ABSTRACT

Background: Prasugrel is recommended over clopidogrel in poor/intermediate CYP2C19 metabolizers with acute coronary syndrome (ACS) and planned percutaneous coronary intervention (PCI), reducing the risk of ischemic events. CYP2C19 genetic testing can guide antiplatelet therapy in ACS patients.

Objective: The purpose of this study was to evaluate the cost-effectiveness of genotype-guided treatment, compared with prasugrel or generic clopidogrel treatment without genotyping, from the US healthcare provider’s perspective.

Methods: A decision model was developed to project lifetime economic and humanistic burden associated with clinical outcomes (myocardial infarction [MI], stroke and major bleeding) for the three strategies in patients with ACS. Probabilities, costs and age-adjusted quality of life were identified through systematic literature review. Incremental cost-utility ratios (ICURs) were calculated for the treatment strategies, with quality-adjusted life years (QALYs) as the primary effectiveness outcome. Relative risk of developing myocardial infarction and stroke between patients with and without variant CYP2C19 when receiving clopidogrel were estimated to be 1.34 and 3.66, respectively. One-way and probabilistic sensitivity analyses were performed.

Results: Clopidogrel cost USD19,147 and provided 10.03 QALYs versus prasugrel (USD21,425, 10.04 QALYs) and genotype-guided therapy (USD19,231, 10.05 QALYs). The ICUR of genotype-guided therapy compared with clopidogrel was USD4,200. Genotype-guided therapy provided more QALYs at lower costs compared with prasugrel. Results were sensitive to the cost of clopidogrel and relative risk of myocardial infarction and stroke between CYP2C19 variant vs. non-variant. Net monetary benefit curves showed that genotype-guided therapy had at least 70% likelihood of being the most cost-effective alternative at a willingness-to-pay of USD100,000/QALY. In comparison with clopidogrel, prasugrel therapy was more cost-effective with <21% certainty at willingness-to-pay of >USD170,000/QALY.

Conclusions: Our modeling analyses suggest that genotype-guided therapy is a cost-effective strategy in patients with acute coronary syndrome undergoing planned percutaneous coronary intervention.

Keywords: Clopidogrel; Prasugrel; Acute Coronary Syndrome; Polymorphism, Genetic; Genetic Testing; Costs and Cost Analysis; United States

INTRODUCTION

Coronary heart disease is the most common cause of death in the US, responsible for 1 in every 6 deaths in 2010. Every year, approximately 620,000 Americans experience a new incident of myocardial infarction (MI) or coronary heart disease death, and an estimated 295,000 experience a recurrent event. The treatment of these patients can place a substantial financial burden on the US healthcare system. The estimated annual direct and indirect cost for coronary heart disease is approximately USD204.4 billion of which a large portion is due to acute coronary syndrome. Hence, analyses to identify cost-effective treatment options are imperative.

Clopidogrel, in combination with aspirin, is widely accepted as the current standard of treatment and has demonstrated efficacy in preventing atherothrombotic events after the occurrence of acute coronary syndrome, including unstable angina, non-ST-elevation myocardial infarction, and ST-elevation myocardial infarction. Clopidogrel is a prodrug that requires metabolic activation catalyzed by several cytochrome P450 (CYP) isoenzymes. Results of studies that evaluated the association between genetic polymorphism in the CYP2C19 enzyme (at least one of the reduced function allele) and risk of adverse events are inconsistent. Three retrospective observational studies have found an increase in the risk of stent thrombosis among clopidogrel-treated patients with genetic polymorphism (OR range 1.59:5.60). However, other observational studies and substudies of randomized clinical trials have failed to find similar results. Given these inconsistent results, it is prudent to draw conclusions via a meta-analysis of
all published studies. A meta-analysis by Bauer et al. found statistically significant association between genetic polymorphism and stent thrombosis (OR 1.77 95%CI 1.31:2.40) but not composite end point (OR 1.11 95%CI 0.89:1.39).10 However, a more recent meta-analysis that includes more studies has shown that genetic polymorphism increases the risk of composite end point (OR 1.50 95%CI 1.21:1.87), myocardial infarction (OR 1.62 95%CI 1.35:1.95) and ischemic stroke (OR 2.14 95%CI 1.36:3.38).4 The most common reduced-function allele is the CYP2C19*2.11 Approximately 50% of Chinese, 34% of African Americans, 25% of Whites, and 19% of Mexican Americans carry at least 1 copy of the reduced function CYP2C19*2 allele.12 Additionally, about 14% of Chinese, 4% of African Americans, and 2% of Whites are considered poor metabolizers (two variant alleles).12,13

Given the evidence of reduced clopidogrel effectiveness in patients with reduced-function CYP2C19 variants, the US Food and Drug Administration (FDA) issued a black box warning and advised clinicians to consider genetic testing for CYP2C19 as an aid in determining clinical treatment strategy.13 The Current Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines recommend the use of an alternate therapy, such as prasugrel, for CYP2C19 poor metabolizers if no contraindication is present.14 Prasugrel, a newer thienopyridine, is not affected by the CYP2C19 polymorphism.14

Genotype-guided therapy offers a promising approach in individualizing therapeutic options, in which prasugrel is indicated for patients with CYP2C19 reduced-function variants and clopidogrel is reserved for patients with no genetic variation. Two studies evaluated the cost-effectiveness of genotype-guided antiplatelet therapy from a payer's perspective.16,17 Reese et al. found that genotype-guided antiplatelet therapy strategy was dominant (less costly and more effective) compared with treatment with prasugrel for all patients regardless of genotype, and was cost-effective when compared with generic clopidogrel (hypothetical cost of USD1/day). However, the study used number of events avoided (thrombotic plus bleeding) as the unit of effectiveness.17 As thrombotic and bleeding events have a different impact on patient quality of life, the evaluation of this combined endpoint in a cost-effectiveness ratio may be misleading. Lala et al. found genotype-guided therapy to be the dominant strategy for base-case analysis at 15 months.16 However, their study ignored long-term costs associated with outcomes.

The aim of our study was to evaluate the cost-utility of genotype-guided antiplatelet therapy, compared with clopidogrel and prasugrel therapy without genotyping in acute coronary syndrome patients with planned percutaneous coronary intervention (PCI), from a healthcare provider’s perspective.

METHODS

Decision model

A 15-month decision-analysis model was developed using TreeAge Pro 2014 (TreeAge Software Inc., Williamstown, MA) to account for clinical outcomes in patients with moderate-to-high risk acute coronary syndrome and planned PCI.18,19 Both costs and quality-adjusted life years (QALYs) associated with clinical outcomes were evaluated and extrapolated to the patients’ life expectancy (Figure 1). The model was designed to compare prasugrel plus aspirin, clopidogrel plus aspirin, and genotype-guided therapy for patients receiving bare-metal stent or drug-eluting stent. In the genotype-guided therapy arm, patients with CYP2C19 reduced-function polymorphism (at least one of the following reduced-function alleles: *1A, *2A, *3, *4, *5A, *6, *7, *8, *9, *10, *12, *13, *14, *17) were given prasugrel plus aspirin whereas patients without the polymorphism were given clopidogrel plus aspirin.

Outcomes modeled were divided into two periods, immediate hospitalization (first 30 days) and long-term (2nd to 15th month), based on the time frames that most clinical trials reported results. Clinical outcomes modeled included myocardial infarction (nonprocedural and procedural), urgent target vessel revascularization, major bleeding, stroke, death due to bleeding, and death due to other cardiovascular causes. Death was assumed to occur only due to myocardial infarction, ischemic stroke, major bleeding, or other cardiovascular causes like dysrhythmia, cardiogenic shock, hypertension, pulmonary embolism or atherosclerotic vascular disease. Major bleeding not related to coronary artery bypass graft was defined as intracranial, retroperitoneal bleeding or bleeding requiring transfusion of 4 units or more (when decrease in hemoglobin is 5 g/dL or more).20 Incremental cost-utility ratios (ICUR) were calculated as the ratio of the differences in costs and QALYs of two treatment strategies. The ICUR for a more costly treatment was interpreted as the additional cost (relative to the less costly treatment) that would be incurred for a unit gain in QALY. A willingness-to-pay threshold of USD100,000 per additional QALY was used to identify the most cost-effective treatment strategy. In the base case analysis, point estimates obtained via literature review were used to calculate the costs and QALYs associated with each treatment. In addition, the impact of uncertainty associated with point estimates on the ICUR and net monetary benefit was evaluated by sensitivity analyses.

Probabilities

As described above, the model was divided into initial (30-day) and long-term outcomes. In the absence of reported outcomes at 30 days, we estimated that fifty-nine percent of outcomes (myocardial infarction, stroke, cardiovascular death, major bleeding) occurred during the first 30 days from reported Kaplan-Meier curves.19
Patel V, Lin FJ, Ojo O, Rao S, Yu S, Zhan L, Touchette DR. Cost-utility analysis of genotype-guided antiplatelet therapy in patients with moderate-to-high risk acute coronary syndrome and planned percutaneous coronary intervention. Pharmacy Practice 2014 Jul-Sep;12(3):438.

Figure 1. Antiplatelet treatment strategies for ACS patients with planned PCI. Clinical outcomes were modeled for two periods post-index PCI i.e. first 30 days, 2nd-15th month. Only patients who developed myocardial infarction post-index PCI underwent target vessel revascularization.

UA= unstable angina; NSTEMI= non-ST elevation myocardial infarction; STEMI= ST elevation myocardial infarction; PCI= percutaneous coronary intervention; MI= myocardial infarction; ASA= aspirin; TVR= target vessel revascularization; CYP2C19= cytochrome P450 2C19.

* The subtree consisting of stroke, major bleeding and death was repeated for patients without myocardial infarction. Similarly, the subtree consisting of major bleeding and death was repeated for patients without stroke. Death was included as a possible terminal outcome only if the patient had experienced any of the event(s).
Table 1. Values for model probabilities

| Outcome                          | Prasugrel therapy | Clopidogrel therapy |
|----------------------------------|-------------------|---------------------|
|                                  | Base case (95% CI) | Beta distribution parameters | Base case (95% CI) | Beta distribution parameters |
| In patients who received DES     | 0.471 (0.462:0.480) | 5743 6461           | 0.471 (0.462:0.480) | 5743 6461           |
| Nonfatal MI                      | 0.067 (0.061:0.073) | 191 2674            | 0.085 (0.078:0.092) | 245 2633            |
| Fatal stroke                     | 0.003 (0.003:0.003) | 10 2855             | 0.005 (0.004:0.005) | 14 2864             |
| Nonfatal stroke                  | 0.010 (0.008:0.013) | 29 2836             | 0.010 (0.008:0.013) | 29 2849             |
| Fatal stroke                     | 0.001 (0.001:0.001) | 2 2863              | 0.001 (0.001:0.001) | 3 2875              |
| Nonfatal major bleeding*         | 0.010 (0.008:0.012) | 29 2836             | 0.009 (0.007:0.011) | 25 2853             |
| Fatal major bleeding*            | 0.003 (0.002:0.003) | 8 2857              | 0.001 (0.001:0.001) | 3 2875              |
| Other CV death**                 | 0.010 (0.005:0.015) | 29 2817             | 0.013 (0.007:0.020) | 38 2820             |
| Urgent TVR***                    | 0.284 (0.258:0.306) | 57 144              | 0.444 (0.404:0.480) | 115 144              |

| Outcome                          | Prasugrel therapy | Clopidogrel therapy |
|----------------------------------|-------------------|---------------------|
| In patients who received BMS     | 0.529 (0.521:0.538) | 6461 5743           | 0.529 (0.521:0.538) | 6461 5743           |
| Nonfatal MI                      | 0.076 (0.069:0.083) | 247 2990            | 0.096 (0.087:0.102) | 305 2919            |
| Fatal                              | 0.004 (0.003:0.004) | 12 3225             | 0.006 (0.005:0.006) | 18 3206             |
| Nonfatal stroke                   | 0.010 (0.007:0.012) | 32 3205             | 0.010 (0.008:0.012) | 32 3192             |
| Fatal                              | 0.001 (0.001:0.001) | 3 3234              | 0.001 (0.001:0.001) | 3 3221              |
| Nonfatal major bleeding*          | 0.010 (0.008:0.013) | 33 3204             | 0.009 (0.007:0.011) | 28 3196             |
| Fatal major bleeding*             | 0.002 (0.002:0.003) | 8 3229              | 0.001 (0.001:0.001) | 3 3221              |
| Other CV death**                  | 0.021 (0.010:0.031) | 66 1347             | 0.020 (0.010:0.030) | 65 3135             |
| Urgent TVR***                     | 0.375 (0.341:0.404) | 97 162              | 0.300 (0.273:0.324) | 97 226              |

This table summarizes the probabilities of outcomes for 15-month trial period. Probabilities for the first 30 days and 2nd-15th months were separately calculated and entered in the decision model.

DES = drug-eluting stent; BMS = bare-metal stent; CV = cardiovascular; TVR = target revascularization; MI = myocardial infarction.

** Proportion of patients suffering bleeding outcomes for prasugrel vs clopidogrel were calculated using the following information: intracranial hemorrhage (0.3% vs 0.3%); retroperitoneal bleeding (0.3% vs 0.2%); transfusion (0.7% vs 0.5%).

** Proportion of patients who received urgent TVR was conditional on them experiencing MI.

Probability of receiving baseline- or drug-eluting type of stent among both prasugrel and clopidogrel groups was estimated to be 0.5 as the clinical trial data indicated that approximately the same number of patients received either type of stent.21

Probabilities for clinical outcomes (myocardial infarction, urgent target vessel revascularization, major bleeding) were calculated using the following information: intracranial hemorrhage (0.3% vs 0.3%); retroperitoneal bleeding (0.3% vs 0.2%); transfusion (0.7% vs 0.5%).19,22,23

Other CV death** was conditional on shock, hypertension, arrhythmia, thrombosis, and atherosclerotic vascular disease. Probability of death due to MI, stroke and major bleeding was conditional on patient experiencing these events. Therefore, among patients treated with clopidogrel, those with CYP2C19 polymorphism had higher risk of death than those without CYP2C19 polymorphism.

Urgent target vessel revascularization was modeled as a conditional probability with the assumption that only those who develop acute myocardial infarction may undergo urgent target vessel revascularization. Given that only nonfatal myocardial infarction and nonfatal stroke were reported in the study27, we estimated proportion of fatal to total events by combining data from the TRITON-TIMI 38 trial and Cardiovascular and Renal Drugs Advisory Committee of the U.S. Food and Drug Administration.22 Site-specific bleeding proportion was assumed to be the same between clopidogrel and prasugrel.9,12,23 Since bleeding is due to the drug and not the type of stent, we assumed that the risk of bleeding did not change by the type of stent.

Studies have shown that CYP2C19 polymorphism is associated with worse outcomes for patients on clopidogrel therapy,3 but not for prasugrel therapy.15 Rates of MI and stroke were different between patients with and without variant CYP2C19 in the clopidogrel group.2 Relative risk of developing MI and stroke between patients with and without CYP2C19 were estimated to be 1.34 and 3.66, respectively.3,15 The prevalence of CYP2C19 polymorphism varies between races3,4, and thus a weighted average of 30.54% was estimated for the overall patients and used in the model.25
Cost of care

Costs have been expressed as 2011 US dollars (Table 2). Costs were varied between ±50% for one-way sensitivity analyses. Cost estimates have been expressed as 2011 USD.

Life expectancy and quality of life

The Declining Exponential Approximation of Life Expectancy (DEALE) was used to estimate the life expectancy. Age- and complication-adjusted life expectancy was estimated to be 20 years (Table 3). EQ-5D score for 61 years old individuals in the U.S. population was reported to be 0.85. Age-adjusted quality of life (QOL) scores for patients who developed myocardial infarction and intracranial hemorrhage were identified from studies that used the EQ-5D instrument. QOL for stroke patients was obtained from a meta-analysis study that combined scores obtained by direct and indirect methods. Disutilities associated with long-term complications like thrombotic stroke, myocardial infarction and intracranial hemorrhage were calculated as the difference between 0.85 and QOL of patients who developed complications. A conservative QOL of zero was assumed for the duration of inpatient stay (average of 3 days) contributed by the PCI procedure. Disutilities associated with myocardial infarction, stroke, and intracranial hemorrhage were estimated to be 0.15, 0.33 and 0.23, respectively. QALYs beyond the first year were discounted at a 5% rate.

Table 2. Cost estimates

| Outcome | Cost in USD (standard error) | Reference | Notes |
|---------|-----------------------------|-----------|-------|
| Myocardial infarction | | | |
| Hospitalization | 23,524 (3,827) | 18, 19, 30, 42-46 | Cost of MI excludes PCI. Cost of hospitalization had been multiplied by a factor of 1.089 to account for recurrent events. 1.089 is the ratio of number of MI events to the number of patients. |
| Post-discharge cost for 1st year | 19,933 (3,243) | 45, 46 | |
| Cost per year after 1st year | 2,575 (419) | 45, 46 | |
| Urgent target vessel revascularization | | | |
| CABG | 30,332 (354) | 43 | Weighted costs of TVR were calculated for patient subgroups i.e. DES and BMS type of stent during index PCI procedure. Weight applied to the cost of CABG=0.12; weight applied to the cost of BMS/DES=0.88. Weights represent proportion of patients undergoing CABG vs. PCI. |
| BMS as type of PCI | 5,921 (3,375) | 44, 47 | |
| DES as type of PCI | 9,770 (5,569) | 44, 47 | |
| Stroke | | | |
| Hospitalization | 9,650 (2,837) | 46, 48 | Estimate obtained by subtracting hospitalization cost from the first year total cost of USD505,582. |
| Post-discharge cost for 1st year | 40,932 (12,034) | 46, 48, 49 | |
| Cost per year after 1st year | 19,238 (5,656) | 46, 49 | |
| Major bleeding | | | |
| Hospitalization a, b | 8,978 (988) | 20, 48, 50-52 | Hospitalization cost of ICH was subtracted from the first year total cost of ICH=USD72,926 - USD28,120=USD44,806. |
| Post-discharge cost for 1st year | 10,722 (1,180) | 20, 48, 49 | |
| Cost per year after 1st year a, b | 2,304 (253) | 20, 49 | |

Mi= myocardial infarction; BMS= bare-metal stent; DES= drug-eluting stent; CABG= coronary artery bypass graft; PCI= percutaneous coronary intervention; ICH= intracranial hemorrhage.

a All costs inputs were varied between ±50% for one-way sensitivity analyses. Cost estimates have been expressed as 2011 USD.

b Cost of care was not included for patients who developed a fatal event during the first 30 days. Only inpatient costs were considered for retroperitoneal bleeding and transfusion while both inpatient and long-term costs were considered for MI, stroke, and intracranial hemorrhage. 

Weighted costs of TVR were calculated for patient subgroups i.e. DES and BMS type of stent during index PCI procedure. Weight applied to the cost of CABG=0.12; weight applied to the cost of BMS/DES=0.88. Weights represent proportion of patients undergoing CABG vs. PCI.

b We assumed that only ICH incurred post-discharge cost.
Sensitivity analyses

One-way sensitivity analyses were performed on all variables to assess the robustness of results to the uncertainty associated with probabilities, disutilities and costs individually. The purpose of one-way sensitivity analyses was to assess the impact of each variable on the expected cost and QALYs of each treatment. The results were considered to be robust to the uncertainty associated with a variable when the incremental cost-utility ratio (ICUR) did not cross the USD100,000/QALY willingness-to-pay threshold. We have provided the values of variables at which the ICUR crosses this threshold or preference for a therapy changes. Upper and lower limits of 95% confidence intervals were used as ranges for the one-way sensitivity analyses for probabilities, relative risks and disutilities. The prevalence of polymorphism (at least one CYP2C19 reduced-function allele) and cost of genetic test were varied over a broad range (15% to 75% and USD150 to USD900, respectively) due to the potential differences between races. Studies reported costs of complications that were substantially different from each other for a variety of reasons, including differences in patient mix, assessed charges and not costs, duration of follow-up, geographical variation, sample size, and single vs. multiple institution data. Therefore, we used a range of 50% of the original cost in one-way sensitivity analyses. The daily maintenance cost of clopidogrel was varied between 2% and 5%.

As previously mentioned, clopidogrel is a prodrug that is metabolized to its active compound by CYP2C19. When clopidogrel metabolism is reduced, there is a higher risk of thrombosis. Although statistically significant findings were observed in the composite endpoint of death from cardiovascular causes, myocardial infarction, or stroke, Mega et al. found consistent, but not statistically significant differences in the individual endpoints of myocardial infarction or stroke. In addition, there were differences between patients in this genetic substudy and the overall trial. The proportion of patients with STEMI, Caucasians, and females was higher while the proportion of patients with hypercholesterolemia was lower in the genetic substudy compared with the overall trial (P<0.05). Therefore, using one-way sensitivity analyses, we varied the risk of having myocardial infarction or ischemic stroke in those with CYP2C19 polymorphism relative to those without to assess the impact of this important factor on choice of therapy.

Probabilistic sensitivity analyses (multiway) was conducted to assess the overall model variability. The purpose of multiway sensitivity analysis was to assess the impact of all variables on the expected costs and QALYs of treatments simultaneously. All relevant probabilities and utilities were assigned beta distribution while the costs of outcomes were assigned gamma distribution for 2nd order Monte Carlo simulation (10,000 iterations). Results have been presented as net monetary benefit curves. Net monetary benefit curves indicate the probability that a strategy is most cost-effective at various willingness-to-pay thresholds (USD0 - USD500,000/QALY).

RESULTS

Base-case analysis

Clopidogrel (USD19,147, 10.03 QALYs) therapy was the least costly and least effective treatment compared to prasugrel (USD21,426, 10.04 QALYs) and genotype-guided therapy (USD19,231, 10.05 QALYs) across the willingness-to-pay range (USD0 - USD100,000/QALY). The results of the sensitivity analyses are presented in Table 4.

| Strategy                  | Life years | Cost (USD) | QALYs | ∆ Cost (USD) | ∆ QALYs | ICUR (USD) | MB at USD50,000/QALY | MB at USD100,000/QALY |
|---------------------------|------------|------------|-------|--------------|---------|------------|-----------------------|------------------------|
| Clopidogrel               | 19,1204    | 19,147     | 10.03 | -            | -       | -          | $482,353              | $983,853                |
| Genotype-guided therapy   | 19,1326    | 19,231     | 10.05 | 84           | 0.02    | 4,200      | $483,269              | $985,769                |
| Prasugrel                 | 19,1305    | 21,425     | 10.04 | 2,194        | -0.01   | Dominated  | $480,575              | $982,575                |

QALY = quality-adjusted life years; ICUR = incremental cost-utility ratio; MB = monetary benefit; ∆ = incremental.
There was a modest gain in QALYs (Table 4). There was a modest gain in QALYs from the use of genotype-guided therapy. Compared to clopidogrel therapy, genotype-guided therapy increased QALYs by an additional 0.02 QALYs at an increased cost of USD84, resulting in an ICUR of USD4,200 per QALY gained. Prasugrel therapy was more costly and less effective than genotype-guided therapy. The ICUR of prasugrel therapy, when compared with clopidogrel therapy, was USD2,278, resulting in an increase in both QALYs and cost by an additional 0.01 and USD2,278, respectively.

**Sensitivity analyses**

One-way sensitivity analyses showed that the cost-utility of genotype-guided therapy (vs. clopidogrel therapy) was sensitive to the uncertainty associated with the relative risk of developing MI/stroke between patients with and without CYP2C19 polymorphism. However, it was robust to the uncertainty associated with prevalence of CYP2C19 polymorphism, discount rate, all disutilities, probability of myocardial infarction/stroke, and cost of genetic testing. Compared to clopidogrel therapy, genotype-guided therapy was cost-effective when the relative risk was between 1.13-1.40 as ICUR was <USD50,000/QALY and dominated clopidogrel at all relative risks ≥1.40. The ICUR for genotype-guided therapy compared to clopidogrel was >USD50,000/QALY when the relative risk of developing myocardial infarction (CYP2C19 variant vs. non-variant) was <1.10 and <1.02, respectively. Similarly, when the risk of ischemic stroke was varied, relative risk of <1.65 and <0.77 resulted in ICURs of >USD50,000/QALY and >USD100,000/QALY, respectively. The genotype-guided therapy dominated clopidogrel therapy when relative risk of ischemic stroke was ≥4.07. Compared to prasugrel therapy, the cost-utility of genotype-guided therapy was robust to the uncertainty associated with disutilities, costs and probabilities of outcomes. However, the ICUR for genotype-guided therapy increased to >USD50,000/QALY when the cost of clopidogrel was more than USD9.88 per day.

When compared with clopidogrel, the cost-utility of prasugrel therapy was robust to the uncertainty associated with discount rate, all disutilities, and cost of myocardial infarction. Prasugrel therapy was cost-effective only when the prevalence of CYP2C19 polymorphism and cost of clopidogrel was ≥45% and USD3.99 per day, respectively. Prasugrel therapy became attractive (vs. clopidogrel therapy) when the relative risk (CYP2C19 variant...
vs. non-variant) of developing myocardial infarction was ≥ 1.67 as ICUR dropped to <USD100,000/QALY; clopidogrel therapy was dominant or ICUR for prasugrel therapy was >USD100,000/QALY when the relative risk of developing MI was <1.67. Prasugrel therapy was dominant or ICUR was <USD100,000/QALY when the relative risk (CYP2C19 variant vs. non-variant) of developing stroke was ≥ 6.75.

Results from probabilistic sensitivity analyses have been presented as net monetary benefit curves in Figure 3. Considerable variation in ICURs was observed in the ICUR scatter plot for all three comparisons due to small differences in QALYs between the three strategies. Regardless of the willingness-to-pay threshold, genotype-guided therapy had a higher likelihood of being the cost-effective strategy compared to prasugrel therapy. Genotype-guided therapy had >70% likelihood of being the most cost-effective strategy for willingness-to-pay ≥ USD60,000/QALY. For all willingness-to-pay thresholds ≥USD10,000/QALY, genotype-guided therapy had a higher probability (≥0.5) of being cost-effective compared to clopidogrel therapy. In the scenario where genetic testing is not available, clopidogrel therapy is the treatment of choice (vs. prasugrel therapy) due to the higher likelihood of it being cost-effective when willingness-to-pay ≤USD170,000/QALY. The choice of therapy would change at a very high willingness-to-pay (>$USD170,000/QALY) as the probability of clopidogrel being the most cost-effective alternative is less than that of prasugrel.

DISCUSSION

For the base case analysis, our results showed that genotype-guided therapy was cost-effective when compared with clopidogrel, with an ICUR below USD50,000 per QALY. In general, differences in QALYs between the three treatment strategies were minimal. We found that genotype-guided antiplatelet therapy strategy was less costly and more effective than prasugrel therapy. When genetic testing is not an option for clinicians, clopidogrel is likely preferred, as prasugrel is not likely an efficient option with an ICUR of USD227,800 per QALY gained. Multiway sensitivity analysis gave us confidence that genotype-guided antiplatelet therapy would be the preferred option for a wide range of willingness-to-pay per additional QALY values in spite of the uncertainties in point estimates.

To our knowledge, three published studies have looked at the value of genotype-guided antiplatelet therapy, although only one assessed the cost-effectiveness of alternate strategies. Both Reese et al. and Lala et al. evaluated the cost-effectiveness of genotype-guided antiplatelet therapy from a payer’s perspective. Both Reese et al. and Lala et al. found this strategy to be dominant (less costly and more effective) compared with treatment with prasugrel (ICER -USD11,710 per event avoided) or clopidogrel (ICER -USD6,760). When the generic cost of clopidogrel at an estimated USD1/pill was considered, genotyping was still more cost effective than prasugrel (ICER -USD27,160) but less cost savings were realized when compared with clopidogrel (ICER USD2,300 per event avoided) for all patients, regardless of genotype. The interpretation of these results is limited because of the use of a composite outcome (number of events avoided) combining thrombotic and bleeding events. As the average severity and impact on quality of life of thrombotic and bleeding events is considerably different, the composite outcome does not accurately reflect an appropriate weight for each event. Quality of life or utility measures (i.e. QALYs) are a much more appropriate methodology for pooling together both thrombotic and bleeding outcomes. Lala et al. found genotype-guided therapy to be dominant to both prasugrel and clopidogrel at both 15 months and 10 years.
Although similar to our findings, our model found genotype-guided therapy dominated prasugrel, but not clopidogrel therapy. Our study differs from Lala et al. in that Lala et al. did not take into account long-term costs associated with myocardial infarction, stroke and bleeding, major bleeding was defined differently with higher rates of bleeding, and patients with CYP2C19 carriers were given a higher bleeding rate than were non-carriers. Difference in bleeding between carriers and non-carriers administered clopidogrel was found to be similar and not significantly different (hazard ratio=1.01; p=0.98). It is not clear why Lala et al. used a major bleeding rate that was higher in carriers than non-carriers, therefore biasing the analysis towards prasugrel and genotype-guided therapy. Genotype screening of acute coronary syndrome patients undergoing PCI was also evaluated in a risk benefit assessment study by Guzauskas et al. The results showed that the genotype-guided strategy had a greater probability of greater net benefit as compared to prasugrel (+0.03 QALY; 95%CI -0.13:0.24) and clopidogrel (+0.05 QALY; 95%CI -0.02:0.11). Although this study did not intend to evaluate the economic implications on patient outcomes, the findings concur with our study, highlighting the value of genetic testing for guiding antiplatelet therapy.

With regard to the comparison of empirical prasugrel and clopidogrel treatment, our findings are not consistent with the previous studies, which suggested that prasugrel is cost-effective in patients with acute coronary syndrome undergoing PCI. Mahoney et al. evaluated the cost-effectiveness of prasugrel versus clopidogrel from the perspective of the US healthcare system, using actual TRITON-TIMI 38 trial patient-level data subset from eight countries, rather than the overall TRITON-TIMI 38 trial patients. Prasugrel was the dominant strategy in the initial 30 days of treatment, as long as the difference in drug price was less than USD7.67/day. For treatment over the full study duration (median follow-up of 14.7 months), prasugrel (USD5.45/day) had higher medication costs than generic clopidogrel (USD1.00/day) with a difference in acquisition costs of USD996 per person. Prasugrel also increased QALY (difference=0.0955) with a corresponding ICUR of USD10,429 per QALY gained. The study findings were mainly driven by the difference of rehospitalization costs of USD517 per person (favoring prasugrel), which was derived from a study subset of 8 countries participating the TIMI-38 trial, and the risk reduction by prasugrel (absolute risk reduction of 3.6%) in PCI during rehospitalization. While the absolute risk reduction for target vessel revascularization (includes PCI & coronary artery bypass graft) for all patients in the TRITON-TIMI 38 trial has been reported elsewhere as 1.2%, Mahoney et al. could have overestimated the benefits of prasugrel. Furthermore, this study applied the same costs to all survivors beyond 15 months, but not taking into account differences in long-term costs of treating ischemic stroke or intracranial hemorrhage beyond the first 15 months.

Another cost-effectiveness study was conducted by Maukopf et al. from a managed care organization perspective, simply with life expectancy gains as the unit of effectiveness in the analysis. In this analysis, the cost per life year gained, with the use of prasugrel, ranged from USD6,642 to USD13,906, based on the lower cost of generic clopidogrel. As with Mahoney et al., this study did not adequately consider differences in long term cost of care for survivors of ischemic stroke or intracranial hemorrhage. Neither of these studies considered the cost-effectiveness of genotype guided therapy.

We found our study results, however, to be sensitive to the relative risk of developing MI/stroke in clopidogrel-treated patients with and without CYP2C19 polymorphism. Our results indicate that genotype-guided therapy would be a cost-effective approach if the relative risk of developing myocardial infarction (between CYP2C19 polymorphism carrier and non-carrier) is higher than 1.02, with the threshold of ICUR set at USD100,000/QALY. Similarly, genotype-guided management would be cost-effective if the relative risk of developing stroke is higher than 0.77. In a recent meta-analysis by Holmes et al., the overall relative risks of developing myocardial infarction and stroke in CYP2C19 polymorphism carriers are 1.37 (95%CI 1.13:1.65) and 1.98 (95%CI 0.77:5.09), respectively. The relative risk of myocardial infarction associated with CYP2C19 polymorphism in most study populations are above the threshold of 1.02, suggesting that our study results remain robust irrespective of the relative risk for myocardial infarction across different populations. On the other hand, the relative risk of stroke associated with CYP2C19 greatly varies across the limited number of studies with a wide confidence interval that contains the null value, indicating that our findings may be sensitive to the relative risk for stroke in the corresponding study population.

Although clopidogrel was shown to be more cost-effective than prasugrel, its use may be hampered by potential drug-drug interaction (e.g., with proton-pump inhibitors) and delayed onset of action. On the other hand, prasugrel is not without its own limitations, including higher bleeding risk and FDA restrictions on its use. The subgroup analysis of TIMI-38 clinical trial suggests that prasugrel should be contraindicated in patients with a history of stroke or transient ischemic attack and that it appears to be less effective in patients ≥75 years old and those <60 kg. Additionally, prasugrel is only approved for patients with acute coronary syndrome undergoing planned PCI while clopidogrel is approved for recent stroke, myocardial infarction (treated with PCI or medically) and peripheral artery disease. Hence, the choice of medication should be based on physician and patient preferences and characteristics as well as economic considerations.

Our analysis is not without limitations. First, the reliance on TRITON-TIMI 38 study and its substudies as the source of clinical data may limit the generalizability of study results. Our model accounts for events occurring within 15 months of index PCI because no data is available to project the outcomes beyond the study follow-up period. In
addition, given that the vast majority (92%) of the study participants in the TRITON-TIMI 38 trial were Caucasians, there is a concern that the results may not adequately represent the broader population since the prevalence of CYP2C19 polymorphism varies across racial groups. However, one-way sensitivity analysis (clopidogrel vs. genotype-guided therapy) revealed that results are robust to variation in the prevalence of variant genotypes across racial groups. The ICUR for genotype-guided therapy decreased from USD18,254/QALY to -USD4,615/QALY as the prevalence of polymorphism increased from 15% to 75%. Compared with clopidogrel, prasugrel therapy was the most cost-effective strategy only when the prevalence of CYP2C19 polymorphism was ≥45%. We also assumed that the genotyped subgroup of TIMI-38 trial patients who were allocated prasugrel and clopidogrel are representative of the overall study cohort, in terms of response to medication and treatment outcomes.

CONCLUSIONS

Our economic analysis demonstrated that, despite initiation costs, genotype-guided antiplatelet therapy is cost-effective when compared with clopidogrel and dominant when compared with prasugrel. When genetic testing is not available, clopidogrel is a more cost-effective strategy when compared with prasugrel, but the choice should be based on patient characteristics as well as economic considerations.

CONFLICT OF INTEREST

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