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Modified Thromboelastography for Peri-interventional Assessment of Platelet Function in Cardiology Patients: A Narrative Review

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Abstract

Viscoelastic testing (VET), such as thromboelastography, can measure whole blood coagulation dynamics in real time and is used across a range of clinical settings, including cardiac surgery, liver transplant, and trauma. The use of modified thromboelastography with platelet function assessment (TEG(R) PlateletMapping(R) Assay) can provide an analysis of platelet contribution to hemostasis, including the contribution of the P2Y12 receptor and thromboxane pathway to platelet function. The TEG PlateletMapping Assay has shown high correlation with the current gold standard test of platelet function, light transmission aggregometry, to measure arachidonic acid and adenosine diphosphate agonist-induced platelet activation. Studies have also shown comparable results with other whole blood platelet function tests. In this review, we explore the clinical applications of modified thromboelastography with platelet function assessment. This includes guiding dual antiplatelet therapy in relation to cardiac procedures, such as percutaneous coronary interventions, transcatheter aortic valve replacement, and left atrial appendage closure. We also explore the developing use of thromboelastography in the emergency care setting of coronavirus disease 2019, which is commonly associated with a hypercoagulable and hypofibrinolytic state. Despite a general lack of high-quality, grade 1 evidence regarding the use of modified thromboelastography with platelet function assessment in these disease areas, the ability of the TEG PlateletMapping Assay to measure global hemostasis and platelet reactivity rapidly and to view and evaluate results at the point of care makes it a promising area for further study for managing patient treatment and optimizing hemostatic therapy.

Keywords
- cardiology
- platelet function
- platelet function testing
- thromboelastography
- TEG
- COVID-19
- percutaneous coronary interventions
- PCI
- TAVR
- LAAC

Thromboelastography, as with other forms of viscoelastic testing (VET), is a whole blood testing method in which clotting is observed in real time in an in vitro system that mimics physiological conditions.[1–3] Thromboelastography has been widely used for patient management in clinical areas such as trauma,[4,5] cardiovascular surgery,[6,7] and liver transplant surgery,[8,9] all of which share both hemorrhage and coagulopathy as common features.

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Recently, there has been growing interest in the use of viscoelastic methods in the understanding and diagnosis of thrombotic conditions. In trauma, thromboelastography has been used to predict the development of pulmonary embolism (PE) following the acute stage.[10] In the coronavirus disease 2019 (COVID-19) pandemic, viscoelastic parameters have been explored as a means to assess the risk for thromboembolic complications, such as venous thromboembolism.[11–14] Most recently, modified thromboelastography with platelet function assessment has been studied for its predictive potential for complications, such as graft thrombosis and infection, following vascular surgery in patients with peripheral artery disease.[15]

Modified thromboelastography with platelet function assessment (TEG(R) PlateletMapping(R) Assay, Haemonetics Corp., Boston, MA) provides specific additional functionality, given that standard thromboelastography is not able to specifically detect hemostatic changes introduced by platelet-inhibiting agents. The specific design of assays for the arachidonic acid (AA) and adenosine diphosphate (ADP) pathways provides a measure of platelet reactivity via pathways (partially) blocked by aspirin and ADP receptor inhibitors (e.g., clopidogrel, ticagrelor), respectively.[16] This introduces the concept of measuring both platelet reactivity and therapeutic responses to these agents.

The TEG PlateletMapping Assay is a whole blood platelet function test (PFT) that is rapid, simple, and can be viewed and evaluated at the point of care. This makes it particularly attractive for use in cardiovascular medicine, where randomized controlled trials (RCTs) of other PFTs, such as the laboratory-based light transmission aggregometry (LTA), have repeatedly demonstrated large inter-individual response to antiplatelet agents.[17–19] This wide variability of individual response has also been repeatedly demonstrated using the TEG(R) 5000 technology (Haemonetics Corp., Boston, MA). Such variability inevitably raises concerns that patients with relatively low response to antiplatelet drugs will be at increased risk of thrombotic/ischemic events, whereas patients with an exaggerated response could be at increased bleeding risk. This hypothesis has consistently been supported by a wide range of observational studies using a variety of platelet function assays, including TEG assays, but randomized trials confirming a benefit to manipulating individual responses are not so far available.

Findings from several earlier RCTs using standard laboratory PFTs did not demonstrate clear clinical benefit of PFT-guided individualized antiplatelet therapy.[20–22] It is perhaps notable that the latter trials all employed the VerifyNow(R) assay to detect low response to clopidogrel, and concerns have been raised about the accuracy of this test in this context (see below). However, the recent TROPICAL-ACS RCT demonstrated a potential role for PFTs (Multiplate(R) analyzer, Roche Diagnostics, Indianapolis, IN) to guide de-escalation of antiplatelet therapy and was included in a recent expert consensus statement,[23] as well as the 2018 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization.[24] Modified thromboelastography with platelet function assessment, in the form of the TEG 6s Analyzer, represents a convenient, whole blood methodology for testing individual response to antiplatelet medications that provides a more comprehensive overview of hemostasis.

We review the potential role of modified thromboelastography with platelet function assessment in the clinical setting of (1) peri-interventional cardiology and (2) for assessment of COVID-19 disease status and management.

The TEG Platelet Mapping Assay

Alongside the clotting dynamics measurements provided by the TEG hemostasis analyzer, the TEG PlateletMapping Assay is able to provide a semiquantitative analysis of platelet function through evaluation of the contribution of the ADP or thromboxane A2 (TxA2) receptors. While standard VET uses an activator such as kaolin or tissue factor in a whole blood sample to accelerate the coagulation process, the TEG PlateletMapping Assay also adds ADP or AA agonists to assess platelet reactivity in response to these agonists. These responses can be assessed relative to (1) the standard kaolin-activated TEG assay, which is taken as the maximal hemostatic activity, and (2) the assay run with the addition of heparin, which can be considered to correspond to the baseline platelet function. By adding the ADP and AA platelet activators into the sample with heparin, the contribution of ADP and TxA2 receptors to the formation of the clot can be measured (►**Fig. 1**).[25,26] These channels of measurement thus provide an assessment of the response to ADP and AA agonists relative to the maximum platelet-induced clot for that individual and, further, can be used to estimate their response to antiplatelet medication.

The next-generation TEG 6s device uses resonance-frequency whole blood viscoelasticity to assess hemostasis during clot initialization, formation, and lysis. As the whole blood sample coagulates to form a clot, the modulus of elasticity—and, therefore, the resonant frequency of the sample—increases. The variations in resonant frequency are measured by the analyzer and displayed as a TEG assay trace. This system requires a much lower blood volume (~340 µL) for coagulation analysis compared with the previous generation TEG 5000 device, which uses a rotating cup and a static pin to measure the sheer viscosity of the coagulating sample. Furthermore, the TEG 6s device uses a disposable four-channel cartridge to process whole blood samples for assays, and this simplified assay procedure increases the ease of use and substantially reduces the time required for results compared with the TEG 5000 device.[27,28] The TEG 6s device has been tested and validated for the assessment of coagulation dynamics in cardiology patients,[29] trauma patients,[30] and in cardiothoracic surgery,[31] showing high within-device reliability, good diagnostic accuracy, and a close correlation of results with the previous generation TEG 5000 device.[32] With the TEG 6s device, the PlateletMapping assay comes as a single cartridge, containing all necessary components to evaluate the activity of the AA and ADP pathways. This cartridge correlates well with the TEG 5000 PlateletMapping assay in the detection of individual response to P2Y12 inhibitors.[28]

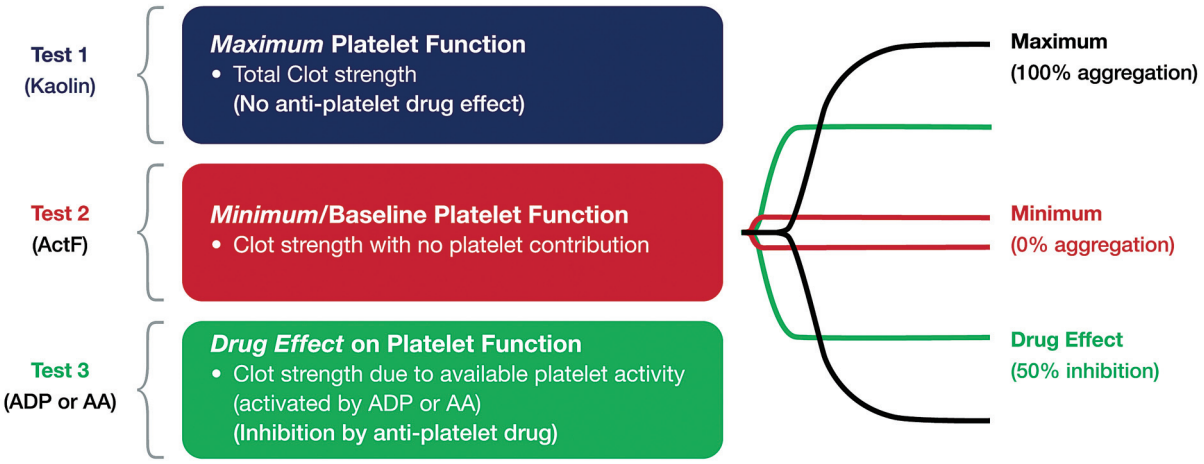

Fig. 1 Use of platelet receptor-specific tracing to identify platelet inhibition and aggregation. AA, arachidonic acid; ActF, activator F; ADP, adenosine diphosphate.

Comparison of the TEG PlateletMapping Assay with Other PFTs

The TEG PlateletMapping Assay has shown high correlation with LTA, the current gold standard PFT, when used to measure the ability of AA and ADP agonists to induce in vitro platelet-to-platelet activation.[33] A correlation between the TEG PlateletMapping Assay and LTA has also been seen in clinical trials, such as the DIVIDE study (http://clinicaltrials.gov/show/NCT03062462), which used both assays to assess the response to P2Y12 receptor inhibitors in Chinese patients with acute coronary syndrome (ACS) to compare the antiplatelet action of half-dose ticagrelor and high-dose clopidogrel.[34]

Studies have also been performed comparing TEG PlateletMapping Assay results against those of other whole blood PFTs, including VerifyNow, Multiplate, and PFA-100 assays. Comparison of three whole blood PFTs (TEG PlateletMapping Assay, VerifyNow PFT system [Werfen, Bedford, MA], and Multiplate) for in vitro P2Y12 receptor-induced platelet inhibition showed the performance of the TEG PlateletMapping Assay to be similar—and in some respects superior—to the other assays, with the TEG PlateletMapping Assay showing lower variability versus VerifyNow and Multiplate.[35] In contrast to VerifyNow, the TEG PlateletMapping assay does not include prostaglandin E1 as an agonist for assessing the inhibition of the P2Y12 pathway. Data suggest that this provides a more accurate assessment of platelet aggregation in patients on clopidogrel compared with VerifyNow.[36,37] As the TEG PlateletMapping Assay—in a similar manner to LTA—is able to directly indicate inhibition of cyclooxygenase, it is also likely to give a more accurate measure of high on treatment platelet reactivity (HTPR) with aspirin compared with nonspecific laboratory measurements, which are affected by other platelet activation pathways and can, therefore, overestimate HTPR with aspirin.[38] This is with the caveat that previous data derived using the TEG PlateletMapping Assay in cardiology, acute stroke, and vascular surgical patients suggested that AA-induced clotting is subject to intra-individual variability in patients on aspirin[39–41] and that an inducible and/or recruitable cyclo-oxygenase independent pathway, not fully blocked by aspirin, probably accounts for the apparently high levels of HTPR with aspirin seen in such patient groups.[42,43]

A large-scale proficiency testing program performed by the College of American Pathologists assessed data from over 1,000 American laboratories from 2012 to 2016 for several PFT devices: PFA-100, LTA, PlateletWorks (Helena Laboratories, Beaumont, TX), and TEG 5000 analyzer with the PlateletMapping Assay.[44] The highest percentage of correct results compared with a standard reference was observed with PFA-100 and a much lower percentage with TEG 5000; although it has been noted[45] that this did not take into account the context relating to the TEG device as the only comprehensive, whole blood test included in the program that encompasses additional contributors to coagulation, such as platelet fibrin linkage. Additionally, given the relative complexity of the assays, there is likely to be higher operator variability in the TEG 5000 device used in this study compared with the TEG 6s analyzer. Other studies using the TEG 5000 PlateletMapping Assay also show a range of correlations with whole blood PFTs, with no single platelet function assay consistently found to be preferable.[46–48] Such comparisons inevitably raise fundamental questions as to how to define and use a "reference" with which to produce a measure of relative efficacy. Specifically, the longest established reference test could perform sub-optimally compared with a newer assay, but the assumption in traditional comparative pathways would assume the reverse was true.

Clinical Applications

In the setting of cardiovascular disease management, there are several areas where knowledge of a patient's platelet reactivity can be valuable. First, platelet reactivity may be variable, and manipulated, at all stages of the patient treatment pathway; thus, there may be value in knowing

individual reactivity at these stages when prescribing, or when trying to assess risk of bleeding or thrombotic events. For example, cardiac surgery is often associated with perioperative blood loss and a high risk of requiring allogenic blood transfusion.[49] Second, it is well established that patients receiving drug-eluting coronary stents have a variable response to the antiplatelet drugs that they are prescribed, and that such individual responses are not routinely taken into account in our current "one size fits all" protocols. As a third example, consensus suggests that there is a need to identify COVID-19-positive patients (and possibly also some people receiving vaccinations) who are at the highest risk of thrombotic complications. There are, therefore, several specific clinical applications in which PFT has the potential to optimize and personalize therapy, thereby reducing patient risk.

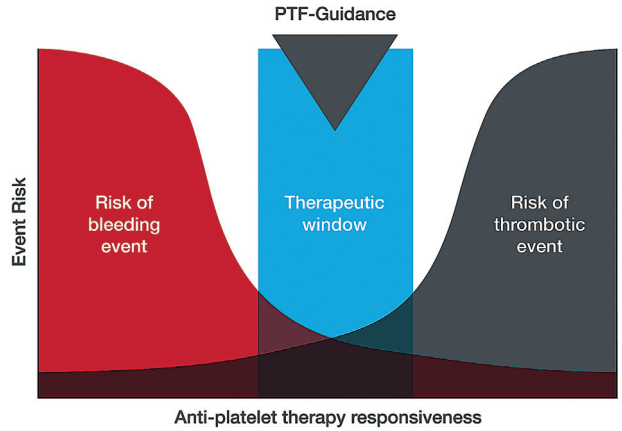

Fig. 2 Use of platelet-function tests for guiding and personalizing antiplatelet therapy based on platelet responsiveness. PFT, platelet function test.

Percutaneous Coronary Interventions

Percutaneous coronary intervention (PCI) is the commonest revascularization method for the treatment of obstructive coronary artery disease. An essential component of a successful intervention, especially involving stent implantation, is to inhibit platelet aggregation to avoid the development of ischemic complications. To this end, patients are treated with antiplatelet therapy both before and following the PCI procedure.[19]

Despite currently missing validated treatment alternatives, it is nevertheless remarkable that, despite the well-documented inter-individual variation in response to aspirin and P2Y12 inhibitors, no assessment of patient response is routinely made in clinical practice. Furthermore, the prevailing agenda in the field of PCI practice is to minimize the bleeding risk for post-stent patients by cutting down the time that patients are on dual antiplatelet therapy (DAPT).[50] While most trials have dropped the P2Y12 inhibitor early and left the patient on aspirin alone, there have been studies stopping the aspirin early and retaining either clopidogrel alone or ticagrelor as the sole antiplatelet agent.[51–53] Given the well-documented prevalence of hypo-responsiveness to clopidogrel[54] (and to a lesser extent both prasugrel and ticagrelor) and the historic association with ischemic complications, such strategies taken in the absence of any personalized measures of response are difficult to justify.

In reality, therefore, while it is not currently common practice to test for platelet function in patients undergoing PCI with stents, there remains a significant percentage of patients who experience adverse outcomes while receiving DAPT, either bleeding events due to low on-treatment platelet reactivity or thrombotic events due to hypo-responsiveness to antiplatelet therapy.[55] There is therefore potential utility for assays for platelet reactivity to monitor the individual response to DAPT following PCI, to optimize effectiveness by identifying the ideal therapeutic window between the risks of bleeding and thrombosis (►**Fig. 2**).[41,56] For example, in the large randomized, controlled CREATIVE (Clopidogrel Response Evaluation and AnTi-platelet InterVEntion in High Thrombotic Risk PCI Patients, NCT01779401) trial, 1,078 patients were stratified to standard or intensified antiplatelet therapies based on TEG PlateletMapping Assay results. For patients who showed low responsiveness to clopidogrel treatment, an intensified antiplatelet treatment regime significantly improved clinical outcomes with reduced rates of adverse cardiac and cerebrovascular events 18 months following PCI, without increasing the risk of major bleeding.[57] There is an increasing amount of data from East Asia which suggest that patients have more HTPR with DAPT compared with European and American populations, potentially due to genetic factors such as the higher prevalence of CYP2C19 polymorphisms in this population.[58] A literature review of studies published in East Asian centers revealed a body of data focused on the use of the TEG PlateletMapping Assay to escalate DAPT treatment and personalize post-PCI antiplatelet therapy.[59] This may be particularly pertinent given the recent evidence suggesting benefit from early single antiplatelet therapy using clopidogrel alone.[52,53]

Whole blood PFTs may thus be used to potentially predict patient risk following cardiology interventions. Patients with high ADP-induced platelet aggregation, particularly those on intensive clopidogrel therapy, have been shown to be at higher risk for ischemic events following PCI,[60] with TEG hemostatic assays and other PFTs showing prognostic utility for predicting long-term ischemic events, including ischemic and bleeding events over 3 years.[55] The ADP-induced platelet inhibition rate measured by the TEG PlateletMapping Assay has been shown to correlate with long-term outcomes. For example, in a study of 451 patients with ACS, patients who experienced ischemic events had significantly lower ADP-induced platelet inhibition compared with those that had no events ($p < 0.001$), with 76% inhibition rate acting as a cut-off for prediction of rehospitalization for unstable angina within 1 year.[61] Furthermore, multiple other studies have demonstrated an association between relative hypo-responsiveness to clopidogrel, or other P2Y12 inhibitors, and stent thrombosis.[62–64] The evidence of a link between responsiveness to antiplatelet

therapy and ischemic events, as well as the increasing use of more potent antiplatelet therapies, indicates that there may be a benefit of measuring individual response to P2Y12 inhibitors to modify therapy where appropriate.[64] The availability of a simple, quick, accurate, reproducible PFT that can be viewed and evaluated at the point of care could render the concept of routine testing and tailored therapy for patients receiving coronary stents to optimize outcome highly plausible.

TAVR

Transcatheter aortic valve replacement (TAVR) is a nonsurgical treatment for aortic stenosis in which a replacement valve is fitted percutaneously, using large bore introducer sheaths most commonly via femoral or subclavian arteries, that is associated with bleeding complications.[65] The risk of bleeding relates not just to the arterial access, but also to systemic anticoagulation during the procedure with unfractionated heparin, as well as pretreatment with antiplatelet medication (usually aspirin alone). There are no specific guidelines that address the use of hemostasis assays or PFTs during or after this procedure, and there is a paucity of evidence. However, VET has been reported to identify a prothrombotic signal during TAVR,[66] with the interesting observation that TAVR is more prothrombotic than PCI, possibly because it is associated with greater endothelial damage and much more extensive vascular instrumentation as well as contact activation on the device.[67] Using TEG hemostasis assays to measure the strength of the fibrin clot immediately following the procedure has also been shown to be predictive of short-term major bleeding complications.[68] Although the clinical implications remain uncertain, this indicates that further research should determine whether there is a role for the routine use of coagulation monitoring plus or minus platelet function assessment, e.g., with the TEG PlateletMapping Assay during this specific intervention.

Left Atrial Appendage Closure

Left atrial appendage closure (LAAC) using the WATCHMAN (R) device (Boston Scientific, Marlborough, MA) is deployed for patients with nonvalvular atrial fibrillation as an alternative to long-term anticoagulation therapy.[69] The device has a high success rate, with a low incidence of adverse events. However, a small proportion of patients show device-related thrombus formation following the procedure.[70] Detailed thrombogenicity phenotyping using thromboelastography together with biomarker assessment determined a baseline prothrombogenic profile associated with device-related thrombosis following LAAC in one prospective case–control study.[71] Major bleeding following the procedure was also associated with low platelet reactivity. While the study did not assess the use of PFTs to measure platelet reactivity, this would be an interesting further area of research.

Timing of Cardiac Surgery

Cardiac surgery can either be performed as an urgent/emergency procedure, in the event of ACSs, recurrent ischemia or acute valve presentations, or as elective surgery. Cardiac surgery is often associated with perioperative blood loss requiring allogenic blood transfusions.[72] The use of TEG technology is well established in clinical practice to assess hemostasis and platelet function throughout the surgical procedure. Algorithms that monitor platelet function alongside assessment of hemostasis during surgery have been shown to reduce bleeding and the requirement for allogenic blood transfusions.[73] Prior to surgery, patients are required to stop some or all antiplatelet therapy whenever possible to reduce the likelihood of perioperative bleeding, with guidelines recommending waiting times of 5 to 7 days after stopping these medications.[74] However, the use of a TEG PlateletMapping Assay-based management strategy to stratify patient waiting times based on platelet reactivity was shown to reduce the waiting time after stopping antiplatelet medications (most commonly clopidogrel) to an average of 2.7 days, without increasing the bleeding risk or the use of blood products during surgery.[75,76] A similar study of patients in China, using the TEG PlateletMapping Assay to stratify presurgical timing for patients on DAPT, also showed a reduced waiting time to 3.2 days prior to coronary artery bypass grafting, with no statistically significant difference in blood transfusions during surgery.[66]

COVID-19

COVID-19 has been characterized as an infectious viral thromboinflammatory disease associated with dysfunction of hemostasis, most commonly a hypercoagulable and hypofibrinolytic state. Around 20% of COVID-19 patients rapidly progress to a severe illness that includes extensive thrombotic complications.[77] Patients may experience both thrombotic and hemorrhagic symptoms, due to overactivation of platelets altering normal clotting, or to secondary inflammation resulting in decreased platelet count and low fibrinogen, usually as a result of consumption.[12]

If left untreated, the development of severe COVID-19 can involve serial iterations of thrombotic and bleeding or thrombocytopenic states, caused in large part by fluctuating levels of circulating inflammatory biomarkers.[78] Depending on the severity and progression of the disease, patients can present with widely differing clinical profiles, which would likely be easier to manage if a full analysis of circulating biomarkers, clotting profile, and platelet function could be deployed to formulate a personalized, patient-specific approach.[78] Typical laboratory hemostasis tests such as prothrombin time and activated partial thromboplastin time only analyze plasma and, therefore, cannot measure the contribution of platelets or fibrin to the clotting process. As clinical status can change in COVID-19 patients very swiftly, a rapid test that provides a comprehensive assessment of whole blood clotting and platelet reactivity and can be viewed and evaluated at the point of care could offer great potential for early detection and management of clotting abnormalities with the intention to prevent clinical deterioration.[77] The TEG 6s device represents a plausible candidate as such a test.

Studies using thromboelastography to monitor changing coagulation in patients with COVID-19 suggest that there is

often a prognostic hypercoagulable profile with both an increased maximal amplitude and reduced fibrinolytic activity.[12,79] In children who develop multisystem inflammatory syndrome related to coronavirus, some observational and retrospective studies have shown unique TEG assay profiles,[80] with TEG parameters correlating with disease severity and length of stay in intensive care.[81] There are already some data to suggest that TEG assay parameters may be used to predict thrombotic risk in COVID-19 patients with moderate or severe disease,[82] and to identify the ideal therapeutic window for heparin treatment to prevent thrombosis without increasing the risk of bleeding.[83]

The use of whole blood PFTs, such as the TEG PlateletMapping Assay, adds an extra layer of information regarding the hemostatic status and response to treatment in patients with COVID-19. A study of 100 patients from a U.S. tertiary care center indicated that the use of a treatment algorithm incorporating TEG PlateletMapping assessments was associated with a lower risk of requiring mechanical ventilation (relative risk = 10.9; $p < 0.0001$), acute kidney injury (relative risk = 2.3; $p = 0.0017$), kidney dialysis (relative risk = 7.8; $p < 0.0001$), and death (relative risk = 7.7; $p < 0.0001$) compared with patients not guided by the treatment algorithm.[14] Specifically, platelet hyperactivity in patients with COVID-19, assessed by AA- and ADP-maximal amplitude, was associated with thrombotic or ischemic complications, while decreased platelet activity was associated with hemorrhagic complications.[14] A study using the TEG PlateletMapping Assay in a largely African-American COVID-19 population identified a high proportion of patients with a suboptimal pharmacodynamic response to anticoagulants and aspirin, with patients on high dose aspirin still showing inadequate therapeutic response (50% of patients) and thromboinflammation (25% of patients).[84]

Due to the nature of COVID-19 and SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) as a relatively novel and infectious disease agent, there is a lack of high-quality evidence from large-scale clinical trials on the use of whole blood PTFs for diagnosis, and as part of treatment management. The currently ongoing TARGET-COVID study (NCT04493307) aims to evaluate hospitalized COVID-19 patients using a mix of thromboelastography, PFT, and biomarker analysis to determine individual patient thrombotic and bleeding risk to help personalize therapy and potentially improve clinical outcomes.[82]

Conclusion

The facility for the TEG PlateletMapping Assay to assess global hemostasis and platelet reactivity in a rapid assay that can be viewed and evaluated at the point of care makes it a plausible potential candidate to be used routinely in several clinical settings to optimize patient care. Specifically, the failure to routinely assess the response of individuals receiving antiplatelet therapy in the context of drug-eluting stent PCI procedures is illogical, given the well-described variability in individual responses to these agents, and the delicate balance between bleeding and ischemic events. Personalized, tailored antiplatelet therapy in such patients would be an attractive goal, and further research on the use of the TEG device is warranted. The use of TEG assays in TAVR patients to minimize bleeding complication rates also has an intuitive appeal, just as the more widespread use in cardiac surgery may offer considerable clinical outcome and bed occupancy advantages. Finally, the characteristic COVID-associated prothrombotic and bleeding sequelae of the highly complex vascular inflammatory response that the infection induces may well be routinely tracked, with reactive therapeutic interventions in the future. Ongoing large-scale studies such as the RISTRATAVI (Risk Stratification Post TAVI Using TEG, NCT03649594) trial on the use of TEG assays to stratify risk following TAVI interventions and the TARGET-COVID trial (NCT04493307) assessing the use of TEG assays and PTFs in hospitalized COVID-19 patients may help to answer some of the open questions regarding the clinical utility of the TEG PlateletMapping Assay.

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Conflict of Interest
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