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Viewpoint

The Case for Routine Genotyping in Dual-Antiplatelet Therapy

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Over 1 million coronary stent procedures are performed annually in the U.S., with dual-antiplatelet therapy, which includes the use of both aspirin and clopidogrel, being a cornerstone in the management of these patients after coronary intervention. Now, recent data have surfaced demonstrating altered active metabolite levels of clopidogrel in patients harboring hepatic cytochrome gene variants. These variants, which have been validated through genome-wide association as the dominant explanation for the marked heterogeneity of clopidogrel response, are linked to a significant increase in the risk for bleeding, stent thrombosis, myocardial infarction, and death. With viable alternatives to clopidogrel now available, including higher clopidogrel maintenance and loading doses, prasugrel, and ticagrelor, clinicians can now effectively guide therapy in those with at-risk gene variants by simple genotyping. Such an individualized approach can potentially prevent tens of thousands of adverse cardiovascular events in the over 30% of those with European ancestry and over 40% of those with Asian or African ancestry who harbor these important clopidogrel gain-of-function and loss-of-function alleles. (J Am Coll Cardiol 2010;56:109–11) © 2010 by the American College of Cardiology Foundation

Approximately 25% of all outpatient prescription drugs filled in the U.S. are taken by patients with genetic polymorphisms that affect these drugs' absorption, metabolism, or excretion (1). These gene variants affect both drug safety and efficacy, but clinicians have only rarely exploited this knowledge to improve patient outcomes. Recently, multiple large cohort studies have incontrovertibly linked genetic polymorphisms in the hepatic cytochrome 2C19 (CYP2C19) system to an alteration in the metabolite levels of clopidogrel (2–6). Now, a recent genome-wide association study has proven that common variants in the CYP2C19 gene locus are the dominant explanation for the genomic variance in clopidogrel antiplatelet response (5). The consequences of these variants include significantly increased risk for bleeding, myocardial infarction, stent thrombosis, and death (3–6). Herein, we provide a rationale for individualizing antiplatelet therapy on the basis of this vital pharmacogenetic information.

CYP2C19 Variants

In 2006, investigators documented a >25% reduction in platelet responsiveness to clopidogrel in healthy volunteer carriers of a reduced-function CYP2C19 allele (7). Several candidate gene studies involving thousands of patients have since validated and extended these initial findings to patients on clopidogrel therapy for acute coronary syndromes and coronary artery disease (2–4). Most important, over one-third of Europeans and over 40% of patients of African and Asian ancestry harbor these common gain-of-function and loss-of-function variants (5,6). Furthermore, loss-of-function allele carriers have a striking 3-fold increase in the risk of stent thrombosis, myocardial infarction, and cardiovascular death, while gain-of-function allele carriers have an approximate 2-fold increase in the risk of Thrombolysis In Myocardial Infarction major and minor bleeding (3–6).

Surprisingly, despite the robust nature of the data outlined here, detractors have cited numerous "holes" in the evidence base preventing widespread acceptance of the results. First, they reference the variability in gene dosage impact seen in the Simon et al. (2) study, in which only those carrying multiple alleles of CYP2C19 gene variants experienced increases in cardiovascular events. Critics also attest to the presence of alternative genetic and environmental factors, such as polymorphisms in drug absorption (ABCB1) (2), other variants in drug metabolism (2B6) (4) or the P2Y12 receptor, smoking, and obesity as significant mediators of clopidogrel response.

While these are all valid concerns, these arguments do not fully consider the enormous breadth of evidence implicating CYP2C19 gene variants as the root cause of adverse cardiovascular events during clopidogrel treatment. To further reconcile and solidify all existing data on genetic modifiers of clopidogrel response, Shuldiner et al. (5) conducted a very timely genome-wide association study.

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Abbreviations and Acronyms

CYP2C19 = hepatic cytochrome 2C19

PFT = platelet function testing

These investigators first measured platelet aggregation in a healthy cohort at baseline and within 1 h after the last dose of clopidogrel on day 7. They then assessed over 400,000 single-nucleotide polymorphisms for association to platelet activity. Not surprisingly, the most significant single-nucleotide polymorphisms (1.5×10^{-13}) clustered around chromosome 10q24, which is in high linkage disequilibrium with the previously established reduced-function CYP2C19*2 allele, the most common loss-of-function CYP2C19 gene variant. Importantly, these single-nucleotide polymorphisms did not associate with platelet aggregation at baseline, thereby confirming CYP2C19 as the major genetic mediator of clopidogrel response. In the next stage, the investigators examined the effect of the CYP2C19 variant in patients undergoing percutaneous coronary intervention. At 1-year follow-up, carriers of this variant had a dramatic 340% increase in stent thrombosis and cardiovascular death, closely mirroring the 3-fold increase in risk for major adverse events seen in previous studies (2–4).

Individualized Options for Dual-Antiplatelet Therapy

Investigators have recently demonstrated an 8-fold reduction in stent thrombosis by administering additional clopidogrel loading doses in patients with poor baseline response (8). In some instances, up to 2,400 mg was required to obtain an adequate antiplatelet effect. In addition, recent data have shown that strategies aimed at doubling the clopidogrel maintenance dose in the period immediately after stenting can confer a significant clinical benefit (9). Furthermore, prasugrel, a newly approved thienopyridine with more rapid and greater inhibition of platelets, has now also emerged as a viable option to standard clopidogrel therapy. A recent clinical trial that used prasugrel in patients with acute coronary syndromes found a 20% reduction in ischemic end points and a >50% reduction in the rate of stent thrombosis compared with individuals randomized to the clopidogrel arm (10). Unfortunately, also observed was a significant increased risk for major bleeding. Accordingly, a selective strategy of giving clopidogrel solely to patients harboring reduced function alleles would most likely magnify prasugrel's efficacy and limit the proportion of patients exposed to its heightened bleeding risk.

Despite all of the current options outlined here, the most commonly used alternative to clopidogrel in the near future will likely be ticagrelor. The first of a new class of orally active nonthienopyridine agents, ticagrelor has a reversible antiplatelet effect and does not require hepatic activation (11,12). Furthermore, this agent confers a faster, more consistent antiplatelet effect compared with clopidogrel (11,12). Most recently, ticagrelor demonstrated significant superiority to clopidogrel in preventing ischemic events and, for the first time, a significant mortality benefit (13). With U.S. Food and Drug Administration approval of ticagrelor likely to be expedited because of its observed mortality benefit and lack of excess bleeding, some experts may argue for the across-the-board use of this agent over clopidogrel. However, such calls would be premature for several reasons. First, similar to prasugrel, the modest 1.9% absolute risk reduction of ischemic events seen with ticagrelor therapy was likely predominantly conferred by patients in the clopidogrel arm of the study who harbored resistance alleles. Therefore, for this reason and because of the anticipated generic availability of clopidogrel in 2011, ticagrelor may be better suited for those who are genetically poor responders or have failed clopidogrel therapy.

Our Pharmacogenetic Future

Many experts will continue to call for results from randomized prospective trials before individualizing antiplatelet therapy on the basis of CYP2C19 carrier status, despite the overwhelming evidence presented here. This doggedness represents a false premise for a number of reasons and denies current patients state-of-the-art care. Certainly, large-scale efforts prospectively validating systematic genotyping should be performed and will be a valuable addition to the current compendium of existing data. However, with stent thrombosis rates in carriers of CYP2C19 as high as 11% (3), mortality associated with such events close to 50%, and a near 2-fold increase in the risk of bleeding in CYP2C19*17 carriers, we cannot afford to wait years for results from these trials that to date have yet to be initiated. In the interim, we should implement all potential interventions to help prevent the catastrophic outcomes of stent thrombosis and death in the tens of thousands of patients currently at risk. Consistent with this line of reasoning, the U.S. Food and Drug Administration has now appropriately added a boxed warning to the clopidogrel label emphasizing this increased risk of adverse cardiovascular outcomes in individuals harboring the poor metabolizer genotypes (14). This notice also advocates, as we have outlined here, implementing strategies aimed at adjusting clopidogrel dosing or the use of alternative antiplatelet agents in these high-risk individuals.

Further, it should be duly noted that there will be substantial challenges in planning a comprehensive prospective trial aimed at validating any pharmacogenetic approach to clopidogrel therapy. First, we will need to incorporate all the various combinations and permutations of treatment and surveillance strategies, including a clopidogrel maintenance dose of 75 mg versus 150 mg, standard versus repeat 600-mg clopidogrel loading doses, prasugrel 5 mg versus 10 mg, ticagrelor, and the effects of other antiplatelet agents yet to emerge. Additional strategies will also include point-of-care platelet function testing (PFT) and the duration of increased dosing of clopidogrel. Finally, it should also be

noted that no current viable randomized design exists to fully account for patient frailty, coronary anatomy, and left ventricular function with respect to bleeding risk and clinical outcomes.

Critics of CYP2C19 genotyping will also suggest that PFT after percutaneous coronary intervention is a better alternative for measuring both genetic and environmental mediators of platelet response. However, data from a recently published study would indicate otherwise (15). In this trial, investigators used 6 separate commonly used methods to assess baseline platelet function after appropriate clopidogrel loading in over 1,000 patients who received coronary stents. At 1-year follow-up, only 3 of the 6 assays were prognostic for adverse cardiovascular events, with only 1 of the 6 assays being predictive for stent thrombosis. Furthermore, the predictive capacities of these tests were modest compared with genotyping and, notably, did not foretell a patient's risk for bleeding (3–6,15). Other problems with PFT include results that are inconsistent and dynamic when assessed at different times in the same patient, lack of a standard definition of suboptimal platelet response, and disagreement on the best method for measuring platelet function (16). In contrast, CYP2C19 genotyping could be performed rapidly before percutaneous coronary intervention, thereby identifying a subset of patients at high risk for bleeding or thrombotic events who could then be monitored with point-of-care PFT for adequate clopidogrel response or potentially switched to an alternative agent such as prasugrel or ticagrelor.

The use of genotyping, with or without PFT, represents the prototype of individualized medicine for the future (17). The clopidogrel story involves the second most highly prescribed medicine in the U.S. and one of the most common medical procedures performed, in over 1.2 million patients each year (18). We believe that the evidence threshold supporting individualized clopidogrel therapy has been clearly surpassed, leveraging new knowledge from pharmacogenomic and epidemiologic studies to select the right drug for the right patient. Translational medicine is not just a matter of bringing science to the practice of medicine; it also requires the appropriate timing and making the call that adequate data have accumulated to change the routine clinical care of patients. Such is the case for genotyping with the use of clopidogrel.

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REFERENCES

1. Frueh FW, Amur S, Mummaneni P, et al. Pharmacogenomic biomarker information in drug labels approved by the United States food and drug administration: prevalence of related drug use. Pharmacotherapy 2008;28:992–8.
2. Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med 2009;360:363–75.
3. Collet JP, Hulot JS, Pena A, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. Lancet 2009;373:309–17.
4. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360:354–62.
5. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA 2009;302:849–57.
6. Sibbing D, Koch W, Gebhard D, et al. Cytochrome 2C19*17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. Circulation 2010;121:512–8.
7. Hulot JS, Bura A, Villard E, et al. Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. Blood 2006;108:2244–7.
8. Bonello L, Camoin-Jau L, Armero S, et al. Tailored clopidogrel loading dose according to platelet reactivity monitoring to prevent acute and subacute stent thrombosis. Am J Cardiol 2009;103:5–10.
9. Mehta SR. CURRENT OASIS-7: benefit to doubling clopidogrel dose in ACS patients undergoing PCI. Paper presented at: European Society of Cardiology 2009 Congress; August 30, 2009; Barcelona, Spain.
10. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.
11. Kowalczyk M, Banach M, Mikhailidis DP, Hannam S, Rysz J. Ticagrelor—a new platelet aggregation inhibitor in patients with acute coronary syndromes. An improvement of other inhibitors? Med Sci Monit 2009;15:MS24–30.
12. Storey RF, Husted S, Harrington RA, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. J Am Coll Cardiol 2007;50:1852–6.
13. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.
14. Food and Drug Administration. FDA drug safety communication: reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug [safety announcement]. March 12, 2010. Available at: http://www.fda.gov. Accessed April 26, 2010.
15. Breet NJ VWJ, Bouman H. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. JAMA 2010;303:754–62.
16. Angiolillo DJ, Suryadevara S, Capranzano P, Zenni MZ, Guzman LA, Bass TA. Antiplatelet drug response variability and the role of platelet function testing: a practical guide for interventional cardiologists. Catheter Cardiovasc Interv 2009;73:1–14.
17. Lesko LJ. Personalized medicine: elusive dream or imminent reality? Clin Pharmacol Ther 2007;81:807–16.
18. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119:480–6.

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