expert roundtable »

The Role of Platelet Function Testing in Improving Clinical Outcomes

Scan this code with your smartphone camera to access this article on-the-go from our website.

Moderated by: **Lisa K. Jennings, PhD**[1]

Discussants: **David J. Schneider, MD**[2]**; Jerrold H. Levy, MD**[3]**; Dominick J. Angiolillo, MD, PhD**[4]

The following Expert Roundtable Discussion was held on November 1, 2017.

The discussion focused primarily on: (1) Factors that contribute toward inadequate antiplatelet drug responsiveness; (2) personalizing antiplatelet therapy to improve clinical outcomes; (3) the limitations of platelet function testing; (4) what is the optimal timing for platelet function testing: at the time of ACS or post-treatment; (5) the role of ROTEM and TEG in addressing clot integrity and platelet function; and (6) the current role for platelet function testing in evaluating patients and outcomes. [Published online ahead of print May 14, 2018.] (Med Roundtable Cardiovasc Ed. 2018 May 14.)

This roundtable was supported by AstraZeneca. The discussants (authors) developed the discussion and reviewed the transcript for important intellectual content, and approved the final version for publication. The authors maintained control of the discussion and the resulting content of this article.

STUDIES DISCUSSED:
GRAVITAS, ARCTIC, TROPICAL-ACS

COMPOUNDS DISCUSSED:
Clopidogrel, heparin, adenosine diphosphate, bivalirudin, argatroban, prasugrel

From the Department of Internal Medicine, The University of Tennessee Health Science Center, Memphis, TN and CirQuest Labs[1]; Cardiovascular Services, The University of Vermont Health Network, Burlington, VT[2]; Cardiothoracic Intensive Care Unit, Duke University School of Medicine, Durham, NC[3]; Division of Cardiology, University of Florida College of Medicine, Jacksonville, FL[4]

Address for correspondence: Lisa K. Jennings, PhD, D334 Coleman Building, 956 Court Avenue, Memphis, TN 38163-2116 • Email: ljennings@uthsc.edu

DR. JENNINGS: The purpose of this roundtable discussion is to reach out to clinical cardiologists and translational investigators to discuss the role of platelet function testing in improving clinical outcomes. We are interested in discussing the implications of platelet function testing in terms of assessing the risk for thrombosis, or for bleeding, and where it may play a role in improving clinical outcomes for patients, particularly acute coronary syndrome (ACS) patients.

Thank you very much for attending. We will begin with some introductions. I am Dr. Lisa Jennings, Clinical Professor at the University of Tennessee Health Science Center. I am also Founder of CirQuest Labs, a specialty platelet function and coagulation laboratory. My area of expertise is hemostasis and thrombosis.

DR. SCHNEIDER: I am Dr. David Schneider, a Professor of Medicine and Director of Cardiovascular Services at the University of Vermont Health Network. I have a long-standing research interest in platelet function assessment.

DR. LEVY: I am Dr. Jerrold Levy, an intensivist and a cardiac anesthesiologist. I am Co-Director of a 32-bed cardiothoracic intensive care unit at Duke, where we manage patients following major cardiovascular surgery including ventricular-assist devices, and extracorporeal membrane oxygenation (ECMO).

I have a long-standing interest in this topic. I am interested in both inhibiting and activating thrombin generation, and developing purified and recombinant strategies for treating life-threatening hemorrhage as well as anticoagulation for extracorporeal circulation. Thank you for the opportunity to participate.

DR. JENNINGS: Thank you. Dr. Angiolillo?

DR. ANGIOLILLO: Thank you for having me. I am Dr. Dominick Angiolillo, Professor of Medicine at the Univer-

sity of Florida in Jacksonville, where I practice as an interventional cardiologist.

I am also the Director of Cardiovascular Research and Program Director for the Interventional Cardiology Fellowship Program, and my interest for the past two decades has been on pharmacodynamic testing, and I have been involved with the development of a series of antiplatelet agents.

DR. JENNINGS: Thank you all for participating as faculty in this important discussion. For the purpose of this discussion, we will address if, or when, platelet function testing may serve a role in patient evaluation, and aid in improving clinical outcomes. Hopefully today we will touch on the many factors that play into evaluating platelet function in the setting of ACS, and post-treatment.

Let's participate in an open-ended discussion. I can start by posing some questions, and I think we all, with our vast experience, will add some insight or identify some areas where platelet function testing may serve a purpose, and where some limitations still exist.

There has been much discussion about inadequate antiplatelet drug responsiveness, and so the question is really, what contributes to this? Is it an inadequate loading or maintenance dose of an antiplatelet therapy? Is there a need to consider other antiplatelet agents in the treatment of patients? How personalized should we be, in terms of treating our patients, to improve critical outcomes?

We have talked about drug resistance, or perhaps low levels of platelet inhibition that may lead to increased risk of thrombosis. So, I would appreciate anyone's viewpoint in terms of antiplatelet drug responsiveness?

DR. SCHNEIDER: I think that it is a complicated situation. Individuals have varying platelet function, even over the course of a given day, so when we look at the response to an antiplatelet drug, we start from a background of variation in platelet function between individuals, and even within an individual over a period of time.

Then, as you move beyond the inter-individual variability, you add, on top of that—particularly with some of the drugs, such as clopidogrel—differences in absorption of the drug, differences in the metabolism of the drug, and then, ultimately, differences in its ability to achieve its end-organ effect, which ultimately can lead to rather substantial variability in the antiplatelet effect.

"I think the field has begun to move away from looking at percent inhibition with respect to a given drug, and toward looking at the residual platelet reactivity during treatment, and how we can associate that with outcomes in patients. Certainly, there have been ample studies demonstrating that high on-treatment platelet reactivity is associated with a greater risk of subsequent cardiovascular events.[1–3]"

~ David J. Schneider, MD

I think the field has begun to move away from looking at percent inhibition with respect to a given drug, and toward looking at the residual platelet reactivity during treatment, and how we can associate that with outcomes in patients. Certainly, there have been ample studies demonstrating that high on-treatment platelet reactivity is associated with a greater risk of subsequent cardiovascular events.[1–3]

DR. ANGIOLILLO: I wanted to echo what David just said. Also, based on your question, it is obviously a complex topic. It is not a matter of the loading dose or the maintenance dose. The loading dose is a one-time thing. We really define resistance or impaired response once the patient theoretically should have received the full therapeutic effect of a drug, which we evaluate during maintenance dosing.

In addition to that, not only can we speak about impaired response, but sometimes there is excessive response, where there have been studies in which patients with very low levels of platelet reactivity have been associated with an increased risk of bleeding, although they are not as consistent as observed for patients with impaired response.

DR. LEVY: I think these are interesting points. The other important point is, we are focusing on platelet reactivity in the milieu of a complexity of various degrees of vascular-endothelial activation, along with other factors that affect hemostasis.

In critically ill patients, there are multiple events that can occur to influence coagulation. Heparin causes microparticalization, and all the things that in the milieu in which we function, we focus on platelet reactivity, a critically important factor, but there are other obviously modulating factors that we do not routinely measure or really think about.

I think we need to better focus on platelets, but platelet function in bleeding and critically ill patients may be difficult to evaluate, and there may also be important influencing factors that we do not routinely measure.

DR. JENNINGS: Those are all relevant points. As we think about platelet function testing, Dominick mentioned that not only do we have issues around thrombotic complications—e.g., post-ACS—we also have bleeding risk, and there has been a continual search for tests that might assess bleeding risk, as well as patients that are at risk for thrombosis. We will try to touch on assessment of bleeding risk later in the discussion.

We still have a considerable amount of work to do. We can identify many platelet function tests (Table).[4,5] Briefly, there are light transmission aggregometry (LTA); lumi-aggregometry that combines platelet aggregation testing with measuring platelet secretion; impedance aggregometry that utilizes whole blood; and there is thromboelastography (TEG) or rotational thromboelastometry (ROTEM). There are platelet-activation tests such as flow cytometric tests, particularly for P2Y12 receptor signaling, using the vasodilator-stimulated phosphoprotein phosphorylation (VASP) assay and flow cytometric tests for platelet activation markers and for platelet signaling. There are also the point-of-care tests such as the PFA-100 and the VerifyNow® System (Accriva Diagnostics, San Diego, CA). The multi-plate electrode aggregometry might be considered an intermediate point-of-care test. I do not think many studies have proven that the correlation between these assays is high—in fact, at best, correlation can be modest to dismal and data from one test cannot be translated to another type of test. We have considerable work to do to define these thresholds of platelet reactivity for each available test that are associated with adverse events, whether it be thrombosis or bleeding.

For example, in VerifyNow®, a point-of-care instrument, there have been various thresholds recommended for residual high-platelet reactivity. We have not readily identified acceptable reactivity thresholds for LTA.

I am interested in your viewpoints as to when we talk about the limitations of platelet function testing, whether it is because we really do not know the values to associate with risk of adverse events, or are there other limitations that remain to be addressed?

DR. LEVY: I have a question. When you are doing P2Y12 testing, my understanding is that there is quite a variability in the concentration of adenosine diphosphate (ADP) that is used. We don't even know the EC50 for clopidogrel, and there are other people who isolated the active metabolite.

Not to diverge, but a partial thromboplastin time (PTT) on bivalirudin, a PTT on argatroban, and a PTT on heparin of the same number may be totally different in terms of thrombin generation.

"Many times, when we are doing prospective studies and evaluating how platelet function testing can be used to individualize therapy, we are assessing platelet function at a single time-point, and maybe not at the best time-point. For example, after undergoing percutaneous coronary intervention (PCI), there are a lot of factors that are involved with the thrombotic profile of that patient, which may include the procedure, per se, as well as characteristics of the patient. You may take that same patient and evaluate their platelet reactivity, and after a few weeks, or after a month, it may be completely different."

~ Dominick J. Angiolillo, MD, PhD

Have we standardized P2Y12 testing to the actual concentration of ADP? My gestalt is, it is variable from 5, 10, 20 µmol, and I think that is just one of the many different reasons—just a small part of it. Can you answer that?

DR. JENNINGS: Point well taken. My thinking is that when we talk about ADP testing, for example, with LTA, we have both the flexibility and the conundrum of what dose of ADP we might use, whereas some of the point-of-care tests—basically within a cartridge, so to speak—the concentration of ADP or combination of reagents that may initiate a platelet activation or aggregation is fairly set, which may provide a consistent test, but may not be the ideal concentration for a particular drug combination therapy or a particular drug itself.

The thing that I wrestle with often in platelet function testing is that we know that ADP comes from the dense granule of the platelet, and so the platelet must be activated for ADP to be released in the first place, and then of course it binds to the P2Y1 and P2Y12 receptors.

I have often asked, when we add exogenous ADP, whether it be a point-of-care or LTA, how well does that addition of exogenous ADP mimic what is going on with the platelet compared to when it becomes activated and releases its ADP to bind to its receptors?

I have added another wrinkle in this discussion, but I think the ADP question is quite challenging, because we are adding exogenous ADP, and there is a lot of variability in terms of which concentration of ADP one uses, whether it be LTA or in a point-of-care–type cartridge.

If high concentrations of ADP are used, then the platelets are challenged to their maximum. Is that result what we want to know? Do we want to know to what extent the platelets can become activated by the exposure or addition of ADP, or are we asking more if low levels of ADP are released from the platelets—e.g., during small activation events—then how well is the platelet inhibited?

Those questions are what we are faced with in evaluating platelet reactivity, and we are faced with trying to understand what would be the appropriate test in a trial, or when we are trying to evaluate the benefit of a particular drug combination therapy.

DR. SCHNEIDER: I will add another level of complexity, and then Domi-

nick, who has worked extensively in this area, can address these comments.

I have become particularly interested in the sensitivity of these assays for platelet function. Another variable with currently used assays is that we are taking blood out of the body. The manner in which you handle the blood can influence how platelets respond. Back to the sensitivity issue, what we know is that within an individual, we see changes in platelet function within the day, from day to day, and over time. I think that this issue is perhaps at the core of the challenge that we have in using the currently-available assays to guide individualized antiplatelet therapies.[6]

I think the concept of individualized therapy holds merit, but a useful analogy is diabetes (and glycemic control)—we are currently attempting to define glycemic control based on a random glucose, rather than a hemoglobin A1C. We need an assay approach that assesses average platelet function over the course of a period of time that is longer than a day, or even a week.

The goals of individualized therapy would be well-served if we could identify a measure of platelet function that is a more stable or a more consistent marker—we know that a patient who is high today is more likely to be high tomorrow, and a week from now, and a month from now, and I think that is likely to be a better guide for long-term care of patients.

DR. ANGIOLILLO: That is a great point. Many times, we tend to speak about inter-individual variability in response, but there is also the intra-individual variability, and this is something that is a little bit less explored.

Many times, when we are doing prospective studies and evaluating how platelet function testing can be used to individualize therapy, we are assessing platelet function at a single time-point, and maybe not at the best time-point. For example, after undergoing percutaneous coronary intervention (PCI), there are a lot of factors that are involved with the thrombotic profile of that patient, which may include the procedure, per se, as well as characteristics of the patient. You may take that same patient and evaluate their platelet reactivity, and after a few weeks, or after a month, it may be completely different.

This is something that we experienced in the GRAVITAS trial,[7] which was the first prospective randomized trial in patients who were identified as non-responders at the time of randomization. Around 40% of patients who were randomized to remain on clopidogrel 75 mg became responders after 30 days, and so this is to get back to the point that this adds an additional level of complexity on defining thresholds. Subsequent trials, such as ARC-TIC,[8] looked into adjusting treatment even a bit more beyond the peri-PCI phase and were not able to demonstrate a benefit. Indeed, the complexity of defining the ideal threshold and time point on when to modify treatment are potential contributors to these findings.

> ***"I absolutely think that looking at recovery of platelet function can be used as a guide to when it is safer to do an invasive procedure. In our institution, we are using testing to target replacement, rather than throwing the kitchen-sink at patients. I think that this is where the strongest evidence in support of testing exists."***
>
> *~ David J. Schneider, MD*

What we can say is that, for the most part, we have more information with the VerifyNow®, simply because, being a point-of-care instrument, it has been used more broadly and extensively studied, compared with LTA and VASP, which are a lot more tedious to perform.

From consensus documents, now there is support of the cutoff of platelet reactivity units (PRU) at 208, which has been considered in other prospective randomized studies of tailored therapy using platelet function testing.

Nevertheless, there is still a lot of debate on the optimal cutoff value. Another factor to consider is ethnicity—there is the so-called East Asian paradox, where their cutoffs are completely different. All this leads to the complexity of implementing platelet function testing routinely in clinical practice for decision making.

DR. JENNINGS: I think everyone brought up some very relevant points, because there have been trial results, as you mentioned, Dominick, and also both David and Jerry have indicated that variability of response, and the question of platelet inhibition versus platelet reactivity—say at the time of ACS, or peri-procedurally—may certainly be different.

The question is, is the degree of platelet inhibition at the time of ACS as important as post-treatment platelet reactivity? So, is platelet function testing early—e.g., after PCI—not as informative as some period of time post-treatment?

Then, certainly it is easier to gain experience with some of the point-of-care instruments such as VerifyNow®, and the experience has been varied. Some choose to use that instrument as kind of an all-or-none type of readout with the accepted cutoff of 208 PRU versus for triaging for various levels of platelet reactivity.

We also have the challenge of understanding what the acceptable reactivity threshold is for LTA. Going from an LTA maximal aggregation response of

75% down to 65% or 62% or 60%, may or may not be sufficient to reduce thrombotic events. Do we have the clinical trial data to really support what that definition of threshold reactivity is for LTA with a particular agonist and agonist concentration?

So, the acceptable reactivity threshold for LTA can certainly be variable, and it does beg the question of how we should be assessing platelet reactivity for this test. The appeal of LTA is that one can select the agonist and agonist concentration for evaluating platelet lag time to response, shape change, extent of aggregation, and aggregate stability.

There are multiple pathways involved in platelet reactivity, and so in some cases we have considered using, e.g., an agonist cocktail to understand, a little more broadly, the platelet reactivity in terms of not only ADP activation of platelets, but perhaps collagen/collagen-related peptide, or the PAR1 receptor, using, for example, thrombin receptor activating peptide.

Do you think getting a little more creative in our platelet function testing, where we are not limited to a single-pathway assessment, might serve us well? Where do you think we are in perhaps refining or modifying our approach for platelet function testing?

DR. ANGIOLILLO: I am very supportive of this concept of looking at the overall phenotype. So, again, as you highlighted, one of the limitations of the test that we use is, we are looking at a specific pathway, but it does not look at the full picture. Having some type of assessment of global thrombogenicity, or as global as you can get with a cocktail-of-agonists approach, is definitely an area of interest.

The problem becomes, to better understand its prognostic value. We do need prospective studies—cohort studies—to understand, at the end of the day, what does this all mean? So, it is a little bit premature for certain things.

Now, it is very good for research purposes, but if we want to move the field forward, I believe that we will need to integrate these tests with cocktails of agonists and larger cohort studies, and try to define how these are associated with different outcomes—and if they are. Also, what are the sensitivity and specificity of these tests?

DR. JENNINGS: Jerry, you have had experience with ROTEM or TEG. In some ways, that is a way of addressing not only clot integrity, but platelet function. Do you have any insights that seem to be a test that is being used in some of the procedure rooms, as well as maybe even a way of assessment of bleeding risk? Do you have any comments about that particular test?

DR. LEVY: It's like playing golf, where you use multiple clubs in your bag to figure out how to get the ball in the hole. I feel like the platelet story—in a lot of critically-ill patients that I deal with—is that it's a difficult variable to figure out, so we use all the other variables, where I would like to have a better understanding of platelet function, especially after all the drugs, after blood-surface interface, and extra-corporeal circulation.

The problem is that the viscoelastic tests are very fibrinogen-dependent, which is good and bad. The TEG-variable platelet function testing has been evaluated, not the best test I think, however this is often in association with an algorithm, any algorithm is better than just empiric therapy.

I am not a big fan of these tests for platelet function, but I think they have an interesting role, especially getting back to my original comment about the milieu of clot. I think it was mentioned earlier about all the things involved, and looking for what you call the phenotype.

I guess your phenotype definition is thrombosis, and these tests are part of the concern that I have. There are things like cytochalasin and the six murine monoclonal antibodies or different tests used to modulate, and try to look better at the platelet function. I am not a big fan of those tests.

Multiplate is another test. These tests are interesting, but I think they all have issues, whether your single agonist—in traditional platelet function, you do EC50, so you are looking at multiple variables and multiple concentrations. I think there are so many factors. To summarize, I am not a fan of those tests, and although they have been modified to look at platelet function, I think they still have issues, and I would appreciate everybody else's perspective on this, but that is my opinion on using them for platelet function testing.

DR. SCHNEIDER: Because of your clinical practice, I would be interested in your comments on the use of TEG as a guide to replacement therapy in a patient who is bleeding, particularly after a procedure? Do you see a utility there?

DR. LEVY: Totally. I previously was at Emory and worked with Andreas Grunzig, and worked in the era of the stents. In that scenario, I agree. In a bleeding ECMO patient, I follow the tissue-factor viscoelastometry test, what is called the EXTEM Assay (TEM Systems Inc., Durham, NC) because to me, that's the physiologic and pathophysiologic activation epitope.

In that scenario, I think it's helpful. The bottom line is, if you're clotting and you have normal whole-blood clot function that looks at all the factors of whole blood—and if you are bleeding, it means you have got a hole, a vascular defect, or there is something else I need to be looking for.

I think it's a great test in that scenario, and I know you all are quite familiar with the whole concept of massive transfusion coagulopathy, and

the studies that have looked at varying degrees of plasma to red cells, and all those scenarios. The reality is that the move now is, let's use TEG and ROTEM to determine if we have adequately repleted factors with massive hemorrhage.

Part of the problem is that fibrinogen gets lost in the equation. So, to answer your question, I think it's great in that scenario—with massive bleeding, with trauma, even with ventricular-assist devices, because you can have an international normalized ratio of 3 to 3.5, and you can still be clotting off due to other factors that cause hypercoagulability.

In that scenario, I think it's a helpful test, but I prefer the ROTEM, because there is the tissue factor assay. In general, people using TEG use kaolin, which is such a nonspecific activator of platelets, and I think a lot has to do with the activator, but I think in that scenario, it has important applications.

DR. JENNINGS: This has been a great discussion for the clinical cardiologist and healthcare practitioners. I am interested to hear from each of you, where you think platelet function testing has its role currently, and if you have any types of recommendations as to when it may be informative in terms of evaluating your patients, or for patient outcomes, and where you think it may still fall into the realm of research—if you would still put it in the research arena.

I think it would be helpful to conclude with your bottom line, in terms of how you use platelet function testing, or when you use it for your patients.

DR. ANGIOLILLO: At our center, we do a lot of platelet function testing, but we do it in the context of research, not necessarily for clinical decision-making. This is largely based on the fact that, to date, most trials have been largely negative.

The first and only prospective randomized study to meet the primary end-point was the TROPICAL-ACS trial,[9] which implements a concept of guided de-escalation therapy—going from a more potent to a less potent P2Y12 inhibitor, without having an increase in ischemic events. There was a trend toward a reduction in bleeding, but it did not reach statistical significance. As a concept, it is very interesting, and I think the study finally identified the right patient population to test this in.

The problem becomes, it is not that practical because to see a response to a given drug, the patient needs to be on the drug, and so the trial did imply de-escalating, but also escalating, in nearly 40% of patients. It is a starting point that we can build upon, with more trials to come. This is one setting. I think another setting is defining time-to-surgery in a patient on a P2Y12 inhibitor.

DR. LEVY: I agree. I think it is especially helpful in the patient who is on clopidogrel—maybe even prasugrel—and there is a concern about when to go for surgery because of the variability of effectiveness and resistance, etc. I think that is where it is effective.

Where I think we need significant additional work is the patient who has been on one of these agents, who has bled, who is a bit factor-depleted, thrombocytopenic, and you are concerned whether you still have an effect or not.

Yet these tests are dependent on certain things like hematocrit. They are dependent on some of the whole-blood tests, in particular. They are dependent on platelet number and, therefore, can be quirky and not informative when you have a critically bleeding patient.

So, in the maintenance phase and in the waiting-for-surgery phase, yes, I think they have a role. Where they really need additional development is in the patient who is bleeding, and the ability to measure platelet function is something that we really lack and needs additional investigation, in my opinion.

If a patient comes in with ACS, and has gotten into some trouble and they have bled, and you are resuscitating, that is where it is very helpful to have an idea of how much the platelets are contributing. Even though you do an EXTEM, you get a whole-blood clot, but it is still very much driven by fibrinogen. So again, critical bleeds in factor-depleted patients, we need to have a better assay that helps us understand.

DR. SCHNEIDER: I absolutely think that looking at recovery of platelet function can be used as a guide to when it is safer to do an invasive procedure. In our institution, we are using testing to target replacement, rather than throwing the kitchen-sink at patients. I think that this is where the strongest evidence in support of testing exists.

I firmly believe that we need to get, someday, to an evidence-based support for using individualized therapy. Sadly, I agree with Dominick that we are not there yet, and I think we should continue our efforts to refine the assays, as we have talked about a variety of ways to do that during our conversation today, and keep working on this issue from that perspective.

I also think, in development of antiplatelet agents, and looking for antiplatelet effects of other anticoagulants, the testing is pivotal. A lot of what Dominick does is what I do, as well, and so I think it is valuable in early-phase trials, and even Phase 4 trials, as we are trying to refine treatment.

For an average patient going to the catheterization lab, I agree with Dominick, we are not using platelet function testing to guide our therapy today, because of the failure of the trials that we have.

DR. JENNINGS: This exchange has been great. I think that we have had a very meaningful discussion and your discussion points are all terrific. It certainly does reflect where we are in the art of platelet function testing. To conclude, I think we all agree that platelet function testing is relevant for both assessment of thrombosis risk and for bleeding risk.

We need to continue to strive for evidence-based support. We all recognize its importance for early-phase trials, research and development, for looking at mechanisms of action, and of combination therapies. We have identified some ways that we might improve the assessment of platelet function, that tailoring treatment based on a single-agonist test may not be sufficient. There are attributes and deficiencies associated with these different tests.

We continue to work toward improved testing and improved assessment for looking at ways of improving patient outcomes. One thing we did not touch on due to time limitations is that there are obviously patient comorbidities—e.g., diabetes—and certain other factors can contribute to the assay results, and confound test interpretations.

It takes a lot of focus, a lot of work, and a lot of discussion such as what we have had today to move the field forward, and to improve our assessment of patients, and their risk for either thrombosis or bleeding.

Thanks so much to all of you for serving as faculty. I hope those who will be reading this and participating with us in our comments will find this to be useful, and encourage more discussion among us all, in terms of how to enhance platelet function testing for the improvement of clinical outcomes.

REFERENCES

1. Nührenberg TG, Stratz C, Leggewie S, et al. Temporal variability in the antiplatelet effects of clopidogrel and aspirin after elective drug-eluting stent implantation. An ADAPT-DES substudy. *Thromb Haemost.* 2015;114(5):1020–1027.
2. Hochholzer W, Ruff CT, Mesa RA, et al. Variability of individual platelet reactivity over time in patients treated with clopidogrel: insights from the ELEVATE-TIMI 56 trial. *J Am Coll Cardiol.* 2014;64(4):361–368.
3. Frelinger AL 3rd, Bhatt DL, Lee RD, et al. Clopidogrel pharmacokinetics and pharmacodynamics vary widely despite exclusion or control of polymorphisms (CYP2C19, ABCB1, PON1), noncompliance, diet, smoking, co-medications (including proton pump inhibitors), and pre-existent variability in platelet function. *J Am Coll Cardiol.* 2013;61(8):872–879.
4. Paniccia R, Priora R, Liotta AA, Abbate R. Platelet function tests: a comparative review. *Vasc Health Risk Manag.* 2015;11:133–148.
5. Hayward CP, Rao AK, Cattaneo M. Congenital platelet disorders: overview of their mechanisms, diagnostic evaluation and treatment. *Haemophilia.* 2006;12(Suppl 3):128–136.
6. Madsen NJ, Holmes CE, Serrano FA, et al. Influence of preparative procedures on assay of platelet function and apparent effects of antiplatelet agents. *Am J Cardiol.* 2007;100(4):722–727.
7. Price MJ, Berger PB, Teirstein PS, et al. for the GRAVITAS Investigators. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA.* 2011;305(11):1097–1105.
8. Collet JP, Cayla G, Cuisset T, et al. Randomized comparison of platelet function monitoring to adjust antiplatelet therapy versus standard of care: rationale and design of the assessment with a double randomization of (1) a fixed dose versus a monitoring-guided dose of aspirin and clopidogrel after DES implantation, and (2) treatment interruption versus continuation, 1 year after stenting (ARCTIC) study. *Am Heart J.* 2011;161(1):5.e5–12.e5.
9. Sibbing D, Aradi D, Jacobshagen C, et al. on behalf of the TROPICAL-ACS Investigators. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicenter trial. *The Lancet.* 2017;390(10104):1747–1757.

Clinical Implications

- **The role of residual platelet reactivity during treatment is important to monitor.**
- **There have been studies that show that high on-treatment platelet reactivity is associated with a greater risk for cardiovascular events.**
- **Platelet function tests use variable concentrations of ADP. This can impact the results. There needs to be more consistency in the concentration of ADP used.**
- **There are multiple pathways involved in platelet reactivity. An assessment of all pathways may give a better overall phenotype.**
- **Recovery of platelet function can be used as a guide to determine when it is safer to do an invasive procedure.**

Table. Different methodologies for assessment of platelet function

Method	Sample	Method application	Method principle
Bleeding time	Native WB	Screening test (obsolete)	In vivo measurement of time needed for bleeding to stop
Tests based on platelet aggregation			
Light transmission aggregometry (LTA)	Citrated PRP	Assessment of platelet function and mild bleeding disorders due to a platelet defect	Extent of light transmission through a stirring suspension of platelets that corresponds to platelet aggregate formation
Lumiaggregometry	Citrated WB	Detection of granule storage/release disorders	LTA or WB aggregometry combined with luminescence that measures nmoles released ATP
Plateletworks	Citrated WB	Monitoring of the platelet in response to platelet agonists	Platelet counting pre- and post-agonist activation in WB
Tests based on platelet adhesion under shear stress			
PFA-100; Innovance PFA-200	Citrated WB	Assessment of bleeding risk due to vWD or aspirin failure	Time evaluation of high shear WB flow through an aperture containing collagen and/or epinephrine
Impact; Cone and Plate(let) Analyzer	Citrated WB	Screening of primary hemostasis	Shear-induced platelet adhesion based on platelet surface coverage and aggregation
Global thrombosis test (GTT)	Native WB	Evaluation of platelet function and thrombolysis	Assesses platelet reactivity, endogenous fibrinolytic and thrombin generating potential
Platelet function methods combined with viscoelastic test			
TEG/platelet mapping system	Citrated WB	Assessment of global hemostasis by assessing dynamics of clot development, stabilization and dissolution	Assesses clot formation and strength; influenced by coagulation capacity, platelet count, platelet function and fibrinogen concentration
ROTEM platelet	Citrated WB	Assessment of global hemostasis by assessing dynamics of clot development, stabilization and dissolution	Assesses clot formation and strength; influenced by coagulation capacity, platelet count, platelet function and fibrinogen concentration
Platelet analysis based on flow cytometry			
Flow cytometry	Citrated WB, PRP, W-Plt	Platelet aggregation, platelet activation by extent of expression of surface and/or cytoplasmic biomarkers, and platelet-leukocyte aggregates	Laser-based detection of fluorescent tagged platelets or platelet-leukocyte aggregates
Evaluation of Thromboxane metabolites			
Radio-or enzyme-linked immunoassays	Serum, urine, citrated Pls	Measurement of TxA2 metabolites (and beta-TG, PF4, soluble P-selectin, CD40L)	Assesses soluble biomarkers for platelet activation

Abbreviations: ATP, adenosine triphosphate; beta-TG, beta-thromboglobulin; Pls, plasma; PRP, platelet-rich-plasma; ROTEM, rotational thromboelastometry; TEG, Thromboelastography; TxA2, thromboxane A2; WB, whole blood; W-Plt, washed platelets; vWD, Von Willebrand disease.

Adapted with permission from Dove Medical Press Ltd.[4]