Research Article

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Pharmacogenomics

CYP2C19-guided antiplatelet therapy: a cost–effectiveness analysis of 30-day and 1-year outcomes following percutaneous coronary intervention

Aim: Determine whether using *CYP2C19* genotype to optimize antiplatelet therapy selection is cost effective over the initial 30 days and 1-year following percutaneous coronary intervention. **Materials & methods:** A cost–effectiveness analysis compared 30-day and 1-year outcomes and cost across three treatment strategies (universal clopidogrel, universal prasugrel, genotype-guided) in a hypothetical cohort. **Results:** Base-case scenario results at 30 days indicated that the incremental cost per major cardiovascular or bleeding event avoided for genotype-guided treatment was US$8525 and US$42,198 compared with universal clopidogrel and prasugrel, respectively. Probabilistic sensitivity analysis demonstrated that genotype-guided treatment was cost effective over 30 days and 1 year in 62 and 70% of simulations, respectively. **Conclusion:** Implementing a *CYP2C19* genotype-guided approach to antiplatelet therapy could have a positive economic impact by preventing readmissions following percutaneous coronary intervention.

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Keywords: clopidogrel • cost–effectiveness • CYP2C19 • genotype • pharmacogenomics • prasugrel • readmission

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Approximately 600,000 percutaneous coronary interventions (PCI) with intracoronary stent placement are performed annually in the USA in coronary artery disease (CAD) patients [1]. Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is indicated following PCI for stable CAD or an acute coronary syndrome (ACS) event [2–4]. Platelet activation and aggregation play a central role in the pathophysiology of CAD, leading to increased risk of major adverse cardiovascular events (MACE) including death, myocardial infarction, ischemic stroke and stent thrombosis (ST). DAPT is indicated to reduce the risk of thrombotic MACE and ST events, but increases the risk for major and minor bleeding events [4]. Selection of the $P2Y_{12}$ inhibitor is based on clinical factors, such as indication for PCI and risk factors for bleeding, and economic considerations. In the USA, clopidogrel remains the most commonly prescribed $P2Y_{12}$ inhibitor [5,6].

Clopidogrel is a prodrug that requires biotransformation by cytochrome P450 enzymes, specifically CYP2C19, to generate its active metabolite. Loss-of-function (LOF) polymorphisms in *CYP2C19* are common and confer a reduced capacity for clopidogrel bioactivation and platelet inhibition [7]. Retrospective analyses of data from clinical trials and patient registries have demonstrated a higher risk for MACE and ST in clopidogrel-treated patients with one (intermediate metabolizer) or two (poor metabolizer) *CYP2C19* LOF alleles after PCI compared with clopidogrel-treated patients without an LOF allele (normal metabolizer) [8–10]. In contrast, *CYP2C19* genotype does not alter the pharmacokinetics, antiplatelet effects or clinical response to prasugrel or ticagrelor [10,11], which have shown

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superior efficacy compared with clopidogrel in ACS patients following PCI in clinical trials [12,13]. However, these alternative $P2Y_{12}$ inhibitors are more expensive than clopidogrel, which is available generically, and are associated with an increased bleeding risk [4,14–16].

Due to the clinical availability of *CYP2C19* genotype testing, clinicians can now personalize antiplatelet therapy so the more potent and expensive alternatives to clopidogrel can be selectively prescribed in the subset of patients most likely to derive an inadequate response to clopidogrel [7]. However, there remains debate and uncertainty surrounding whether a *CYP2C19* genotype-guided approach should be routinely used to optimize antiplatelet therapy selection following PCI as a means to improve patient outcomes and lower healthcare costs [17]. A number of recent studies have evaluated the cost–effectiveness of *CYP2C19* genotyping for individualized antiplatelet therapy over 12–15 months of treatment [18–26]; however, the economic impact on the US healthcare system within the initial 30 days remains unclear. The Patient Protection and Affordable Care Act uses 'quality indicators' to adjust payments to hospitals as part of value-based purchasing [27]. Thirty-day hospital readmission rate is a proposed quality indicator for PCI by the National Quality Foundation; consequently, hospital readmissions within 30 days following PCI could lead to decreased reimbursements for health systems. Approximately 60–70% of MACE, ST and major bleeding events occur within the first 30 days following PCI [12–14,28–30]. These clinical events require readmission, confer significant morbidity and mortality to the patient, and in turn cause significant economic burden on the payer and the healthcare system. Therefore, identifying cost-effective strategies that improve the precision of $P2Y_{12}$ inhibitor selection and minimize risk of major cardiovascular and bleeding events within 30 days of PCI is critical to healthcare systems, payers, providers and patients. The objective of the current study was to determine whether using a *CYP2C19* genotype-guided strategy to optimize $P2Y_{12}$ inhibitor selection in CAD patients is cost effective over the initial 30 days and 1 year following PCI.

Materials & methods

Model structure & inputs

A decision tree model (Figure 1) was developed based on the US healthcare payer's perspective to compare three strategies for antiplatelet therapy in a hypothetical closed cohort of CAD patients undergoing PCI and treated with aspirin and a $P2Y_{12}$ inhibitor for at least 12 months according to clinical practice guidelines [2,3]: universal clopidogrel (clopidogrel for all individuals without genotyping); universal prasugrel (prasugrel for all individuals without genotyping); and genotype-guided therapy (*CYP2C19* genotyping with subsequent use of prasugrel for individuals carrying 1 or 2 LOF alleles and clopidogrel for individuals with 0 LOF alleles). For patients undergoing *CYP2C19* genetic testing, we assumed that all LOF allele carriers would receive prasugrel instead of clopidogrel, as recommended by the Clinical Pharmacogenetics Implementation Consortium guidelines [7]. It was also assumed that information on *CYP2C19* genotype would be available either pre-emptively or with prompt turnaround to sufficiently guide drug selection during the index PCI hospitalization, as described by institutions that have implemented *CYP2C19* genotyping into clinical practice [31–33]. Two time horizons were investigated with the same decision tree model: 30 days to evaluate early outcomes (primary analysis) and one year to evaluate total outcomes (secondary analysis). Publicly available data sources and published studies were used for all model inputs. The prevalence of one or two *CYP2C19* LOF alleles in the population was assumed to be 30%, which is consistent with the frequency of the CYP2C19 intermediate or poor metabolizer phenotype in US populations [31,32]. The event rate probabilities for MACE (defined as composite of cardiovascular death, myocardial infarction or ischemic stroke events), ST (defined as definite or probable ST events according to the Academic Research Consortium criteria) and major bleeding (defined as major bleeding events unrelated to coronary artery bypass graft surgery according to the Thrombolysis in Myocardial Infarction [TIMI] criteria) at 30 days and 1 year were obtained from the meta-analysis by Mega and colleagues, which included nine studies of CAD patients undergoing PCI, with enrichment from the TRITON TIMI-38 clinical trial that compared clinical outcomes following randomization to either clopidogrel or prasugrel in ACS patients undergoing PCI [9,13]. The cost estimates used in the analysis are reported in 2014 US dollars ($) and are based on Medicare reimbursement rates. The input parameters and assumptions used in the early outcome and total outcome analysis are summarized in Table 1, and are described in detail in the Supplementary Material.

Analysis

A cost–effectiveness analysis was conducted from the US healthcare payer's perspective.

In the model, a simulated cohort of 10,000 patients was assigned to each treatment strategy. The base-case scenario analysis assumed the base-case value for all parameters listed in Table 1. Model outcomes were calculated as the number of MACE, ST and major bleeding events avoided in the genotype-guided treatment arm compared with use of either universal clopidogrel or universal prasugrel per 10,000 patients treated.

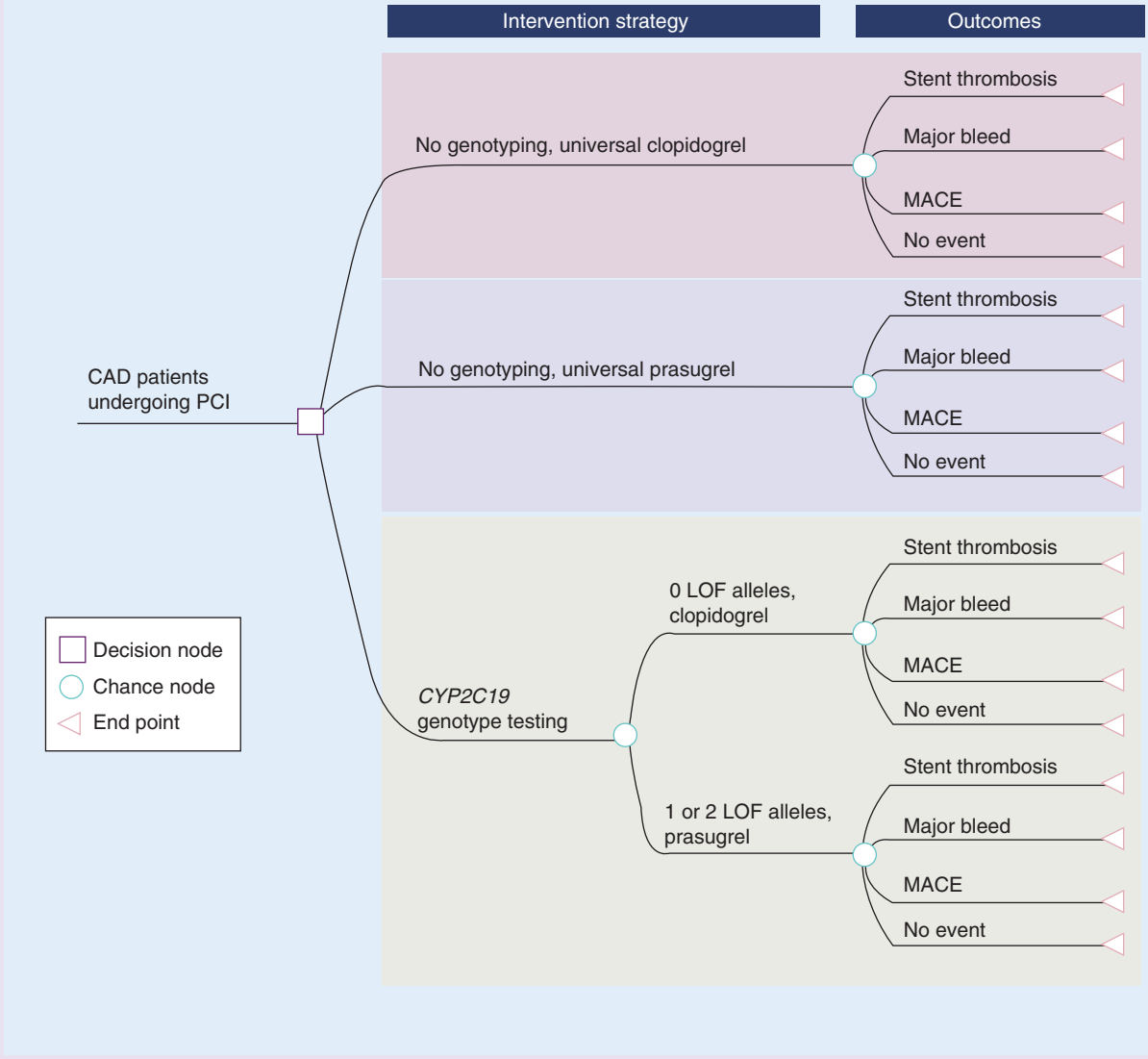

Figure 1. Model structure for the cost–effectiveness analysis. The structure of the decision tree is provided. Simulated patients enter the decision tree and proceed into one of the three intervention strategies: universal clopidogrel, universal prasugrel, or *CYP2C19* genotype-guided treatment selection. Squares represent decision nodes, circles represent chance nodes and triangles represent terminal nodes.
CAD: Coronary artery disease; LOF: Loss-of-function; MACE: Major adverse cardiovascular events; PCI: Percutaneous coronary intervention.

The expected event costs per treated patient and the incremental cost–effectiveness ratio were also calculated. The incremental cost–effectiveness ratio value represents the cost to avoid a major cardiovascular or bleeding event.

Probabilistic sensitivity analyses were performed using 10,000 Monte Carlo simulations to investigate the impact of parameter uncertainty on the early outcome and total outcome cost–effectiveness results. All model inputs were parameterized using a triangular distribution with the base-case value representing the peak value and reported 95% confidence intervals or ranges, when available, or ± 20% of the base-case value representing the minimum and maximum values for individual input parameters (Table 1). All analyses were performed using TreeAge Pro 2016 (TreeAge Software, Inc., MA, USA).

Table 1. Model input values used in the cost–effectiveness model.

Parameter	Base-case value†	Lower limit‡	Upper limit‡
Costs (2014 US$)			
Clopidogrel (generic) – per 30-day supply	13	6	23
Prasugrel (brand) – per 30-day supply	324	260	390
CYP2C19 genotype test	292	100	350
MACE	8883	8715	16,611
ST event	21,463	15,791	23,313
Major bleeding event	8222	6623	11,258
Event rate probabilities			
MACE on clopidogrel without genotype testing			
Early (30 days)	0.0610	0.055	0.070
Total (1 year)	0.0960	0.089	0.106
MACE on clopidogrel with 0 LOF allele			
Early (30 days)	0.0500	0.042	0.057
Total (1 year)	0.0820	0.070	0.089
MACE on prasugrel with 1–2 LOF allele or without genotype testing			
Early (30 days)	0.0500	0.042	0.057
Total (1 year)	0.0820	0.070	0.089
ST on clopidogrel without genotype testing			
Early (30 days)	0.0132	0.010	0.016
Total (1 year)	0.0195	0.014	0.024
ST on clopidogrel with 0 LOF allele			
Early (30 days)	0.0064	0.004	0.008
Total (1 year)	0.0104	0.007	0.012
ST on prasugrel with 1–2 LOF allele or without genotype testing			
Early (30 days)	0.0064	0.004	0.008
Total (1 year)	0.0104	0.007	0.012
Major bleed on clopidogrel without genotype testing			
Early (30 days)	0.0088	0.007	0.011
Total (1 year)	0.0165	0.013	0.020
Major bleed on clopidogrel with 0 LOF allele			
Early (30 days)	0.0088	0.007	0.011
Total (1 year)	0.0165	0.013	0.020
Major bleed on prasugrel with 1–2 LOF allele or without genotype testing			
Early (30 days)	0.0109	0.008	0.015
Total (1 year)	0.0205	0.015	0.028

Assumptions: the risk of MACE and ST was equivalent for clopidogrel with 0 LOF allele and prasugrel with 1–2 LOF alleles or without genotype testing; the risk of major bleeding was equivalent for clopidogrel regardless of genotype [8,11,30].
†A detailed description of the input parameters and references is provided in the Supplementary Material.
‡Upper and lower limits are derived from 95% confidence intervals or ranges, when available, or ±20% of base-case values. The selected range of genotype test cost ($100–350) is consistent with ranges reported in other publications [18].
LOF: Loss of function; MACE: Major adverse cardiovascular event; ST: Stent thrombosis.

Table 1. Model input values used in the cost–effectiveness model (cont.).

Parameter	Base-case value†	Lower limit‡	Upper limit‡
Other information (genetic test)			
Prevalence of 0 LOF alleles in the population	0.70	0.65	0.75
Prevalence of 1 or 2 LOF alleles in the population	0.30	0.25	0.35
Sensitivity of the genetic test	0.9999	0.95	1
Specificity of the genetic test	0.9999	0.95	1

Assumptions: the risk of MACE and ST was equivalent for clopidogrel with 0 LOF allele and prasugrel with 1–2 LOF alleles or without genotype testing; the risk of major bleeding was equivalent for clopidogrel regardless of genotype [8,11,30].
†A detailed description of the input parameters and references is provided in the Supplementary Material.
‡Upper and lower limits are derived from 95% confidence intervals or ranges, when available, or ±20% of base-case values. The selected range of genotype test cost ($100–350) is consistent with ranges reported in other publications [18].
LOF: Loss of function; MACE: Major adverse cardiovascular event; ST: Stent thrombosis.

Results

Base-case scenario

Early outcomes

When compared with universal clopidogrel, a genotype-guided treatment strategy was predicted to avoid 178 major cardiovascular events within 30 days (including 68 ST events) per 10,000 patients, while causing 6 major bleeding events, and would cost an additional US$147 per patient (Tables 2 & 3). When compared with universal prasugrel therapy, a genotype-guided strategy was predicted to prevent 15 major bleeding events within 30 days per 10,000 patients and cost an additional US$62 per patient. Taking into account the cost of genetic testing, and assuming that all LOF allele carriers were treated with prasugrel, the incremental cost per major cardiovascular or bleeding event avoided for genotype-guided treatment was US$8525 compared with universal clopidogrel and US$42,198 compared with universal prasugrel, respectively (Table 3).

Total outcomes

When compared with universal clopidogrel, a genotype-guided treatment strategy was predicted to avoid 231 major cardiovascular events within 1 year (including 91 ST events) per 10,000 patients, while causing 12 major bleeding events, and would cost an additional US$1102 per patient (Tables 4 & 5). The incremental cost per major cardiovascular or bleeding event avoided for genotype-guided treatment was US$50,308 compared with universal clopidogrel. When compared with universal prasugrel therapy without genotype testing, a genotype-guided strategy was dominant since it was predicted to prevent 28 major bleeding events within

Table 2. Base-case scenario results (early outcomes): number of major cardiovascular and bleeding events avoided over 30 days by genotype-guided therapy per 10,000 patients treated.

Strategy	MACE (composite) events†	Stent thrombosis events‡	Major bleeding events§	Total (sum) events
Universal clopidogrel	610	132	88	830
Universal prasugrel	500	64	109	673
Genotype-guided therapy	500	64	94	658
– Number of events avoided# (vs universal clopidogrel)	110	68	-6	172
– Number of events avoided# (vs universal prasugrel)	0	0	15	15

†MACE defined as the composite of cardiovascular death, myocardial infarction or ischemic stroke events.
‡Defined as definite or probable stent thrombosis events according to the ARC criteria.
§Defined as major bleeding events unrelated to coronary artery bypass graft surgery according to the TIMI criteria.
#A negative number indicates that the number of events in the genotype-guided therapy group is higher compared with the designated reference group.
ARC: Academic Research Consortium; MACE: Major adverse cardiovascular event; TIMI: Thrombolysis in myocardial infarction.

Table 3. Base-case scenario results (early outcomes): cost–effectiveness of genotype-guided therapy over 30 days per patient treated.

Strategy	Cost per patient (US$)	Incremental cost (US$)	Adverse events per patient	Incremental effectiveness (events avoided)	Incremental cost–effectiveness ratio (cost per event avoided, US$)
Universal clopidogrel	910.53	–	0.0830	–	–
Universal prasugrel	995.13		0.0673		
– vs universal clopidogrel†		84.60		0.0157	5389
Genotype-guided therapy	1057.16		0.0658		
– vs universal clopidogrel†		146.63		0.0172	8525
– vs universal prasugrel†		62.03		0.0015w	42,198

†Reference group.

1 year per 10,000 patients at a cost of US$2343 less per patient.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis for early outcomes illustrated that genotype-guided treatment was predicted to be the most cost-effective strategy at a willingness-to-pay (WTP) threshold above US$12,000, and genotype testing was increasingly cost effective compared with the other two options as the WTP threshold increased (Figure 2A). At a WTP threshold of US$50,000, genotype testing was cost effective in 62% of the simulations, whereas prasugrel without genotype testing was cost effective in 38% of simulations. Universal clopidogrel was rarely cost effective over the initial 30 days. For total outcomes at 12 months, genotype-guided treatment was predicted to be the most cost-effective strategy at WTP thresholds above US$40,000, and genotype testing was increasingly cost effective compared with the other two options as the WTP threshold increases (Figure 2B). At a WTP threshold of US$50,000, genotype-guided treatment was cost effective in 70% of the simulations, whereas universal clopidogrel was cost effective in 30% of simulations. Universal prasugrel was rarely cost effective due to the cost of prasugrel treatment over the course of 1 year.

Discussion

Implementation of a *CYP2C19* genotype-guided approach to optimize antiplatelet therapy selection following PCI offers the potential to lower risk of major cardiovascular and bleeding events and lower healthcare costs [7]. However, the economic impact within the initial 30 days following PCI, when the risk for readmission due to a MACE, ST or bleeding event is highest, had not been evaluated. In the current investigation of a hypothetical US cohort of CAD patients undergoing PCI, selecting antiplatelet therapy based on a *CYP2C19* genetic test result (LOF allele carrier: prasugrel, no LOF allele: clopidogrel)

Table 4. Base-case scenario results (total outcomes): number of major cardiovascular and bleeding events avoided over 1 year by genotype-guided therapy per 10,000 patients treated.

Strategy	MACE (composite) events†	Stent thrombosis events‡	Major bleeding events§	Total (sum) events
Universal clopidogrel	960	195	165	1320
Universal prasugrel	820	104	205	1129
Genotype-guided therapy	820	104	177	1101
– Number of events avoided# (vs universal clopidogrel)	140	91	-12	219
– Number of events avoided# (vs universal prasugrel)	0	0	28	28

†MACE, defined as the composite of cardiovascular death, myocardial infarction or ischemic stroke events.
‡Defined as definite or probable stent thrombosis events according to the ARC criteria.
§Defined as major bleeding events unrelated to coronary artery bypass graft surgery according to the TIMI criteria.
#A negative number indicates that the number of events in the genotype-guided therapy group is higher compared with the designated reference group.
ARC: Academic Research Consortium; MACE: Major adverse cardiovascular event; TIMI: Thrombolysis in myocardial infarction.

Table 5. Base-case scenario results (total outcomes): cost– effectiveness of genotype-guided therapy over 1 year per patient treated.

Strategy	Cost per patient (US$)	Incremental cost (US$)	Adverse events per patient	Incremental effectiveness (events avoided)	Incremental cost–effectiveness ratio (cost per event avoided, US$)
Universal clopidogrel	1562.96	–	0.1320	–	–
Universal prasugrel	5008.17		0.1129		
– vs universal clopidogrel[†]		3445.21		0.0191	180,378
Genotype-guided therapy	2664.70		0.1101		
– vs universal clopidogrel[†]		1101.74		0.0219	50,308
– vs universal prasugrel[†]		-2343.47[‡]		0.0028	(dominant)[§]

[†]Reference group.
[‡]A negative number indicates that the incremental cost in the genotype-guided therapy group is lower compared with the universal prasugrel group.
[§]Universal prasugrel was predicted to be less effective and more expensive than (dominated by) genotype-guided therapy.

was projected to be more cost effective than either universal clopidogrel or universal prasugrel without *CYP2C19* genotyping over the initial 30 days following PCI. Moreover, when considering outcomes and medication costs over 1 year, a genotype-guided strategy was predicted to be more effective and less costly than universal prasugrel as well as cost effective compared with universal clopidogrel. Taken together, these results suggest that routinely implementing a *CYP2C19* genotype-guided approach to optimize $P2Y_{12}$ inhibitor use in clinical practice would have a positive economic impact on the US healthcare system.

Selection of medications that account for individual genetic differences has been proposed as a cornerstone of precision medicine [34]. As the evidence base grows and genetic tests are more readily available, clinicians have begun to implement genetic test results into treatment decisions for individual patients [35]. It is pertinent to understand the clinical and economic implications of genotype-guided prescribing on healthcare systems [36]. A series of previous cost–effectiveness studies conducted in the US healthcare setting to understand the economic impact of *CYP2C19* genotype testing to guide antiplatelet therapy selection following PCI have focused on longer term (12–15 months and lifetime) outcomes [18–24]. These studies have collectively concluded that *CYP2C19* genotype-guided treatment strategies are cost effective when compared with universal clopidogrel or universal prasugrel treatment without genotype testing. Our 1-year results are consistent with these findings. However, it is equally important to understand the early economic impact of genotype testing, especially since there is a shift in the economic burden for hospital readmissions during the first 30 days following a PCI. Institutional protocol and the Center for Medicaid and Medicare Services mandates dictate that healthcare organizations could bear the burden of hospital readmissions in patients within the first 30 days of PCI compared with the later readmissions that are typically reimbursed by insurance.

The current investigation focuses on 30-day outcomes and costs, which has not been evaluated previously, and offers valuable new insight into the cost–effectiveness of a *CYP2C19* genotype-guided treatment strategy during a critical time period when patients undergoing PCI are at highest risk for readmission due to adverse cardiovascular and bleeding outcomes. Base-case scenario results at 30 days indicated that genotype-guided therapy costs 16 and 7% more than universal clopidogrel and prasugrel, respectively, and is predicted to avoid MACE and ST events compared with universal clopidogrel and avoid major bleeding events compared with universal prasugrel. Consequently, the cost per major cardiovascular or bleeding event avoided for genotype-guided therapy was US$8525 when compared with universal clopidogrel and US$42,198 when compared with universal prasugrel. The base-case scenario and the probabilistic sensitivity analysis results indicated that a genotype-guided strategy is cost effective in the initial period after a PCI, and suggest that routine *CYP2C19* testing might help healthcare institutions and payers save money by avoiding early readmissions after PCI. The projected cost savings to healthcare systems would be even more pronounced if reimbursement was reduced or eliminated due to hospitals being penalized for early readmissions.

When comparing the economic and clinical outcomes over 1 year to those observed at 30 days, the cost–effectiveness of a genotype-guided strategy appeared to be lessened when compared with universal clopidogrel

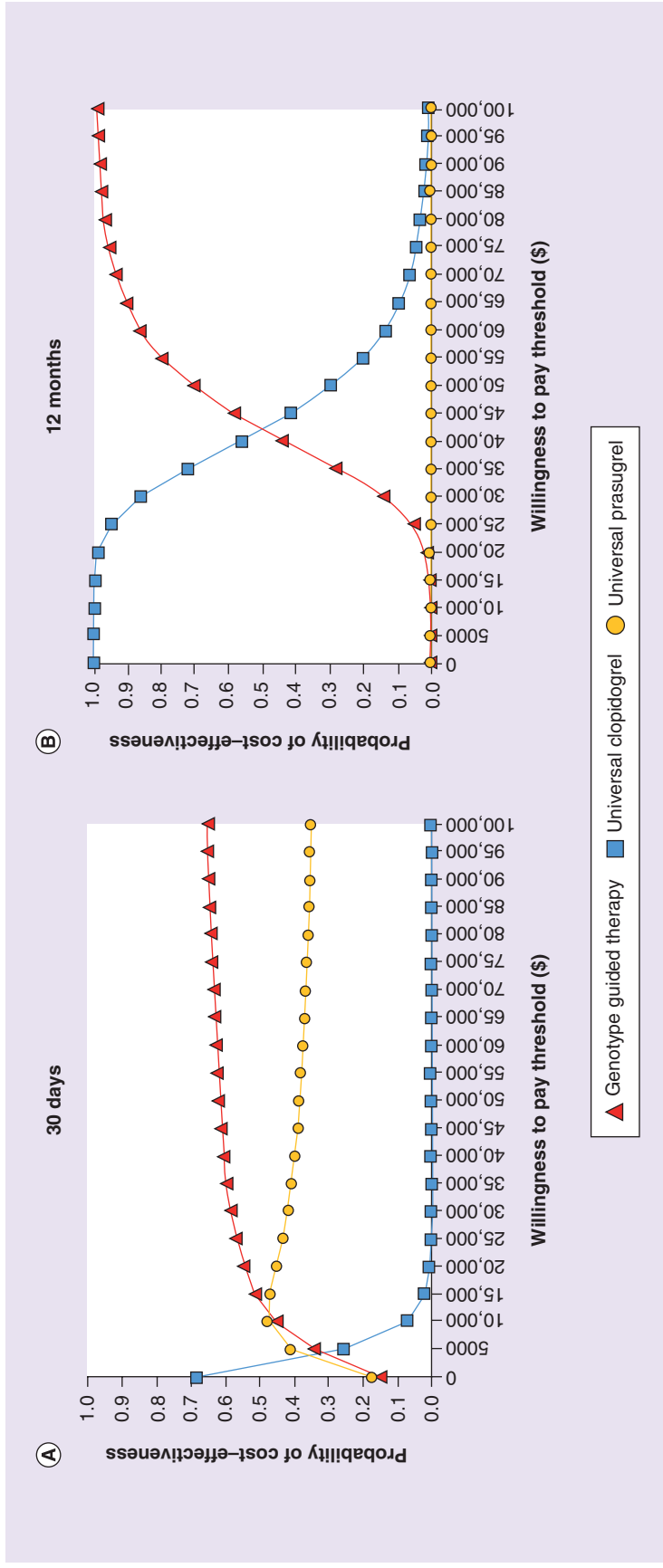

Figure 2. Probabilistic sensitivity analysis for early and total outcomes. Cost–effectiveness acceptability curves representing the probability that each treatment strategy (universal clopidogrel, universal prasugrel, genotype-guided therapy) is cost effective (y-axis) for a given willingness-to-pay threshold in US dollars per major event avoided (x-axis). Separate curves are provided for **(A)** early (30 day) outcomes, and **(B)** total (1 year) outcomes.

and magnified when compared with universal prasugrel. Genotype-guided therapy was predicted to cost 70% more than universal clopidogrel and cost 47% less than universal prasugrel therapy. These differences were driven by the cost of prasugrel treatment over the course of 1 year. Taking uncertainty across multiple input parameters in the probabilistic sensitivity analysis, genotype-guided treatment was predicted to be the most cost-effective strategy at a WTP threshold of US$50,000 with cost–effectiveness predicted 62% of the time over 30 days and 70% of the time over 1 year. In comparison, universal prasugrel was predicted to be cost effective 38% of the time over 30 days and rarely over 1 year. Although universal prasugrel appears to be a cost-effective alternative to genotype-guided therapy over the first 30 days following PCI, the cost associated with prolonged prasugrel treatment made universal prasugrel the least cost effective option over the course of 1 year. Given that DAPT is indicated following PCI for at least 12 months in high risk patients [2,3], and universal clopidogrel is associated with the highest risk of 30-day and 1-year MACE and ST events, universal genotyping with targeted use of prasugrel in CYP2C19 intermediate and poor metabolizers appears to be the preferred strategy in terms of cost–effectiveness in both the short- and long-term.

Although this study integrated critical parameter inputs and projected 30-day cost and effectiveness estimates for genotype-guided antiplatelet therapy for the first time, there are limitations to the current investigation that must be considered. First, projected event rate probabilities for genotype-guided therapy were derived from retrospective analyses of clinical trials and patient registries, and not an outcome-driven prospective randomized controlled trial. Although a clinical trial that will compare the impact of *CYP2C19* genotype-guided antiplatelet therapy on MACE and bleeding outcomes to universal clopidogrel has been initiated (NCT01742117), it will not be completed until 2020. Second, only major cardiovascular and bleeding events resulting in readmission were taken into consideration in this analysis, and patients could only experience one event over each time horizon in the model. Compared with clopidogrel, it is well-established that prasugrel also lowers the risk of other ischemic events such as unstable angina and target vessel revascularization, and increases the risk of minor bleeding events [13]. Since these events are directly related to the intensity of antiplatelet therapy, the number of events avoided with genotype-guided therapy may have been underestimated. Third, the main outcome in this analysis, cost per major cardiovascular or major bleeding event avoided, should be interpreted with caution. Although this outcome has been used in previous analyses [19,37], major cardiovascular and major bleeding events are the most clinically relevant outcomes leading to readmission following PCI, and a WTP threshold of US$50,000 is generally considered cost effective for an additional quality-adjusted life year, a WTP threshold value for the cost of a healthcare technology to avoid a major cardiovascular or major bleeding event has not been established and each event could impact quality of life differently. Our model costs were based on the current Center for Medicaid and Medicare Services reimbursement rates, which may not be generalizable for all commercially insured plans. Furthermore, only direct inpatient medical costs associated with the major cardiovascular or bleeding event were considered. The cost–effectiveness of preventing these events may have been underestimated since these events incur additional downstream medical costs, such as follow-up outpatient encounters and chronic treatment, which were not considered. Moreover, since the true costs extend beyond the payer's perspective, future analyses from the societal perspective that include indirect (e.g., lost time from work), direct nonmedical (e.g., transportation) and intangible costs (e.g., pain and suffering) are needed.

It is also important to note that the decision tree was simplified with a few key assumptions that may not reflect real-world clinical practice. First, although ticagrelor is an alternative antiplatelet therapy that is not impacted by *CYP2C19* genotype, our analysis focused on prasugrel since prasugrel is the most commonly prescribed alternative antiplatelet therapy at institutions that have implemented *CYP2C19* genotyping into clinical practice [31–33]. Evaluating the cost–effectiveness of a genotype-guided strategy compared with universal ticagrelor over 30 days and 1 year was beyond the scope of the current analysis, and will require subsequent investigation. Furthermore, since the antiplatelet therapy prescribing decision will include factors beyond *CYP2C19* genotype, such as risk for bleeding, our assumption that all CYP2C19 intermediate and poor metabolizers would receive prasugrel instead of clopidogrel may overestimate the benefits of the genotype-guided strategy. Indeed, early adopters of this strategy have reported that approximately 70–80% of LOF allele carriers have been prescribed alternative therapy in clinical practice [31,32]. It was also assumed that the *CYP2C19* genotype result would be available to sufficiently guide drug selection during the index PCI hospitalization. This would require either a reactive genotyping approach with on-site genotyping and prompt turnaround or a pre-emptive genotyping approach, as described [31,32]. Consequently, successful implementation of a reactive genotyping approach may not be feasible at all institutions. If the genotyping test

result was delayed, our results suggest that a universal prasugrel strategy during the first 30 days may be a cost-effective alternative to genotype-guided therapy that could be considered to minimize readmission for early MACE or ST events until the genotype result is available and the patient is beyond the high-risk 30-day period. An alternative approach would be to use a pre-emptive genotyping strategy, which would involve identifying and genotyping a larger patient cohort with the understanding that only a subset of genotyped patients will require a PCI, antiplatelet therapy and actionable use of the *CYP2C19* result in the near future. The cost–effectiveness of pre-emptive genotyping strategies, which typically involve panel-based testing for multiple genetic markers, are not well-described in the literature and beyond the scope of the current analysis. Future analyses will be needed to ascertain the relative cost–effectiveness of reactive and pre-emptive approaches to genotype-guided antiplatelet therapy for health systems and payers.

Conclusion

In the current investigation of a hypothetical US cohort of CAD patients undergoing PCI, selecting antiplatelet therapy based on a *CYP2C19* genetic test result was projected to avoid major cardiovascular or bleeding adverse events at reasonable costs over the course of 30 days and 1 year following PCI when compared with universal clopidogrel and universal prasugrel. Taken together, these results suggest that implementing a genotype-guided approach to optimize $P2Y_{12}$ inhibitor selection in clinical practice could help health systems achieve lower readmission rates within the first 30 days following PCI, and that reimbursement for *CYP2C19* genetic testing appears to be a worthwhile investment from the perspective of third party payers. Given the high potential for a positive economic impact on the US healthcare system, the direct effects of implementing a *CYP2C19* genotype-guided selection strategy on clinical outcomes in real-world clinical practice, and the associated costs, should be evaluated.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/pgs-2017-0075

Summary points

Background & methods

- There remains uncertainty surrounding whether *CYP2C19* genotype should be routinely used to guide antiplatelet therapy selection following percutaneous coronary intervention (PCI).
- The current study evaluated the cost–effectiveness of a *CYP2C19* genotype-guided strategy from the US healthcare payer's perspective.
- A decision tree model projected major cardiovascular and bleeding outcomes and cost across three treatment strategies (universal clopidogrel, universal prasugrel and genotype-guided therapy) over 30 days and 1 year following PCI in a hypothetical closed cohort of 10,000 PCI patients.

Results

- The base-case incremental cost per major cardiovascular or bleeding event avoided at 30 days was US$8525 and US$42,198 for a genotype-guided strategy compared with universal clopidogrel and prasugrel, respectively.
- Probabilistic sensitivity analysis demonstrated that genotype-guided treatment was cost–effective over 30 days and 1 year in 62 and 70% of simulations, respectively, at a willingness-to-pay threshold of US$50,000.

Conclusion

- These results suggest that a *CYP2C19* genotype-guided strategy to optimize antiplatelet therapy would have a positive economic impact on the healthcare system by lowering readmission rates for major cardiovascular and bleeding events within the first 30 days and 1 year following PCI.

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