Cardiovascular Drugs and Therapy (2019) 33:533–546
https://doi.org/10.1007/s10557-019-06896-8

ORIGINAL ARTICLE

Cost-Effectiveness of Strategies to Personalize the Selection of $P2Y_{12}$ Inhibitors in Patients with Acute Coronary Syndrome

Kibum Kim[1] · Daniel R. Touchette[2,3] · Larisa H. Cavallari[4] · Amer K. Ardati[5] · Robert J. DiDomenico[2,6]

Published online: 31 July 2019

Abstract

Purpose Perform a cost-effectiveness analysis comparing strategies for selecting $P2Y_{12}$ inhibitors in acute coronary syndrome (ACS).

Methods Six strategies for selection of $P2Y_{12}$ inhibitors in ACS were compared from the US healthcare system perspective: (1) clopidogrel for all (universal clopidogrel); (2) ticagrelor guided by platelet reactivity assay (PRA; clopidogrel + phenotype); (3) ticagrelor use only in *CYP2C19* poor metabolizers (genotype + conservative ticagrelor); (4) ticagrelor use in both *CYP2C19* intermediate and poor metabolizers (genotype + liberal ticagrelor); (5) ticagrelor use only in patients with *CYP2C19* polymorphisms and clopidogrel nonresponse by PRA (genotype + phenotype); and (6) ticagrelor for all (universal ticagrelor). A decision model was developed to model major adverse cardiovascular events and bleeding during 1 year of treatment with a $P2Y_{12}$ inhibitor. Model inputs were identified from the literature. Lifetime costs were adjusted to 2017 US dollars; quality-adjusted life-years (QALYs) were projected using a Markov model. The primary endpoint was the incremental cost-effectiveness compared to the next best option along the cost-effectiveness continuum. Sensitivity analyses were performed on all model inputs to assess their influence on the incremental cost-effectiveness.

Results In the base case analysis, incremental cost-effectiveness ratios (ICER) for the clopidogrel + phenotype, genotype + liberal ticagrelor, and universal ticagrelor strategies were $12,119/QALY, $29,412/QALY, and $142,456/QALY, respectively. Genotype + conservative ticagrelor and genotype + phenotype were not cost-effective due to second-order dominance. Genotype + liberal ticagrelor compared to clopidogrel + phenotype demonstrated the highest acceptance (97%) at a willingness to pay (WTP) threshold of $100,000/QALY.

Conclusion Cost-effective strategies to personalize $P2Y_{12}$ inhibition in ACS include clopidogrel +phenotype and genotype + liberal ticagrelor. Universal ticagrelor may be considered cost-effective at a higher WTP threshold ($150,000/QALY). Genotype + liberal ticagrelor exhibited the highest acceptability compared to clopidogrel + phenotype over the widest range of WTP thresholds and may be preferred.

Keywords Acute coronary syndrome · Personalized medicine · Ticagrelor · Clopidogrel · $P2Y_{12}$ inhibitors · Cost-effectiveness

✉ Robert J. DiDomenico
rdidom1@uic.edu

1 Department of Pharmacotherapy and Pharmacotherapy Outcomes Research Center, University of Utah, Salt Lake City, UT, USA

2 Center for Pharmacoepidemiology and Pharmacoeconomic Research, University of Illinois at Chicago, Chicago, IL, USA

3 Department of Pharmacy Systems, Outcomes and Policy, University of Illinois at Chicago, Chicago, IL, USA

4 Department of Pharmacotherapy and Translational Research and Center for Pharmacogenomics, University of Florida, Gainesville, FL, USA

5 Division of Cardiology, University of Illinois at Chicago, Chicago, IL, USA

6 Department of Pharmacy Practice, University of Illinois at Chicago, Chicago, IL, USA

Introduction

Acute coronary syndrome (ACS), which includes ST-elevation myocardial infarction (MI), non-ST-elevation MI, and unstable angina, accounts for more than 1.3 million discharges annually (primary and secondary diagnoses) and is among the top 10 most expensive conditions treated in the USA [1]. For most patients with ACS, current guidelines recommend dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor to prevent major adverse cardiovascular events (MACE) [2–4]. Although clopidogrel is most commonly prescribed, the availability of prasugrel and ticagrelor introduce more options—and complexity—to therapeutic decision-making in ACS [5, 6].

$P2Y_{12}$ inhibitors bind to the $P2Y_{12}$ receptor on platelets preventing adenosine diphosphate from binding, thereby inhibiting platelet activation and aggregation. Clopidogrel is a prodrug that requires conversion to the active metabolite via the *CYP2C19* enzyme. However, in patients with *CYP2C19* generic polymorphisms (carriers of the loss-of-function [LOF] alleles *2 and/or *3), conversion of clopidogrel to its active metabolite is reduced in both intermediate metabolizers (*1/*2, *1/*3, *2/*17) and poor metabolizers (*2/*2, *2/*3, *3/*3) and may contribute to high on-treatment platelet reactivity (HTPR) [7]. Several studies have demonstrated that clopidogrel effectiveness decreases in patients with coronary artery disease (CAD) at high-risk for MACE (e.g., those with ACS undergoing percutaneous coronary intervention [PCI]) who are intermediate or poor metabolizers of *CYP2C19* [8, 9]. Prasugrel and ticagrelor are alternative $P2Y_{12}$ inhibitors in patients with ACS that are unaffected by *CYP2C19* genotype, more effective than clopidogrel in preventing MACE, but incur higher bleeding risk and cost [10, 11]. Thus, personalizing therapy with $P2Y_{12}$ inhibitors to maximize cost-effectiveness and minimize risk is desirable and recommended by both the Clinical Pharmacogenetics Implementation Consortium (CPIC) and US Food and Drug Administration (FDA) [7, 12]. While both organizations recommend personalizing $P2Y_{12}$ inhibitor therapy, the optimal approach is uncertain and the routine use of either strategy is not currently recommended for patients with ACS [3, 4].

More recently, genotype-guided $P2Y_{12}$ inhibitor therapy in which prasugrel or ticagrelor are used in patients identified as poor or intermediate metabolizers of clopidogrel has been shown to reduce the rate of MACE in patients with CAD undergoing PCI, including those hospitalized for ACS [13–18]. Studies in this setting have found that this approach is cost-effective compared with universal clopidogrel [19–24]. Yet, under certain conditions, universal ticagrelor use without genotyping may be a cost-effective strategy [19, 21]. While several institutions have implemented *CYP2C19* testing to guide $P2Y_{12}$ inhibitor selection, local challenges (e.g., stakeholder buy-in, laboratory contracts with the hospital, development of clinical decision support, billing/reimbursement) and lack of guideline endorsement have limited more widespread adoption of this practice [25].

An alternative to genotype-guided $P2Y_{12}$ inhibitor selection in ACS is phenotype-guided therapy in which a platelet reactivity assay (PRA) is used to characterize the antiplatelet activity of clopidogrel and an alternative $P2Y_{12}$ inhibitor is selected for patients demonstrating HTPR. Although limited, recent evidence suggests a phenotype-guided strategy for selecting $P2Y_{12}$ inhibitors in patients with ACS is at least as effective and may be superior to universal clopidogrel or prasugrel [26–28]. This approach has also been shown to be cost-effective compared with the universal use of any of the $P2Y_{12}$ inhibitors in patients with ACS [29, 30]. Implementation of phenotype-guided therapy has been met with many of the same challenges as genotype-guided approaches.

Given the prevalence of ACS, the costs associated with its treatment, and the complexities of selecting $P2Y_{12}$ inhibitors, identifying a cost-effective strategy for personalizing $P2Y_{12}$ inhibitor therapy in patients with ACS would be beneficial. Although pharmacoeconomic evaluations have been conducted on both genotype- and phenotype-guided strategies for selecting $P2Y_{12}$ inhibitors in patients with ACS, to our knowledge, no study has compared the cost-effectiveness of these strategies to one another [19–24, 29–31]. The objective of this study was to evaluate the cost-effectiveness of several strategies to personalize $P2Y_{12}$ inhibitor selection in patients with ACS in an effort to identify a preferred strategy for personalizing $P2Y_{12}$ inhibitor therapy.

Methods

Target Population and $P2Y_{12}$ Selection Strategies

A cost-effectiveness model (Fig. 1) was developed to evaluate six selection strategies for $P2Y_{12}$ inhibitors in patients with ACS: (1) clopidogrel for all patients (universal clopidogrel); (2) clopidogrel for all patients followed by PRA testing and switching clopidogrel non-responders to ticagrelor (clopidogrel + phenotype); (3) selection based on *CYP2C19* genotype where ticagrelor is reserved for poor metabolizers (two LOF alleles) and clopidogrel for all other genotypes (genotype + conservative ticagrelor); (4) selection based on *CYP2C19* genotype where ticagrelor is used for both intermediate (one LOF allele) and poor metabolizers and clopidogrel for all other genotypes (genotype + liberal ticagrelor use); (5) based on both genotype and phenotype in which ticagrelor is used in *CYP2C19* poor metabolizers, a phenotype-driven approach is used for intermediate metabolizers (to identify intermediate metabolizers with HTPR), and clopidogrel used for all other genotypes (genotype + phenotype); and (6) ticagrelor for all patients (universal ticagrelor).

We assumed that both genotype and phenotype information would be available from the beginning of the patient follow-up based on the availability of point-of-care testing with a median turnaround time for the *CYP2C19* genotype test is as short as 96 min at a local laboratories [32, 33]. Given that the classification of CPIC recommendations differs between intermediate and poor metabolizers, we chose to model different approaches (genotype + conservative ticagrelor, genotype + liberal ticagrelor) to these patients to evaluate the incremental cost-effectiveness of both approaches. Prasugrel was not included in this model because our assumptions allowed for a portion of patients to be managed medically—without PCI

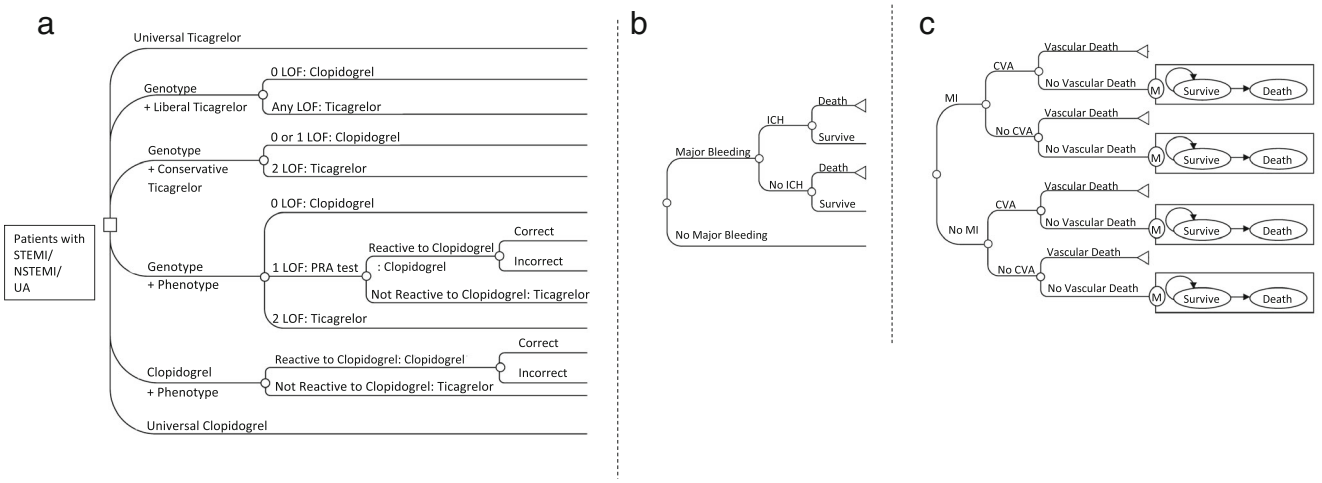


Fig. 1 Decision tree. **a** Main decision tree. **b** Outcomes associated with major bleeding complications for each decision alternative. **c** Outcomes associated with myocardial infarction for each decision alternative. *STEMI* ST segment-elevation myocardial infarction, *NSTEMI* non-ST segment-elevation myocardial infarction, *UA* unstable angina, *LOF* loss of function allele(s), *PRA* platelet reactivity assay, *ICH* intracranial hemorrhage, *MI* myocardial infarction, *CVA* cerebrovascular accident (stroke)

(see below); prasugrel is only recommended to treat ACS in patients who undergo PCI [3, 34].

The model utilized a hypothetical cohort of patients aged 62 years with ACS requiring DAPT similar to clinical trial data [10]. We assumed that 72% of patients had a planned invasive treatment strategy and 64% would have PCI performed [10]. We assumed all patients—regardless of PCI status—would be treated with DAPT with the selected $P2Y_{12}$ inhibitor for a duration of 12 months during which the direct benefits associated with the antiplatelet strategy were assumed. Switching between $P2Y_{12}$ inhibitors was not factored into the model. The primary outcome was incremental cost-effectiveness defined as the incremental cost/quality-adjusted life-years (QALY) gained over the lifetime horizon. Following the Second Panel on Cost-Effectiveness in Health and Medicine recommendations, the analysis was conducted from the US health care sector's perspective and includes formal health care sector costs paid by third-party payers [35]. Patient out-of-pocket costs and a societal perspective were not included in this analysis, as this detailed information was not available. All six $P2Y_{12}$ inhibitor selection strategies were considered in order of increasing QALY and an incremental cost-effectiveness ratio (ICER) was calculated for each strategy by dividing the incremental cost (compared to strategy that yielded the next most QALY) by the incremental benefit (difference in QALY gained between the two strategies). $P2Y_{12}$ inhibitor selection strategies that displayed either first-order (more costly, less effective) or second-order (higher ICER than the comparator) dominance were not deemed cost-effective and were excluded from calculation of the final ICERs. A 3% annual discount rate for both costs and QALY was used.

Model Structure and Clinical Pathways

A simple decision tree was developed using TreeAge Pro (TreeAge Pro 2013, Williamstown, MA, USA) modeling the first 12 months of therapy, followed by a Markov model with a lifetime time horizon. The model included the costs, QALYs, and the following adverse events derived from clinical trial data during the first 12 months of therapy: MI, ischemic stroke, intracranial hemorrhage (ICH), non-ICH major bleeding, or death [10, 36]. Lifetime costs and QALYs were calculated using a Markov model for patients who survived the first year of therapy. To conservatively estimate the benefits of the DAPT strategies over the first year after the onset of ACS, the model included two Markov states, life and death [2–4]. The Markov model ran on 1-year cycles using age-dependent mortality rates, adjusted for survival post-ACS, until the annual mortality for each strategy was greater than 90% [37, 38]. The expected annual mortality was adjusted for complications (e.g., recurrent MI, ischemic stroke) that patients experienced during the first year of treatment [38].

Model Inputs for Base-Case Analysis

Model inputs were extracted from a targeted review of the literature and the opinion of senior authors (AKA, RJD) who have clinical expertise in treating patients with ACS including personalizing $P2Y_{12}$ inhibitor selection (Table 1) [9, 10, 36–52]. For effectiveness inputs (MI, ischemic stroke), 12-month risk ratios were obtained from clinical trial data and included in the model [10, 36]. Bleeding risk was estimated using the Thrombolysis in Myocardial Infarction criteria and clinical trial data [10, 36].

Based on meta-analyses evaluating the influence of *CYP2C19* polymorphisms on platelet reactivity in more than

Table 1 Base case model variables and ranges in sensitivity analysis

Variable	Base case	One-way sensitivity analysis		Monte Carlo simulation		References
		Lower	Upper	Type	Inputs	
Discount rate	0.03	0.01	0.05	Uniform		EO
Costs (2017 US dollars)						
Aspirin 81 mg daily[a]	$0.05	$0.02	$0.75			EO
Clopidogrel 300 mg (loading dose)	$9.27	$4.64	$14.00			[39]
Clopidogrel 75 mg daily[a]	$4.36	$2.18	$6.54	Triangular		[39]
Ticagrelor 90 mg twice daily[a]	$14.12	$7.06	$21.18	Triangular		[39]
Non-ICH bleeding, immediate	$1355.00	$678.00	$2034.00			[40]
ICH, hospitalization	$24,853.00	$12,426.00	$37,279.00			[41]
ICH, long-term care—1st year	$33,409.00	$16,705.00	$50,114.00			[40]
ICH, long-term care—2nd year	$10,239.00	$5119.00	$15,358.00			[40]
ICH, long-term care—3rd year or later	$3763.00	$1882.00	$5,645.00			[40]
Myocardial infarction, hospitalization	$23,831.00	$11,916.00	$35,747.00			[41]
Myocardial infarction, annual chronic care	$5345.00	$2672.00	$8017.00	Triangular		[19]
Ischemic stroke, hospitalization	$14,169.00	$7084.00	$21,253.00			[41]
Ischemic stroke, long-term care—1st year	$27,365.00	$13,682.00	$41,047.00			[40]
Ischemic stroke, long-term care—2nd year	$7389.00	$3695.00	$11,084.00			[40]
Ischemic stroke, long-term care—3rd year or later	$5380.00	$2690.00	$8070.00			[40]
Cost ratio, additional MI vs. index MI	0.5	0	1			EO
Genotyping	$293.40	$146.70	$440.10	Gamma	$\alpha = 25, \lambda = 0.085$	[43]
Phenotyping	$39.80	$19.90	$59.70			[43]
Probabilities						
Sensitivity of PRA	0.8330	0.7330	0.9330	Triangular		[44, 45]
Specificity of PRA	0.8400	0.7440	0.9440	Triangular		[44, 45]
Major bleeding, clopidogrel	0.0770	0.0716	0.0824	Beta	$\alpha = 707, \beta = 8479$	[10, 36]
RR of major bleeding, ticagrelor vs. clopidogrel	1.0260	0.9300	1.1500	LogNormal	$\mu(\log) = 0.026, \sigma(\log) = 0.054$	[10, 36]
Non-ICH bleeding death, clopidogrel	0.0336	0.0195	0.0477	Beta	$\alpha = 21, \beta = 604$	[10]
RR of non-ICH bleeding death, ticagrelor vs. clopidogrel	0.4225	0.1950	0.9152			[10, 36]
ICH, clopidogrel	0.0204	0.0094	0.0313	Beta	$\alpha = 13, \beta = 625$	[10, 36]
RR of ICH, ticagrelor vs. clopidogrel	1.7181	0.8780	3.3619	LogNormal	$\mu(\log) = 0.54, \sigma(\log) = 0.34$	[10, 36]
ICH death, clopidogrel	0.1538	0.0423	0.3500	Beta	$\alpha = 2, \beta = 11$	[10]
RR of ICH death, ticagrelor vs. clopidogrel	3.1100	0.8104	6.5000			[10]
Myocardial infarction, clopidogrel	0.0692	0.0640	0.0744	Beta	$\alpha = 641, \beta = 8624$	[10]
RR of myocardial infarction, ticagrelor vs. clopidogrel	0.8403	0.7522	0.9387	LogNormal	$\mu(\log) = -0.17, \sigma(\log) = 0.056$	[10]
Mortality ratio, secondary MI vs. no secondary MI	1.5000	0.7500	2.2500	Uniform		[38]

Table 1 (continued)

Variable	Base case	One-way sensitivity analysis		Monte Carlo simulation		References
		Lower	Upper	Type	Inputs	
Vascular death, clopidogrel	0.0511	0.0467	0.0556	Beta	$\alpha = 474$, $\beta = 8791$	[10]
RR of vascular death, ticagrelor vs. clopidogrel	0.7910	0.6826	0.9166	LogNormal	$\mu\,(\log) = -0.23$, $\sigma(\log) = 0.068$	[10]
Non-vascular death, clopidogrel	0.1538	0.0000	0.3200	Beta	$\alpha = 46$, $\beta = 9287$	[10]
Ischemic stroke, clopidogrel	0.0102	0.0082	0.0123	Beta	$\alpha = 95$, $\beta = 9170$	[10]
RR of ischemic stroke, ticagrelor vs. clopidogrel	1.1760	0.8959	1.5437	LogNormal	$\mu(\log) = 0.16$, $\sigma(\log) = 0.14$	[10]
Mortality ratio, stroke vs. no stroke	1.5000	0.7500	2.2500	Uniform		[38]
Extensive metabolizer (EM)	0.7000	0.6000	0.8000	Uniform		[9]
Intermediate metabolizer (IM, 1 LOF allele), if non-EM	0.9200	0.8500	0.9500	Uniform		[9]
Poor metabolizer (PM, 2 LOF alleles)	(1-EM) × (1-PM)					
Clopidogrel responders, if IM	0.2800	0.2000	0.4000	Uniform		[9, 46]
RR of composite endpoint, IM vs. EM	1.5500	1.1100	2.1700	LogNormal	$\mu\,(\log) = 0.44$, $\sigma(\log) = 0.17$	[9, 46]
RR of composite endpoint, PM vs. EM	1.7600	1.2400	2.5000	LogNormal	$\mu\,(\log) = 0.57$, $\sigma(\log) = 0.18$	[9, 46]
RR of major bleeding, IM or PM vs. EM	0.8400	0.7500	0.9400			[47]
Annual mortality of PLATO Population	$0.0098e^{(0.0954(\text{Age}-62))} \times 2$					[37, 38]
Utilities						
Utility, general health status	0.8500	0.6540	1.0000	Beta	$\alpha = 9.99$, $\beta = 1.77$	[48]
Disutility, non-ICH bleed	0.0150	0.0075	0.0300			[49]
Disutility, ICH	0.2300	0.2065	0.2535			[50]
Disutility, myocardial infarction	0.1470	0.1340	0.1600			[51]
Disutility, ischemic stroke	0.1780	0.1630	0.1930			[51]

EO expert opinion, *ICH* intracranial hemorrhage, *PRA* platelet reactivity assay, *RR* relative risk, *LOF* loss-of-function, *ACS* acute coronary syndrome

[a] Drug costs represented as cost/day

50,000 patients treated with clopidogrel, we estimated 30% of ACS patients to be intermediate or poor metabolizers of *CYP2C19* [9, 47]. The model assumed all normal metabolizers and 28% of intermediate metabolizers would have an appropriate antiplatelet response to clopidogrel, while all other clopidogrel recipients had a poor response [9]. Based on this calculation, the model assumed that 22% of patients are true candidates for ticagrelor, which is a midpoint of prevalence data from recent PRA studies [19, 52, 53]. The risk of complications in patients who were poor responders to clopidogrel were assumed to be same as those who were *CYP2C19* poor metabolizers [9, 46].

Daily cost of antiplatelet agents was calculated from the average wholesale price available from RedBook® [39]. The cost of acute care for the index hospitalization was extracted from Healthcare Cost and Utilization Project (HCUP) national statistics [54]. Costs for the short-term (initial hospitalization) and long-term (years 1–3 or later) complications (recurrent MI, ischemic stroke, ICH, or non-ICH major bleeding) were derived from HCUP national statistics and previous reports in the literature [40, 42, 54, 55]. The expected cost of PRA and genotyping were extracted from the Clinical Laboratory Fee Schedule data [43]. All cost inputs were converted to 2017 US dollars using the Consumer Price Index for Medical Care [56]. The utility of each complication was identified from published studies reporting utility scores derived from EQ-5D® [48–51]. Estimated disutility values for corresponding adverse event encounters were subtracted from the EQ-5D® scores of US adults aged from 55 to 64 years. For patients who suffered multiple complications, the disutility of each complication were added together and this sum subtracted from the EQ-5D® score to calculate the final utility score [57]. Patients who died were assigned a utility score of zero. In the base case analysis, point estimates using the inputs described above were used to calculate total costs and QALYs associated with each treatment.

Sensitivity Analysis

One-way sensitivity analysis was performed for all variable inputs using the ranges shown in Table 1. We also performed three scenario analyses in which the daily clopidogrel cost decreased to $0.50, daily ticagrelor cost decreased to $7.06 and to $3.53 (e.g., 50% and 25% of the base case ticagrelor cost, respectively) to further assess the influence that lower-cost generics had on ICERs for each strategy. Probabilistic sensitivity analysis, using Monte Carlo simulation (10,000 iterations), was performed including variables that changed the ICER more than $5,000/QALY from each two-arm comparison after excluding first- or second-order dominated options. Beta distribution was assigned for rates of clinical outcomes to ensure that sampling distributions were centered on the base case estimate. Risk ratios between ticagrelor and clopidogrel followed a log-normal distribution which was defined by mean and standard deviation extracted from the clinical trial data. Gamma distribution was assigned to cost inputs, if applicable, using shape (α) and rate (λ) parameters. When 95% confidence interval could not be obtained from published studies, a range of 50–150% of the base case value for each variable was used in one-way sensitivity analyses and a triangular distribution for each input was assumed for the Monte Carlo simulations. Results from these analyses were presented on both the cost-effectiveness plane and as cost-effectiveness acceptability curves (probability a therapy would be cost-effective). Although incremental cost-effectiveness was evaluated using different willingness-to-pay (WTP) thresholds, a WTP threshold of $100,000 per QALY gained was generally deemed cost-effective.

Results

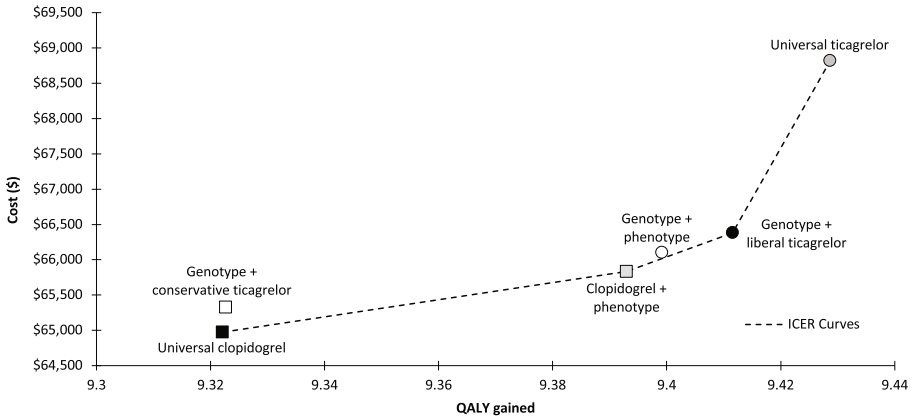
Base Case Analysis

Compared to universal clopidogrel (9.3221 QALY gained), each alternative $P2Y_{12}$ inhibitor selection strategies increased QALY gained (Fig. 2). The most effective strategy was universal ticagrelor (9.4287 QALY gained) while the genotype + conservative ticagrelor yielded the smallest increase in QALY gained (9.3227). Similarly, all $P2Y_{12}$ inhibitor strategies increased total costs compared to universal clopidogrel ($64,974); universal ticagrelor was the most costly ($68,818).

Three alternatives to universal clopidogrel were cost-effective depending on one's WTP. The ICERs for both the genotype + conservative ticagrelor and the genotype + phenotype strategies were higher than the next most effective strategies (universal clopidogrel and clopidogrel + phenotype, respectively). Thus, due to second-order dominance, both of these strategies were excluded. Among the four remaining $P2Y_{12}$ inhibitor selection strategies, clopidogrel + phenotype had the lowest ICER ($12,119/QALY compared to universal clopidogrel) followed by genotype + liberal ticagrelor ($29,412/QALY compared to clopidogrel + phenotype), and universal ticagrelor ($142,456/QALY compared to genotype + liberal ticagrelor). At a WTP threshold of $100,000/QALY, both the clopidogrel + phenotype and genotype + liberal ticagrelor strategies were considered cost-effective.

One-Way Sensitivity Analysis

In one-way sensitivity analyses, the remaining alternative $P2Y_{12}$ inhibitor selection strategies were sensitive to the risk ratios of the ischemic and bleeding events included in the model (Fig. 3). Compared to universal clopidogrel, the ICER for the clopidogrel + phenotype strategy ranged from $5,830/QALY to $1,164,000/QALY depending on the risk



STRATEGY	COST ($)	QALY gain	Incremental cost ($)	Incremental effect (QALY)	ICER ($/QALY)	DOMINATED	Final ICER ($/QALY) (excluding 2nd order dominance strategies)
Universal clopidogrel	64,974	9.3221	-	-	-		-
Genotype + conservative ticagrelor	65,326	9.3226	352	0.0005	704,000	2nd order	-
Clopidogrel + phenotype	65,832	9.3929	506	0.0703	7,198		12,119
Phenotype + genotype	66,102	9.3992	270	0.0063	42,857	2nd order	-
Genotype + liberal ticagrelor	66,382	9.4116	280	0.0124	22,581		29,412
Universal ticagrelor	68,818	9.4287	2,436	0.0171	142,456		142,456

Fig. 2 Base case analysis. Each box represents the cost and quality-adjusted life years (QALY) gained associated with each $P2Y_{12}$ inhibitor selection strategy. Incremental cost-effectiveness ratios (ICERs) were calculated for each $P2Y_{12}$ selection strategy with the strategy that yielded the next most QALY serving as the comparator. $P2Y_{12}$ inhibitor selection strategies that displayed either first-order (more costly, less effective; strictly dominated) or second-order dominance (higher ICER; extended dominance) were not deemed cost-effective and were excluded from calculation of the final ICERs

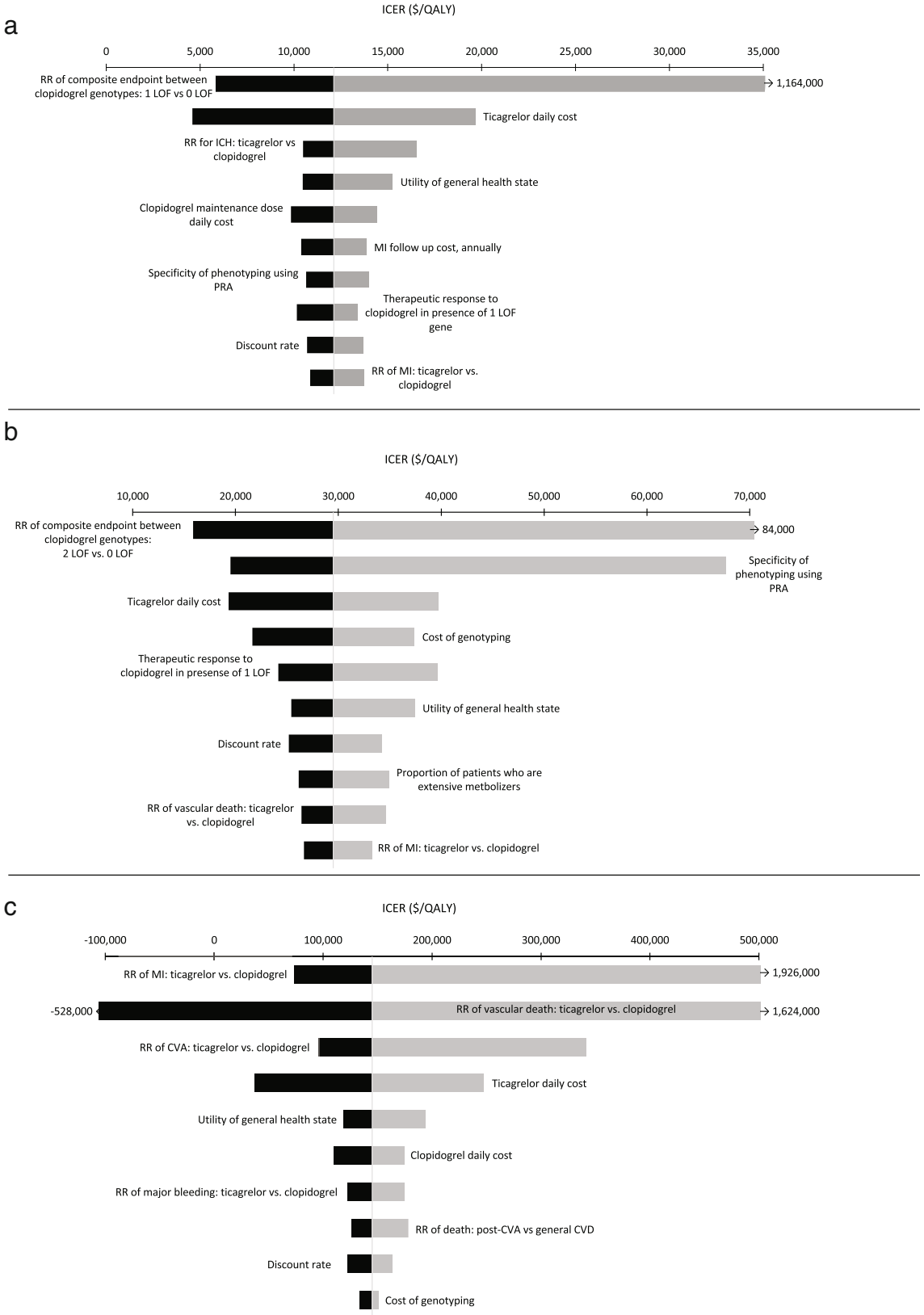
ratio for the composite endpoint between patients who carry one *CYP2C19* LOF allele and those without the polymorphism (Fig. 3a). The ICER for the genotype + liberal ticagrelor (compared to clopidogrel + phenotype) was most sensitive to the risk ratio of the composite endpoint between patients with two *CYP2C19* LOF alleles and those without the polymorphism and also the specificity of phenotyping using PRA (Fig. 3b). However, the ICER for genotype + liberal ticagrelor was consistently less than $100,000/QALY for all sensitivity analyses conducted. The ICER for universal ticagrelor strategy demonstrated the most variance (compared to the genotype + liberal ticagrelor strategy) depending on the risk ratios of MI, vascular death, and ischemic stroke as well as the daily cost of ticagrelor (Fig. 3c).

In the scenario analyses (Table 2), lowering the daily cost of clopidogrel to $0.50 did not influence the ranking of ICERs for the various strategies but did impact the relative cost-effectiveness somewhat. The ICERs for the clopidogrel + phenotype and genotype + liberal ticagrelor strategies compared to the next best option increased slightly ($13,762/QALY and $34,125/QALY, respectively). But, the ICER for the universal ticagrelor vs. the genotype + liberal ticagrelor strategy exceeded $200,000/QALY and was no longer cost-effective. In contrast, lowering the daily cost of ticagrelor to $7.06 dramatically reduced the ICER of universal ticagrelor compared to the genotype + liberal ticagrelor ($37,633/QALY) making it a cost-effective option. Universal ticagrelor exhibited dominance over all other $P2Y_{12}$ inhibitor selection strategies when the daily ticagrelor cost was reduced to 25% of the base case (third scenario analysis) and resulted in an ICER of $122/QALY compared to universal clopidogrel.

Probabilistic Sensitivity Analysis

Results from the probabilistic sensitivity analyses demonstrate that both incremental costs and effectiveness were variable when comparing the four $P2Y_{12}$ inhibitor strategies to one another (Fig. 4). Compared to universal clopidogrel, the clopidogrel + phenotype strategy demonstrated the greatest variation in incremental effectiveness. The universal ticagrelor strategy had the greatest variation in incremental costs compared to the genotype + liberal ticagrelor strategy. The strategy with the least variation in both incremental costs and effectiveness was the genotype + liberal ticagrelor compared to the clopidogrel + phenotype strategy.

As the WTP threshold increased, the acceptable $P2Y_{12}$ inhibitor selection strategy changed (Fig. 5a). The probability of universal clopidogrel being cost-effective decreased rapidly as WTP threshold increased. The probabilities of both the clopidogrel + phenotype and genotype + liberal ticagrelor rose rather sharply as the WTP threshold increased. However, the probability for clopidogrel + phenotype also deceased rapidly, whereas the decrease in acceptability for the genotype + liberal ticagrelor was less and more gradual. The probability that the universal ticagrelor strategy would be cost-effective gradually and consistently increased as the WTP threshold increased. At a WTP threshold of $100,000/QALY, the probability of being cost-effective for the genotype + liberal ticagrelor, universal ticagrelor, clopidogrel + phenotype, and universal clopidogrel strategies were 63%, 33%, 3%, and 1%, respectively. When the WTP threshold increased to $150,000/



QALY, the universal clopidogrel and clopidogrel + phenotype strategies were rarely preferred leaving the genotype + liberal ticagrelor and universal ticagrelor approaches as acceptable options with little difference observed between them. When evaluated as two-way comparisons between $P2Y_{12}$ inhibitor selection strategies, at a WTP threshold of

◀ **Fig. 3** One-way sensitivity analysis. **a** One-way sensitivity test for clopidogrel + phenotype vs. universal clopidogrel strategies. **b** One-way sensitivity test for genotype + liberal ticagrelor vs. clopidogrel + phenotype strategies. **c** One-way sensitivity test for universal ticagrelor vs. genotype + liberal ticagrelor strategies. For each figure, the ten variables that had the greatest impact on the incremental cost-effectiveness ratio (ICER) are shown; black bars indicate that the ICER was lower than the ICER from the base case analysis while gray bars indicate the ICER was greater than the base case analysis in response to varying the input value for the respective model variable. *QALY* quality-adjusted life years gained, *RR* relative risk, *LOF* loss of function allele(s), *ICH* intracranial hemorrhage, *MI* myocardial infarction, *PRA* platelet reactivity assay, *CVA* cerebrovascular accident (stroke), *CVD* cardiovascular disease

$100,000/QALY, acceptability rates for the clopidogrel + phenotype (compared to universal clopidogrel), genotype + liberal ticagrelor (compared to clopidogrel + phenotype), and universal ticagrelor (compared to genotype + liberal ticagrelor) were 98%, 97%, and 33%, respectively (Fig. 5b). At a WTP of $150,000/QALY, the clopidogrel + phenotype and genotype + liberal ticagrelor strategies were preferred to the next most effective strategy in 98% and 99% of the simulations, respectively, but acceptability rate of universal ticagrelor was only 50%.

Discussion

Although prasugrel and ticagrelor have been shown to be superior to clopidogrel in preventing MACE in patients with ACS, their high cost relative to clopidogrel has contributed to the underutilization of these agents. Personalizing $P2Y_{12}$ inhibitor therapy by identifying patients with ACS who are known (phenotype) or predicted (genotype) to respond poorly to clopidogrel may be a cost-effective approach. While several studies have evaluated the cost-effectiveness of genotype- or phenotype-guided strategies to personalize $P2Y_{12}$ inhibitor therapy in patients with ACS, to our knowledge, this is the first evaluation that comprehensively compares the cost-effectiveness of these two approaches and addresses the influence of the analytic validity (e.g., sensitivity and specificity varied by PRA cut-off) of the phenotype approach [19–24, 29–31]. Our analysis found that three strategies for selecting alternatives to clopidogrel in patients with ACS, each representing a different philosophical approach, were cost-effective depending on one's WTP. In the base case, a phenotype-guided approach (clopidogrel + phenotype) was more cost-effective than universal clopidogrel. Although probabilistic sensitivity analyses suggested that this strategy was subject to considerable variation in

Table 2 Incremental cost-effectiveness ratios resulting from scenario analyses

Strategy	ICER ($/QALY)	Dominated	Final ICER ($/QALY) (excluding 1st- and 2nd-order dominance strategies)
Scenario analysis 1: daily clopidogrel cost = $0.50			
Universal clopidogrel	Reference		Reference
Genotype + conservative ticagrelor	46,380	2nd order	–
Clopidogrel + phenotype	10,416		13,762
Phenotype + genotype	42,252	2nd order	–
Genotype + liberal ticagrelor	30,037		34,125
Universal ticagrelor	201,431		201,431
Scenario analysis 2: daily ticagrelor cost = $7.06 (50% of base case)			
Universal clopidogrel	Reference		Reference
Genotype + conservative ticagrelor	34,143	2nd order	
Clopidogrel + phenotype	335		3,481
Phenotype + genotype	42,312	2nd order	
Genotype + liberal ticagrelor	7,110		18,892
Universal ticagrelor	37,633		37,633
Scenario analysis 3: daily ticagrelor cost = $3.53 (25% of base case)			
Universal clopidogrel	Reference		Reference
Genotype + conservative ticagrelor	29,937	1st order	–
Clopidogrel + phenotype	− 2,927	2nd order	–
Phenotype + genotype	42,312	2nd order	–
Genotype + liberal ticagrelor	423	1st order	–
Universal ticagrelor	− 15,351		122

ICER incremental cost-effectiveness ratio

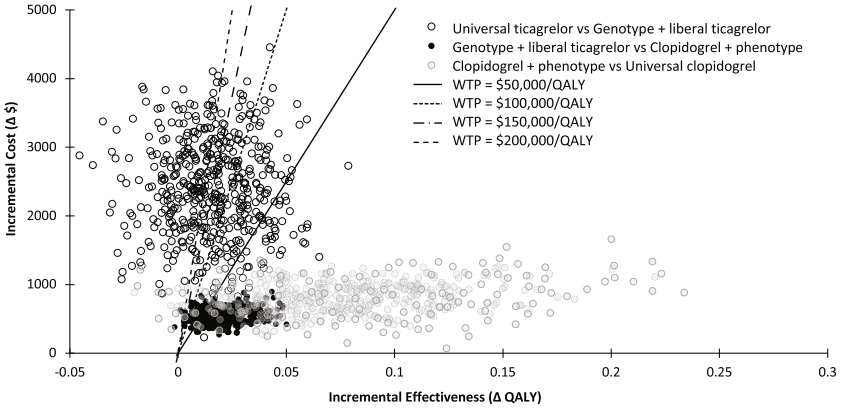


Fig. 4 Incremental costs and effectiveness from the Monte Carlo simulations. *WTP* willingness to pay, *QALY* quality-adjusted life years gained. Each circle reflects the incremental costs and incremental effectiveness from each Monte Carlo simulation compared to the next option ordered by QALY gained. The various WTP thresholds are depicted by the straight lines. The ICER for data points to the right of each WTP threshold are less than the threshold value (cost-effective) while the ICER for data points to the left of each WTP threshold are more than the threshold value (not cost-effective)

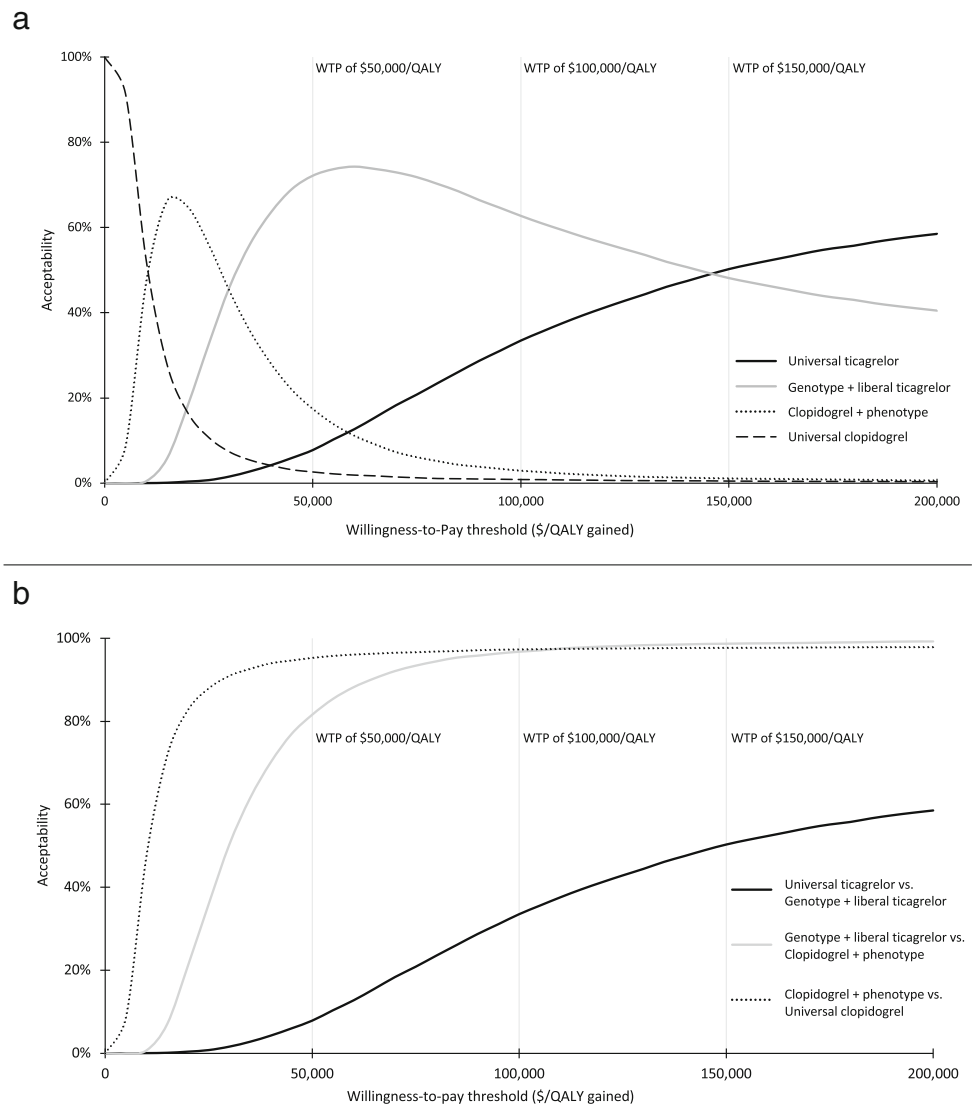


Fig. 5 Cost-effectiveness acceptability curves. **a** Simultaneous comparison of four $P2Y_{12}$ inhibitor selection strategies. **b** Series of two-way comparisons between $P2Y_{12}$ inhibitor selection strategies. Incremental cost-effectiveness ratios (ICERs) were calculated for each $P2Y_{12}$ selection strategy with the strategy that yielded the next most QALY serving as the comparator. $P2Y_{12}$ inhibitor selection strategies that displayed either first-order (more costly, less effective; strictly dominated) or second-order dominance (higher ICER; extended dominance) were not deemed cost-effective and were excluded from calculation of the final ICERs. For each $P2Y_{12}$ inhibitor selection strategy, the point at which the line crosses the vertical willingness-to-pay thresholds indicates the probability that the decision to use the selected strategy will be cost-effective. *QALY* quality-adjusted life years gained, *WTP* willingness to pay.

cost-effectiveness, at a WTP of $100,000/QALY, the probability that this strategy would be cost-effective compared to universal clopidogrel exceeded 90%. Personalizing $P2Y_{12}$ inhibitor selection based on genotype was also cost-effective, depending on the trigger for switching to ticagrelor. When ticagrelor was substituted for clopidogrel in patients with either one or two LOF alleles (genotype + liberal ticagrelor), the genotype-guided strategy was cost-effective in the base case (compared to the clopidogrel + phenotype strategy) and over a wide range of WTP range thresholds in probabilistic sensitivity analyses. Compared to the clopidogrel + phenotype strategy, acceptability of the genotype + liberal ticagrelor strategy exceeded 80% at a WTP threshold of $50,000/QALY and 97% at a WTP threshold of $100,000/QALY. In contrast, when ticagrelor was substituted for clopidogrel only in patients with two LOF alleles (genotype + conservative ticagrelor), the ICER was unacceptably high and the strategy was eliminated due to second-order dominance. If one is willing to accept a higher WTP threshold, a strategy of universal ticagrelor is also cost-effective, although it is subject to considerable uncertainty which limits the acceptability of this approach even at high WTP thresholds (58% at a WTP threshold of $200,000/QALY).

For the genotype-guided $P2Y_{12}$ inhibitor selection strategy, our findings are generally consistent with previous analyses which found this approach either dominated (lower cost, more effective) or was a cost-effective alternative to universal clopidogrel with ICERs less than $50,000/QALY [19–24]. In two previous analyses in which the genotype-guided strategy dominated universal clopidogrel, the cost inputs for both clopidogrel and alternative $P2Y_{12}$ inhibitors were considerably lower than those included in our analysis which may explain, in part, why the genotype-guided strategy dominated while another model, conducted prior to the availability of generic clopidogrel, used the cost of branded clopidogrel [20, 22, 24]. When the cost of generic clopidogrel was substituted for the branded product in the latter analysis, the genotype-guided $P2Y_{12}$ inhibitor selection strategy had an ICER of $2,300/QALY [24]. Lowering the daily cost of clopidogrel to $0.50 in our analysis resulted in only modest changes in the ICER for personalized strategies. Unlike previous models, some of which used long-term or lifetime horizons, cardiovascular events occurring after the first year were assumed to be independent from event rates during the 1 year of DAPT in our model [19–22]. Consequently, our estimates are more conservative. Despite differences in model structure, the number of QALY gained using the genotype + liberal ticagrelor strategy in our analysis compared to clopidogrel (0.0895) was similar to several previous analyses, validating our assumptions [19–21].

In previous decision models comparing a genotype-guided approach to other $P2Y_{12}$ inhibitor selection strategies, universal use of an alternative $P2Y_{12}$ inhibitor (prasugrel or ticagrelor) have produced discordant results. A genotype-guided approach dominated the universal use of alternative $P2Y_{12}$ inhibitors in most studies [20, 22–24]. In contrast, two previous analyses found that the universal ticagrelor strategy was a cost-effective alternative (ICER $42,456/QALY–$52,600/QALY) [19, 21]. However, the cost of ticagrelor used in these models was 38–61% lower than that used in our model, likely impacting the ICERs. In our model, universal ticagrelor was of intermediate value (ICER $142,456/QALY) but was no longer cost-effective when the daily cost of clopidogrel was lowered to $0.50.

Similar to our decision analysis, previous decision models have found that a phenotype-guided $P2Y_{12}$ inhibitor selection strategy is cost-effective (ICERs between $40,000/QALY–$50,000/QALY) [29, 30]. As we found in our model, decision analyses evaluating phenotype-guided strategies are sensitive to changes in drug-specific hazard ratios for MACE [29]. While the phenotype-guided strategy could be cost-effective compared to clopidogrel, above a WTP threshold of $29,516/QALY, alternative strategies (e.g., genotype + liberal ticagrelor) are more cost-effective.

Although a prior decision model found that utilization of both genotype and phenotype to personalize $P2Y_{12}$ inhibitor therapy in ACS patients was less costly and more effective than alternative strategies, our analysis found that this approach was subject to second-order dominance and was excluded [31]. There are important differences in assumptions related to *CYP2C19* intermediate metabolizers between the two models. In the previous model, high-dose clopidogrel (225 mg daily) was used for *CYP2C19* intermediate metabolizers; switching to an alternative $P2Y_{12}$ inhibitor only in patients with HTPR on high-dose clopidogrel, whereas our model utilized ticagrelor as the alternative for both *CYP2C19* intermediate metabolizers and patients with HTPR [31]. Because the cost input for high-dose clopidogrel was ~50% lower than the cost of alternative $P2Y_{12}$ inhibitors, this likely contributed to the first-order dominance observed [31].

Our observations that a genotype-guided strategy for selecting $P2Y_{12}$ inhibitors in patients with ACS may be preferred over other strategies is consistent with recent clinical evidence. While most of the evidence supporting a genotype-driven strategy for selecting $P2Y_{12}$ inhibitors have not focused on patients with ACS but rather patients with CAD undergoing PCI, a recent trial of 888 patients with ACS found a genotype-guided strategy reduced the risk of MACE by 42% compared to standard care without genotype information [14]. Interpretation of these findings is limited because the study was terminated early after enrolling only 25% of the prespecified sample size. However, it is one of the first and largest prospective studies to support the use of a genotype-guided approach specifically in patients with ACS [14]. At least two ongoing, large-scale, prospective clinical trials are investigating the effectiveness and cost-effectiveness of a genotype-guided approach in high-risk patients with CAD undergoing PCI, including those with ACS (clinicaltrials.gov,

NCT01742117 and NCT01761786, respectively). While the evidence supporting a genotype-guided strategy is growing, there is debate regarding the utility of a phenotype-guided approach. In clinical trials that utilized PRA testing to personalize $P2Y_{12}$ inhibitors in ACS, the phenotype-guided approach was either no different or noninferior to universal therapy with prasugrel [26, 28]. In contrast, observational data suggests that a phenotype-guided strategy in patients with ACS is associated with a lower risk of MACE [27]. Given uncertainty surrounding the clinical utility of using a phenotype-guided approach, growing evidence to support a genotype-guided strategy, and our data suggesting the genotype + liberal ticagrelor is cost-effective compared to clopidogrel + phenotype, the genotype-guided approach should be preferred.

Our data should be interpreted in the context of several potential limitations. The impact of clopidogrel and ticagrelor on the risk of MACE were estimated from a single controlled trial [10]. Although this trial included more than 18,000 patients from 43 different countries, the results may not be generalizable to patients who differ significantly from our assumptions (e.g., age, race, cardiovascular risk, treatments received, adherence, etc.). Although the real-world effectiveness of these therapies may differ from that observed in clinical trials due to differences in one or more of these characteristics or technological advances in the diagnosis and treatment of ACS, recent observational analyses suggest that the clinical trial results are reproducible, validating our use of this data for model inputs [10, 58, 59]. Additionally, the ICERs for the alternative $P2Y_{12}$ inhibitor strategies were relatively stable in response to changes in rates of MACE with the exception of the universal ticagrelor strategy, which was sensitive to changes in several variables including the risk of MACE. Another limitation of our study is that the differences between subgroups who might benefit from particular therapies could not be thoroughly evaluated in the model due to insufficient evidence. Although our model assumed that all normal metabolizers had an appropriate antiplatelet response to clopidogrel, multiple factors besides *CYP2C19* genotype contribute to variability in platelet reactivity following clopidogrel administration. Therefore, a proportion of patients may have a poor antiplatelet response to clopidogrel despite being categorized as normal metabolizers based on genotype, resulting in an overestimation of clopidogrel efficacy in our model. Ethnicity, age, principal diagnosis, comorbidities, and bleeding risk may alter the effectiveness, safety, and, therefore, cost-effectiveness of $P2Y_{12}$ inhibitors. Because the cost of generic clopidogrel has continued to decline and a generic formulation of ticagrelor will soon be available, our cost inputs for both drugs may have overestimated the cost of therapy resulting in potentially lower ICERs for alternative therapies. However, based on one-way sensitivity analyses (Fig. 3) and scenario analyses, the cost of clopidogrel had a relatively low impact on the ICERs for the clopidogrel + phenotype and genotype + liberal ticagrelor strategies, but eliminated universal ticagrelor as a cost-effective strategy. In contrast, lowering the cost of ticagrelor in the scenario analyses significantly lowered the ICERs of universal ticagrelor, making it a more cost-effective option in both scenarios. Our study did not consider switching or premature discontinuation of the antiplatelet strategy. In real-world practice, many patients switch their initial $P2Y_{12}$ inhibitor to an alternative option [60, 61]. However, because the impact of $P2Y_{12}$ inhibitor switching on long-term outcomes has not been well-studied, our model did not incorporate switching $P2Y_{12}$ inhibitors nor premature discontinuation of these agents. Prasugrel was not evaluated as a $P2Y_{12}$ inhibitor strategy in this study. Since our model assumed that 36% of patients would not be treated with PCI, a population for whom prasugrel is not recommended, we believe we were just excluding prasugrel [3, 34]. Finally, although our results were relatively robust to a broad range of sensitivity analyses related to model assumptions, uncertainty around some of the model inputs, their assigned distributions, and the combined impact of multiple inputs may have influenced our results in ways we did not detect.

Conclusions

Our analysis found that two strategies (clopidogrel + phenotype and genotype + liberal ticagrelor) for selecting alternatives to clopidogrel in patients with ACS were cost-effective at a WTP threshold of $100,000/QALY and a third (universal ticagrelor) was cost-effective at a WTP threshold of $150,000/QALY. However, above a WTP of $29,516/QALY, the probability that the genotype + liberal ticagrelor strategy was cost-effective exceeded that of the clopidogrel + phenotype strategy and demonstrated less uncertainty compared to universal ticagrelor in probabilistic sensitivity analyses. Consequently, the genotype + liberal ticagrelor strategy may be preferred.

Acknowledgements The authors would like to acknowledge and thank Marty Calabrese, PharmD for his assistance in collecting and analyzing background information on treatment trends and economics of cardiovascular diseases, including acute coronary syndrome.

Compliance with Ethical Standards

Conflict of Interest Dr. DiDomenico received an honorarium from Amgen Inc. for preparation of a heart failure drug monograph for *Pharmacy Practice News*. He also served as an Otsuka America Pharmaceuticals, Inc. heart failure advisory board member. Dr. Touchette received an unrestricted grants from Cardinal Health, Sunovion Pharmaceuticals Inc. He has also served as a consultant to and Director of the American College of Clinical Pharmacy Practice-Based Research Network on a study funded by Pfizer Inc.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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