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Cost-effectiveness of *CYP2C19*-guided antiplatelet therapy in patients with acute coronary syndrome and percutaneous coronary intervention informed by real-world data

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Abstract

Current guidelines recommend dual antiplatelet therapy (DAPT) consisting of aspirin and a P2Y12 inhibitors following percutaneous coronary intervention (PCI). *CYP2C19* genotype can guide DAPT selection, prescribing ticagrelor or prasugrel for loss-of-function (LOF) allele carriers

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(genotype-guided escalation). Cost-effectiveness analyses (CEA) are traditionally grounded in clinical trial data. We conduct a CEA using real-world data using a 1-year decision-analytic model comparing primary strategies: universal empiric clopidogrel (base case), universal ticagrelor, and genotype-guided escalation. We also explore secondary strategies commonly implemented in practice, wherein all patients are prescribed ticagrelor for 30 days post PCI. After 30 days, all patients are switched to clopidogrel irrespective of genotype (nonguided de-escalation) or to clopidogrel only if patients do not harbor an LOF allele (genotype-guided de-escalation). Compared with universal clopidogrel, both universal ticagrelor and genotype-guided escalation were superior with improvement in quality-adjusted life years (QALY's). Only genotype-guided escalation was cost-effective ($42,365/QALY) and demonstrated the highest probability of being cost-effective across conventional willingness-to-pay thresholds. In the secondary analysis, compared with the nonguided de-escalation strategy, although genotype-guided de-escalation and universal ticagrelor were more effective, with ICER of $188,680/QALY and $678,215/QALY, respectively, they were not cost-effective. *CYP2C19* genotype-guided antiplatelet prescribing is cost-effective compared with either universal clopidogrel or universal ticagrelor using real-world implementation data. The secondary analysis suggests genotype-guided and nonguided de-escalation may be viable strategies, needing further evaluation.

Introduction

The introduction of percutaneous coronary intervention (PCI) and P2Y12 receptor antagonists clopidogrel, prasugrel [1], and ticagrelor [2] have significantly improved outcomes in patients with acute coronary syndrome (ACS) [3].

For patients undergoing PCI, dual antiplatelet therapy (DAPT) consisting of aspirin and a P2Y12 inhibitor is recommended [4]. P2Y12 inhibitor selection is based on an individual's risk of bleeding and therapeutic failure, and medication costs. Although the use of ticagrelor and prasugrel (alternative antiplatelets) is increasing, clopidogrel remains widely used [5]. The efficacy of clopidogrel is influenced by variants in the cytochrome P450 2C19 gene (*CYP2C19*), with patients possessing *CYP2C19* loss-of-function (LOF) alleles (**2*:rs4244285, **3*:rs4986893), experiencing an increased risk for stent thrombosis and major adverse cardiovascular events (MACE) [6]. In contrast, *CYP2C19* genotype does not influence the efficacy of prasugrel or ticagrelor [7, 8]. Both have demonstrated superior efficacy compared with clopidogrel, albeit without prospective genotype substratification and at increased bleeding risk and higher medication costs [2]. Clinical trial results have also informed cost-effectiveness analysis (CEA) of alternative antiplatelets versus clopidogrel [9–12] and of *CYP2C19* genotype-guided DAPT [13–15].

With the availability of rapid genotyping, guidance from the FDA and Clinical Pharmacogenetics Implementation Consortium (CPIC) [16], and the potential to improve outcomes by guiding P2Y12 inhibitor selection, implementation of genotype-guided DAPT has been a major focus of precision medicine efforts [17–19]. The Implementing GeNomics In pracTicE Network Pharmacogenetic Working Group recently showed that among patients prescribed clopidogrel (versus alternative antiplatelets), possession of *CYP2C19* LOF allele was associated with twofold increase in MACE risk in patients undergoing PCI (HR = 2.3;

95% CI: 1.2–4.3; $p = 0.013$) and almost threefold increase in MACE risk in patients undergoing PCI for ACS (HR: 2.9; 95% CI 1.3–6.19, $p = 0.013$) [20].

Using these real-world effectiveness data, we conducted a CEA of genotype-guided DAPT versus empiric DAPT following ACS and PCI. Unlike prior efforts, which conducted CEA using data from clinical trials, our analysis is based on event rates observed in routine clinical practice. In addition, unlike prior analyses, which assumed treatment strategies do not change over time, we explored secondary strategies informed by clinical practice wherein treatment is modified at 30 days post PCI.

Methods

A decision-analytic model was designed to simulate costs and outcomes across treatment strategies using the payer perspective (Fig. 1) [21]. For each strategy, we simulated the expected outcomes for 2,000,000 ACS patients (Table 1) following PCI over a 1-year time horizon. During this time, a patient might experience no event, stent thrombosis, nonfatal stroke, nonfatal MI, major bleeding, or cardiovascular death.

The *primary strategies* we compared were universal empiric clopidogrel (base case), universal ticagrelor, and *CYP2C19* genotype-guided escalation. Genotype-guided escalation included genotyping at time of PCI, with ticagrelor prescribed for all LOF allele carriers and clopidogrel prescribed for patients without an LOF allele for 12 months. The *secondary strategies* included strategies commonly implemented in practice, wherein all patients are prescribed ticagrelor for the first 30 days post PCI, followed by universal de-escalation to clopidogrel (without genotyping) or genotype-guided de-escalation to clopidogrel only in patients without an LOF allele for the remaining 11 months [22, 23].

Model structure and inputs

The CE model was created as a discrete event simulation using our implementation study and literature-based values for variant frequencies, clinical outcomes, secular death, utilities, and costs. Health state utilities and costs were assigned to each event in 1-month cycles. Model input parameters are presented in Table 2. The LOF allele frequency (32%) was informed by prior reports [16, 19, 20, 24]. Recognizing that LOF allele frequency varies across racial groups, we include additional analysis varying the LOF allele frequency from 20 to 70%, in 5% increments. We assumed that genotyping was 100% sensitive and 100% of physicians use the information from genetic testing if already available. To account for variation in physician acceptance, we include additional analysis varying the acceptance from 60 to 100% in 10% increments.

For genotype-guided strategies, we modeled the DAPT regimens based on CPIC guidelines [16]. As ticagrelor is preferentially used over prasugrel in post ACS/PCI settings [5], it was included as the alternative antiplatelets in all analyses. We assumed that patients possessing LOF alleles would receive ticagrelor, whereas patients with gain-of-function (**1*/**17*, **17*/**17*), or normal function (**1*/**1)* alleles, would be treated with clopidogrel. Because one increased function allele does not completely compensate for one LOF allele (**2*/**17*) such persons would receive ticagrelor consistent with CPIC recommendations.

The rates and timing of adverse events (MACE events MI, stroke, and death) were informed by observed event rates as a function of *CYP2C19* allele status [6, 20, 24]. Treatment-related incidence of bleeding was estimated from randomized trials. As the 30-day de-escalation strategies were not directly implemented or measured, we considered these strategies secondary; the simulation used different subpopulations of the implementation cohort when calculating early (0–30 days) versus late (31–365 days) event rates.

For clopidogrel treated patients, we estimated the incidence of MACE events from ACS patients in our prospective study [20], and from clinical trials, observational data, U.S. life tables, Medicare claims, guidelines, and other publications. [1, 2, 25–30] The event rates in the other gene-treatment groups were estimated using rate ratios relative to patients on clopidogrel from our recent report [20]. As the effects of ticagrelor are unaffected by *CYP2C19* genotype, we assumed that LOF allele carriers and noncarriers have similar outcomes [28]. Based on results from Platelet Inhibition and Patient Outcomes study, we assumed that ticagrelor reduced cardiovascular deaths without a corresponding increase in fatal bleeding [2, 25].

Quality-of-life estimates and costs

We estimated age-specific quality of life [31]. We assumed that patients who had an MI or stent thrombosis had a 0.12 permanent quality-of-life decrement [32]. We included direct medical costs (such as admissions, procedures, clinical visits, and drugs) and induced costs (such as cost of procedural complications) but not indirect costs (such as lost wages and caregiver costs). Cost estimates were derived from Medicare reimbursement rates, the Nationwide Inpatient Sample, and key publications in the health economics literature [33, 34]. We estimated age-specific costs from the Agency for Healthcare Research and Quality's Medical Expenditure Panel Survey [15].

We assumed current monthly prescription costs (goodrx. com) for generic clopidogrel (base case $10/month; range $5–60/month), and ticagrelor (base case $360/month; range $20–460/month) in the sensitivity analyses. The 6-month average costs were used as the reference. We estimated cost of genotyping (base case $100/test) from a survey of retail process of commercially available tests but included a range ($50–250/test).

We present results in 2016 U.S. dollars, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs). ICERs were calculated using the difference in cost divided by the difference in their effect. Strategies are considered cost-effective if the associated ICER is below the willingness-to-pay (WTP) threshold of $100,000 per QALY [35]. To facilitate comparisons across the strategies in sensitivity analyses we calculated the net monetary benefit (NMB), calculated by multiplying QALY × WTP and subtracting the cost for each strategy. We conducted one-way sensitivity analyses to explore the impact of variation in the cost of genotyping and drug therapy, and a probabilistic sensitivity analysis (PSA) using the Saltelli method to account for uncertainty across all clinical risks, utilities, and costs simultaneously [36]. The results of the PSA for the probability of the primary strategies being cost-effective compared with the reference strategy across a wide range of WTPs are presented using cost-effectiveness acceptability curves (CEAC). The simulation and sensitivity analyses were conducted using the simmer package in R (Version 3.6.3).

Results

For the primary strategies, both universal ticagrelor and genotype-guided escalation had a higher number of QALYs compared with universal clopidogrel (base case; Table 3). Genotype-guided escalation was cost-effective at $42,365/QALY, while universal ticagrelor was not (ICER of $227,044/QALY).

Among the secondary strategies, (Table 4) universal clopidogrel and genotype-guided escalation were dominated by the nonguided de-escalation strategy, which was more effective and less expensive. Compared with the nonguided de-escalation strategy, the genotype-guided de-escalation and universal ticagrelor were more effective and more expensive. However, genotype-guided de-escalation (ICER of $188,680/QALY) and universal ticagrelor (ICER $678,215/QALY) were not cost-effective.

One-way sensitivity analyses were conducted by varying the cost of testing and prescription costs for clopidogrel and ticagrelor. The relative rankings of strategies considered in our primary and secondary analyses remained unchanged from the reference case across the entire range of cost of testing considered (Supplementary Fig. 1a, b). Similarly, our reference case results were robust to varying monthly clopidogrel prescription costs from $5 to $60 (Supplementary Fig. 2a, b).

However, we did find our findings were sensitive to the assumptions made about the monthly ticagrelor prescription costs. When WTP is set at $100,000/QALY, the preferred strategy was universal ticagrelor when ticagrelor costs were less than $130/month, genotype-guided escalation when ticagrelor ranged from $130 to $380/month, and universal clopidogrel when ticagrelor costs exceed $380/month (Supplementary Fig. 3a) In the secondary analysis, the preferred strategy was universal ticagrelor when ticagrelor costs were less than $58/month, genotype-guided de-escalation when these costs ranged from $58 to $191/month, and nonguided de-escalation when they exceeded $191/month (Supplementary Fig. 3b).

Sensitivity analysis also revealed our primary and secondary findings were robust to assumptions made about bleeding risk among ticagrelor versus clopidogrel users [15] (Supplementary Fig. 4a, b). Variation in *CYP2C19* LOF allele frequency (Supplementary Fig. 5a, b) did not alter the preferred strategy, which remained genotype-guided escalation in the primary analysis and nonguided de-escalation in the secondary analysis across a broad range of LOF allele frequency (20–70%). Sensitivity analysis also revealed our primary and secondary findings were robust to varying acceptance of genotype-based recommendations (Supplementary Fig. 6a, b).

Probabilistic sensitivity analysis showed that results were most sensitive to assumptions about the risk of post-PCI myocardial infarction (Fig. 2a, b). Further, as demonstrated by the CEAC (Fig. 3), genotype-guided escalation had the highest probability of being cost-effective when compared with universal clopidogrel or universal ticagrelor across all conventional WTP thresholds.

Discussion

The paucity of clinical and cost-effectiveness data are often cited as barriers to pharmacogenetic implementation [37, 38]. To address these barriers, among patients undergoing *CYP2C19* genotyping after PCI as part of clinical care, we previously showed that prescribing alternative antiplatelets versus clopidogrel to those with an LOF allele reduced the risk for MACE [20]. Utilizing these real-world data, our primary CEA demonstrates that genotype-guided antiplatelet therapy is cost-effective compared with either universal clopidogrel or universal ticagrelor.

Previous cost-effectiveness studies used event rates and probabilities from clinical trials and consistently showed that genotype-guided DAPT after ACS and/or PCI was cost-effective compared with universal clopidogrel or prasugrel [39–41]. The data with ticagrelor are more variable [12], but more recent studies showed that genotype-guided DAPT was cost-effective versus universal ticagrelor following ACS and PCI [14, 15]. A recently completed randomized controlled trial (POPular Genetics NCT01761786 examined the clinical utility of genotype-guided DAPT after PCI in STEMI patients. Patients received ticagrelor or prasugrel (control group) or genotype-guided DAPT. Genotype-guided DAPT patients with LOF alleles received ticagrelor or prasugrel, and noncarriers received clopidogrel. genotype-guided DAPT group had a 0.7% lower absolute risk of MACE or major bleeding ($p < 0.001$ for noninferiority, $p = 0.4$ for superiority), and a significantly lower bleeding risk (HR 0.78; 95% CI, 0.61–0.98; $p = 0.04$) compared with universal alternative therapy [42]. This supports the clinical utility of genotype-guided DAPT, which is being further evaluated in an ongoing randomized controlled trial of patients undergoing PCI for either an ACS or non-ACS indication (Tailor-PCI NCT01742117).

Our study provides cost-effectiveness data in the context of real-world implementation of genotype-guided DAPT. Our results are congruent with data from the Netherlands, wherein, prescription of prasugrel for patients with two LOF alleles undergoing elective PCI was cost-effective compared with universal clopidogrel [43]. Our study extends these findings to a population of patients with ACS undergoing emergent PCI and where alternative antiplatelet therapy was recommended for patients with one or two LOF alleles, consistent with CPIC guidelines [16]. Our sensitivity analysis demonstrates that genotype-guided escalation remains cost-effective despite a higher bleeding risk among ticagrelor users (versus clopidogrel).

We also examined the cost-effectiveness of two de-escalation strategies compared with continuation of ticagrelor in a secondary analysis. The rationale for a de-escalation approach is that, while shown to be superior to clopidogrel in reducing MACE, prasugrel and ticagrelor are associated with higher medication cost and greater bleeding risk, which appears to be greatest with use beyond the early post-PCI period [44, 45]. Thus, use of a more potent P2Y12 inhibitor early after PCI when the risk for atherothrombotic events is highest, then de-escalating to clopidogrel for chronic therapy to minimize bleeding risk and lower medication costs is emerging in clinical practice [22, 23]. Recently, a de-escalation strategy guided by platelet function testing was shown to be noninferior to continued use of prasugrel for the net composite outcome of atherothrombotic and bleeding events [46].

De-escalation strategies could be potentially useful in real-world settings [47], allowing institutions without in-house genotyping facilities to obtain genotype results through a reference laboratory. However, the cost-effectiveness of de-escalation has not been evaluated. With this approach, alternative antiplatelets could be continued for those with the LOF allele, whereas therapy could be de-escalated to clopidogrel for patients with no LOF, thereby reducing costs and bleeding risk. We show that nonguided de-escalation from ticagrelor to clopidogrel after the initial 30 days is cost-effective (and less expensive) compared with a genotype-guided de-escalation approach or universal ticagrelor. However, this secondary analysis was based on estimated parameters from our implementation study receiving the primary strategies. Moreover, given the discordant outcomes data with a nonguided de-escalation strategy [22, 48], we recommend these results be considered as hypothesis generating, highlighting the need for studies evaluating the effectiveness and cost-effectiveness of the de-escalation strategies.

We focused our analysis on high-risk patients with ACS who underwent PCI, a group in whom we previously demonstrated a significantly lower risk for MACE when alternative therapy was prescribed over clopidogrel for *CYP2C19* LOF carriers [20]. Studies have consistently demonstrated associations between *CYP2C19* genotype and clopidogrel effectiveness in the setting of ACS and PCI [6, 8, 28, 49], whereas the association is less clear in those with stable coronary disease or ACS managed medically [50, 51].

The study was rigorously conducted and meets the standards of the Panel on Cost-Effectiveness in Health and Medicine. To our knowledge, this is the first analysis based on data from real-world practice without the eligibility restrictions of clinical trials, which tend to exclude/limit higher risk patients. As might be expected, our event rates were higher than those observed in trials and may better reflect event rates in the general population. This unique strength is of particular relevance to decision makers. As genotyping was conducted as part of clinical care, unlike previous CEAs, our analysis was not limited by assumptions regarding the availability genotype data in a timeline conducive for clinical care [17].

We used standardized costs for the post-PCI outcomes. While it may be intuitive to use institutional costs, locally negotiated contracts determine cost-to-charge ratios, are not readily available or shared, and are subject to change. We recognize that we did not account for indirect costs, such as lost time from work secondary to adverse events and our inability to estimate the proportion of patients treated with ticagrelor with treatment switched at 30 days, as this is not a strategy previously reported in clinical trials or observational studies [22]. The event rates modeled were from a population predominately European American (78%), with African Americans (15.7%) and other race groups (6.3%) contributing smaller proportions. As LOF allele frequencies are similar across European Americans and African Americans, we expect our findings are generalizable to these race groups. Although we model cost-effectiveness by varying the LOF allele frequencies from 20–70%, confirmation of these results in non-European race groups, with different LOF frequencies, is needed. Although guidelines recommend ticagrelor or prasugrel over clopidogrel in patients with ACS and PCI [4] based on superior efficacy of these drugs compared with clopidogrel [1, 2], we focused on ticagrelor as the alternative antiplatelet in our analysis. Data suggest similar efficacy of prasugrel and clopidogrel in patients without an LOF allele [52] while ticagrelor

demonstrated superior efficacy in patients with ACS irrespective of genotype [8]. Moreover, current P2Y12 inhibitor prescription data demonstrate preferential use of ticagrelor [53]. We recognize the limitations of the implementation data, wherein no events were accrued for some endpoints for the ticagrelor group. This may represent inability to capture all events in the real-world setting. Therefore, we conducted sensitivity analysis across reported ranges for these events to demonstrate no significant change in the results. We also recognize that models did not discount QALYs for the higher bleeding risk or dyspnea associated with ticagrelor or switching to clopidogrel in patients with ticagrelor associated-dyspnea [54]. We recognize that acceptance of genotype-based recommendations is not 100%. However, the CEA was robust to observed variability in acceptance. Finally, we did not collect information on medication adherence and assumed 100% adherence in our models. We recognize that if adherence was substantially lower than 100%, then the relative cost difference between treatment strategies would be attenuated. More complex models that incorporate a discontinuation (and crossover) rate need to be evaluated.

In summary, our analysis demonstrates cost-effectiveness of genotyping at the time of PCI to guide escalation of antiplatelet therapy. Our analysis also suggests that benefit of nonguided and genotype-guided de-escalation strategies on clinical outcomes and cost warrants further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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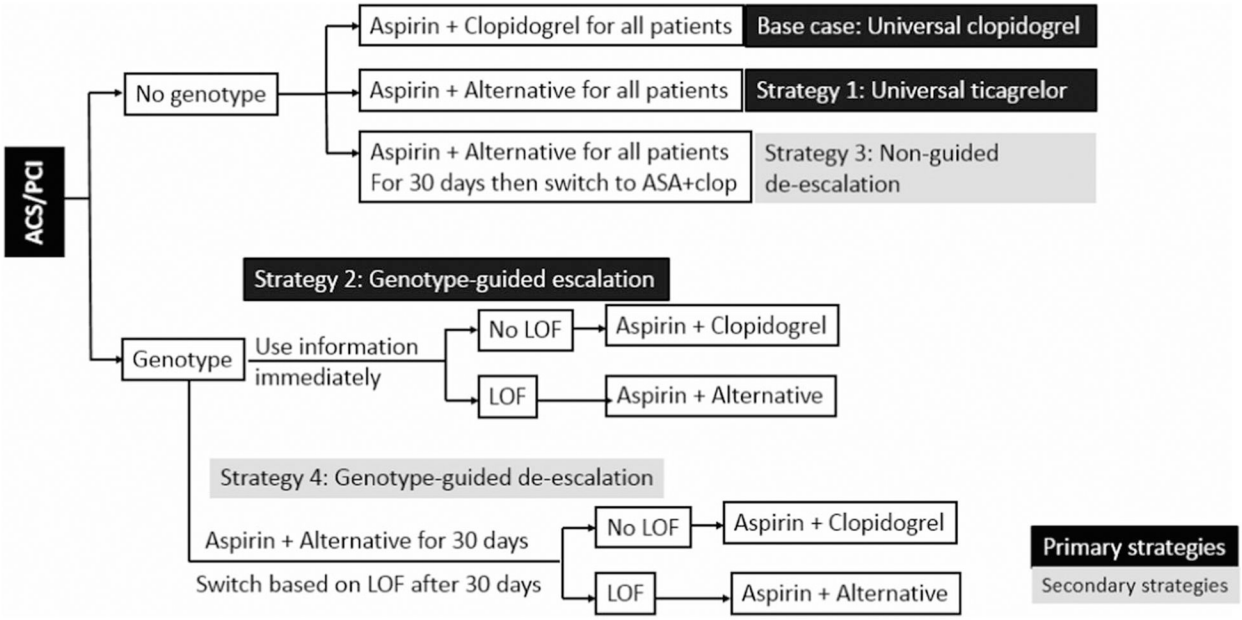

Fig. 1. Decision-analytic model simulating outcomes of five strategies over a 1-year horizon.
The primary strategies were universal clopidogrel (base case), universal ticagrelor, and *CYP2C19*-guided escalation. The secondary strategies were de-escalation at 30 days (unguided strategy 3; genotype-guided strategy 4).

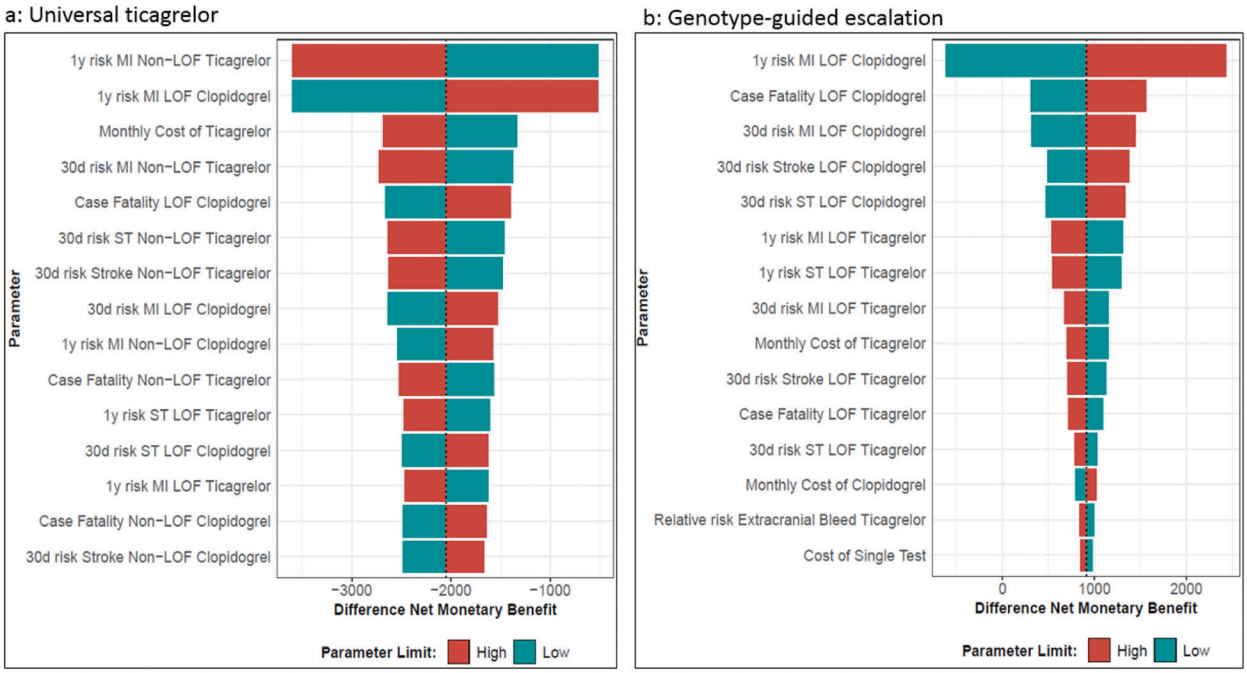

Fig. 2. Tornado plots of influential factors from the probabilistic sensitivity analyses (PSA).

Tornado plots of fifteen most influential factors from the probabilistic sensitivity analyses (PSA) of universal ticagrelor scenario (**a**) or genotype escalation scenario (**b**) compared with the reference scenario, universal clopidogrel. Parameter ranges used in PSA are given in Table 2; parameter values greater than base case are represented in red while values lower than base case are represented in green. Willingness to pay is set to 100,000/QALY. The difference in net monetary benefit on *x*-axis shows parameter values for which the alternative strategy is cost-effective (difference is positive) or when reference strategy is more cost-effective (difference is negative).

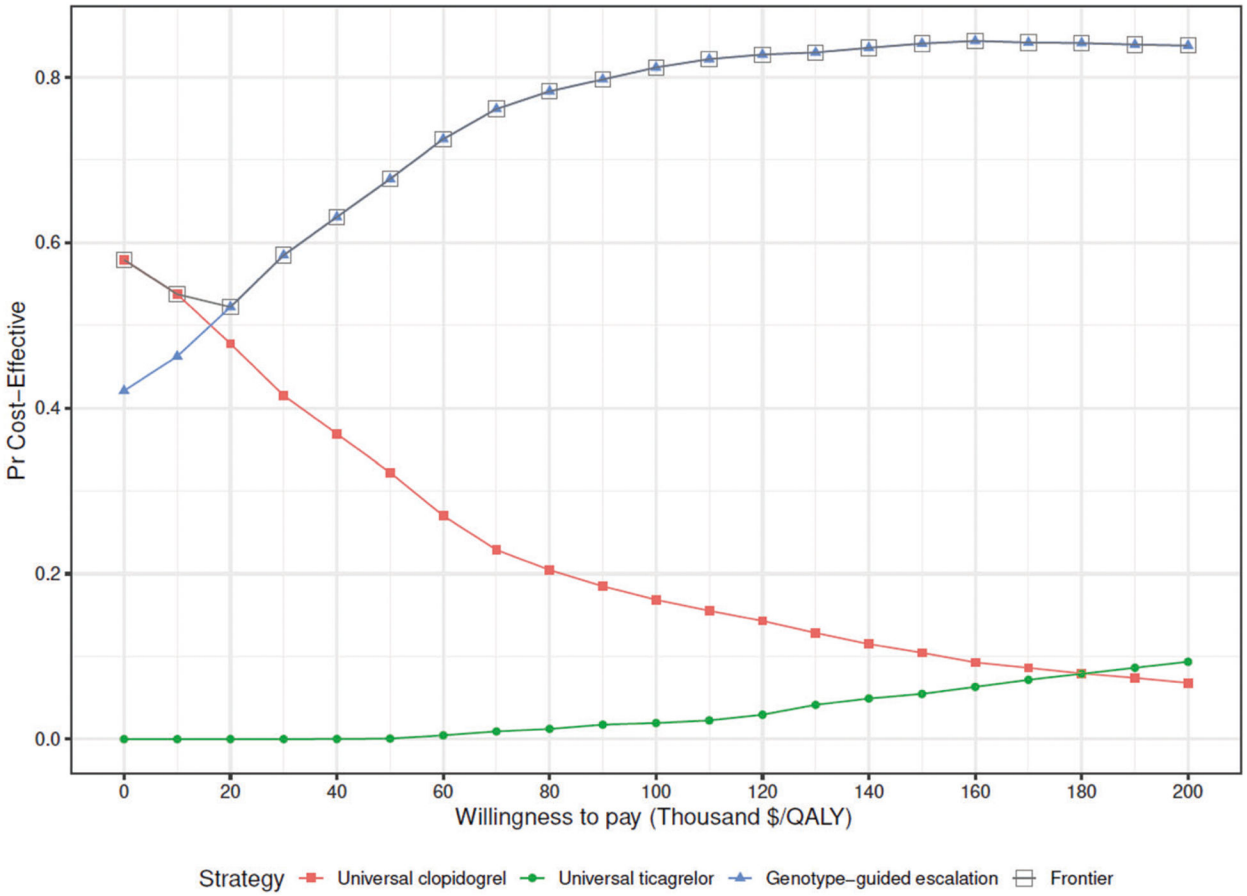

Fig. 3.

Cost-effectiveness acceptability curve and frontier; *y*-axis values indicate probability of a strategy being cost-effective across a wide range of willingness-to-pay thresholds.

Table 1

Adverse events experienced postpercutaneous coronary intervention under varying dual antiplatelet.

	Primary strategies			Secondary de-escalation strategies at 30 days[a]	
	Universal clopidogrel	**Universal ticagrelor**	**Genotype-guided escalation**	**Nonguided**	**Genotype-guided**
Patient population simulated	2,000,000	2,000,000	2,000,000	2,000,000	2,000,000
Received genotyping	-	-	2,000,000	-	1,989,912
Drug exposure					
Clopidogrel	2,000,000	-	1,359,024	1,989,912	1,351,774
Ticagrelor	-	2,000,000	640,976	2,000,000	2,000,000
Aspirin	2,000,000	2,000,000	2,000,000	2,000,000	2,000,000
Adverse events rates 0–30 days					
Stent thrombosis-related MI	11.87	4.53	4.99	4.53	4.53
MI without stent thrombosis	29.40	11.89	18.30	11.89	11.89
Stroke	8.20	NO	6.118	NO	NO
Revascularization	8.61	8.72	8.67	8.72	8.72
Bleeding	3.62	4.44	4.08	4.44	4.44
Mortality rate 0–30 days					
Secular death	1.46	1.44	1.49	1.44	1.44
Fatal bleed	0.11	0.10	0.11	0.10	0.10
Cardiovascular death	6.79	NO	3.06	NO	NO
Adverse event rates 31–365 days					
Stent thrombosis-related MI	9.07	7.72	16.53	9.03	16.63
MI without stent thrombosis	66.12	43.10	36.01	67.02	35.78
Stroke	4.54	NO	4.54	4.58	4.52
Revascularization	92.32	94.02	93.20	93.39	93.52
Bleeding	40.45	49.17	44.22	40.54	44.26
Mortality rate 31–365 days					
Secular death	15.88	15.92	15.90	15.81	15.87
Fatal bleed	1.39	1.24	1.25	1.35	1.29
Cardiovascular death	12.54	NO	5.14	12.72	5.29

NO denotes not observed in the 1800 patient prospective multi-institutional cohort.

Bleeding events includes both major and minor bleeding.

[a]Regarding the secondary de-escalation strategies at 30 days: 2,000,000 represents patients receiving ticagrelor for first 30 days. The number of patients in de-escalation strategies at 30 days reflects patients surviving and free of CABG at 30 days post PCI. (1) Under the nonguided de-escalation strategy, DAPT was discontinued in patients undergoing CABG. (2) Under genotype-guided de-escalation strategy, all survivors were genotyped (1,996,901) with 1,351,774 receiving clopidogrel on day 30 and 638,138 continuing Ticagrelor.

Table 2

Summary of key model parameters.

Variables	Base case value	Range
Population-level allele frequencies		
Population-level allele frequency distribution: poor metabolizer (loss-of-function) [20]	0.32	
Population-level allele frequency distribution: rapid metabolizer [20]	0.26	
Population-level allele frequency distribution: unknown metabolizer [20]	0.038	
Risk[a]		
Stent thrombosis		
30-day risk of stent thrombosis: Non-LOF patients receiving clopidogrel [20]	0.0074	0.0024–0.0173
31–365 day risk of stent thrombosis: Non-LOF patients receiving clopidogrel [20]	0.0135	0.0037–0.0347
30-day risk of stent thrombosis: Non-LOF patients receiving ticagrelor [20]	0.0067	0.0002–0.0371
31–365 day risk of stent thrombosis: Non-LOF patients receiving ticagrelor [20]	0	0.0000–0.0049
30-day risk of stent thrombosis: LOF patients receiving clopidogrel [20]	0.021	0.0043–0.0615
31–365 day risk of stent thrombosis: LOF patients receiving clopidogrel [20]	0	0.0000–0.0074
30-day risk of stent thrombosis: LOF patients receiving ticagrelor [20]	0	0.0000–0.0156
31–365 day risk of stent thrombosis: LOF patients receiving ticagrelor [20]	0.0244	0.0050–0.0712
Case fatality [20]		
Case fatality—cardiovascular death for myocardial infarction: Non-LOF patients receiving clopidogrel [20]	0.15	0.0010–0.3000
Case fatality (cardiovascular death) for myocardial infarction: Non-LOF patients receiving ticagrelor [20]	0	0.0000–0.3000
Case fatality (cardiovascular death) for myocardial infarction: LOF patients receiving clopidogrel [20]	0.18	0.0010–0.3600
Case fatality (cardiovascular death) for myocardial infarction (ST/non-ST) Events: LOF patients receiving ticagrelor [20]	0	0.0000–0.3000
Nonfatal stent thrombosis: Probability of coronary artery bypass grafting (CABG) [55, 56]	0.08	0.040–0.1200
Annual risk of noncardiovascular death (used as secular death risk): Non-LOF patients receiving clopidogrel [20]	0.0175	0.0000–0.1000
Myocardial infarction (Ml)		
30-day risk of myocardial infarction (not stent thrombosis related): Non-LOF patients receiving clopidogrel [20]	0.0225	0.0126–0.0371
31–365 day risk of myocardial infarction (not stent thrombosis related): Non-LOF patients receiving clopidogrel [20]	0.0379	0.0189–0.0679
30-day risk of myocardial infarction (not stent thrombosis related): Non-LOF patients receiving ticagrelor [20]	0.0133	0.0016–0.0481
31–365 day risk of myocardial infarction (not stent thrombosis related): Non-LOF patients receiving ticagrelor [20]	0.0484	0.0100–0.1416
30-day risk of myocardial infarction (not stent thrombosis related): LOF patients receiving clopidogrel [20]	0.0427	0.0157–0.0929
31–365 day risk of myocardial infarction (not stent thrombosis related): LOF patients receiving clopidogrel [20]	0.1262	0.0410–0.2945

Variables	Base case value	Range
30-day risk of myocardial infarction (not stent thrombosis related): LOF patients receiving ticagrelor [20]	0.0085	0.0010–0.0307
31–365 day risk of myocardial infarction (not stent thrombosis related): LOF patients receiving ticagrelor [20]	0.0327	0.0089–0.0838
Myocardial infarction (not stent thrombosis related): probability of CABG [29, 55, 56]	0.08	0.04–0.12
Myocardial infarction (not stent thrombosis related): probability of percutaneous coronary intervention (PCI) [55, 56]	0.55	0.45–0.65
Myocardial infarction (not stent thrombosis related): probability of medical management [55, 56]	0.37	0.23–0.51
Stroke [20]		
30-day risk of stroke: Non-LOF patients receiving clopidogrel [20]	0.009	0.0033–0.0196
31–365 day risk of stroke: Non-LOF patients receiving clopidogrel [20]	0.0068	0.0008–0.0245
30-day risk of stroke: Non-LOF patients receiving ticagrelor [20]	0	0.0000–0.0240
31–365 day risk of stroke: Non-LOF patients receiving ticagrelor [20]	0	0.0000–0.0047
30-day risk of stroke: LOF patients receiving clopidogrel [20]	0.0067	0.0002–0.0374
31–365 day risk of stroke: LOF patients receiving clopidogrel [20]	0	0.0000–0.0075
30-day risk of stroke: LOF patients receiving ticagrelor [20]	0	0.0000–0.0158
31–365 day risk of stroke: LOF patients receiving ticagrelor [20]	0	0.0000–0.0025
Annual risk of revascularization [57]	0.1	0.05–0.15
Surgical revascularization: probability of CABG [29]	0.25	0.15–0.35
Bleeding risk		
Annual risk of TIMI major nonfatal extracranial bleeds while receiving Clopidogrel and Aspirin [15]	0.023	0.015–0.070
Annual risk of TIMI major nonfatal intracranial bleed [15]	0.0015	0.0010–0.0020
Annual risk of TIMI minor bleed [15]	0.02	0.01–0.06
Annual risk of fatal bleed [15]	0.0015	0.0010–0.0030
Annual risk of CABG-related TIMI major bleeding [15]	0.022	0.013–0.031
Relative risk of extracranial bleeds for ticagrelor and aspirin users, relative to clopidogrel and aspirin [15]	1.3	1.05–1.61
Relative risk of intracranial bleeds for ticagrelor and aspirin users [15]	1.15	0.55–2.41
Relative risk of minor bleeds for ticagrelor and aspirin users [15]	1.07	0.91–1.26
Relative risk of fatal bleeds for ticagrelor and aspirin users [15]	0.87	0.48–1.59
Relative risk of CABG-related TIMI major bleeds for ticagrelor users [15]	1.08	0.85–1.36
Relative risk of bleeds among LOF patients treated with clopidogrel relative to noncarriers [15]	0.84	0.75–1.00
Costs [US dollars)		
Cost of single test	100	50–250
Monthly cost of clopidogrel (year 2018) [34]	10	9–70

Variables	Base case value	Range
Monthly cost of ticagrelor (year 2018) [34]	400	300–425
Monthly cost of aspirin (year 2018) [34]	2	
Cost of nonfatal extracranial bleed [15, 34]	10,120	5060–20,240
Cost of nonfatal intracranial bleed [15, 34]	20,740	10,370–41,480
Cost of nonfatal minor bleed) [15, 34]	79	40–158
Cost of fatal bleed #36795;Kazi, 2014 #25591}	17,920	8960–35,840
Cost of CABG-related bleed [15, 34]	35,570	17,790–71,140
Cost of cardiovascular death (fatal myocardial infarction) [15, 34]	24,540	12,270–49,080
Cost of ST CABG [15, 34]	67,720	33,860–135,440
Cost of ST PCI [15, 34]	27,840	13,920–55,680
Cost of MI CABG [15, 34]	67,720	33,860–135,440
Cost of MI medical management [15, 34]	17,200	8600–34,400
Cost of myocardial infarction PCI [15, 34]	27,840	13,920–55,680
Cost of revascularization CABG [15, 34]	50,560	25,280–101,120
Cost of revascularization PCI [15, 34]	20,670	10,340–41,340
Cost for stroke (year 2007) [58]	21,537	12,000–34,000
Quality of life (utilities)		
Disutility of nonfatal myocardial infarction (ST/Non-ST) [31, 32, 51, 56, 59, 60]	0.12	0.07–0.16
Disutility of nonfatal extracranial bleed [31, 32, 51, 56, 59, 60]	0.2 for 14 days	7–21 days
Disutility of nonfatal intracranial bleed [31, 32, 51, 56, 59, 60]	0.61	0.4–0.8
Disutility of nonfatal minor bleed [31, 32, 51, 56, 59, 60]	0.2 for 2 days	0–7 days
Disutility of CABG-related bleed [31, 32, 51, 56, 59, 60]	0.5 for 7 days	3–14 days
Disutility of revascularization CABG [31, 32, 51, 56, 59, 60]	0.5 for 14 days	7–21 days
Disutility of revascularization PCI [58, 60]	0.5 for 7 days	3–14 days
Disutility of stroke [58, 60, 61]	0.64	0.34–0.89

[a]IGNITE Implementation Study 30-day risks are per patient month, 31–365-day risks are per patient year.

LOF loss-of-function allele, *Non-LOF* absence of loss-of-function allele, *ST* stent thrombosis, *CABG* coronary artery bypass grafting, *PCI* percutaneous coronary intervention.

Table 3

Incremental cost-effectiveness of dual antiplatelet selection strategies following percutaneous coronary intervention in acute coronary syndrome (ACS) patients: universal clopidogrel, universal ticagrelor, and genotype-guided escalation (primary analysis).

Strategy	QALY	Total cost	Test cost	Drug cost	Event cost	ICER	NMB
Universal clopidogrel	0.948	6047	0	139	5909	NA	88,767
Genotype-guided escalation[a]	0.959	6493	94	1451	4949	42,365	89,374
Universal ticagrelor	0.969	8832	0	4231	4602	227,044	88,065

[a]Patients with LOF CYP2C19 alleles prescribed ticagrelor, non-LOF with clopidogrel.

Table 4

Incremental cost-effectiveness of dual antiplatelet selection strategies following percutaneous coronary intervention in acute coronary syndrome (ACS) patients: universal clopidogrel, universal ticagrelor, genotype-guided escalation, nonguided de-escalation, and genotype-guided de-escalation (secondary analysis).

Strategy	QALY	Total cost	Test cost	Drug cost	Event cost	ICER	NMB
Universal clopidogrel	0.948	6047	0	139	5909	dominated	88,767
Genotype-guided escalation	0.959	6493	94	1451	4949	dominated	89,374
Nonguided de-escalation	0.961	5680	0	488	5191	NA	90,452
Genotype-guided de-escalation	0.965	6467	93	1689	4685	188,680	90,082
Universal ticagrelor	0.969	8832	0	4231	4602	678,215	88,065