EDITORIAL COMMENT

Post-Thienopyridine Platelet Response, Cardiovascular Outcomes, and Personalized Therapy

En attendant Godot*

Sotirios Tsimikas, MD;† Gregor Leibundgut, MD†‡
La Jolla, California; and Basel, Switzerland

In Samuel Beckett’s tragicomedy “En attendant Godot” (1) (later translated to English from the original French version by the author as “Waiting for Godot” [2]), Vladimir and Estragon wait excitedly by a tree on a country road for Godot, who is quite late in arriving with news of some important matter that will significantly impact them. Even though they each claim to know him personally, in fact, neither knows him well at all. While anxiously waiting for Godot to arrive, they occupy themselves with multiple diversions, some of which border on the absurd, including vaudeville exhibitions and discussions on death, human existence, ethics, rhetoric, time, and money. This play is thought to prominently represent the Theater of the Absurd Movement, and its content has led to different philosophical, political, psychological, biblical, and other interpretations of the play’s meaning.

See page 648

The current unresolved status of the clinical utility of post-thienopyridine platelet response—and primarily clopidogrel hyporesponsiveness—parallels some of the themes in Waiting for Godot by engendering different interpretations of the data, controversy, and vibrant debate in how to currently use such information, pending definitive trials. The main issues relate broadly to: 1) accurate measurement and definition of platelet hyporesponsiveness after thienopyridine administration; 2) developing methodologies that are accurate, precise, reproducible, easy to use, and cost-effective; 3) defining when and in whom platelet hyporesponsiveness should be measured; 4) developing consensus on appropriate criteria for platelet hyporesponsiveness that predict optimal reduction of future events as well as bleeding; 5) understanding the role of multiple genotypes, such as CYP2C19, that mediate poor response to clopidogrel; and 6) defining the role of emerging P2Y12 receptor antagonists that have superior efficacy compared with clopidogrel.

The importance of inhibiting platelet function in patients with acute coronary syndromes (ACS) and after percutaneous coronary intervention (PCI) takes on a supreme role when one considers that there are approximately 785,000 new and 470,000 recurrent coronary events, 195,000 silent myocardial infarctions, 795,000 strokes (2009 data), and 1,313,000 PCI procedures in the U.S. (2006 data) (3). Percutaneous coronary intervention carries an attendant 0.5% to 2% risk of stent thrombosis over the first year, and for some drug-eluting stents (DES) the risk might continue to increase at a low but measurable rate over at least the next 5 years. Such concerns have led to the empiric recommendation that the duration of dual antiplatelet therapy be increased to a minimum of 1 year after placement of a DES, pending randomized controlled trials such as the DAPT (Dual Antiplatelet Study, clinical trial number: NCT00977938), which is testing 12 versus 28 months of dual antiplatelet therapy. Therefore, relevant information on optimal antiplatelet therapy from the perspectives of appropriate drug, dosage, timing, and duration will be critical in improving clinical outcomes.

In that regard, in this issue of JACC: Cardiovascular Interventions, French investigators represented by El Ghanmoudi et al. (4) document higher 9-month cardiovascular mortality in a prospective registry in subjects undergoing urgent and elective PCI with inadequate response to clopidogrel, measured by the vasodilator-stimulated phosphoprotein test (VASP). On the basis of the VASP platelet reactivity index (PRI) of ≥61% as determined by receiver operating characteristic curve analysis, 40% of patients were low-responders to clopidogrel. The use of DES, impaired renal function, high C-reactive protein, and low responsiveness to clopidogrel were all predictive of cardiovascular mortality. This study adds to the rapidly growing observational study database on post-clopidogrel platelet hyporesponsiveness and clinical outcomes. Although there is currently no consensus regarding the appropriate methodology and criteria that define on-treatment platelet hyporesponsiveness, several studies using a variety of assays have consistently shown that inadequate response to clopidogrel predicts risk of future major adverse cardiac events in patients undergoing PCI (Table 1).

Definitive outcomes data do not yet exist showing that modifying therapy on the basis of a platelet function test leads to improved outcomes. However, the recognition of the highly variable response of clopidogrel, the fact that 20% to 40% of patients are hyporesponsive, and the associated risk this entails is appropriately driving further research in the utility of platelet function testing. Clopidogrel is a
produg that is converted to active metabolites by the cytochrome system in the liver, and particularly CYP2C19, which then bind irreversibly to the P2Y12 platelet receptor, ultimately leading to inhibition of platelet aggregation. There are several tests that measure platelet responsiveness to thienopyridines (5). Light transmission aggregometry (LTA) measures increased light transmission in response to the thrombin receptor agonist iso-TRAP and to ADP (LTA5/10, CPA 6 Reduced MACE). The data are presented as absolute P2Y12 reaction units and as a percentage inhibition of response to the thrombin receptor agonist iso-TRAP and to ADP. The PRI is then expressed as a mean percentage of activated platelet reactivity is established in response to PGE1, and interventions. The VerifyNow (Accumetrics, San Diego, California) requires a dedicated clinical laboratory with trained techni-
cians. The VerifyNow (Accumetrics, San Diego, California) documented that only the LTA, Plateletworks (Helena Laboratories Corp., Beaumont, Texas), and VerifyNow (Accumetrics, San Diego, California) system is a bedside test that measures enhanced light transmission after agglutination of fibrinogen-coated beads in response to the thrombin receptor agonist iso-TRAP and to prostaglandin E1 (PGE1) and ADP. The data are presented as absolute P2Y12 reaction units and as a percentage inhibition of the basal (iso-TRAP) and ADP induced values. In the VASP method, phosphorylated VASP is detected with fluorescently labeled anti-P-VASP antibodies with flow cytometry. Resting platelet reactivity is established in response to PGE1, and activated platelet reactivity is established in response to PGE1 plus ADP. The PRI is then expressed as a mean percentage of platelet reactivity. Lower PRI values are associated with higher antiplatelet efficacy (6).

Recently, the POPULAR (Do Platelet Function Assays Predict Clinical Outcomes in Clopidogrel-Pretreated Patients Undergoing Elective PCI?) study (7) has overcome several of the limitations of prior studies evaluating clopidogrel hyporesponsiveness, including small sample size, low event rates, different cutoffs for hyporesponsiveness, and lack of comparison of different platelet function tests, by performing a head-to-head comparison of 6 platelet function tests, determining cutoff values for high on-treatment platelet reactivity on the basis of receiver-operator characteristic curves and then evaluating their relationship to major adverse cardiac events and Thrombolysis In Myocardial Infarction bleeding. They documented that only the LTA, Plateletworks (Helena Laboratories Corp., Beaumont, Texas), and VerifyNow (Accumetrics, San Diego, California) P2Y12 tests predicted clinical outcomes in patients pre-treated with clopidogrel undergoing elective PCI. Interestingly, it seemed that the aggregation tests were better predictors of events than the shear-based tests. However, all tests had low positive predictive value after taking into account conventional risk factors and procedural variables, and none predicted bleeding. Further studies are needed to assess their predictive value in higher-risk subsets such as ST-segment elevation myocardial infarction, ACS, and complex coronary anatomy and interventions.

Because clopidogrel is converted to its active metabolite by the hepatic cytochrome enzymes and because several loss-of-function single-nucleotide polymorphisms have been identified that reduced the bioavailability of clopi-
ticagrelor, a debate has emerged as to whether universal genotyping would provide enhanced predictive value. However, individual or even a collection of relevant single-nucleotide polymorphisms explain only a modest amount of the variability in clopidogrel response as measured by LTA (8). Additional demographic (obesity, ACS, diabetes), environmental (drugs, noncompliance), biochemical (high fibrinogen levels [9]), procedural (unrecognized dissections and poor stent apposition), and other parameters ultimately mediate clinical events. Finally, most subjects with clopidogrel hyporesponsiveness will not have a future event, which provides an imperative to primarily screen the highest-risk patients. By contrast, with the complexity of the cytochrome P450 system, designing a genotype-driven clinical trial where patients are randomized to different therapies on the basis of loss of function alleles will be challenging. Therefore, it remains to be determined how this aspect of “personalized” therapy will evolve in the near future.

Do we even need genotyping or phenotyping, in the form of platelet function tests, with the approval of prasugrel and, in the future, ticagrelor and other P2Y12 antagonists, which have platelet function tests, with the approval of prasugrel and, in the future.

this aspect of “personalized” therapy will evolve in the near future.

Do we even need genotyping or phenotyping, in the form of platelet function tests, with the approval of prasugrel and, in the future, ticagrelor and other P2Y12 antagonists, which have more potent antiplatelet effects and very low incidence of platelet hyporesponsiveness (10)? Although prasugrel is associated with better efficacy and also more bleeding, ticagrelor demonstrated reduced cardiovascular mortality with similar bleeding rates (11). With clopidogrel becoming available as a generic drug soon, cost issues might ultimately drive the debate about when and if to genotype or measure platelet function.

Unlike in Waiting for Godot (2) where Godot does not ultimately appear and Vladimir and Estragon do not find out the “news”, randomized trials are underway to help clinicians individualize treatment of antiplatelet therapies. These trials will measure platelet responsiveness after clopidogrel and randomize patients either to standard therapy versus a higher dose of clopidogrel (GRAVTAS [Gauging Responsiveness With A VerifyNow Assay–Impact On Thrombosis And Safety] [NCT00645918], DANTE [Dual Antiplatelet Therapy Tailored on the Extent of Platelet Inhibition] [NCT00774475], and ARCTIC [Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy] [NCT00827411]) or to prasugrel (TRIGGER-PCI [Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel] [NCT00910299]). Ultimately, for selected patients, particularly those at high risk of thrombotic events, it is possible that data derived from platelet function testing might be useful in improving patient outcomes. The resolution of these issues in the next few years will ultimately allow clinicians to effectively individualize and prescribe optimal antiplatelet therapies in patients with ACS and particularly those undergoing PCI.

Key Words: acute coronary syndrome • clopidogrel resistance • percutaneous coronary intervention • platelet • thienopyridines.