Evaluating the clinical usefulness of platelet function testing: Considerations for the proper application and interpretation of performance measures

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Summary

Various diagnostic and prognostic performance measures have been used to describe the clinical usefulness of platelet function testing in the evaluation and management of patients taking P2Y12 inhibitors, which reduce the risk for thrombosis due to their action on the platelet P2Y12 receptor. Platelet function tests are used to confirm the presence of an antiplatelet effect of a P2Y12 inhibitor, and confirmation that the pharmacodynamic effect is associated with a reduction in the rate of thrombosis. Despite this clear association, enthusiasm for the clinical usefulness of platelet function testing has been tempered based on observed sensitivity, specificity, and positive predictive value for the detection of future thrombotic events. However, evaluating the prognostic utility of a test based on diagnostic performance indicators is not appropriate because prognostic tests are not used to diagnose which patients will have events; instead, they are used to assist in risk stratification. Therefore, when evaluating the usefulness of platelet function testing, diagnostic performance measures such as sensitivity, specificity, and predictive values should focus on diagnostic performance in identifying a pharmacodynamic effect, and prognostic performance should be evaluated using prognostic performance measures such as hazard ratios and net reclassification improvement, which are comparable to other well-established risk factors for cardiovascular events.

Keywords

Platelet function testing, antiplatelet agents, test statistics, platelet reactivity

Background on P2Y12 inhibitors and platelet function testing

The use of dual antiplatelet therapy (DAPT) with the P2Y12 receptor inhibitor clopidogrel and aspirin to reduce thrombosis in patients with high risk for coronary artery disease is well established (1-3), but is also associated with an increased risk for spontaneous bleeding and peri-surgical bleeding compared to aspirin monotherapy (2-6). P2Y12 Receptor antagonists are administered to minimise the platelet activation and aggregation that play a critical role in arterial thrombus formation, and their clinical efficacy (reduced thrombosis) and risk (increased bleeding) is attributable to this specific pharmacodynamic effect, i.e. the inhibition of the platelet P2Y12 receptor that mediates platelet activation induced by adenosine diphosphate (ADP) (7). The antiplatelet effect of P2Y12 inhibitors can be evaluated through measurements of *ex vivo* ADP-induced platelet function. The use of biochemical and physiological measurements to monitor the drug effect is not a novel concept. For example, blood pressure monitoring is routinely used while managing patients with antihypertensive medications, cholesterol measurements are made to assess the response to statin therapy, glucose levels are regularly measured in patients with diabetes treated with insulin and other antihyperglycaemic agents; the international normalised ratio (INR) is used to guide warfarin therapy, and serum brain natriuretic peptide (BNP) is measured to assess the severity of heart failure and the response to therapy.

Platelet function testing (PFT) using ADP as the agonist provides a direct measurement of the pharmacodynamic effect of the P2Y12 receptor inhibitor. During the initial development stages of antiplatelet agents, PFT is used to identify candidate agents and select the optimal dose to be subsequently studied in the clinical trials that evaluate efficacy and safety. For example, PFT was used to support both the dose selection of clopidogrel (8), plus the newer and more potent P2Y12 inhibitors, prasugrel and ticagrelor (9, 10) to provide a greater, more consistent antiplatelet effect than the Food and Drug Administration (FDA) approved and guideline recommended dose of clopidogrel, thereby overcoming the inter-
patient variability in response and high-on-treatment platelet activity (HPR) observed during clopidogrel therapy. Consistent with the observations made by PFT during phase I and II development, these more potent P2Y12 inhibitors demonstrated a further reduction in the rate of thrombotic events at the expense of increased bleeding compared with clopidogrel (11, 12). Despite this proven role of PFT during the development of P2Y12 inhibitors that led to optimal dosing and superior outcomes with these agents versus clopidogrel therapy in large scale clinical trials, controversy remains about the clinical usefulness of PFT in routine practice to confirm an adequate antiplatelet effect.

Methods for measuring the antiplatelet effect of P2Y12 inhibitors

The four most established and clinically validated methods of PFT are light transmittance aggregometry (LTA), VerifyNow P2Y12 Reaction Unit (PRU) results (Accumetrics, San Diego, CA, USA), flow cytometry-based vasodilator-stimulated phosphoprotein (VASP) phosphorylation analysis (BioCytex, Marseille, France), and the Multiplate® ADPtest HS multiple electrode aggregometry method (13-19). There is no true “gold standard” for PFT, which can be attributed to the fact that the tests are measurements of biological function and not measurements of analyte concentrations. There are similarities and differences in the methodologies and scientific principles underlying these tests. LTA and VerifyNow measurements evaluate the combination of both platelet activation and aggregation, while VASP measurements only identify the potential for platelet activation. The Multiplate measurement is based on the combination of platelet activation and aggregation of activated platelets to a foreign surface. The VerifyNow, VASP, and Multiplate assays include prostaglandin E1, which provides a more specific measurement of the effect of P2Y12 receptor inhibitors than LTA, because the LTA result is influenced by the activity of both the P2Y12 and P2Y1 receptors on the platelet. Finally, VerifyNow can be considered a true point-of-care test because it uses direct, unprocessed whole blood samples and does not require pipetting, whereas LTA requires platelet-rich plasma preparation, VASP requires platelet fixation and permeabilisation, and both LTA and Multiplate require sample pipetting as well as reagent preparation and pipetting. Despite these differences and the lack of standardisation, each method correlates significantly with P2Y12 inhibitor active metabolite concentrations, with the highest correlations reported for the VerifyNow PRU result and VASP, and weaker correlations reported for LTA and Multiplate (20, 21). High on-treatment platelet reactivity as defined by each method has been significantly associated with an increased occurrence of thrombotic and ischaemic events after percutaneous coronary intervention (PCI) in high-risk patients (21-23). Data reported using the VerifyNow method is the focus of this review as it is the most extensively and internationally evaluated method and, in some cases, the only method whose performance has been described using all of the statistical techniques described herein. Other methods have either been primarily evaluated regionally or have not been described using all of the statistical techniques to be discussed. Further, the VerifyNow method is a closed system that is not associated with the same repeatability and specificity concerns as the other methods, as poor repeatability and specificity can be significant sources of error in assessments of test performance.

Clinical scenarios where platelet function testing is used

PFT is mainly used in two clinical scenarios. The first scenario is after P2Y12 inhibitor therapy has been administered to reduce the risk of thrombosis, for example, in association with PCI. The second scenario is after P2Y12 inhibitor therapy has been interrupted to reduce the risk of bleeding, for example, prior to a major surgical procedure. In both scenarios, the same basic question is being asked – is there evidence of a significant antiplatelet effect from the P2Y12 inhibitor?

In the clinical context where the P2Y12 inhibitor is administered for the reduction of thrombosis, the physician is seeking confirmation of a significant antiplatelet effect because i) there is variability in the response to clopidogrel, and ii) HPR has been linked to increased risk of thrombosis (23-38). One might consider simply administering the newer, more potent P2Y12 inhibitors for all patients. However, contraindications and boxed warnings of significantly increased bleeding risk in association with the use of these newer, more potent agents have been deterrents to this potential one-size-fits-all approach (39, 40). Very low levels of platelet reactivity produced by more potent P2Y12 inhibition appear to be associated with increased bleeding risk, leading to proposals for the definition of therapeutic windows of platelet reactivity associated with optimal outcomes (41). The availability of generic versions of clopidogrel that are substantially less expensive than the newer, more potent agents has also raised the possibility that using PFT to identify patients with a clear antiplatelet effect while receiving clopidogrel may provide economic benefit. Several health plans in the United States have already instituted prior authorisation requirements to prescribe prasugrel and ticagrelor, with some plans specifying that HPR to clopidogrel – which can only be demonstrated through PFT – fulfills prior authorisation requirements (42, 43).

In the pre-surgical setting, the presence of clopidogrel and other P2Y12 inhibitors is associated with increased risk for peri-surgical bleeding. Accordingly, the prescribing information for P2Y12 inhibitors recommends discontinuation – if possible – for a period of time prior to surgery to reduce the risk of bleeding (4-6, 39, 40, 44). However, it is also advantageous to minimise the amount of time that P2Y12 inhibitor therapy is interrupted, since patients will not be receiving the antiplatelet effect while therapy is discontinued, placing them at increased risk for thrombosis. Therefore, PFT may be beneficial in reducing the length of time between interruption of P2Y12 inhibitor therapy and surgery by helping the physician identify when there is no longer evidence of a significant P2Y12 inhibitor effect (39, 40, 44-49).
Methods for describing laboratory test performance

Descriptors of laboratory test performance are selected on the basis of how the information provided by the test will be incorporated into clinical decision-making. Tests may be used either for the purpose of diagnosis or prognosis (i.e., risk assessment), and the techniques for evaluating the utility of a test differ markedly depending on how the test will be used. A summary of common techniques for describing test performance in these scenarios is provided in Table 1.

Test cut-offs

The first step in evaluating the performance of a laboratory test is to establish a decision point or “cut-off” to facilitate dichotomisation of results as positive or negative. It is critical to consider how the test will be used clinically when selecting a cut-off, because some clinical situations require high sensitivity while others require high specificity. There are two primary methods for establishing a cut-off. First, a cut-off may be established by identifying a reference range. A reference range that is derived from a population of subjects without the condition of interest will typically result in a cut-off that is highly sensitive for the condition of interest. This approach is sometimes used to establish a rule-out test cut-off when false negative results could lead to significant consequences.

Rather than defining cut-offs to maximise either sensitivity or specificity, it may be desirable in certain cases to use a cut-off that provides the highest combination of sensitivity and specificity for the condition of interest. In this regard, the second approach for establishing a cut-off is through the use of a receiver-operating characteristic (ROC) curve. The ROC curve is a plot of the true positive rate (sensitivity) versus the false positive rate (1-specificity) across the spectrum of all possible cut-offs for a continuous variable (54). When the ROC curve approach is used, the Youden index, calculated as [(sensitivity + specificity) - 1], at each cut-off is determined, and the test result value associated with the largest Youden index is often selected as the “optimal” cut-off (55).

Describing diagnostic test performance

The performance of a diagnostic test to detect the condition of interest is typically described in terms of sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV). These descriptors reflect the use of the test as a stand-alone method for detection of the condition; the classification determined by the test can be compared to another established diagnostic method or gold standard. Sensitivity, also referred to as the true positive rate, describes how often subjects with the condition have a positive test result. Specificity, also referred to as the true negative rate, describes how often subjects without the condition have a negative test result. Accuracy is the percent of subjects correctly classified by the test. PPV describes how often the condition is present when the test is positive, and NPV describes how often the condition is absent when the test is negative. PPV and NPV can sometimes be misleading because these descriptors are greatly influenced by the prevalence of the condition of interest. This phenomenon is illustrated in Figure 1. When the prevalence of the condition is very low, the PPV will also be low even when the test specificity is very high, and the NPV will be high even when the test sensitivity is very low. Sensitivity and specificity are not affected by the prevalence of the condition, but can be influenced by various factors, including demographics and clinical features present within the groups with and without the condition.

Likelihood ratios, calculated from diagnostic sensitivity and specificity, may also be used in the evaluation of diagnostic test performance through Bayesian inference techniques (56). Bayesian inference is based on the iterative process of gathering and integrating new information in the decision-making process. It requires an initial assessment using current knowledge to identify a pre-test probability for the condition, followed by a revised assessment after incorporating test results to arrive at a post-test probability. At a minimum, the pre-test probability may simply be the rate or incidence of the condition in the population being tested. The post-test probability is calculated as the pre-test probability multiplied by the likelihood ratio.

Table 1: Techniques used to describe laboratory test performance (adapted from [50]). The techniques used to describe risk assessment are substantially different from those used to describe diagnostic testing.

<table>
<thead>
<tr>
<th>Type of use</th>
<th>Evaluation</th>
<th>Descriptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic Testing</td>
<td>Test characteristics</td>
<td>Sensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Specificity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive predictive value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Accuracy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative predictive value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Likelihood ratios</td>
</tr>
<tr>
<td>Risk Assessment</td>
<td>Association</td>
<td>Odds ratio</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hazard ratio</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative risk</td>
</tr>
<tr>
<td>Discrimination</td>
<td>ROC curve (AUC, c-statistic)</td>
<td>Discrimination</td>
</tr>
<tr>
<td>Calibration</td>
<td>Hosmer-Lemeshow c2statistic</td>
<td>Calibration</td>
</tr>
<tr>
<td>Reclassification</td>
<td>Net reclassification improvement</td>
<td>Reclassification</td>
</tr>
<tr>
<td></td>
<td>Integrated discrimination improvement</td>
<td>Integrated discrimination improvement</td>
</tr>
</tbody>
</table>
ROC curves are central to the evaluation of test performance, regardless of whether the test is used for diagnostic purposes or risk assessment. The ability of a test to discriminate subjects with the condition from those without the condition is described through a calculation of the area under the curve (AUC), also called the c statistic. The c statistic can range from 0.5, which indicates no discriminatory ability, to 1.0, which indicates perfect discriminatory ability, and represents the probability that a randomly selected individual from the group with the condition of interest will have a test result that is greater (or lower, depending on the directionality of the test) than a randomly selected individual from the group without the condition (54). When cut-offs are selected using the ROC curve approach, the c statistic should be greater than 0.5 and reach statistical significance, and the uncertainty of cut-off selection decreases as the c statistic increases.

Describing prognostic test performance
Risk assessment tests or methods are most frequently described using odds ratios (OR) or hazard ratios (HR), which describe the multiplicative risk of the condition or hazard. A test that has a statistically significant OR or HR is considered to be predictive of in-
increased risk for the outcome. Multivariate models are frequently employed to evaluate whether the test is an independent predictor of the outcome. However, simply demonstrating that the test result is significantly associated with the risk for the outcome is not sufficient for concluding that the test is clinically useful. For example, small differences can easily achieve statistical significance in studies with large populations, but not all statistically significant associations are clinically meaningful. Other statistical techniques must be employed to demonstrate that the test has additive value to other established risk assessment indices and improves the overall risk assessment (57). One technique is to evaluate the change in the ROC curve c statistic when the test result is added to another risk prediction model. A statistically significant increase in the c statistic when the test result is included in the model indicates that the test result provides information that improves the ability of the physician to discriminate a patient at higher risk from a patient at lower risk. One limitation of this approach is that the test result may yield a statistically significant improvement in the c statistic, but the absolute increase in the c statistic is modest, which could lead to mistakenly concluding that the test is not clinically useful (58).

Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) can be used to evaluate the usefulness of risk assessment tools (57, 59-61). NRI evaluates a test’s ability to improve risk categorisation based on event-specific reclassification tables; it requires a priori establishment of meaningful risk categories (57). NRI is useful in demonstrating the ability of a new test to improve risk stratification and alter treatment decisions and is much more sensitive than the ROC curve c statistic (59, 60). IDI is a measure of a test’s ability to improve integrated (average) sensitivity while maintaining integrated (average) specificity, and is influenced by the incidence of the outcome of interest (57, 59).

The use of certain performance measures to debate the usefulness of platelet function testing should be reconsidered

HPR is consistent with the proposed Wilson-Jungner requirements for a meaningful risk marker (62) because i) it has biological plausibility since it is a measure of the potential for platelet acti-
vation and aggregation in vivo, which is the physiological process being targeted by the P2Y₁₂ inhibitor; ii) there is a strong, consistent association of HPR with worse outcome across multiple studies, including observational studies, analyses of randomised clinical trials, and meta-analyses (23, 28-38); iii) HPR precedes the event; and iv) there is evidence of a dose-response relationship between the degree of platelet reactivity and outcome (35). Despite this clear association, the clinical usefulness of PFT has been disputed, frequently based on conclusions drawn from misapplication and/or misinterpretations of statistical measures that are more appropriately suited for the evaluation of diagnostic tests, not prognostic indicators.

In diagnostic testing, the outcome has already occurred but is unknown to the investigator at the time of testing. In prognostic modeling or risk stratification, the outcome has not yet occurred at the time of testing and there is no guarantee that the outcome will occur, nor is there an indication of when an event will occur. Future disease status can only be estimated as a probability or risk (58). Interpretation of the utility of a risk assessment tool using diagnostic test statistics will frequently result in the rejection of prognostic indicators that are in fact clinically useful. For example, low PPV, sensitivity, specificity, accuracy, ROC curve c statistic, and a low area between the post-test probabilities based on a positive or negative test result have been cited as major limitations in the clinical usefulness of PFT for predicting adverse outcomes (63, 64).

HPR and positive predictive values

A low PPV has often been cited as a limitation of PFT for the use of identifying patients at risk for stent thrombosis. However, the rates of stent thrombosis in the cohorts that have been studied are typically no more than 1-2%. As noted above, PPV is critically dependent on the prevalence of a disease (or incidence of an outcome); the PPV for a prognostic test for stent thrombosis will always be low because the incidence of stent thrombosis in these studies is very low (Figure 1).

HPR, likelihood ratios, and Bayesian pre- and post-test probabilities

While sensitivity, specificity, PPV and NPV describe diagnostic performance (i.e. they indicate the ability of the test to detect the presence of a condition of interest), the purpose of PFT is to measure the antithrombotic effect of the P2Y₁₂ inhibitor, which in turn may facilitate identification of patients that have a sub-optimal P2Y₁₂ inhibitor effect and as a result are at increased risk for future major adverse cardiovascular events (MACE ) because they are not receiving the expected pharmacodynamic effect of the drug. In other words, the test helps to identify whether patients are at increased risk for MACE and is not used to identify whether or not the patient will have MACE. Accordingly, plots of pre-test probability versus post-test probability stratified by test result as described by Krishna et al. (64) have limited utility in the evaluation of PFT because they utilise likelihood ratios that are calculated from diagnostic sensitivity and specificity. Again, the purpose of the test is to assess risk, not to diagnose whether or not a future event will occur. Figure 2 illustrates the inappropriate use of such Bayesian plots to ascertain the clinical utility of a risk predictor. In this example, plots of pre-test probability versus post-test probability are stratified by whether the risk factor is present or absent for HPR (35) and for two other well-established risk predictors: diabetes (63) and non-compliance with P2Y₁₂ inhibitor therapy (3). Therefore, the clinical importance of diabetes and non-compliance with P2Y₁₂ inhibitor therapy on cardiovascular outcomes would be rejected using this technique to assess the performance of a risk factor.

Table 2: Comparison of reported net reclassification improvement values for various measures associated with cardiovascular risk. Platelet reactivity provides equivalent or better net reclassification improvement compared to several other established risk assessment tools. FRS = Framingham Risk Score; ATP III = National Cholesterol Education Panel Adult Treatment Panel III guidelines.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Reference</th>
<th>Number of Subjects</th>
<th>Referent Risk Classification</th>
<th>NRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>VerifyNow PRU</td>
<td>35</td>
<td>3,059</td>
<td>Clinical Risk Score</td>
<td>23% (p = 0.001)</td>
</tr>
<tr>
<td>VerifyNow PRU</td>
<td>Kirtane et al., presented at ACC 2012</td>
<td>8,575</td>
<td>ACS/Diabetes/Stent Length</td>
<td>29% (p &lt; 0.001)</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>57</td>
<td>3,264</td>
<td>FRS</td>
<td>12% (p &lt; 0.001)</td>
</tr>
<tr>
<td>C-reactive Protein</td>
<td>67</td>
<td>3,006</td>
<td>FRS</td>
<td>12% (p = 0.009)</td>
</tr>
<tr>
<td>Carotid Intima-Media Thickness</td>
<td>68</td>
<td>2,965</td>
<td>FRS</td>
<td>7.6% (p = 0.01)</td>
</tr>
<tr>
<td>Coronary Artery Calcification</td>
<td>69</td>
<td>4,129</td>
<td>FRS ATP III</td>
<td>22.4% (p = 0.009)</td>
</tr>
<tr>
<td>Family History of premature CAD</td>
<td>70</td>
<td>22,841</td>
<td>FRS</td>
<td>-2.0%</td>
</tr>
</tbody>
</table>
HPR and performance measures for risk assessment

HPR as a risk indicator has also been evaluated by for its clinical usefulness in addition to other clinical and procedural risk factors. The ROC curve approach has been used to evaluate the additive usefulness of HPR to a model that includes other risk factors, and HPR contributed to a statistically significant increase in the c statistic of the model (35). NRI has been recently used to evaluate the additive utility of HPR to existing tools for risk assessment, and the clinical usefulness of HPR compares favorably with other established risk indicators, as described in Table 2.

Considerations for defining HPR and interpreting PFT results

Another frequently debated topic is the selection of a cut-off to define HPR by PFT. When selecting such a cut-off, one must consider the purpose for the information that the test is providing. Although HPR should not be evaluated for its diagnostic performance in predicting outcomes, PFT can be evaluated for its diagnostic performance in identifying an antiplatelet effect due to a P2Y12 inhibitor. PRU results are highly accurate in detecting the presence of P2Y12 inhibition, with a c statistic of 0.95 (64). A PRU reference range of 194-418 has been established based on the 95% confidence interval of a P2Y12 inhibitor-naïve population (51), and results less than 194 are highly specific (~98%) diagnostic evidence of an antiplatelet effect due to a P2Y12 inhibitor. Many studies have confirmed the prognostic utility of HPR and have reported "optimal" PRU cut-offs generally ranging between 208-272 using the ROC curve/Youden index approach (28-32, 35, 36, 41). In fact, these cut-offs most likely represent decision points related to the fundamental principle of the test in measuring the level of P2Y12 receptor blockade relative in comparison to baseline platelet reactivity to ADP, and results below the cut-offs provide evidence of an antiplatelet effect of the P2Y12 inhibitor. Not surprisingly, evidence of a P2Y12 inhibitor effect is associated with a lower MACE rate. The clinical value of PFT to "diagnose" the presence of a P2Y12 inhibitor effect is also supported by the reported NRI for PRU results, where the majority of the benefit was in reducing the risk categorisation of subjects without events when there is evidence of a P2Y12 inhibitor effect.

There are several important considerations when selecting cut-offs for prognostic indicators using the ROC curve approach. Several factors can introduce uncertainty into an "optimal" cut-off. Uncertainty in the Youden index can result from a low AUC, which is typical of prognostic indicators, and by low event rates, which produce a more jagged appearance of the ROC curve and introduce uncertainty in the estimate of sensitivity and specificity at each possible cut-off. Finally, differences between studied populations also introduce uncertainty, which may explain the different optimal PRU cut-offs that have been reported. Bootstrap analyses of optimal cut-off selection using the ROC curve approach from both small and large studies have described 95% confidence intervals for the optimal cut-off of 174–291 PRU and 190-272 PRU, respectively (28, 35). Within this range of optimal cut-offs, there is evidence that a lower cut-off may have better clinical utility, because there is no apparent further reduction in MACE once PRU results are less than the median value (PRU = 200), and patients who achieve PRU results less than 208 have lower MACE rates (35, 36).

Summarisation

Various diagnostic and prognostic performance measures have used to describe the clinical usefulness of PFT. However, care must be taken in their correct application and interpretation. P2Y12 inhibitors are administered in high-risk patients to reduce the risk for thrombosis, and PFT is used to provide “diagnostic” evidence of a P2Y12 inhibitor effect. Diagnostic evidence of a P2Y12 inhibitor effect is associated with reduced risk for thrombosis due to the pharmacodynamic effect of the drug. Taken together, the existing published evidence for PFT supports the importance of confirming that the patient is receiving the intended therapeutic effect of their P2Y12 inhibitor. Since the antithrombotic properties of P2Y12 inhibitors are solely due to their pharmacodynamic effect, it is intuitive that the goal of treatment with these agents would be the establishment of a P2Y12 inhibitor-induced antiplatelet effect. PFT in high risk populations, particularly in the setting of treatment with a P2Y12 inhibitor associated with an unpredictable and, in some cases negligible effect, should lead to improved outcomes by identifying those patients without adequate P2Y12 inhibition.

Conflicts of interest

J. R. Dahlen is an employee of Accumetrics. M. J. Price has received research/educational grants, honoraria and/or consultancy fees from DSI/Lilly, BMS/Sanoﬁ, AstraZeneca, Accumetrics, Merck, Medicare, Jansen Pharmaceuticals, Quest Diagnostics and Iverson Genetics. P. A. Gurbel has received research/educational grants, honoraria and/or consultancy fees from AstraZeneca, Medtronic, DSI/Lilly, Pozen, Sanoﬁ, Boston Scientific, Bayer, Novartis, Accumetrics, Nanosphere, Boehringer and Merck. H. Parise declares no conﬂicts of interest.

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