Journal of the American College of Cardiology Vol. 58, No. 25, 2011

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.09.031

EDITORIAL COMMENT

Personalized Therapy Following Drug-Eluting Stenting Using Platelet Function Testing and C-Reactive Protein*

Grant W. Reed, MD, Christopher P. Cannon, MD

Boston, Massachusetts

Recent advances in genetics and proteonomics have great potential to help tailor treatment to individual patients in remarkable ways. A focus of intense research is on "clopidogrel nonresponders," who despite treatment with conventional-dose clopidogrel still demonstrate high on-treatment platelet reactivity (HTPR), which has been associated with in-stent thrombosis and recurrent cardiovascular events (1). This decreased response to clopidogrel is thought to affect roughly one-third of patients (2). Several genetic polymorphisms have been linked to reduced hepatic metabolism of clopidogrel (the most prevalent of which is CYP2C19), leading to a lower concentration of the active metabolite (3). This pathophysiological explanation lends itself to clinical applications, because targeting those patients with a positive genetic screen or HTPR after drug-eluting stents (DES) with a more effective antiplatelet agent may prove an effective strategy. Recent trials have shown both prasugrel (TRITON–TIMI 38 [Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38]) and ticagelor (PLATO [PLATelet inhibition and patient Outcomes]) yield benefits over clopidogrel in patients with acute coronary syndromes, and more effectively suppress platelet reactivity (PRINCIPLE–TIMI 44 [Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis In Myocardial Infarction 44 trial], PLATO Platelet), setting the stage for their use as alternatives to clopidogrel.

See page 2630

The 2011 update to the American College of Cardiology/American Heart Association guidelines for the management of unstable angina/non–ST-segment elevation myocardial infarction reflects the growing consensus that genetic and platelet function testing are useful in selected patients, mainly those at a increased risk of future events (4). Currently, platelet function testing carries a Class IIb recommendation, Level of Evidence: B, but has yet to be widely implemented. Among the reasons for this: 1) there are many platelet function assays available, but there is no clear consensus as to which is the best; 2) setting a cutoff value to define HTPR is challenging; and 3) as of yet, there are limited data that alteration of therapy based on HTPR improves outcomes (3). To address these issues, a comparison of platelet function assays suggests that the VerifyNow P2Y12 assay (Accumetrics, San Diego, California) may be the most practical test currently available, as it is inexpensive, easy to use, and yields comparable results to the standard light transmittance aggregometry (5). A cutoff of >235 to 240 $P2Y_{12}$ reaction units (PRU) to define HTPR as measured by VerifyNow was recently endorsed by the American College of Cardiology (3). Moreover, modifying treatment based on the presence of HTPR defined by VerifyNow is the focus of ongoing clinical trials, and GRAVITAS (Gauging Responsiveness With A VerifyNow Assay-Impact on Thrombosis And Safety) was the first large-scale trial to study this, although no benefit was seen of doubling of the clopidogrel dose in patients with HTPR (6).

In the paper by Park et al. (7) in this issue of the *Journal*, the VerifyNow P2Y12 assay failed to demonstrate a significant difference in event rates: the occurrence of the primary endpoint was essentially unchanged in those with HTPR and those without (2.8% vs. 2.4% at 2 years; $p = 0.18$), and the addition of HTPR as a risk factor to a multivariate regression analysis did not improve prognosis of future cardiac events. One strength of this study was that patients were followed a median of 2.2 years, longer than other comparable studies; but a weakness was the low event rate, thus limiting the power of the study. This may in part be explained by the absence of periprocedural myocardial infarction in the primary endpoint, as has been used in recent observational trials with higher event rates (5).

Of interest, in the current study, the prevalence of HTPR was much higher at 58.3%, in contrast to GRAVITAS and prior studies, where the prevalence of HTPR was 40.7%. The reasons for this degree of HTPR are unclear, perhaps due to increased genetic polymorphisms for CYP2C19 in the Korean patient population. Thus, integrating the current study with GRAVITAS and many prior studies, platelet function (perhaps combined with genetic) testing continues to hold promise as a tool to tailor therapy, but the

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts. Dr. Reed has reported that he has no relationships relevant to the contents of this paper to disclose. Dr. Cannon has received research grants/support from Accumetrics, AstraZeneca, GlaxoSmithKline, Merck, and Takeda; has been on the advisory boards (but funds donated to charity) of Bristol-Myers Squibb/Sanofi, Novartis, and Alnylam; has received honoraria for development of independent educational symposia for Pfizer and AstraZeneca; and has been a clinical advisor with equity in Automedics Medical Systems.

verdict is out on whether this will prove clinically useful or lead to meaningful treatment strategies.

In a second aim of the current study, the authors show that individuals with C-reactive protein (CRP) ≥3.0 mg/l are at higher risk for cardiovascular events following DES (5.6% vs. 1.7% at 2 years, $p < 0.001$). The addition of CRP to standard risk factors improved the ability to prognosticate patient outcomes modestly (increase of the C-statistic from 0.729 to 0.759, $p = 0.03$). These results are consistent with a recent meta-analysis that shows CRP concentration has continuous associations with the risk of CAD, ischemic stroke, and vascular mortality (8). Targeting patients with CRP >2 mg/l for primary prevention with statins appears to lead to improved outcomes in patients at intermediate risk (9). In the setting of acute coronary syndromes, elevated CRP was independently correlated with increased 14-day mortality in TIMI 11A. Additionally, in PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22), patients with elevated CRP post-treatment also had increased risk of cardiovascular events. The current study is consistent with prior studies linking CRP to stent thrombosis and cardiovascular events (10), and is supportive of the growing body of evidence suggestive that CRP can be used to indentify high-risk patients who in turn can be targeted for intensive primary and secondary prevention.

Importantly, this study identifies those patients with elevated CRP as a high-risk group following DES, and suggests that patients with both elevated CRP and HTPR are at even higher risk. This raises the question of whether patients with high CRP would benefit the most from platelet function testing and tailored antiplatelet therapy. As CRP is a marker of inflammation, it is plausible that patients with elevated CRP would have higher platelet reactivity at baseline, be more likely to exhibit HTPR, and benefit from more potent antiplatelet agents. Additionally, given the results of this current study, it may be worthwhile to investigate whether treating patients with elevated CRP following DES with intensive statin therapy may be an effective means of secondary prevention, regardless of low-density lipoprotein level.

Integrating the current evidence and practice guidelines, genetic and platelet function testing are suggested in *selected* patients that would benefit the most from testing. This patient group is still being defined, but might include patients with prior stent thrombosis, obese or very low body weight individuals, and (incorporating the current study's results) patients with CRP ≥3 mg/l. As this area of research matures, the comparative utility of genetic versus platelet function testing should be investigated prospectively, and the definition of HTPR further refined. Several ongoing trials seek to elucidate whether treatment strategies of higher dose clopidogrel (NCT01235351 and NCT00827411) and prasugrel (NCT01090336) (or ticagrelor) actually improve outcomes. Personalizing medical therapy to target HTPR and CRP may thus be on the horizon. With the proper focus, this may lead to improved patient outcomes following DES in the near future.

Reprint requests and correspondence: Dr. Christopher P. Cannon, TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. E-mail: cpcannon@partners.org.

REFERENCES

1. Kereiakes DJ, Gurbel PA. Peri-procedural platelet function and platelet inhibition in percutaneous coronary intervention. J Am Coll Cardiol Intv 2008;1:111–21.
2. Holmes DR, Dehmer GJ, Kaul S, Leifer D, O'Gara PT, Stein CM. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents and the American Heart Association. J Am Coll Cardiol 2010;56:321–41.
3. Bonello L, Tantry US, Marcucci R, et al. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol 2010;56:919–33.
4. Wright RS, Anderson JL, Adams CD, et al. 2011 ACCF/AHA focused update of the guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction (updating the 2007 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011;57:1920–59.
5. Breet NJ, van Werkum JW, Bouman HJ, et al. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. JAMA 2010;303:754–62.
6. Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. JAMA 2011;305:1097–105.
7. Park D-W, Lee S-W, Yun S-C, et al. A point-of-care platelet function assay and C-reactive protein for prediction of major cardiovascular events after drug-eluting stent implantation. J Am Coll Cardiol 2011;58:2630–9.
8. Kaptoge S, Di Angelantonio E, Lowe G, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010;375:132–40.
9. Ridker PM, Rifai N, Clearfield M, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N Engl J Med 2001;344:1959–65.
10. Buffon A, Liuzzo G, Biasucci LM, et al. Preprocedural serum levels of C-reactive protein predict early complications and late restenosis after coronary angioplasty. J Am Coll Cardiol 1999;34:1512–21.

Key Words: C-reactive protein ■ drug-eluting stent(s) ■ editorial ■ platelet function test.