiplatelet therapy in various settings, including CABG[92-95], and have predicted post-operative bleeding in patients undergoing cardiac surgery and CPB[96, 97]. However, their clinical efficacy at point-of-care during cardiac surgery and in antiplatet therapy needs to be substantiated.

Can results of a single point-of-care platelet function test sufficiently guide clinical decisions for pre- and perioperative management of cardiac surgery patients on antiplatelet therapy?

Although the various point-of-care tests for platelet function differ in terms of sample volume requirements, use of plasma or whole blood and presence of conditions of shear[98], making it hard to compare them directly, they each provide unique advantages despite their individual shortfalls, and may be used to complement

each other. For example, whilst MEA allows simultaneous measurement of multiple agonists, it overlooks the fact that platelet activity *in vivo* depends on shear stress. On the other hand, PFA-100, which measures platelet functional activity under high shear conditions, is useful in patients with valvular heart conditions, while the Cone and Platelet Analyzer, which measures the interaction of platelets and vWF in whole blood under conditions of shear might be the ideal method to obtain more physiologically relevant results. Therefore, owing to the inherent differences in the principles of these platelet function tests, it is difficult to find correlations between them, as outlined below:

A comparison of VerifyNow and MEA in predicting early clinical outcomes after PCI found a lack of correlation of these platelet function assays in predicting the occurrence of peri-procedural MI and MACE[65]. A recent comparison of MEA and Rotem Platelet® in cardiac surgery patients found no correlation whatsoever[91]. Furthermore, when a range of platelet function testing assays (VerifyNow, PFA-100, PlateletWorks, flow cytometry, LTA, TEG and urinary 11- dehydro thromboxane levels) were compared, only VerifyNow consistently identified high platelet reactivity amongst coronary artery disease (CAD) patients treated with aspirin[36]. Interestingly, a prospective study of platelet function in 27 patients treated with abciximab during PCI found that results from PFA-100 assays were comparable to those from platelet aggregometry[99]. This is in contrast to a study comparing aggregometry and PFA-100 in 50 patients on antiplatelet therapy who were undergoing PCI, which found a disagreement in the ability of the two tests to distinguish aspirin responders from non-responders, suggesting the two assays were not interchangeable when monitoring antiplatelet treatment[100].

When comparing PFA-100 and VerifyNow with light transmission aggregation in 484 CAD patients on dual antiplatelet therapy who were undergoing PCI, significant correlations among the three methods were observed, although there were variations in the level of sensitivity, suggesting that cut-off values for these assays ought to be refined in order to be of clinical relevance[40]. In another study, MEA, PFA-100 and light transmission aggregometry produced similar results when used to detect the effects of aspirin and clopidogrel in 70 pre-operative patients scheduled for elective CABG surgery[101]. However, a recent prospective study examining the relationship between preoperative platelet function and perioperative bleeding in 50 patients undergoing off pump CABG found little correlation between the VerifyNow, PlateletWorks, TEG, and light transmission aggregometry platelet function tests, and no correlations with perioperative bleeding either[102]. These findings put to question the utility of these assays at point-of-care in guiding decisions for patient management. Moreover, PFA-100 and PlateletWorks show limited sensitivity for cyclooxygenase inhibitors and P2Y12 antagonists, while Platelet Mapping, Impact Cone and Platelet Analyzer and VerifyNow fall below standard laboratory platelet aggregometry in terms of sensitivity[103]. These limitations may restrict their clinical utility in the perioperative period in cardiac surgery patients.

Understandably, the lack of agreement between most of these studies can be partially attributed to the fact that the assays are based on different principles; they use different agonists; and measure different aspects of platelet function. However, the huge discrepancies and a lack of correlation amongst them clearly highlights the significant variability of the platelet function tests, and underscores the need for further studies to validate the clinical efficacy of current point-of-care platelet function tests in the accurate prediction of immediate and long-term clinical outcomes for cardiac surgery patients.

CONCLUSIONS

Achieving the delicate balance between the risk of excessive bleeding and thrombotic events is crucial for cardiac patients on antiplatelet therapy who may require cardiac surgery. Point-of-care platelet function testing can facilitate the provision of a personalised treatment and management plan such as increasing, reducing or discontinuing anti-platelet therapy, and allowing accurate determination of when it is safe to perform cardiac surgery. Point-of-care platelet function testing assays have been used to assess the degree of platelet inhibition and correctly predicted major adverse cardiac events [39], as well as

identifying patients at risk of excessive bleeding, and the need for blood product transfusion. Early prediction of these events can inform transfusion laboratories to avail adequate units of screened and cross-matched transfusion products, hence improved preparedness for emergencies. Thus, it can be argued that platelet function testing at point-of-care has made a significant improvement in the care and management of cardiac patients on platelet therapy who undergo cardiac surgery. This is partly because platelet function testing at point-of-care allows for evidence-based treatment and management of patients by providing immediate results on the patient's condition to guide and prompt the transfusion processes, as well as initiation and cessation of anti-platelet therapy.

Besides improving patient care and clinical outcomes, point-of-care platelet function testing has contributed to reduced costs by cutting the in-patient waiting times for hospitalized patients scheduled for cardiac surgery. Platelet function testing at point-of-care has also reduced costs by considerably cutting the number of unnecessary transfusions [81]. This is supported by recent reports showing that transfusion algorithms based on point-of-care testing for both coagulation and platelet function are associated with reduced transfusions [12, 20, 104]; leading to reduced costs and improved management of post-cardiac surgery bleeding. Moreover, reduced numbers of transfusion reduces the risk of alloimmunisation and other side effects of transfusion.

The fact that most of the platelet function tests discussed here use whole blood has the advantage that it allows interaction between plasma clotting factors, platelets, and red cells, thus giving more physiologically relevant measurements. However, point-of-care platelet function tests that can replicate all of the physiological conditions (role of the sub-endothelium, contribution of RBCs and high shear conditions) though highly desirable are still lacking. Current research should focus in this area, as this will enhance the clinical relevance of point-of-care platelet function testing for cardiac surgery patients.

Another important aspect is the fact that different tests measure different parameters of platelet function, and use different agonists, making it difficult to perform a head-to-head comparison of the clinical value of these tests. This is further complicated by vast differences in the study populations in terms of heart disease conditions; high versus low risk of thromboembolic events; types of intervention/surgery; age groups (adult versus paediatric); different antiplatelet therapies (some patients may be given more potent platelet inhibitors); different study designs (prospective, cross-sectional, retrospective, or observational); and varied numbers of study patients. Further clinical studies are required to validate and standardise each of the platelet function testing assays across the various settings, in order to eliminate the enormous variability in predicting blood loss and transfusion requirements. This will in turn minimise the dangers associated with incorrect prediction of thrombotic events in cardiac surgery (excessive haemorrhage and embolism), and will help to save more lives.

However, even in studies where various platelet function assays were compared within similar settings, some still indicated a lack of correlation, and absence of similarities between the assays [40, 101]. This calls for further clinical studies to establish uniform cut-off values that predict the risk of bleeding or thrombosis across various point-of-care platelet function tests and reach a consensus on transfusion triggers. This will be instrumental in the large-scale implementation of guidelines on when to initiate interventions for improved clinical outcomes of cardiac surgery patients. The lack of agreement between the various point-of-care platelet function assays strongly suggests that future practice in the treatment and care of cardiac surgery patients on dual antiplatelet therapy might need to rely on a combination of platelet function assays carried out simultaneously, in order to predict accurately the risk of haemorrhage and thrombotic events. However, this would have huge cost implications, as point-of-care testing is generally expensive.

Abbreviations

DVT: deep vein thrombosis; PE: pulmonary embolism; ACS: acute coronary syndromes; POCT: point of care testing; CHD: coronary heart disease; PCI: percutaneous coronary interventions; CABG: coronary artery bypass graft; MEA: Multiple Electrode Aggregometry; PFA: Platelet Function Analyzer; TEG: Thromboelastography; ROTEM: Rotational Thromboelastometry; ADP: Adenine di-Phosphate; CPB: cardiopulmonary bypass; CAD:

coronary artery disease; LTA: light transmission aggregometry.

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