Cost Is Not a Barrier to Implementing Clopidogrel Pharmacogenetics

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Clopidogrel, in combination with aspirin, is widely prescribed to prevent cardiovascular events in patients with an acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI). Clopidogrel requires biotransformation to its active thiol metabolite, which irreversibly binds to the platelet P2Y12 adenosine diphosphate receptor to inhibit platelet activation. Cytochrome P450 (CYP) 2C19 is involved in both steps of the biotransformation process. Deficient CYP2C19 activity secondary to genetic polymorphism results in lower active metabolite levels and reduced inhibition of platelet aggregation with clopidogrel.1–3

The CYP2C19*1/*1 genotype is the wild-type genotype associated with normal enzyme activity and the extensive metabolizer (EM) phenotype. The CYP2C19*2 (c.681G>A) allele is the most common variant leading to loss of CYP2C19 function, with carriers of 1 (*1/*2) or 2 (*2/*2) CYP2C19*2 alleles deemed intermediate metabolizers (IMs) or poor metabolizers (PMs), respectively. On the other hand, the CYP2C19*17 allele confers increased enzyme activity, higher levels of the active clopidogrel metabolite, and the ultrarapid metabolizer (UM) phenotype.4

Numerous studies have documented an increased risk for cardiovascular events after ACS and PCI in clopidogrel-treated patients with the CYP2C19 PM or IM phenotype compared with similarly treated EMs or UMs.2, 3, 5–7 Some of the most convincing data come from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial, in which patients with ACS and planned PCI were randomized to clopidogrel or prasugrel.8 Clopidogrel-treated patients with a loss-of-function CYP2C19 allele (PM or IM phenotype) had a significantly higher risk for the composite end point of death from cardiovascular causes, myocardial infarction, or stroke, and a 3-fold increase in the risk of stent thrombosis compared with noncarriers.3

In 2010, the clopidogrel labeling was revised to include a boxed warning about reduced drug effectiveness in CYP2C19 PMs.9 The labeling advises health care professionals that genotyping is available and that alternative strategies should be considered in patients found to be PMs. Prasugrel and ticagrelor are third-generation P2Y12 receptor inhibitors that have a more rapid onset of action and are superior in preventing cardiovascular events compared with clopidogrel, but at the cost of increased non-coronary artery bypass graft-related bleeding.8, 10–12 Neither prasugrel or ticagrelor is affected by CYP2C19 loss-of-function genotype; thus, either may be considered as an alternative to clopidogrel in individuals with a CYP2C19 loss-of-function allele.13, 14 However, prasugrel is contraindicated in patients with a history of transient ischemic attack or stroke, and ticagrelor is more expensive than clopidogrel and requires twice-daily dosing, somewhat limiting use of these agents.15 In addition, clopidogrel is expected to be available as a generic formulation in mid- to late-2012, which could significantly widen the cost differential among antiplatelet agents.
The Evidence Gap

For both practitioners and payers, it may be unclear exactly how to balance the differences in clinical effectiveness and safety together with cost implications when choosing 1 antiplatelet drug vs another for patients with an ACS or those undergoing PCI. Using genotyping to guide selection of antiplatelet therapy has been suggested as one means of sorting through these prescribing complexities. However, this has not been widely implemented in clinical practice despite the data supporting reduced clopidogrel effectiveness in CYP2C19 PMs and IMs, and the revised clopidogrel labeling. An obstacle to clinical implementation of pharmacogenomics is the need to establish clinical utility and cost-effectiveness of a genotype-guided therapeutic approach. Trials addressing the clinical utility of genotype-guided antiplatelet therapy are under way. The data presented by Reese et al. in this issue of Pharmacotherapy provide evidence of the cost-effectiveness of such an approach.17

New Findings

Reese et al. conducted a model-based, cost-effectiveness study comparing those receiving genotype-guided antiplatelet therapy with clopidogrel or prasugrel (arm 1) with either those receiving clopidogrel regardless of genotype (arm 2) or those receiving prasugrel regardless of genotype (arm 3).17 Patients included in the model were assumed to have ACS and scheduled PCI. The decision model incorporated the probability that a patient in the genotype-guided therapy arm would have a loss-of-function allele (i.e., IM or PM phenotype), in which case, the patient was assumed to receive prasugrel, whereas those deemed EMs or UMs were assumed to receive clopidogrel.

All 3 arms of the model incorporated the probability that patients would experience a cardiovascular event (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke), a noncardiovascular event (major or minor bleeding), or no event while receiving antiplatelet therapy during the 15 months after the scheduled PCI. The probabilities for these events were obtained from the TRITON-TIMI 38 trial, in which prasugrel was shown to be superior to clopidogrel in preventing adverse cardiovascular events in patients with ACS and planned PCI.8 The probability of the genotype result (i.e., genotype frequencies) was obtained from the TRITON-TIMI 38 genetic substudy.13 Also included in the model were the cost of hospitalization and PCI, the cost of genotyping (only for the genotype arm), the cost of antiplatelet therapy for 15 months, and the cost associated with each cardiovascular or noncardiovascular event. The perspective was that of a third-party payer (e.g., an insurance company), and cost-effectiveness was expressed as the incremental cost for each event avoided in the genotype-guided therapy arm vs the other 2 arms, reported as the incremental cost-effectiveness ratio (ICER).

The investigators performed the analysis by simulating patients in each arm of the model (10,000 patients in each arm) to determine the number of cardiovascular events avoided and then the number of patients who would need to be genotyped in order to prevent the occurrence of 1 cardiovascular event in the other arms (e.g., number needed to treat). Keeping with contemporary practices in decision modeling, probabilistic sensitivity analysis was used to test the robustness of the model results over a range of probability estimates from the literature. Cost-effectiveness acceptability curves (CEACs) were created using Monte Carlo simulations to present the probability that genotype-guided therapy is cost-effective compared with prescribing either clopidogrel or prasugrel for all patients over a range of “willingness-to-pay” (WTP) values, which is explained further below.

The authors found that genotype-guided antiplatelet therapy was more cost-effective than prescribing either clopidogrel or prasugrel treatment for all patients. That is, when one considers the cost of genotyping along with the cost of antiplatelet drug, and other costs associated with treatment (including costs associated with cardiovascular events and bleeding), the genotype-guided approach is both less expensive and more effective. The ICER for the comparison of
genotype-guided antiplatelet therapy with clopidogrel was −$6760, and the ICER for genotyping compared with prasugrel was −$11,710. In pharmacoeconomic terms, when one option is less expensive and more effective, it is considered “dominant” compared with the alternative. The cost-effectiveness of genotype-guided therapy was largely driven by the fact that, among 10,000 patients, this strategy produced 450 fewer cardiovascular events compared with clopidogrel treatment for all and 350 fewer events compared with prasugrel treatment for all. Thus, the number needed to treat with genotype-guided therapy (or essentially the number needed to genotype) to avoid one event compared with clopidogrel and prasugrel was 23 and 30, respectively.

The probabilistic sensitivity analyses conducted by the investigators showed the result to be consistent over a wide range of values. This analysis produced CEACs expressed as the WTP (or cost incurred by the payer) to avoid one event. Essentially, the CEACs showed the proportion of time that genotype-guided therapy is cost-effective compared with prescribing either clopidogrel or prasugrel for all patients at each level of WTP, with the “threshold” being defined as the WTP value where the payer could be 95% certain to avoid one event. For the comparison with clopidogrel, the threshold was $9670, and for prasugrel, it was $22,500. The WTP threshold can be interpreted as the cost of each cardiovascular event avoided above which the third-party decision maker would choose to select the alternative (e.g., clopidogrel or prasugrel) instead of the genotype-guided therapy. These are important values from the standpoint of the third-party payer who may be making policy decisions for large groups of patients. The values suggest that the decision to use genotype-guided therapy is not likely to change unless there are large changes in the costs incorporated in the model.

An example of such a change in costs might be the introduction of generic clopidogrel. In order to anticipate this, the authors conducted a sensitivity analysis where the brand-name drug cost for clopidogrel was substituted with an assumed generic cost of $1/day. They then repeated all of their analyses. Under this scenario, genotype-guided therapy was less cost-effective than generic clopidogrel (although it remained more cost-effective than prasugrel). In fact, the option of prescribing generic clopidogrel for all patients dominated the genotype-guided therapy (ICER $2300). The WTP threshold for this analysis was $3700, meaning that the decision to prescribe generic clopidogrel for all patients instead of genotype-guided therapy would not change until the cost of each event avoided exceeded $3700. It should be noted that this threshold is relatively low; thus, minor changes in the costs or other assumptions used in the analysis might result in a different conclusion.

Unanswered Questions

Reese et al. should be congratulated for conducting one of the first studies to examine the cost-effectiveness of genotype-guided antiplatelet therapy. Although their findings support such an approach, some clinical and economic questions remain and require consideration. First, the authors assumed event rates similar to those in TRITON-TIMI 38, in which the majority of patients (94%) had an ACS and underwent intracoronary stenting (i.e., high-risk patients). Even though the authors examined the most relevant population in terms of cardiovascular risk, their results may not be generalizable to patients at lower risk because event probabilities will be different.

A related issue is that although a majority of patients taking antiplatelet agents are older than 65 years, the TRITON-TIMI 38 study (on which this model was based) included younger patients (median age 61 years). Older patients may have different risks for cardiovascular and noncardiovascular events than were used in this study. Therefore these results may not be applicable to that population.

Further, over 90% of TRITON-TIMI 38 participants were Caucasian. Approximately 25–30% of Caucasians carry a CYP2C19*2 allele, and 2–4% are PMs. Slightly more African-Americans (35%) and about twice as many Asians (60%) carry a loss-of-function allele. The probabilistic sensitivity analysis adjusted for variation in phenotype frequency. However, the efficacy of prasugrel vs clopidogrel in non-Caucasian patients cannot be determined from the TRITON-TIMI 38 data; thus, the cost-effectiveness of genotype-guided therapy in non-Caucasians is unclear.

Whereas the cost-effectiveness study focused solely on the CYP2C19 genotype, other genotypes have been implicated in clopidogrel responsiveness, with ABCB1 3435C>T being the mostly notable. Additional genotyping may
incur additional costs; however, it may also improve the ability to predict clopidogrel responsiveness. One group of researchers recently demonstrated that, among clopidogrel-treated patients, a combined model of clinical and genetic factors (including CYP2C19 and ABCB1 genotypes) was more predictive of risk for early stent thrombosis compared with clinical-only and genotype-only models. Use of such multifactorial models may allow for refinement of risk with clopidogrel and further improve the cost-effectiveness of a pharmacogenetic approach to antiplatelet therapy.

Other important clinical questions are when to genotype and who should be genotyped. The question of when to genotype is particularly relevant for patients with ACS or undergoing PCI, in whom an antiplatelet loading dose is warranted. Patients with a loss-of-function genotype CYP2C19 genotype do not obtain sufficient concentrations of the active clopidogrel metabolite with a standard loading dose and, presumably, would derive greater protection against acute coronary events with an alternative antiplatelet strategy. Rapid or point-of-care genotyping would be required to identify these patients before PCI. In the absence of such, one approach would be to give a loading dose of either prasugrel or ticagrelor to all patients. Then, based on evidence that clopidogrel and prasugrel provide similar protection against cardiovascular events in the absence of a CYP2C19 loss-of-function genotype, patients later genotyped and found to be EMs or UMIs could have their antiplatelet therapy transitioned to clopidogrel. This approach would provide rapid and effective platelet inhibition acutely, and then allow for use of the most cost-effective long-term therapy. As far as who should be genotyped, the National Institutes of Health–supported Clinical Pharmacogenetics Implementation Consortium (CPIC) suggests 1 of 2 approaches: genotype all patients who suffer an ACS or undergo PCI, or genotype only moderate- to-high-risk patients, including those with a history of stent thrombosis, diabetes mellitus, renal insufficiency, or high-risk coronary angiographic features. Consistent with the approach we outline above, standard-dose clopidogrel is recommended in patients without a CYP2C19 loss-of-function allele, whereas substitution of prasugrel or ticagrelor is a recommended strategy for IMs or PMs.

Several economic questions also remain unanswered. Although the study conducted several types of sensitivity analyses, including presentation of CEACs, some basic questions that practitioners and payers are likely to contemplate remain unaddressed. For example, the study conducted by Reese et al. provided results for a scenario of generic clopidogrel at $1/day, but the actual price of generic clopidogrel may be different. Therefore it would be better to know the clopidogrel price threshold at which a different decision would be made (i.e., how expensive does generic clopidogrel have to be for genotype-guided therapy to be the preferred option?) The same is true for the price of prasugrel, which may change in the future with increased competition from generic clopidogrel, ticagrelor, or other new antiplatelet agents. Finally, although ticagrelor was not on the market at the time this study was initiated, it is available now and obviously needs to be part of the clinical decision.

It is also important to highlight that the perspective of this study was that of the third-party payer, and as a result, only direct medical costs were included in the analysis. If the study were conducted from a patient or societal perspective, then indirect costs, such as lost productivity or earnings from work after a cardiovascular or non-cardiovascular event, would have been included. Inclusion of indirect costs would likely make the genotype-guided therapy option even more cost-effective because these costs are reduced when events are avoided, and although this would not change the results of the main analysis (where genotype-guided therapy was the best option), it might change the results of the analysis that includes generic clopidogrel, particularly considering that the WTP threshold for the option involving the change from generic clopidogrel for all patients to the option of genotype-guided therapy for all patients was relatively low.

Despite these remaining questions, this is an important study in that it is one of the first to document that genotyped-guided pharmacotherapy can be both more clinically effective and less expensive than traditional therapy. This has important implications for pharmacists who could play an integral role in prescribing decisions based on personal genetic information. Clinicians at Vanderbilt University recently announced efforts to genotype all potential clopidogrel candidates for CYP2C19 loss-of-function alleles. The genetic data are imbedded in the electronic medical record so that, in the event that a patient is prescribed clopidogrel, the genetic information is available for the clinician to consider. Other health care centers may follow suit. In fact, it is...
conceivable that patients may eventually be broadly genotyped a priori for multiple genotypes with implications for multiple drugs. This would essentially eliminate the cost of genotyping at the time of drug prescribing, since this cost would already be incurred, and eliminate the questions of when to genotype and who should be genotyped, further improving the cost-effectiveness and utility of genotype-guided therapy.

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