Financial Analysis of *CYP2C19* Genotyping in Patients Receiving Dual Antiplatelet Therapy Following Acute Coronary Syndrome and Percutaneous Coronary Intervention

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ABSTRACT

BACKGROUND: Dual antiplatelet therapy is an established standard of care for patients with acute coronary syndrome (ACS) to reduce thrombotic risk. Reduced *CYP2C19* activity impairs clopidogrel bio-activation and increases risk of adverse clinical outcomes. Patients with poor and intermediate *CYP2C19* metabolizers treated with clopidogrel incur higher cardiovascular event rates, including myocardial infarction, stroke, and stent thrombosis, following ACS than patients with normal *CYP2C19* function. Tests are available to identify the *CYP2C19* genotype and can be used to support individualization of antiplatelet therapy.

OBJECTIVE: To estimate the financial impact of *CYP2C19* genotyping in a theoretical cohort of 1,000 patients with ACS, who received percutaneous coronary intervention and coronary stent implantation and were treated with clopidogrel, prasugrel, or ticagrelor in a managed care setting.

METHODS: Differences in overall and average cost per patient were estimated based on the rate of *CYP2C19* genotyping in a theoretical cohort of 1,000 patients. Sensitivity analysis was carried out for varying costs, adherence, and the percentage of patients treated according to genotyping results. All clinical event costs were reported in terms of 2012 U.S. dollars. The budget impact analysis used published event rates from primary literature to estimate costs of events analysis for 3 different scenarios: Scenario A, no *CYP2C19* genotyping; Scenario B, 50% of patients received *CYP2C19* genotyping with appropriate treatment based on genotype; and Scenario C, 100% of patients received *CYP2C19* genotyping with appropriate treatment based on genotype.

RESULTS: According to this model, there was no change in the market share for the 3 antiplatelet agents in Scenario A. Initial market share for clopidogrel, prasugrel, and ticagrelor was 93%, 5%, and 2%, respectively; however, use of *CYP2C19* genotyping is expected to shift market share from clopidogrel to either prasugrel or ticagrelor. In Scenario B, where 50% of the patients received genotyping, clopidogrel market share was reduced to 83%, while prasugrel increased to 12.1% and ticagrelor increased to 4.9%. In Scenario C, where all patients received genotyping, clopidogrel market share was reduced to 73%, prasugrel increased to 19.3%, and ticagrelor increased to 7.7%. Total estimated cost differences when all possible patients were genotyped included annual savings of roughly $444,852.

CONCLUSIONS: Important financial benefits may be realized through use of genotype-guided antiplatelet therapy to reserve prasugrel or ticagrelor use for patients with reduced *CYP2C19* activity to avoid costs associated with adverse cardiac events.

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What is already known about this subject

- Despite demonstrated clinical utility for *CYP2C19* genotyping in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention, broad implementation of such pharmacogenetic testing, particularly outside of academic medical centers, has not occurred.
- Lack of uniform reimbursement for pharmacogenetic testing is a barrier to widespread use. While several published studies suggest the cost-effectiveness of *CYP2C19* genotyping for individualizing antiplatelet therapy, many health systems struggle to assess and develop business cases that support implementation.

What this study adds

- Important financial benefits may be realized by using a genotype-guided approach to reserve prasugrel or ticagrelor use for *CYP2C19* poor and intermediate metabolizers.
- Financial benefit and clinical utility of *CYP2C19* genotyping support clinical implementation across different health care delivery systems.

The field of pharmacogenomics encompasses a growing knowledge base linking genetic variation to drug disposition and response. Yet, despite the fact that the U.S. Food and Drug Administration (FDA) began incorporating genetic information into drug labels in 2007, clinical implementation outside of academic medical centers remains largely absent.[1,2] While completion of the Human Genome Project raised expectations that predicting response to drug therapy is now possible for many patients, debate continues on whether pharmacogenomic testing should be routinely used. Realistic application of genomic technologies to clinical practice requires several steps, including (a) discovery and validation of pharmacogenomic markers in well-designed studies; (b) replication of drug-gene associations and demonstration of utility in at-risk patients; and (c) assessment of the clinical and financial impact of pharmacogenomic testing.

Although clopidogrel is the most frequently prescribed antiplatelet agent, mounting evidence suggests that alternative agents could be prescribed for certain patients, such as

CYP2C19 poor metabolizers.[1,3-6] Although polymorphisms in several genes coding for drug metabolizing enzymes or transport proteins for clopidogrel (e.g., *PON1, ABCB1, CYP1A2, CYP2B6, CYP2C9, CYP3A4/5,* and *CYP2C19*) have been associated with interindividual variability in clopidogrel response, available data for the impact of *CYP2C19* genetic variation in patients with cardiovascular disease receiving clopidogrel arguably remains compelling and actionable information for clinicians.[6] Furthermore, in March 2010, the FDA released a black box warning, stating that the "effectiveness of clopidogrel depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally *CYP2C19*. Tests are available to identify a patient's *CYP2C19* genotype and can be used as an aid in determining therapeutic strategy."[7]

Since 2010, 2 meta-analyses reviewed available studies for major adverse cardiovascular events in patients who received clopidogrel for all cardiovascular indications (e.g., medical and invasive management of coronary artery disease) stratified according to *CYP2C19* genotype.[3,5] Findings suggested that clopidogrel use in *CYP2C19* poor metabolizers (e.g., homozygous for *CYP2C19*2*) and *CYP2C19* intermediate metabolizers (e.g., heterozygous for *CYP2C19*2*) was associated with significantly increased risk for adverse cardiac events, particularly stent thrombosis.[3,5] Despite the demonstrated association between the *CYP2C19* genotype and improved clinical outcomes from antiplatelet therapy use, lingering barriers limit widespread use, including health care provider knowledge gaps, genotyping costs, and lack of uniform reimbursement for pharmacogenomic testing.[8]

Lack of uniform coverage and reimbursement for pharmacogenetic testing is another significant barrier to clinical implementation along with cost-effectiveness of genotyping. While several large organizations (e.g., the Personalized Medicine Coalition) continue to advocate for this testing, it is uncertain whether the current payer systems are ideally prepared to assess clinical utility for pharmacogenomic applications or next-generation sequencing.[9]

Several published studies have evaluated the cost-effectiveness of *CYP2C19* genotyping for individualized antiplatelet therapy; however, opportunities to demonstrate favorable economic impact in different types of health systems exist.[8,10,11] A recent investigation by Kazi et al. (2014) evaluated the cost-effectiveness of *CYP2C19* genotype-guided antiplatelet therapy for patients with acute coronary syndrome (ACS) using a Markov model to evaluate 5 possible scenarios: (1) using empiric clopidogrel, (2) using empiric prasugrel, (3) using empiric ticagrelor, (4) switching from clopidogrel to prasugrel based on *CYP2C19* genotype, and (5) switching from clopidogrel to ticagrelor based upon *CYP2C19* genotype.[8] Based on a cohort of 100,000 patients with ACS who underwent percutaneous coronary intervention (PCI) and received at least 1 drug-eluting stent, the results suggested that *CYP2C19*

genotype-guided therapy was the most cost-effective strategy provided the cost of genotyping did not exceed $358 based on a willingness-to-pay threshold of $50,000 per quality-adjusted life-year.[8] Additional cost-effectiveness analyses support that *CYP2C19* genotype-guided therapy has economic benefits resulting from savings because of prevention of avoidable adverse cardiac events.[8,10,11] Although cost-effectiveness of *CYP2C19* genotype-guided antiplatelet therapy has been investigated, an opportunity to predict economic impact within managed care organizations remains. The objective of this investigation was to model the financial impact of *CYP2C19* genotyping in ACS patients undergoing PCI and treated with clopidogrel, prasugrel, or ticagrelor in addition to aspirin within such an environment.

◼ Methods

Model Overview

A budget impact analysis was conducted over a 1-year time horizon using overall and average cost per patient modeling based on the rate of *CYP2C19* genotyping in a theoretical 1,000 patient cohort. This model assumed all patients suffered ACS and underwent PCI with coronary stent implantation and received dual antiplatelet therapy for 1 year following PCI and reflects methodology used in other published analyses.[10,11] This analysis was intentionally modeled from the payer perspective to practically demonstrate the magnitude of the financial impact from *CYP2C19* genotype-guided antiplatelet therapy.

Model Structure and Input Data

This model identified patients likely to be hyporesponsive to clopidogrel and the possible cost difference if the *CYP2C19* genotype was obtained prior to initiation of dual antiplatelet therapy. Approximately 27% of patients had predicted phenotypes of intermediate (e.g., *CYP2C19 *1/*2*) or poor metabolizer status (e.g., *CYP2C19 *2/*2*), while 73% were predicted to be ultrarapid (e.g., *CYP2C19 *17/*17* or *1/*17*) or extensive metabolizers (e.g., *CYP2C19 *1/*1*) based on published estimates.[12] The analysis adjudicated patients with 1 loss-of-function allele and 1 gain-of-function allele into ultrarapid or extensive metabolizers because no change in treatment is recommended based on the presence of a gain-of-function allele (i.e., *CYP2C19 *17*).

Based on market share rates from a large administrative claims database, the model assumed that market shares for clopidogrel, prasugrel, and ticagrelor were 93%, 5%, and 2%, respectively. Additionally, the model assumed rate and cost for cardiovascular events based on published literature estimates. Specifically, patients receiving clopidogrel have the highest probability of nonfatal myocardial infarction (MI) overall but the lowest probability of cardiovascular death (CVD). Poor metabolizers for *CYP2C19* had a predicted 3-fold increase in nonfatal stroke.[4] Patients receiving prasugrel have a decreased

TABLE 1	Total Estimated Annual Costs of Clinical Outcomes and Antiplatelet Treatment

Outcome/Drug/Procedure	Estimated Costs ($)[a]
Nonfatal MI	26,086
Nonfatal stroke	28,053
CVD	22,267
Nonfatal bleeding	24,829
Fatal bleeding	12,562
Clopidogrel	0.50/day
Prasugrel	8.00/day
Ticagrelor	8.71/day
CYP2C19 genotyping	315

[a]*Estimated costs are based on 2012 costs for events,[12] 2013 Average Wholesale Price (AWP), and market-based CYP2C19 genotyping cost estimate.*
CVD = cardiovascular death; MI = myocardial infarction.

TABLE 2	Budget Impact for 3 Clinical Scenarios

	Scenario A ($)[a]	Scenario B ($)[b]	Scenario C ($)[c]
Total costs	8,866,274	8,643,848	8,421,422
Cost per patient	8,866	8,644	8,421
CVD	75	65	55
Nonfatal MI	229	213	197
Nonfatal bleeding	19	23	26

[a]*No patients received CYP2C19 genotyping.*
[b]*50% of patients received CYP2C19 genotyping.*
[c]*100% of patients received CYP2C19 genotyping.*
CVD = cardiovascular death; MI = myocardial infarction.

TABLE 3	Annual Cost Difference Between Scenarios A, B, and C

	Cost Difference Between Scenarios A and B ($)	Cost Difference Between Scenarios A and C ($)
Total costs	222,426	444,852
Cost per patient	222	445
CVD	10	20
Nonfatal MI	16	32
Nonfatal bleeding	4	7

CVD = cardiovascular death; MI = myocardial infarction.

probability of nonfatal stroke and nonfatal MI; however, they have an increased probability of CVD and nonfatal bleeding. Poor and intermediate *CYP2C19* metabolizers taking prasugrel have a lower probability of nonfatal MI and nonfatal bleeding.[13] Ticagrelor has the lowest rates of nonfatal MI but the highest probability of CVD and death from bleeding. Patients on ticagrelor have the same probability of events regardless of *CYP2C19* metabolism.[14] The probability for each outcome identified was used from previous trials that compared antiplatelet regimens.[4,13,14]

Costs of adverse events, including nonfatal MI, stroke (transient ischemic attack and cerebral vascular accident), bleeds, and CVD were estimated using mean national Medicare reimbursement rates for the corresponding diagnosis-related group code (Table 1).[15] Costs from nonfatal bleeding events were estimated using Medicare reimbursement for inpatient treatment of gastrointestinal hemorrhage.[16] All costs were varied in sensitivity analyses and inflated to 2012 U.S. dollars. Costs for antiplatelet drugs were described in terms of estimated 2012 wholesale drug costs available to a large managed care organization. The model assumed 80% adherence to antiplatelet medications for patients based on previous data.[17] The predicted cost of *CYP2C19* genotyping was set at $315 based on average cost.[8] Total cost for each therapy option was calculated by multiplying the number of patients, the number of adverse events, and cost of the adverse events. This was calculated separately for ultrarapid/extensive metabolizer patients and intermediate/poor metabolizer patients. The results, the cost of the specific therapy, and the cost of genotyping were added together for a total cost per therapy option. The costs included in the analysis were not discounted or adjusted for current market price.

This budget impact analysis explored 3 scenarios (Table 2). Scenario A assumed that none of the patients were genotyped and were allocated to treatment based on current market share of each antiplatelet agent. Scenario B assumed that 50% of patients received *CYP2C19* genotype-guided antiplatelet therapy based on previous published estimates of genotype frequency. Scenario C assumed all patients received *CYP2C19* genotype-guided antiplatelet therapy. Patients who had *CYP2C19* intermediate/poor metabolizing phenotypes and were allocated to clopidogrel were reassigned to either prasugrel or ticagrelor, maintaining the starting market share ratio.

■ Results

In Scenario A (assumes no patients received *CYP2C19* genotyping), there is no change in market share for the 3 different antiplatelet agents. In Scenario B (where 50% of patients received *CYP2C19* genotyping), clopidogrel market share fell to 83%; prasugrel market share increased to 12.1%; and ticagrelor market share increased to 4.9%. In Scenario C (all patients received *CYP2C19* genotyping), clopidogrel market share fell to 73%; prasugrel increased to 19.3%; and ticagrelor increased to 7.7%. The cost and event differences between Scenario A and Scenario B are shown in Table 3. The total cost difference favors Scenario B with annual cost savings of $222,426. Table 3 also compares costs and event differences between Scenario A and Scenario C. When all possible patients are genotyped, these numbers double, saving $444,852 annually.

A sensitivity analysis was conducted to test the robustness of this model and suggested that varying all costs, adherence to therapy, and *CYP2C19* genotyping rates reduced overall costs,

decreased mortality, and increased nonfatal bleeding. Overall, adverse events and associated costs had the largest impact on the results rather than medication or *CYP2C19* genotyping costs.

■ Discussion

The well-characterized drug-gene interaction between clopidogrel and *CYP2C19* represents a clinically significant pharmacogenetic application. Published Clinical Pharmacogenetics Implementation Consortium guidelines provide evidence-based recommendations for antiplatelet drug selection based upon *CYP2C19* genotype, supporting health systems engaged in clinical implementation of pharmacogenetic testing.[6] Despite evidence demonstrating clinical utility for *CYP2C19* genotyping in patients with ACS undergoing PCI, routine clinical use of *CYP2C19* genotyping lags behind. One lingering barrier is the relative lack of evidence for economic viability of genotyping, particularly across health systems other than academic medical centers, despite published examples demonstrating feasibility of clinical pharmacogenomics implementation.

In the point-of-care genetic testing for personalization of antiplatelet treatment study, patients who were undergoing PCI were randomized to receive *CYP2C19* genotype-guided antiplatelet therapy using a point-of-care device able to rapidly return results. Importantly, this study demonstrated that it was feasible to use a targeted genotyping approach within the cardiac catheterization laboratory to individualize therapy.[18] Another small study conducted in a community pharmacy setting by Ferreri et al. (2014) demonstrated the feasibility of providing *CYP2C19* genotyping for patients prescribed clopidogrel along with patient counseling by a pharmacist.[19]

Despite this demonstrated feasibility, only a handful of institutions have successfully implemented and documented clinical implementation of pharmacogenomic testing, using a preemptive genotyping approach where data for multiple pharmacogenes are acquired at the same time and electronically stored for future use.[20] This approach enables decreased individual genotype costs and development of advanced clinical decision support tools for use by frontline pharmacists and other clinicians (similar to, but more advanced than, drug allergy or drug-drug interaction information). In this paradigm, medication order entry automatically triggers a search for relevant drug-gene interactions for the patient; if clinically actionable variants are identified, the system guides the clinician toward appropriate individualized therapy. A particularly appealing feature of this preemptive approach is that testing can be multiplexed, assaying hundreds to thousands of genetic variants at a time. This genetic information can be reused as other drugs are prescribed over a lifetime and as the knowledge base of drug-gene interactions grows.

Additional approaches for demonstrating cost-effectiveness of genotype-guided therapy range from a clinical trial comparing per-patient costs for specific clinical outcomes between genotype-based versus standard regimens or a decision model-based study (i.e., one that uses a simulated patient cohort).[21] Regardless of the specific approach used, the economic impact and cost-effectiveness of pharmacogenetic screening may be affected by different variables. To illustrate this point, 2 studies utilized modeling techniques with simulated patient cohorts to evaluate potential clinical and economic outcomes for genotype-guided warfarin dosing. While the relatively high cost of a *CYP2C9* and *VKORC1* bundled test ($326 to $570) resulted in only modest improvements (quality-adjusted life-years, survival rates, and total adverse rates), investigators also suggested that improvements in the cost-effectiveness can be achieved through further cost reduction of the genotyping test and utilizing a genotype-guided warfarin dosing algorithm in outliers (patients with out-of-range international normalized ratios and/or those who are at high risk for hemorrhage).[22,23] Other variables, such as different population prevalence of a specific variant and cost of alternative treatment approaches, would also impact the economic impact analysis. Ultimately, clinical utility and cost-effectiveness cannot solely determine the relative value of pharmacogenetic testing in optimizing drug therapy for individual patients. Rather, they should be used to supplement the best practices currently in place to achieve optimal drug therapy.

Tailoring antiplatelet therapy regimens according to *CYP2C19* genotype can reduce costs associated with preventable adverse outcomes, particularly stent thrombosis related to low or absent *CYP2C19* activity. Stent thrombosis is a rare but serious complication typically resulting in high cost interventions and increased case fatality risk.[24] At the health care provider level, this increased risk, when ignored, can result in adverse consequences for patients and health care delivery systems. For example, in March 2014, the Hawaii attorney general filed suit against makers of branded clopidogrel for a "failure to adequately market that clopidogrel has diminished effectiveness for East Asians or Pacific Islanders."[25]

Limitations

Foremost among the analysis limitations is that published cost estimates were used to determine budget impact of *CYP2C19* genotyping for clopidogrel. We did not compare published cost estimates with real-world health system costs. Second, our analysis relies on published clinical trial outcomes data from randomized clinical trials, which may not be representative of patient populations at various health systems. Third, our analysis does not compare budget impact according to type of coronary stent implanted (i.e., bare metal vs. drug-eluting or next-generation drug-eluting), which may influence the results.[26] Fourth, our analysis does not consider preemptive pharmacogenetic testing but, rather, assumes targeted *CYP2C19* genotyping based upon indication for clopidogrel (i.e., ACS and PCI). Fifth, the simplifying assumptions that

every patient tested is treated appropriately according to the test result and that medication adherence is not adjusted based on adverse events may under- or overestimate the benefits of genotyping. Finally, these estimates reflect the general population but may underrepresent the benefits gained in specific populations with higher *CYP2C19* loss-of-function allele prevalence (e.g., those of Asian descent). This may underestimate the true financial impact of *CYP2C19* genotype-guided therapy, since many pharmacogenomic array-based tests have similar costs to single gene tests; however, arrays provide genetic variant information on hundreds of pharmacogenes (i.e., not just *CYP2C19*).

Conclusions

In a rapidly evolving national health care system, it is increasingly important to assess the potential economic impact of new technology adoption, such as pharmacogenomic testing. This study modeled a budget impact analysis within a managed care setting and may serve as a template for future analyses in other settings.

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