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Commentary

Genotyping

One Piece of the Puzzle to Personalize Antiplatelet Therapy

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The loss-of-function hepatic cytochrome P450 (CYP) 2C19*2 allele has been associated with reduced clopidogrel active metabolite generation and higher ex vivo platelet reactivity to adenosine diphosphate. Independently, in post hoc analyses, CYP2C19*2 has been associated with worse clinical outcomes during clopidogrel therapy. The controversy surrounding the diminished effectiveness of clopidogrel in poor metabolizers, those having 2 loss-of-function alleles, has been recently highlighted in the "boxed warning" issued by the U.S. Food and Drug Administration. However, much of the variation in clopidogrel response is not explained by the CYP2C19*2 allele (the most frequent loss-of-function allele), and other factors, both genetic and nongenetic, are likely to be important contributors. High on-treatment platelet reactivity to adenosine diphosphate during clopidogrel therapy is a well-documented predictor of recurrent ischemic events in the percutaneous coronary intervention population. While platelet function is dynamic in individual patients because of the influence of variable external factors, the influence of the CYP2C19*2 allele is intrinsically constant. Thus, it may be reasonable to consider both genotyping and platelet function measurement to assess ischemic risk and to guide antiplatelet therapy. Prospective clinical trials to test new algorithms for optimal personalized antiplatelet therapy are needed to provide the evidence base required for the routine adoption of genotyping into clinical practice. (J Am Coll Cardiol 2010;56: 112–6) © 2010 by the American College of Cardiology Foundation

In this issue of the *Journal*, Damani and Topol (1) propose routine genotyping alone to personalize dual-antiplatelet therapy. Here we summarize what we know and what we should know before using routine genotyping alone for personalized antiplatelet therapy.

What We Know

The current "one size fits all" antiplatelet regimens recommended by the American Heart Association, American College of Cardiology, and European Society of Cardiology guidelines are associated with about 10% recurrent ischemic event rates (2). Multiple studies have clearly demonstrated that platelets play a major role in the genesis of both periprocedural and long-term atherothrombotic events, including myocardial infarction and stent thrombosis (2). Adenosine diphosphate (ADP) is an important secondary agonist released in response to other agonists (thromboxane A_2, collagen, thrombin, and shear) that amplifies platelet activation and aggregation. Persistent activation of the glycoprotein IIb/IIIa receptor and subsequent stable thrombus generation at the site of vessel wall injury is highly dependent on continuous ADP-mediated $P2Y_{12}$ receptor signaling. Therefore, the addition of the $P2Y_{12}$ receptor blocker clopidogrel to aspirin has been associated with a significant reduction in major cardiovascular events in high-risk patients. However, nonresponsiveness and high on-treatment platelet reactivity (HPR) measured by ex vivo assays of platelet function have been overwhelmingly associated with increased ischemic event occurrence in clopidogrel-treated patients (2).

Pharmacokinetic studies indicate that clopidogrel is converted into its active metabolite by hepatic cytochrome P450 (CYP) isoenzymes in a 2-step oxidation process involving primarily CYP2C19, CYP1A2, and CYP2B6 isoenzymes in the first step and CYP2C19, CYP2C9, CYP2B6, and CYP3A4 isoenzymes in the second step. The active metabolite (R130964) covalently binds to the platelet $P2Y_{12}$ receptors to irreversibly inhibit ADP-stimulated platelet aggregation. Both CYP2C19 and CYP3A4 have been suggested as major isoenzymes involved in the metabolic activation of clopidogrel (3).

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Multiple lines of evidence show that clopidogrel response variability is due largely to variability in active metabolite generation (4). There are at least 25 single-nucleotide polymorphisms (SNPs) of the gene encoding the CYP2C19 isoenzyme (5). The most widely analyzed and most frequent SNPs are CYP2C19*2, a G→A mutation in exon 5 producing an aberrant splice site leading to the complete absence of CYP2C19 activity, and *17 (-806C>T), a regulatory region variant that has been associated with increased expression and enzymatic activity. The *2 loss-of-function and *17 gain-of-function alleles are in linkage disequilibrium ($D' = 1$, $r^2 = 0.04$), resulting in 3 observed haplotypes and 6 possible diplotypes, which may be grouped into 3 enzymatic activity phenotypes (6,7) (Fig. 1).

Recently, variation in ADP-stimulated platelet aggregation in response to clopidogrel was evaluated in a genome-wide association study in healthy subjects (6). Remarkably, a cluster of 13 SNPs within and flanking the CYP2C18-2C19-2C9-2C8 cluster on chromosome 10q24 (out of about 400,000 SNPs analyzed genome-wide) was strongly associated with clopidogrel response ($p = 10^{-12}$ to 10^{-7}). Further mapping identified the CYP2C19*2 variant, which accounted for most or all of the 10q24 association signal. In a replication study involving patients undergoing percutaneous coronary intervention, carriers of the CYP2C19*2 allele had higher cardiovascular event rates compared with noncarriers (hazard ratio [HR]: 2.42; $p = 0.02$) (6). Candidate gene studies also support an important role of CYP2C19 reduced-function alleles in clopidogrel nonresponsiveness and adverse clinical outcomes. In healthy volunteers, a 32.4% relative reduction ($p < 0.001$) in plasma exposure to the active clopidogrel metabolite and a relative reduction of approximately 25% in mean platelet aggregation ($p < 0.001$) was observed in carriers of at least 1 CYP2C19 reduced-function allele compared with noncarriers (8). Among patients with acute coronary syndromes undergoing stenting and treated with clopidogrel in the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction 38) study, CYP2C19 reduced-function allele carriers had a higher rate of recurrent ischemic events (HR: 1.53; $p = 0.01$), including stent thrombosis (HR: 3.09; $p = 0.02$), compared with noncarriers (8). Similarly, Sibbing et al. (9) demonstrated that CYP2C19*2 carriers had a significantly higher cumulative 30-day incidence of stent thrombosis compared with CYP2C19 wild-type homozygotes (HR: 3.81; $p < 0.007$). In a collaborative meta-analysis of various clinical trials involving 9,684 patients, Mega et al. (10) recently demonstrated that CYP2C19*2 allele carriers had a higher risk of major adverse clinical event occurrence compared with noncarriers (HR: 1.61; $p < 0.001$). Similarly, risk was greater in heterozygotes compared with wild type (HR: 1.50; $p = 0.016$) and in homozygotes compared with wild type (HR: 1.81; $p = 0.004$) (10).

CYP2C19 genotyping is currently available through a number of commercial laboratories. However, the turnaround time is often on the order of several days. Because a large number of events happen within the first several hours after percutaneous coronary intervention, for personalized antiplatelet therapy to be optimally applied, rapid and accurate point-of-care CYP2C19 genotyping will be neces-

Abbreviations and Acronyms

ADP = adenosine diphosphate
CYP = hepatic cytochrome P450
HPR = high on-treatment platelet reactivity
HR = hazard ratio
SNP = single-nucleotide polymorphism

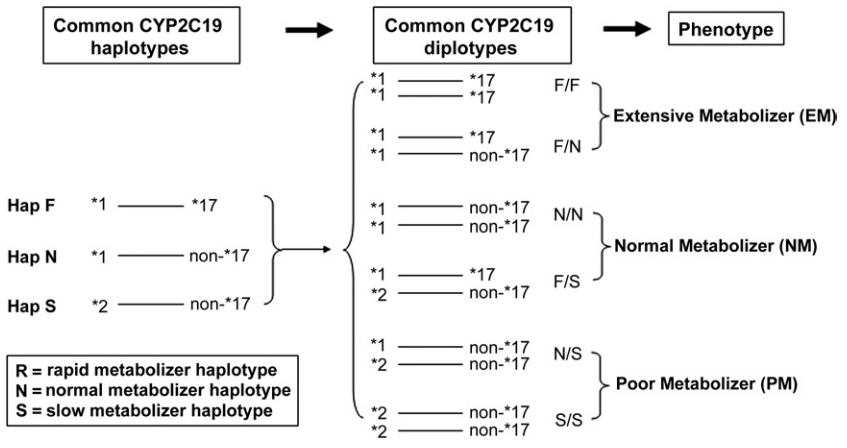

Figure 1 Linkage Disequilibrium and CYP2C19 Haplotypes

Because of linkage disequilibrium between the hepatic cytochrome P450 (CYP) 2C19*2 loss-of-function (slow metabolizer) and *17 gain-of-function (fast metabolizer) variants, only 3 (of 4 possible) haplotypes exist. These 3 haplotypes result in 6 diplotypes, which define 3 main phenotypes: extensive metabolizers, normal metabolizers, and poor metabolizers.

sary. Currently, these assays are used predominantly for research purposes and include the AmpliChip Cyp450 test (Roche Diagnostics GmbH, Mannheim, Germany), Verigene (Nanosphere, Inc., Northbrook, Illinois), and Infinity (AutoGenomics, Inc., Carlsbad, California). These tests can be performed on small amounts of whole blood with a turnaround time of about 3 to 8 h.

What We Should Know

Although Damani and Topol (1) refer to "overwhelming evidence" presented in support of routine, widespread genotyping, as yet, there has not been a single, adequately-powered prospective trial with clinical end points performed to support this premise. It is hypothesized that the *2 allele confers its risk by affecting the pharmacodynamic response to clopidogrel (4). However, no single study has demonstrated a conclusive link between the presence of a loss-of-function genetic polymorphism, suboptimal clopidogrel active metabolite generation (pharmacokinetic measurement), decreased clopidogrel responsiveness (pharmacodynamic measurement), and adverse clinical outcomes.

While most studies show a gene-dose effect, in which CYP2C19*2 homozygotes (approximately 3% to 4% of the general U.S. population) have the worst clopidogrel response and heterozygotes (25% to 30% of the general U.S. population) have intermediate responses between wild-type and *2 homozygotes, a study by Simon et al. (11) suggested that increased risk is limited only to the *2 homozygotes. CYP2C19*2 heterozygotes have 1 normal CYP2C19 allele and maintain partial enzymatic activity, while CYP2C19*2 homozygotes have little or no enzymatic activity (4). Thus, the argument for genotyping may be more persuasive in the case of homozygotes. However, it is unclear how future personalized antiplatelet regimens may differ between those harboring 1 versus 2 CYP2C19*2 alleles.

Because the heritability of clopidogrel response is approximately 70%, and the CYP2C19*2 genotype accounts for only about 12% of clopidogrel response variability (not 50%, as suggested by Damani and Topol [1]), the majority of factors, both genetic and nongenetic, influencing clopidogrel response variability remain unexplained (6). It is likely that several (even many) additional gene variants, both common and rare, exist that once discovered will add to the predictive value of a panel of genetic markers that will include the CYP2C19 genotype. We recently demonstrated that the sensitivity of the *2 carrier state for detecting HPR was only 56% (7). Determination of diplotype status may better identify patients with HPR and associated ischemic risk.

Sibbing et al. (12) demonstrated that CYCP2C19*17 allele carriers had significantly lower ADP-induced platelet aggregation ($p < 0.039$) and a higher risk for bleeding during clopidogrel treatment compared to wild-type carriers ($p = 0.01$). However, platelet function in patients with bleeding was not reported. Whether the CYP2C19*17 allele affects cardiovascular events is less certain. The independent effect of *17 on platelet reactivity during clopidogrel therapy remains unclear (7). Similarly, very little is known about the less common loss-of-function variants (e.g., *3, *4, *5, *6, *7, *8). Greater knowledge of whether these variants (and the diplotypes they produce) affect clopidogrel response will also be critical to optimizing personalized antiplatelet therapy algorithms. Recently, the TT (vs. CT or CC) genotype at rs1045642 of the ABCB1 gene, which encodes a transporter that modulates clopidogrel absorption, has been shown to be associated with clopidogrel response variability by influencing clopidogrel absorption and also with worse clinical outcome (11,13).

In addition to genetics, functional variability in the P450 isoenzyme activity that is influenced by drug–drug interactions also contributes to the clopidogrel response variability. The coadministration of clopidogrel with proton pump inhibitors, lipophilic statins, calcium-channel blockers, caffeine, St. John's wort, smoking, and warfarin, which are metabolized by the CYP2C19, CYP3A4, CYP1A2, and CYP2C9 isoenzymes, has been shown to influence the response to clopidogrel (4,14). How these exogenous modifiers of cytochrome P450 function interact with endogenous genetic modulators of cytochrome P450 function is not known. Furthermore, clopidogrel response may vary with the presence of diabetes as well as the level of glucose control (15) and body mass index (16). Among subjects with diabetes mellitus, clopidogrel response was significantly diminished in the presence of an elevated serum fibrinogen level (17). Although the consequences of these interactions with respect to ischemic event occurrence remain controversial, it is reasonable to consider incorporating these factors into personalized antiplatelet algorithms as well.

Numerous translational research studies have correlated ex vivo measures of platelet function with ischemic event occurrence using multiple $P2Y_{12}$ receptor reactivity assays. A recent consensus has been reached on the definition of HPR to ADP determined by receiver-operating characteristic curve analyses. These cut points of HPR have been associated with adverse ischemic event occurrence, including stent thrombosis: 1) platelet reactivity index >50% by vasodilator-stimulated phosphoprotein phosphorylation analysis; 2) platelet reaction units >235 by VerifyNow $P2Y_{12}$ assay (Accumetrics, Inc., San Diego, California); 3) maximal platelet aggregation >46% in response to 5 μmol/l ADP; and 4) aggregation units over time >468 (in response to ADP) by Multiplate analyzer (Dynabyte Informationssysteme GmbH, Munich, Germany) (18). A recent study with clinical follow-up identified 3 tests of on-treatment platelet reactivity—light transmission aggregometry, VerifyNow $P2Y_{12}$, and the Plateletworks assay (Helena Laboratories Corporation, Beaumont, Texas)—as best correlating with the occurrence of a composite ischemic primary end point to 1 year (19). Interestingly, no correlation between platelet function studies and subsequent bleeding events could be discerned.

Algorithms for Response to Clopidogrel Resistance

Various therapeutic algorithms have been offered (but remain unproven) to ameliorate ischemic risk in patients hyporesponsive or resistant to clopidogrel, including: 1) increasing clopidogrel dose (20); 2) switching to ticlopidine (21); 3) the addition of CYP inducers to enhance clopidogrel conversion (22); 4) the addition of cilostazol (23); 5) periprocedural platelet glycoprotein IIb/IIIa inhibition (24); and 6) novel $P2Y_{12}$ receptor inhibitors such as prasugrel, ticagrelor, and elinogrel (25–27). Although increasing clopidogrel dose may accelerate the time course and enhance the magnitude of subsequent platelet inhibition, despite doses of up to 2,400 mg, an unpredictable approximately 10% of subjects remain unresponsive (20). Similarly, a clopidogrel maintenance dose of 150 g/day will "convert" very few "nonresponders" to "responders" when a platelet reactivity index by vasodilator-stimulated phosphoprotein definition of ≤50% (for response) is used (28). It has been suggested that "tailored treatment" (with clopidogrel) is not the ideal solution for clopidogrel resistance (29). Although periprocedural glycoprotein IIb/IIIa receptor blockade is effective in reducing ischemic events among patients resistant to clopidogrel and/or aspirin (24), long-term outcomes have not been reported. Novel agents provide the greatest promise. Prasugrel, a novel third-generation thienopyridine, provides more effective $P2Y_{12}$ receptor inhibition, which has been ascribed to more rapid, complete, and uniform active metabolite generation (25). Importantly, neither the pharmacokinetic or pharmacodynamic response to prasugrel nor clinical outcomes appear to be adversely influenced by CYP2C19*2 carrier status (25). Clopidogrel-"resistant" patients are invariably responsive to ticagrelor, a novel cyclopentyl triazolopyrimidine nonthienopyridine reversible, direct-acting $P2Y_{12}$ receptor inhibitor. Ticagrelor therapy appears to provide superior inhibition of the $P2Y_{12}$ receptor in both clopidogrel responders and nonresponders and was associated with a very low prevalence of HPR (26). Similarly, elinogrel, a reversible, direct-acting $P2Y_{12}$ receptor inhibitor, significantly reduced aggregation and the portion of subjects with HPR among clopidogrel nonresponders (27). Although Damani and Topol (1) suggest that an unwillingness to perform widespread genotyping "denies . . . patients state-of-the-art care," they offer no guidance as to an appropriate algorithm for response (for either 2C19*2 heterozygotes or homozygotes) and provide no "evidence" as to the relative safety and efficacy of altering therapy in this cohort of patients. This lack of direction regarding appropriate therapy for poor metabolizers on the basis of genotyping mirrors the statement made by the U.S. Food and Drug Administration to "consider use of other antiplatelet medications or alternative dosing strategies for [clopidogrel]." Finally, an appropriate therapeutic response to the presence of CYP2C19*17 (reduce clopidogrel dose) has not been defined.

In a recent study, the influence of both HPR and genotyping on clinical outcomes in a percutaneous coronary intervention cohort was evaluated separately. Although CYP2C19*2 and HPR had comparatively high specificity (72% and 79%), each factor independently identified only 46% of patients with events. Interestingly, 75% of patients with events were identified when both risk factors were combined (30). The latter observation suggests that both genotyping and ex vivo platelet function testing may be more predictive than either alone. This concept makes sense given that the CYP2C19 genotype is invariant and accounts for a constant portion of clopidogrel response variability, while platelet function testing is an integrated measure of many factors, both genetic and nongenetic, and is thus more dynamic in an individual patient. While genotyping assays are straightforward and highly accurate and reproducible, point-of-care platelet aggregation testing platforms are comparatively less accurate because of technical factors.

Finally, we wish to clarify 3 additional points. First, Damani and Topol (1) mention that the relation of genetic polymorphisms to alteration in clopidogrel active metabolite levels was noted in various large-scale clinical investigations involving patients (6,8,11,12,31), but active metabolite levels were analyzed only in healthy volunteers in the study by Mega et al. (8). Second, in the study by Shuldiner et al. (6), in addition to stent thrombosis and cardiovascular death, other events, such as myocardial infarction, ischemic stroke, unplanned target vessel revascularization, unplanned non–target vessel revascularization, hospitalization for coronary ischemia without revascularization, and death secondary to any cardiovascular cause at 1-year follow-up, were also assessed. Third, the proposal by Damani and Topol (1) that ischemic events in the clopidogrel arm of the PLATO (Platelet Inhibition and Patient Outcomes) study may be related to the presence of resistance alleles is speculative and premature, as the results of the genetic substudy of PLATO are not yet available (32).

Conclusions

Recent studies indicate that the CYP2C19 genotype is an important predictor of the laboratory and clinical response to clopidogrel. We share the enthusiasm of Damani and Topol (1) for the promise of genotyping to tailor antiplatelet therapy. Commercially available CYP2C19 genetic testing (and soon point-of-care genetic testing) has now made it possible to use CYP2C19 genotype to "guide" antiplatelet therapy. However, the safety and efficacy of altering therapy in response to genotypic or phenotypic testing are entirely unknown. While neither alone adequately describes the global risk profile of an individual patient treated with clopidogrel, point-of-care platelet function testing to identify HRP combined with CYP2C19 genetic testing may be more effective in identifying high-risk patients for alternative antiplatelet therapies than either alone. Ultimately, prospective randomized clinical trials will be needed to test

specific personalized antiplatelet algorithms to provide the evidence base necessary for widespread adoption into clinical practice.

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Key Words: genotyping ■ antiplatelet therapy ■ CYP2C19*2.