Supplement: Model Details and Supplementary Results

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1. Input Parameters

This section provides additional details on how we arrived at some of the key parameters for patients in the clopidogrel arm of the model (Supplement Figure 1). As noted in the paper, we first estimated the events in the clopidogrel arm and then built the prasugrel, ticagrelor and genotyping arms using rate ratios relative to clopidogrel.

Stent thrombosis

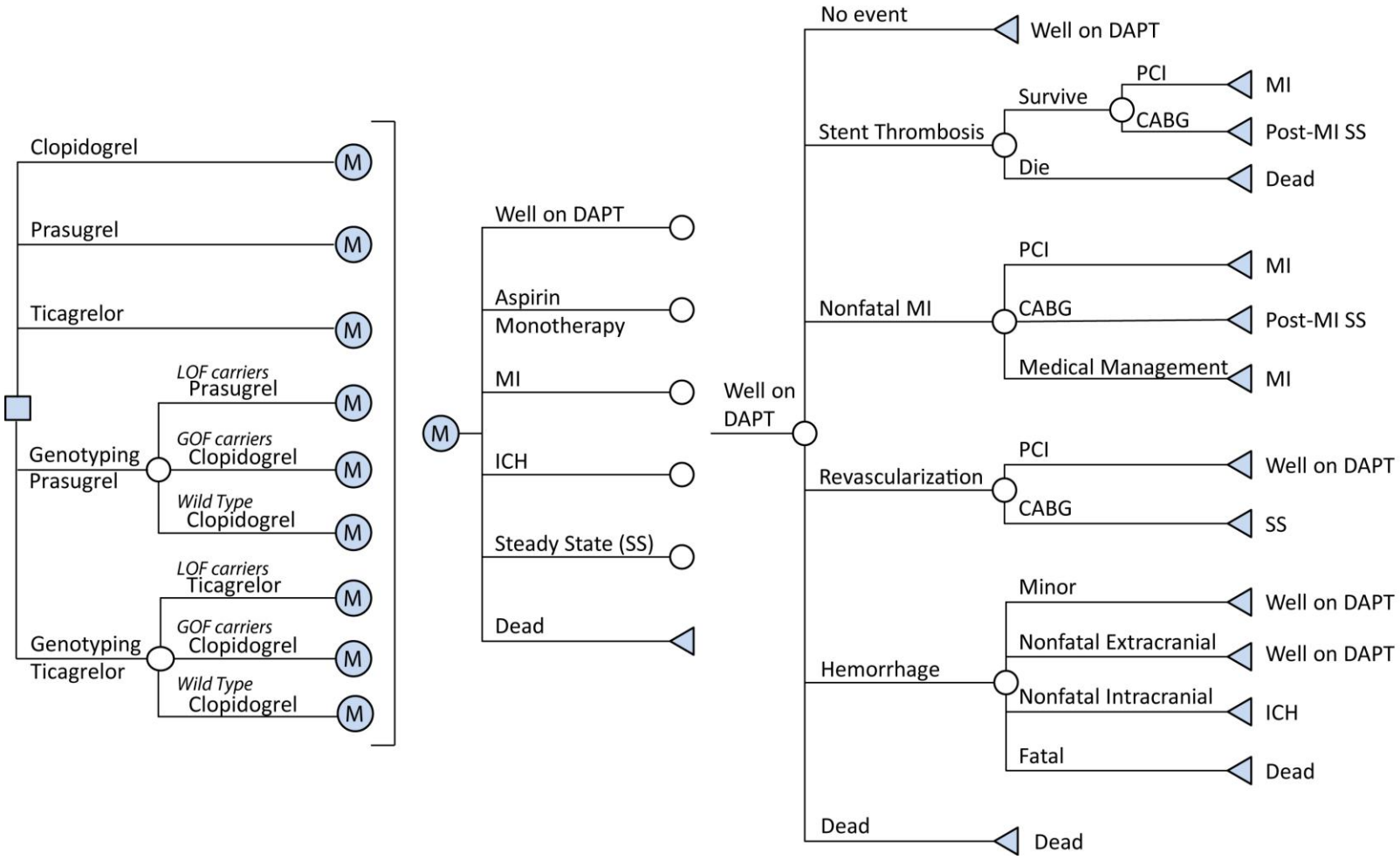
Stent thrombosis is a rare but catastrophic event after percutaneous coronary intervention (PCI). Rates of stent thrombosis are greatest in the first month after the PCI but decline thereafter. Although both bare metal and drug eluting stents are affected, the latter have been associated with episodes of very late stent thrombosis (i.e., more than 1 year after stent implantation), likely related to the delayed endoluminal healing of the angioplasty site. Stent thrombosis is an infrequent yet extremely important clinically because of the high morbidity and mortality associated with the event.

Estimates of the rates of stent thrombosis after PCI vary widely in the published literature (38-46). This is in part due to the fact that early reports utilized disparate definitions of stent thrombosis, making comparisons among different datasets challenging. For instance, angiographically proven cases of stent thrombosis may underestimate the true incidence, as patients may die before the angiogram is obtained. A standardized definition of stent thrombosis (classified as definite, probable and possible in decreasing order of diagnostic certainty) is now widely accepted (48), and for the purpose of the study we considered all events that met criteria for definite or probable stent thrombosis.

Patients undergoing a PCI for ACS experience a two to three fold greater risk of stent thrombosis compared to patients undergoing PCI for stable CAD – thus studies incorporating both kinds of patients are likely to have lower rates of ST compared to those studying only patients who receive a stent for ACS. We therefore assumed ST rates towards the upper end of the range of published estimates.

Using the Academic Research Consortium's definitions for definite and probable stent thrombosis (44), we assumed the rate of early (first 30 days) stent thrombosis in the clopidogrel arm was 1.5%, the rate of late stent thrombosis (31 to 365 days) was 0.6%, and the rate of very late stent thrombosis (beyond 1 year) was 0.22%/year. We assumed the risk of stent thrombosis persisted for four years from the initial PCI, and varied that duration between two and five years in sensitivity analyses. We assumed that all stent thromboses resulted in a myocardial infarction (MI), and 20% were fatal (Appendix Table). Based on expert opinion and a review of the literature, we assumed that 10% (range: 5-15%) of those who survived the episode of ST underwent emergent CABG, and, as a simplifying assumption, the others underwent a repeat PCI with a drug-eluting stent.

Supplement Figure 1. Schema of Markov Model. Five strategies for dual antiplatelet therapy were evaluated in the model. The square node represents a choice among the strategies under examination, circles represent chance nodes at each of the associated downstream points of uncertainty, and triangles represent terminal states. Patients who carry one gain-of-function (GOF) and one loss-of-function (LOF) allele were modeled as LOF carriers. CABG = coronary artery bypass grafting; DAPT = dual antiplatelet therapy; GOF = gain-of-function; ICH = intracranial hemorrhage; LOF = loss-of-function; MI = myocardial infarction; PCI = percutaneous coronary intervention; SS = steady state (into which all patients move 4 years after their initial PCI or after coronary bypass grafting, whichever is sooner).



Myocardial Infarction

Patients were also at risk for MI unrelated to stent thrombosis at a base-case rate of 3.5%/year in the clopidogrel arm (16,19,62). Eight percent of these patients underwent coronary artery bypass grafting (CABG) and 55% underwent a percutaneous coronary intervention (PCI) during the index hospitalization for the nonfatal MI (17,72). Patients who had one or more nonfatal MIs experienced a 30% increase in long-term cardiovascular mortality and recurrent MI (72).

Repeat Revascularization

We estimated rates of repeat revascularization after PCI for acute coronary syndrome (ACS) from Medicare claims data (2001-2006; Appendix Table) (57, 58). Because we modeled revascularizations related to stent thrombosis and MI separately, we subtracted these from the total observed revascularizations to avoid double counting.

Hemorrhage

Based on Thrombolysis in Myocardial Infarction (TIMI) criteria (36), bleeds were classified as minor or major; major bleeds were further divided into extracranial and intracranial. Half of all non-CABG-related major bleeding observed in the first year occurred in the first month after PCI and the hazard was constant over the remaining duration of drug exposure. We also modeled CABG-related TIMI major bleeds and assumed that all excess CABG-related bleeds were extracranial; these were associated with increased costs and decreased quality-adjusted life years (QALYs), but did not increase perioperative mortality.

Mortality

We used the Medicare MEDPAR and denominator files to estimate the 5-year survival for 65-year old patients who underwent PCI for ACS between 2002-2005 (57,58). Based on the practice patterns at the time, it was assumed that the majority of patients in this cohort received clopidogrel after PCI, allowing us to extrapolate mortality data from this real-world cohort to the control arm of our model. All-cause mortality in years two to five in this population was twice that observed in the age-matched general U.S. population (Supplement Figure 2). In order to estimate long-term survival, we assumed that this incremental mortality declined over the next 10 years, but varied the duration and function of the decline in sensitivity analyses.

Genotyping

Several studies have shown that carriers have loss-of-function polymorphisms of the CYP2C19 enzyme achieve lower platelet inhibition when treated with clopidogrel (12). The association between loss-of-function alleles and clinical outcomes among patients treated with clopidogrel has also been extensively examined in a variety of clinical settings, including patients undergoing PCI, medically managed ACS, stable coronary heart disease, and atrial fibrillation. These data have been combined in numerous systematic reviews, with somewhat differing conclusions based on the studies that are

included, definition of individual end-points, and statistical modeling (66). Two meta-analyses in the literature are considered particularly "influential" (12,67) and formed the basis of our modeling.

Mega and colleagues (12 conducted a collaborative meta-analysis of 9 studies which included 9,685 patients, 91.3% of whom had undergone a PCI – a cohort similar to the patients included in our study. They used standardized definitions of end-points, and a random-effects model that allows for between-study differences. In this setting, the investigators noted a strong correlation between carriage of loss-of-function alleles and increased thrombotic events.

Subsequently, Holmes and colleagues (67) conducted a systematic review in which they included all clopidogrel trials in which genotype was also examined. Their analysis included 32 studies, with data on 42,016 patients in a variety of clinical settings, including PCI for ACS (the patients in this analysis), medically managed ACS (for which prasugrel is not indicated), stable coronary disease (for which clopidogrel is not standard of care, and neither prasugrel nor ticagrelor are indicated), as well as atrial fibrillation (for which prasugrel or ticagrelor have not been evaluated and are not indicated). The investigators noted a weaker association between loss-of-function genotype and clinical outcomes than that observed by Mega and colleagues in the post-PCI population, and noted the presence of a small-study bias. However, several experts have commented that the association between loss-of-function genotype and clinical outcomes would be expected to be greater in the post-PCI setting (as examined by Mega and colleagues, and similar to the patients included in our study) compared with the heterogeneous patient population examined by Holmes. Similarly, they have noted that the small-publication bias described by Holmes and colleagues may at least in-part be due to the fact that post-PCI studies in the analysis were generally smaller than non-PCI studies.

Given this uncertainty between the association between loss-of-function genotype and clinical outcomes, we modeled two scenarios. In the "low-discrimination scenario", we assumed weak correlations between loss-of-function genotype and thrombotic outcomes, using point-estimates from Holmes' systematic review. We used this as our base-case for modeling. In a separate, "high-discrimination scenario", we modeled the association between loss-of-function genotype and clinical outcomes that were observed in the systematic review by Mega and colleagues.

Carriers of one or two gain-of-function alleles (*17/*17 or *1/*17) of the CYP2C19 enzyme have increased platelet inhibition with clopidogrel relative to wild-type patients (*1/*1), resulting in increased bleeding and possibly fewer thrombotic events (14,15). Patients who carry one loss-of-function and one gain-of-function allele behave phenotypically like carriers of loss-of-function alleles and achieve lower levels of platelet inhibition with clopidogrel, because the gain-of-function allele cannot fully compensate for the loss-of-function allele (25).

We estimated the baseline distribution of carrier status for gain-of-function and loss-of-function alleles based on an inverse-variance weighted meta-analysis of the proportions reported in several contemporary studies (25, 34, 63-65), which corresponded to the frequencies reported in the 2013 update of the Clinical Pharmocogenetics Implementation Consortium guidelines (25).

Mega and Holmes reported ratio of events among carriers of loss-of-function alleles to noncarriers. The model exploits the algebraic relationship between this ratio, the proportion of carriers in the population, and total number of events observed in the entire population. For instance, in any given cycle, we know:

1. The number of events observed in the entire clopidogrel cohort (based on base-case assumptions),
2. the proportion of patients that are carriers, and
3. the rate ratio for events among carriers relative to noncarriers.

Because the two categories (carriers/noncarriers) are mutually exclusive and collectively exhaustive, we can algebraically determine the proportion of observed events that occurred among carriers. The remaining events (i.e., total events – events among carriers) are assumed to occur in noncarriers. Rigorous internal validation was performed to ensure that the sum of events occurring among carriers and noncarriers equaled the sum of events occurring in the entire cohort in every cycle.

The pharmacokinetics and pharmacodynamics of ticagrelor and prasugrel appear to be unaffected by loss-of-function polymorphisms of the CY2C19 enzyme. As a result, analyses of data from TRITON-TIMI38 and PLATO have shown that loss-of-function carriers and noncarriers have similar outcomes on the drugs (which are better than those achieved on clopidogrel) (34,35). Therefore the net clinical benefit of prasugrel or ticagrelor compared with clopidogrel would be expected to be greater in loss-of-function carriers than in noncarriers (because loss-of-function carriers have more thrombotic events than noncarriers when treated with clopidogrel).

Supplement Table 1. CYP2C19 Alleles: Genotype, Phenotype, and Treatment Strategy.

	Genotype	Alleles	Phenotype	Treatment Strategy
Carriers of LOF alleles	Homozygotes with two LOF alleles	*2-*8/*2-*8	Poor Metabolizers	Prasugrel or Ticagrelor
	Heterozygotes with one LOF allele and one wild-type allele	*1/*2-*8	Intermediate Metabolizers	Prasugrel or Ticagrelor
	Heterozygotes with one LOF and one GOF allele	*2-*8/*17	Unknown Metabolizers	Prasugrel or Ticagrelor
Noncarriers of LOF alleles	Heterozygotes with one GOF allele and one wild-type allele	*1/*17	Rapid Metabolizers	Clopidogrel
	Homozygotes with two GOF alleles	*17/*17	Ultra-Rapid Metabolizers	Clopidogrel
	Homozygotes with two wild-type alleles	*1/*1	Extensive Metabolizers	Clopidogrel

LOF = Loss-of-function; GOF = gain-of-function.

Hospitalization Costs

As shown in the Appendix Table, we estimated most hospitalization costs from the Healthcare Cost and Utilization Project's National Inpatient Sample for 2008 (80). The algorithm deployed was as follows. For a given diagnosis related group – for instance, an admission for CABG – we used the National Inpatient Sample to estimate the charges for Medicare beneficiaries over the age of 65. Next we used the facility-specific Medicare charge-to-cost ratio to estimate the facility costs. Using the ratio of facility costs to professional fees from the SEQOL study which estimated long-term costs of care among patients undergoing revascularization for coronary disease using micro-costing methods (37), we estimated that the total cost of CABG in 2008 dollars. Next we used the GDP deflator to update the estimated costs into 2011 US dollars (84). This algorithm was repeated for each of the cost parameters shown in the Appendix Table, using combinations of DRGs to identify the incremental costs associated with complications or more acute presentations.

Drug Costs

We assumed a base-case cost of $30/month for generic clopidogrel, and included the current average wholesale price of the proprietary formulation ($218/month) in the sensitivity analysis (82). We extended our sensitivity analysis down to a monthly price of $4, the price of generic medications at several U.S. retail pharmacies. We assumed the cost of prasugrel to equal its average wholesale price ($220/month) (82). Ticagrelor has been recently approved by the FDA, and its estimated average wholesale price is $261/month (82). This represents a 19% premium over prasugrel, which is consistent with its U.K. pricing (a 23% price premium over prasugrel). We tested a wide range of prices for prasugrel and ticagrelor ($150-$300) in our sensitivity analyses.

All healthcare costs were updated to 2011 U.S. dollars using the GDP deflator (84).

Adverse Events

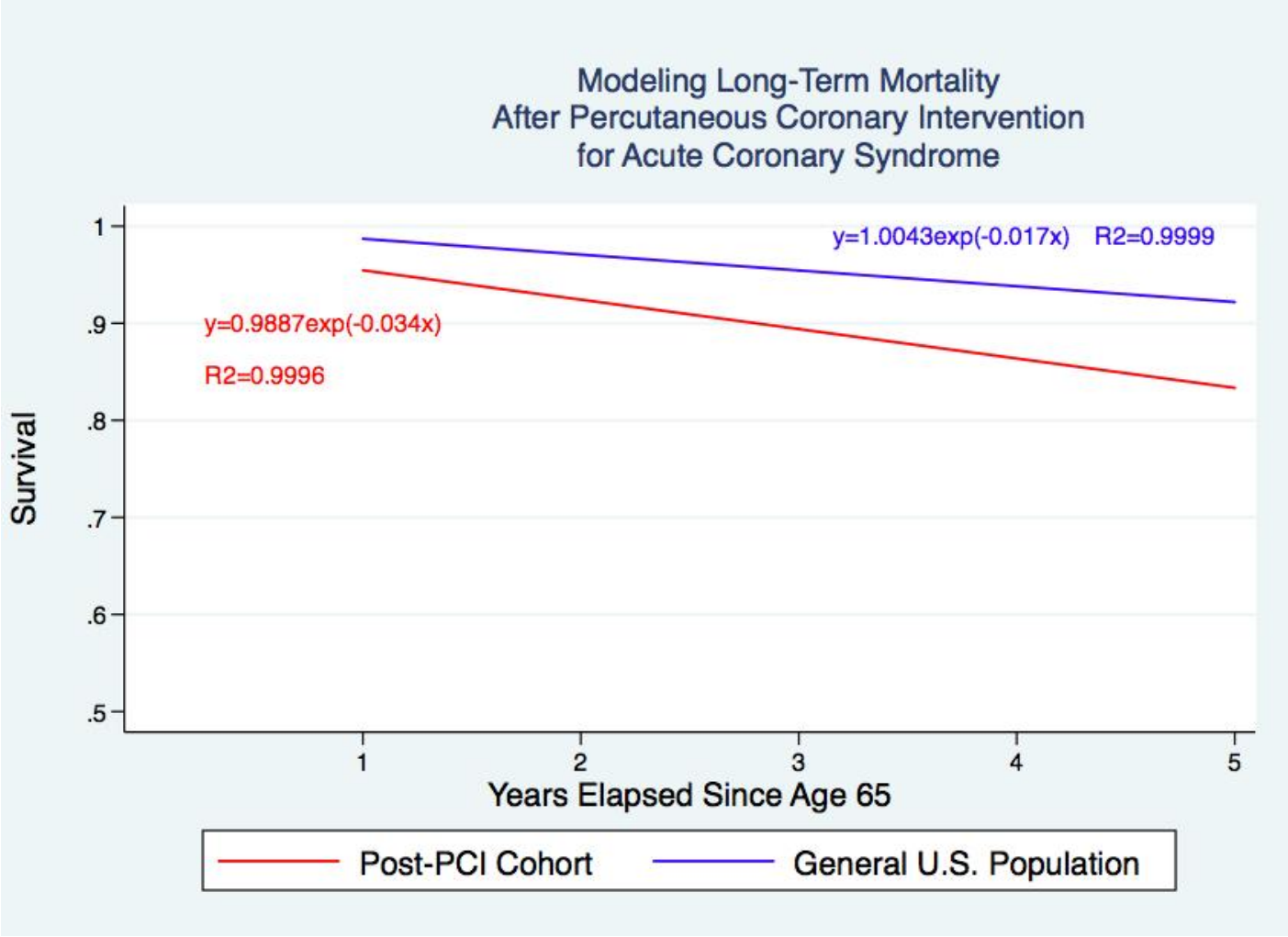
In a phase II trial, ticagrelor was associated with an increased incidence of bradyarrhythmias and ventricular pauses (24). Therefore a subset of patients in the phase III trial (PLATO) had continuous electrocardiographic monitoring to determine the incremental incidence and clinical consequences of bradyarrhythmias among patients receiving ticagrelor. The investigators noted that bradyarrhythmias were common after PCI for ACS, and occurred more frequently in the ticagrelor arm. But most bradyarrhythmias captured on continuous electrocardiographic monitoring were asymptomatic, nocturnal, and occurred in the first month after the initiation of therapy (24). There was a small but statistically insignificant difference in the incidence of symptomatic bradyarrhythmias (1.3%) including syncope (0.2%) between patients receiving ticagrelor and those receiving clopidogrel, which we modeled as our base-case. PLATO investigators noted that more patients in the clopidogrel arm experienced complete heart block or required a pacemaker, so we examined the impact of varying the incidence of bradyarrhythmias in a sensitivity analysis.

Medication Adherence

Adherence to long-term medication regimens is a complex behavior with numerous patient-, physician-, and system-level determinants. Medication non-adherence is significantly greater in the real-world than that observed in randomized clinical trials, and is strongly correlated with adverse clinical outcomes and increased resource utilization. Data from our own group (52) and that of other investigators (53) suggests that adherence to antiplatelet agents is very high in the first month after PCI, but likely declines thereafter.

There are no long-term data on adherence to ticagrelor or prasugrel after PCI, or the clinical consequences of intermittent non-adherence to these drugs. Since cost-effectiveness models evaluate incremental cost-effectiveness, we are most interested in the relative decline in adherence to these drugs. Both clopidogrel and prasugrel are dosed once-daily, whereas ticagrelor is a twice-daily regimen. In a recent systematic review, Coleman and colleagues demonstrated that adherence to twice-daily regimens of cardiovascular drugs was 6.9% lower than that of once-daily regimens (54). In our base-case, we therefore assumed a 93.1% adherence to ticagrelor during months 2 through 12 of therapy after PCI. In a sensitivity analysis, we examined the impact of assuming lower (90%) and higher (100%) rates of adherence on the optimal choice of dual antiplatelet therapy after PCI for ACS.

Supplement Figure 2. All-Cause Mortality After Percutaneous Coronary Intervention for Acute Coronary Syndrome. The red curve indicates observed survival from years 2 through 5 among Medicare enrollees undergoing PCI for ACS at age 65 (Medicare claims data, 5% sample, 2002-06). The blue curve indicates the corresponding survival of the general U.S. population among subjects who are age 65 at the start of the analysis. The fitted exponential curves indicate that the mortality rate in the post-PCI group is twice that of the general U.S. population.



Distributions

For the purpose of the probabilistic sensitivity analysis, all input parameters were assigned a statistical distribution. We used the lognormal distribution for costs because costs are non-negative and positively skewed. We also used the log-normal distribution for rate ratios, because the confidence limits for these are calculated on a log scale. We used beta distributions for probabilities because all probabilities are constrained to the range between zero and one. Although utilities can occasionally assume values less than zero (for states worse than death), this was not the case in our model where they were constrained between zero and one; we therefore represented them by beta distributions. We used the Dirichlet multinomial distribution where probabilities were correlated (e.g., probability of post-MI patients receiving PCI, CABG, or medical management). Finally, because sensitivity and specificity of genetic testing were also constrained between 0 and 1, we used the beta distribution.

2. Clinical Events

Supplement Table 2 depicts the major clinical events observed in the study cohort in the first four years after the initial PCI. These results provide mechanistic insight into the cost-effectiveness analysis. When comparing a drug therapy to the corresponding genotyping arm (e.g., prasugrel vs. genotyping–prasugrel), it is important to note that the carriers of loss-of-function alleles receive the new drug in both arms. Therefore the relative outcomes of the two arms are a function of the outcomes of noncarriers on the new drug compared with noncarriers receiving clopidogrel. In the high discrimination scenario, genetic testing is accurately distinguishes between high-risk and low-risk individuals; it follows that noncarriers have a low incidence of thrombotic events on clopidogrel in this setting. As a result, genotyping–ticagrelor (high-discrimination) has very low thrombotic event rates; in some cases even lower than when all patients receive ticagrelor.

Supplement Table 2. Major Clinical Events In the First Four Years After the Initial Percutaneous Coronary Intervention.[*]

	Clopidogrel	**Prasugrel**	**Ticagrelor**	**Genotyping –Prasugrel**[†§] (Low-Discrimination)	**Genotyping –Ticagrelor**[‡§] (Low-Discrimination)	**Genotyping –Prasugrel**[†§] (High-Discrimination)	**Genotyping –Ticagrelor**[‡§] (High-Discrimination)
Nonfatal myocardial infarction	17.77	15.91	16.84	16.64	16.97	16.45	16.78
Stent thrombosis, definite or probable	2.86	1.77	2.33	2.28	2.44	2.00	2.17
TIMI Major Bleeding							
Fatal	0.45	0.95	0.43	0.61	0.45	0.62	0.45
Nonfatal intracranial	0.26	0.28	0.30	0.27	0.28	0.28	0.29
Nonfatal extracranial	4.79	5.33	5.57	5.06	5.11	5.08	5.13
CABG-related	0.11	0.34	0.12	0.18	0.12	0.18	0.12
TIMI Minor Bleeding	3.54	4.44	3.68	3.66	3.65	3.64	3.63
Repeat Revascularization							
CABG	5.64	5.51	5.58	5.56	5.58	5.55	5.57
PCI	22.67	21.37	22.14	21.91	22.18	21.79	22.05
Cardiovascular deaths	9.87	9.38	9.15	9.49	9.44	9.22	9.17
Noncardiovascular deaths, including fatal bleeding	3.91	4.26	3.65	4.03	3.83	4.05	3.86

TIMI = Thrombolysis in Myocardial Infarction; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

[*] Events reported as percentage of patients who experienced at least one event in the first four years. This is an intention-to-treat analysis, i.e., all events that occur in the first four years in a particular arm of the study are reported, including those that occurred after the study drug is discontinued

[†] In the genotyping–prasugrel strategy, carriers of one or two loss-of-function polymorphisms in CYP2C19 were treated with prasugrel; the others received generic clopidogrel.

[‡] In the genotyping–ticagrelor strategy, carriers of one or two loss-of-function polymorphisms in CYP2C19 were treated with ticagrelor; the others received generic clopidogrel.

[§] The low-discrimination scenario assumes weaker associations between loss-of-function genotype and thrombotic outcomes (i.e., stent thrombosis, MI, and cardiovascular death), whereas the high-discrimination scenario assumes genotype to be strongly predictive of thrombotic outcomes. See text for details.

3. Deterministic Sensitivity Analyses

Sensitivity analyses investigate the impact of clinical or statistical uncertainty in the input parameters on the results of the model. AS with the base-case analysis, we conducted sensitivity analyses using a tiered approach – first investigating prasugrel- and ticagrelor-based therapies separately before conducting a global analysis incorporating all strategies.

In one- or two-way sensitivity analyses, one or two input parameters are varied across a pre-specified range, holding all other parameters constant. Each analysis was conducted under both the low- and high-discrimination scenarios. When necessary, we used an a priori definition of the willingness-to-pay threshold of $50,000/QALY.

One-Way

For the key input parameters, we extended the range tested in one-way analyses beyond those pre-specified in the Appendix Table in order to identify thresholds where the optimal strategy changes from the base-case (Supplement Table 3). In the low-discrimination scenario, modest changes in input parameters such as rates of cardiovascular and noncardiovascular mortality affect the optimal choice of DAPT. These results suggest that in the low-discrimination scenario, treating all patients with ticagrelor is a reasonable alternative to genotyping–ticagrelor in the absence of a hard budget constraint.

In contrast, in the high-discrimination scenario, the choice of genotyping–ticagrelor is the most cost-effective strategy for DAPT after PCI for ACS is robust to variations in the input parameters.

Supplement Table 3. Results of One-Way Sensitivity Analyses Across All Strategies. Variables that affect the choice of the most cost-effective strategy for dual antiplatelet therapy after percutaneous coronary intervention for acute coronary syndrome at a willingness-to-pay threshold of $50,000/QALY under low- and high-discrimination scenarios.*

Variable	Base-Case	Low-Discrimination Scenario Most cost-effective strategy: Genotyping–Ticagrelor†		High-Discrimination Scenario Most cost-effective strategy: Genotyping– Ticagrelor†	
		Threshold for most cost-effective strategy	Optimal Dual Antiplatelet Therapy When Threshold is Crossed	Threshold for most cost-effective strategy	Optimal Dual Antiplatelet Therapy When Threshold is Crossed
Rate ratio for cardiovascular death, ticagrelor relative to clopidogrel	0.79	<0.78	Ticagrelor§	< 0.66 > 0.98	Ticagrelor Genotyping–Prasugrel‡
Rate ratio for noncardiovascular death unrelated to bleeding, ticagrelor relative to clopidogrel	0.63	<0.57	Ticagrelor	-	-
Rate ratio for fatal bleeding, ticagrelor relative to clopidogrel	0.87	<0.54	Ticagrelor	-	-
Rate ratio for nonfatal intracranial bleeding, ticagrelor relative to clopidogrel	1.15	<0.97	Ticagrelor	-	-
Rate ratio for nonfatal myocardial infarction, ticagrelor relative to clopidogrel	0.84	-	-	-	-
Rate ratio for stent thrombosis, ticagrelor relative to clopidogrel	0.75	-	-	-	-
Rate ratio for cardiovascular death, LOF carriers relative to LOF noncarriers‖	-	< 1.32	Ticagrelor	< 1.26	Ticagrelor
Rate ratio for nonfatal myocardial infarction, LOF carriers relative to LOF noncarriers¶	-	<1.09	Ticagrelor	-	-
Proportion of the population that carriers the CYP2C19 loss of function polymorphism	28%	>52.7%	Ticagrelor	> 86.8%	Ticagrelor
Difference in monthly cost of ticagrelor and generic clopidogrel	$231	< 215	Ticagrelor	< $93	Ticagrelor
Sensitivity of Genetic Test for CYP2C19 polymorphisms	100%	<90%	Ticagrelor	< 51%	Ticagrelor

Cost of Genetic Testing	$235	>358	Ticagrelor	-	-
Discount factor	3%	<2.1%**	Ticagrelor	-	-

LOF = loss-of-function; QALY = quality-adjusted life year.

* This table presents results of one-way sensitivity analyses comparing all five antiplatelet strategies in the model, and reports the threshold values of the input parameters where the choice of optimal therapy changes at a willingness-to-pay threshold of $50,000/QALY. The low-discrimination scenario assumes weak associations between LOF carrier status and thrombotic events (67), whereas the high-discrimination scenario assumes stronger associations between LOF genotype and thrombotic events (25). Note that for several key parameters, e.g., drug costs or costs of genetic testing, we tested ranges beyond those pre-specified in the Appendix Table in order to identify thresholds where the optimal choice of therapy switches.

† In the Genotyping–Ticagrelor strategy, patients with one or two LOF polymorphisms in CYP2C19 were treated with ticagrelor; all others received generic clopidogrel.

‡ In the Genotyping–Prasugrel strategy, patients with one or two LOF polymorphisms in CYP2C19 were treated with prasugrel; all others received generic clopidogrel.

§ This can be interpreted as follows: at a threshold of $50,000/QALY, genotyping-ticagrelor is the most cost-effective therapy in the base-case, but if the rate ratio for cardiovascular death on ticagrelor relative to clopidogrel were less than 0.78 (base-case 0.79, 95% confidence interval: 0.69-0.91), ticagrelor would become the most cost-effective therapy in the low-discrimination scenario.

‖ The base-case rate ratio for cardiovascular death among carriers of LOF alleles relative to noncarriers was 1.37 in the low-discrimination scenario (estimated in the model from the rate ratio for death from all causes reported by Holmes, et al.); and 1.84 in the high-discrimination scenario.

¶ The base-case rate ratio for non-fatal myocardial infarction among carriers of LOF alleles relative to noncarriers was 1.48 in the low-discrimination scenario and 1.45 in the high-discrimination scenario.

** This can be interpreted as follows: if the discount rate for costs and outcomes were less than 2.1% a year, ticagrelor would become the most cost-effective strategy at $50,000/QALY. The intuition is that lower discount rates make it more attractive to invest in a more expensive drug like ticagrelor, where the costs are incurred upfront (in the first year after coronary revascularization) whereas the benefits accrue over the patients' lifetime.

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Two-Way

Since the relative effectiveness and cost-effectiveness of the evaluated strategies are largely driven by the relative impact of ticagrelor and prasugrel on fatal events, we conducted two-way sensitivity analyses to investigate how uncertainties in our estimated rates of fatal bleeding and cardiovascular mortality affect the choice of optimal dual antiplatelet therapy (Appendix Figure 2).

Appendix Figure 2 examines the impact of varying the rate ratios for fatal bleeding and cardiovascular mortality for ticagrelor relative to clopidogrel while holding constant the corresponding ratios for prasugrel. Note that genotyping–ticagrelor is the most cost-effective therapy in both the low- and high-discrimination scenarios, but the results are more robust to uncertainty in the estimates of efficacy and safety of ticagrelor in the high-discrimination scenario than in the low-discrimination scenario.

4. Probabilistic Sensitivity Analysis

Another useful tool in defining the robustness of the results of a cost-effectiveness model is probabilistic sensitivity analysis. In contrast to one-way sensitivity analyses, probabilistic sensitivity analyses allow all input parameters to vary simultaneously, with each parameter drawn from an appropriate statistical distribution. Each simulation represents a single draw from each of the parameter distributions; 10,000 such simulations were run on our model. The proportion of such simulations that favor a particular strategy helps illustrate the robustness of the results to uncertainty in the input parameters (Figure 2). In the low-discrimination scenario (Figure 2), genotyping–ticagrelor is the optimal strategy in the $31,500-50,500/QALY range, whereas ticagrelor is the optimal strategy beyond $50,500/QALY. At a threshold of $50,000/QALY, genotyping–ticagrelor and ticagrelor is each the preferred in 42% of the simulations, reflecting the uncertainty in the choice of optimal therapy. The more one is willing to pay per QALY, the more economically attractive the ticagrelor-for-all strategy becomes. In the high-discrimination scenario (Figure 2), which assumes stronger associations between LOF genotype and the rate of thrombotic events, genotyping–ticagrelor is the optimal strategy in the $26,500-78,000/QALY range. At a threshold of $50,000/QALY, genotyping–ticagrelor is the optimal strategy in 63.4% of the simulations.

5. Scenario Analyses

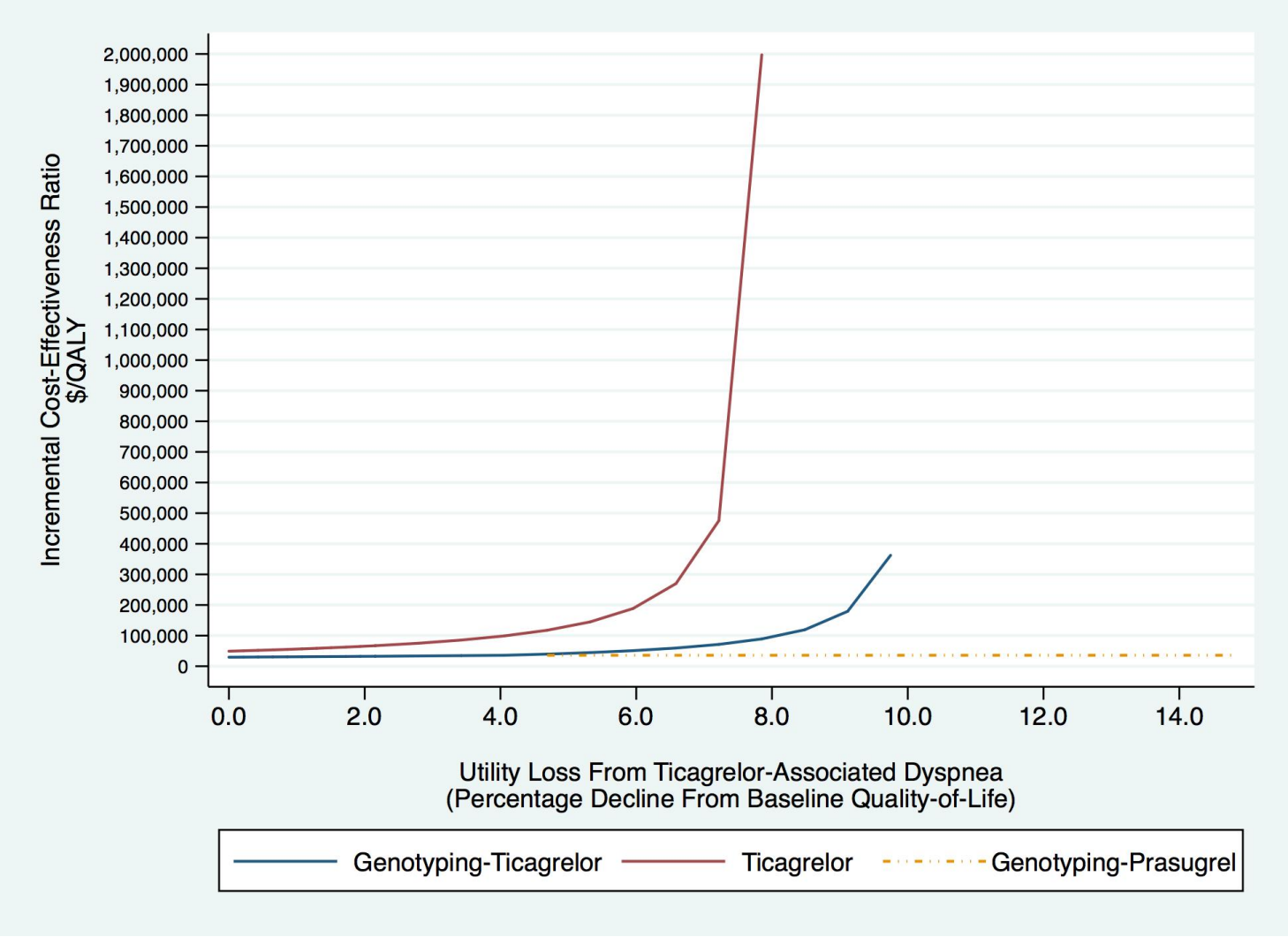
A third kind of sensitivity analysis varies select input parameters in a clinically relevant manner to inform decision-making in certain specific clinical scenarios.

The Impact of Ticagrelor-Associated Dyspnea

Next, we investigated the optimal strategy in a patient unable to tolerate ticagrelor due to ticagrelor-associated dyspnea. In PLATO, the proportion of patients reporting dyspnea as a drug-related adverse event was a 6% greater in the ticagrelor arm

than in the clopidogrel arm; but the proportion of patients with dyspnea requiring discontinuation of the study drug was only 0.8% greater. Therefore about 5.2% of the patients experience mild-to-moderate ticagrelor-associated dyspnea but are able to continue taking the drug. Indeed, the symptoms are likely to resolve in a few months in the majority of patients even if they continue to take the drug, and the syndrome is not associated with any permanent cardiopulmonary dysfunction. We evaluated the optimal choice of dual antiplatelet therapy among patients who experience mild to moderate dyspnea on ticagrelor but continue to take it. The question we asked was: how severe does the quality-of-life decrement on ticagrelor have to be before it was no longer the optimal choice of dual antiplatelet therapy (Supplement Figure 3)? At a threshold of $50,000/QALY, a decrement of 0.049 (or approximately 6% of the baseline quality of life at age 65 years) made genotyping–prasugrel the most cost-effective therapy. In other words, among loss-of-function carriers, a 6% of the baseline quality-of-life due to ticagrelor-associated dyspnea made prasugrel the most cost-effective strategy. Noncarriers crossed over even sooner – even mild ticagrelor-associated dyspnea (a decrement of 0.026, or 3% of baseline quality-of-life at 65 years) made clopidogrel the most cost-effective therapy.

Supplement Figure 3. Cost-Effectiveness of Genotyping Among Patients With Ticagrelor-Associated Dyspnea.



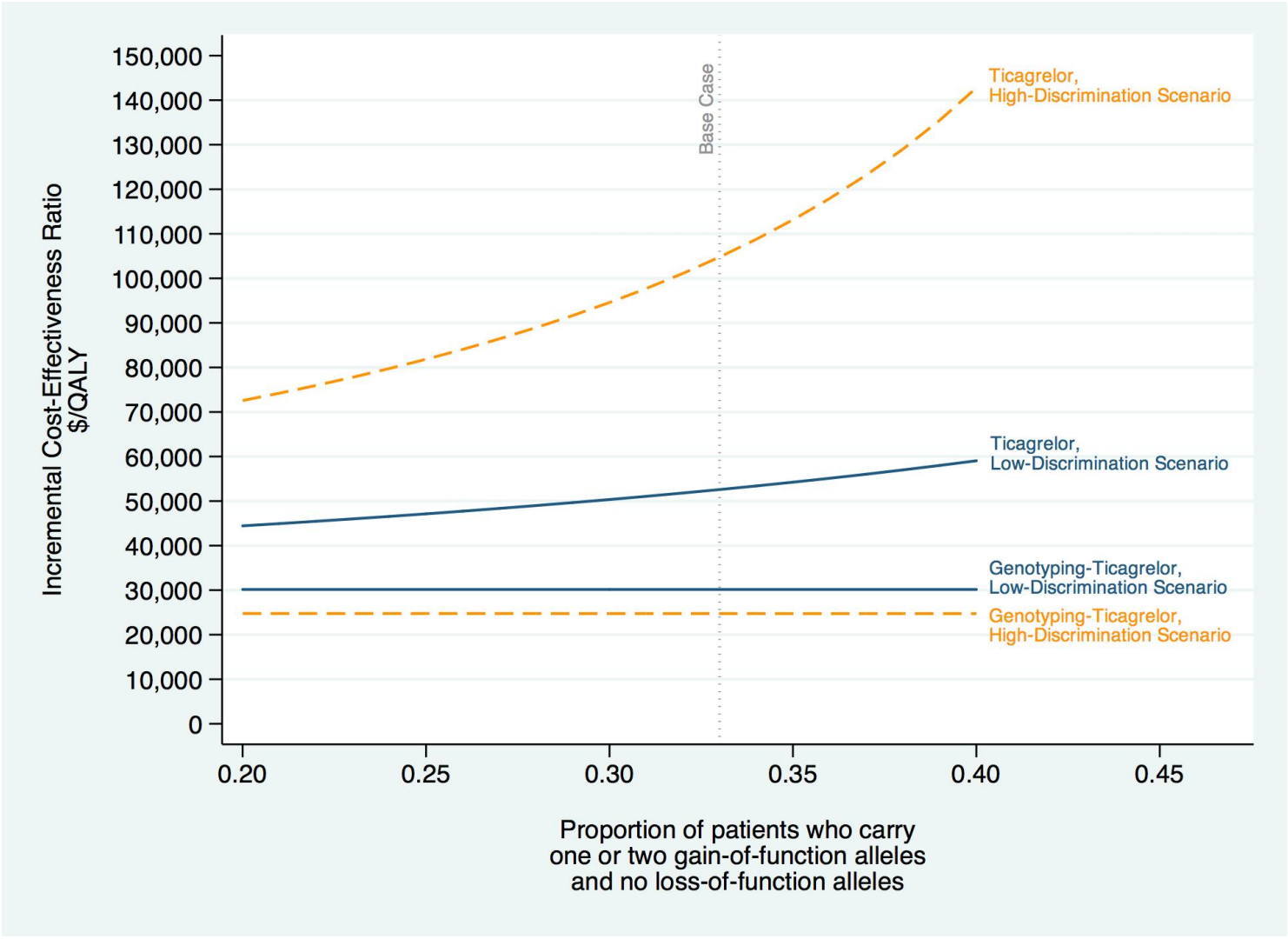
Allele Frequency of Loss-of-Function Polymorphisms

The vast majority of patients included in the initial studies of the impact of genotype on clinical outcomes were white (including 95.8% of the patients in the Mega meta-analysis). However, a large number of subsequent studies in non-white populations have demonstrated that the population frequency of loss-of-function alleles varies significantly by race/ethnicity – being considerably higher in South and Central Asia (35%), East Asia (40%), and the Oceania (76%) than in Europe (13%) or Africa (16%) (25). These studies have shown a similar association between loss-of-function genotypes and platelet reactivity and clinical outcomes as that observed in the original investigations. Despite the small sample size of these studies, the sum of the evidence suggests an increase in thrombotic outcomes among carriers of loss-of-function alleles that is similar in magnitude to that observed in white populations. We specifically examined the impact of population variability in the allelic frequency of loss-of-function polymorphisms. As the proportion of patients who are carriers of loss-of-function alleles increases, both genotyping –ticagrelor and ticagrelor become increasingly cost-effective (Appendix Figure 3). In the low-

discrimination scenario, treating all patients with ticagrelor may be the most cost-effective therapy in populations where loss-of-function carriers constitute more than 52.7% of the population (Appendix Figure 3, solid green lines). In the high-discrimination scenario, genotyping-ticagrelor remains the most cost-effective strategy for dual antiplatelet therapy after PCI for ACS unless loss-of-function carriers constitute 86.8% of the population, which has not been previously described (Appendix Figure 3, broken black lines).

In contrast, an increase in the proportion of patients carrying one or two gain-of-function polymorphisms and no loss-of-function polymorphisms (i.e., rapid and ultra-rapid metabolizers) does not materially alter the cost-effectiveness of genotyping–ticagrelor, but makes treating all patients with ticagrelor less cost-effective (Supplement Figure 4).

Supplement Figure 4. The Impact of Gain-of-Function Allele Frequency on the Optimal Choice of Dual Antiplatelet Therapy after Percutaneous Coronary Intervention for Acute Coronary Syndrome.



Accuracy of Genetic Testing

We investigated the change in cost-effectiveness of the antiplatelet strategies with varying sensitivity and specificity of genetic testing. In the base-case, we had assumed that genotyping has 100% sensitivity and 99.3% specificity for reduced function polymorphisms in CYP2C19. As the sensitivity and specificity of genotyping (or both) declines, giving all patients ticagrelor becomes increasingly more attractive (i.e., the incremental cost-effectiveness ratio of ticagrelor relative to genotyping–ticagrelor gets smaller, Supplement Figure 5). At a sensitivity and specificity of 95%, the ICER for ticagrelor declines to $51,500/QALY, and the ICER for genotyping-ticagrelor increases to $31,500/QALY.

Cost of Genotyping

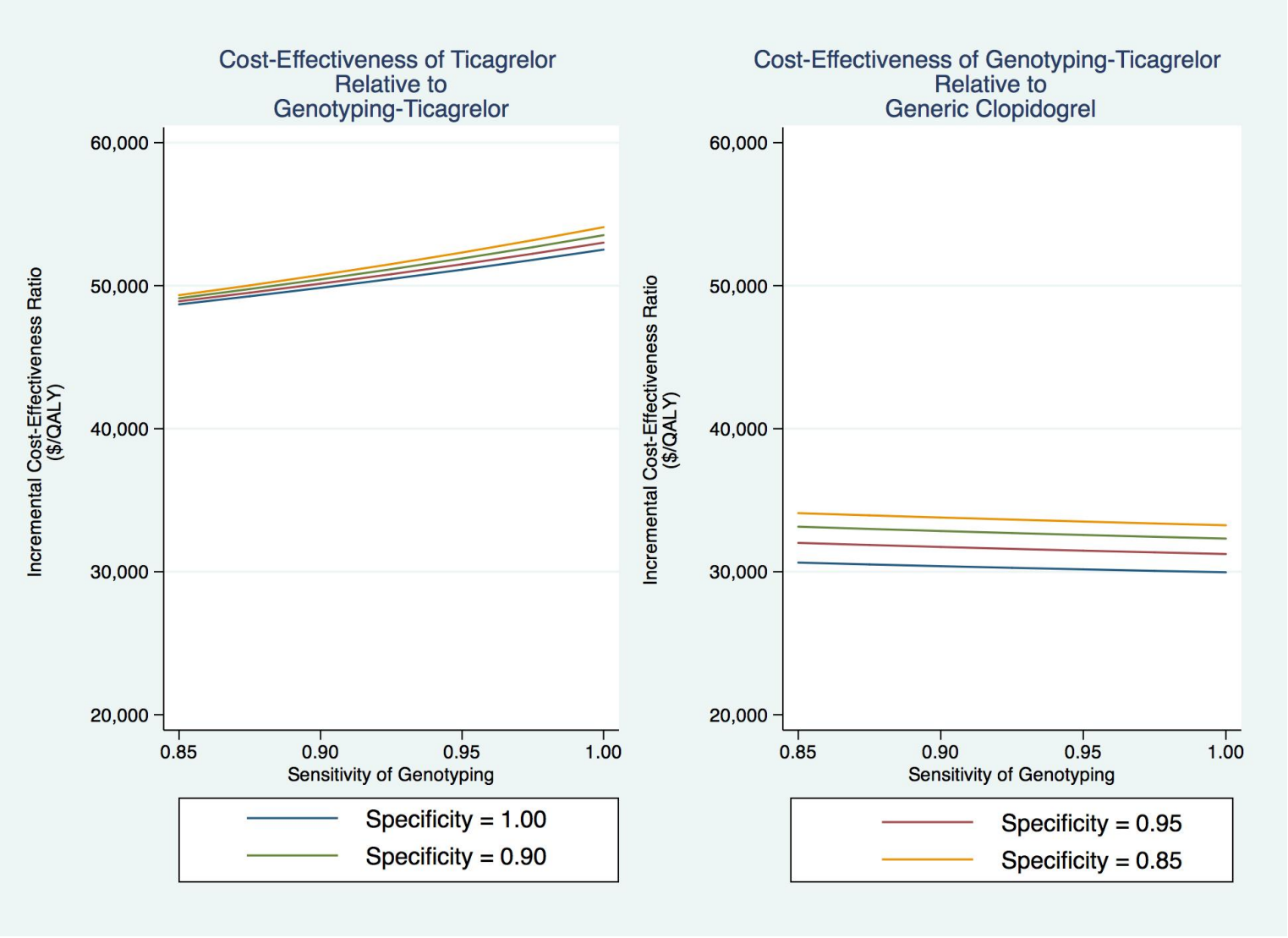
The incremental cost-effectiveness of genotyping-tailored therapies is sensitive to the cost of genetic testing. In the base-case, we assumed that genetic testing cost $235 per test, but the cost of the test may vary substantially over time and region of the country. We therefore conducted an analysis of the impact of the cost of genotyping on its cost-effectiveness (Supplement Figure 6). This analysis guides policy-makers and clinicians on the optimal strategy for dual antiplatelet therapy based on local costs of genetic testing.

Drug Costs

The cost-effectiveness of ticagrelor and genotyping–ticagrelor vary with the relative cost of ticagrelor and clopidogrel. As the difference in the monthly costs of ticagrelor and clopidogrel declines (e.g., ticagrelor becomes less expensive, or clopidogrel becomes expensive than base-case estimates), both ticagrelor and genotyping–ticagrelor become more cost-effective. In the low-discrimination scenario, the ICER for ticagrelor drops below $50,000/QALY when the monthly price difference between ticagrelor and clopidogrel is less than $215. In the high-discrimination scenario, this occurs when the monthly price difference between ticagrelor and clopidogrel is less than $93.

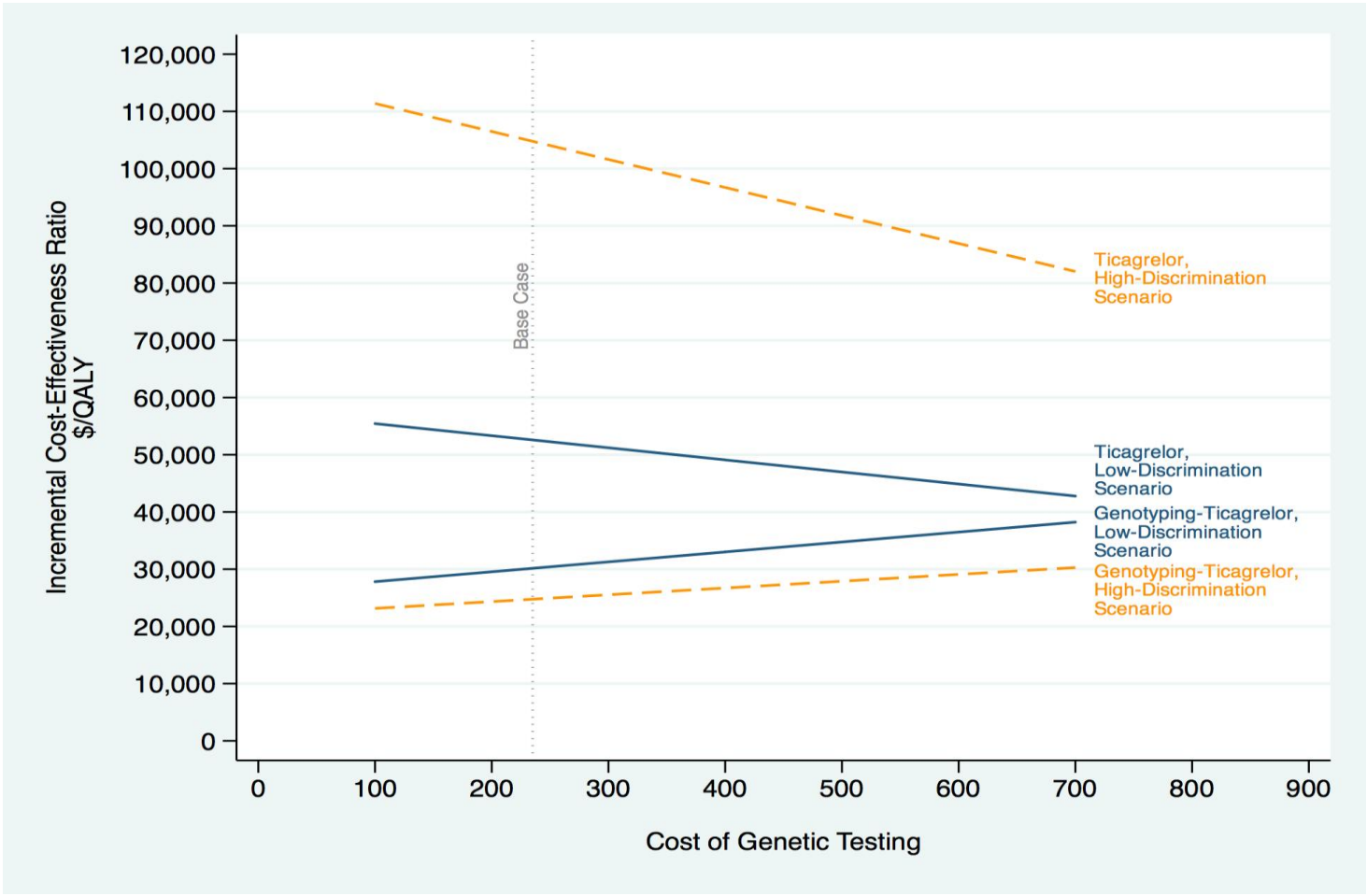
Supplement Figure 5. Scenario Analysis: Accuracy of Genotyping.

In the base-case, the model assumes that genetic testing is 100% sensitive and 99.3% specific for polymorphisms of CYP2C19. In this sensitivity analysis, we examined the impact of decrements in the sensitivity and specificity of the genetic test on the cost-effectiveness of ticagrelor (relative to genotyping-ticagrelor, left panel) and genotyping-ticagrelor (relative to generic clopidogrel, right panel). As the sensitivity and specificity of genotyping decline from 100% (arrow), ticagrelor becomes more cost-effective, and genotyping-ticagrelor becomes less cost-effective. At a sensitivity and specificity of 95%, the ICER for ticagrelor declines to $51,500/QALY, and the ICER for genotyping-ticagrelor increases to $31,500/QALY. QALY = quality-adjusted life year.

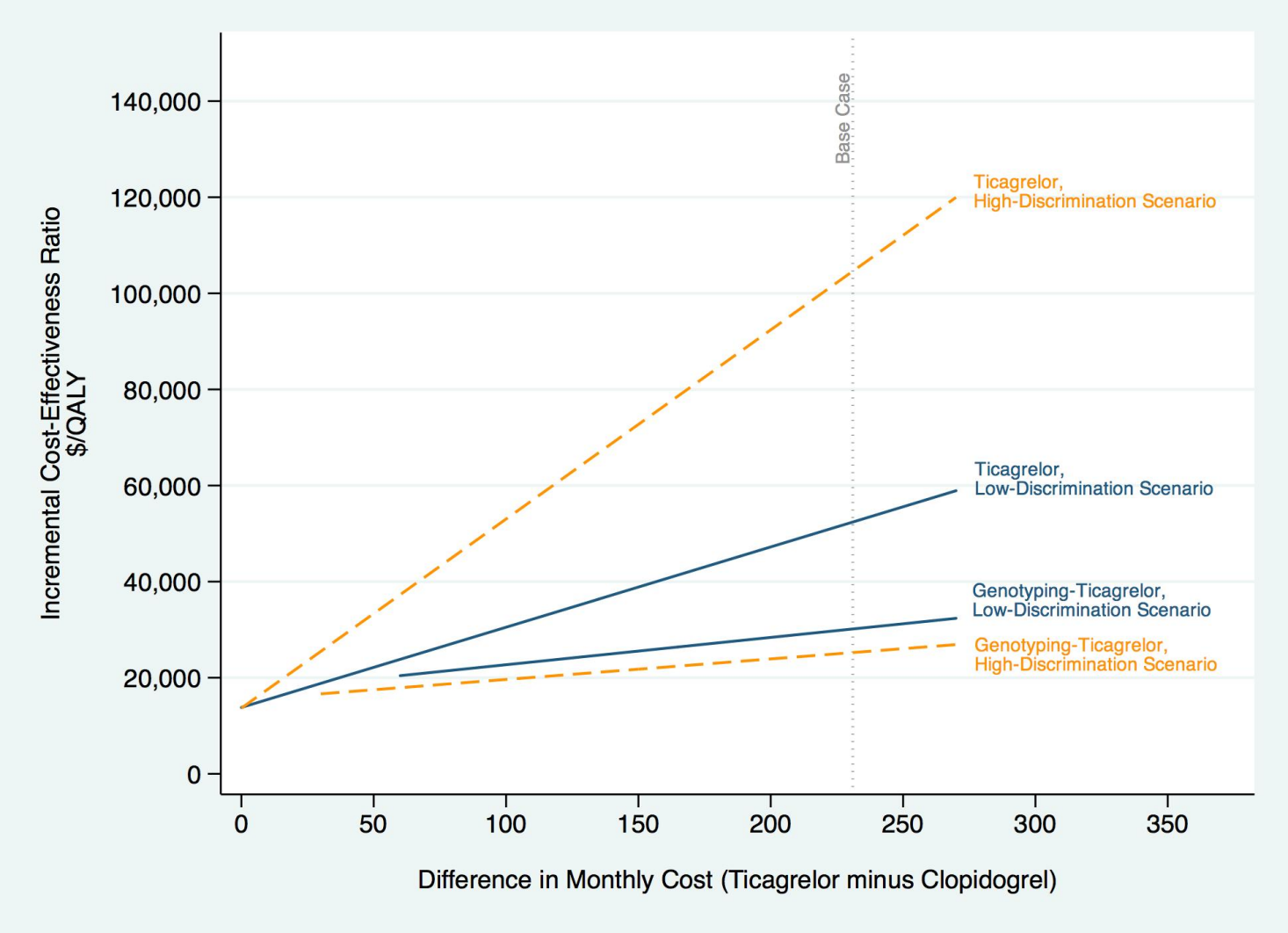


Supplement Figure 6. Impact of Cost of Genotyping.

Because the cost of genetic testing may vary substantially by geography and over time, we examined the impact of varying the cost of genotyping on the optimal choice of dual antiplatelet therapy after percutaneous cutaneous intervention for acute coronary syndrome. Results from both the low-discrimination (solid navy lines) and high-discrimination (broken orange lines) scenarios are shown here. In the low-discrimination scenario, the optimal strategy in the base-case is genotyping–ticagrelor, but ticagrelor-for-all becomes the most cost-effective strategy when the cost of the genetic test exceeds $358. In the optimistic scenario (broken orange lines), genotyping–ticagrelor is the most cost-effective strategy across the entire range of genotyping costs examined ($100-700 per test).



Supplement Figure 7. One-way Sensitivity Analysis on Monthly Drug Costs. The cost-effectiveness of ticagrelor is measured relative to genotyping–ticagrelor and cost-effectiveness of genotyping–ticagrelor is measured relative to clopidogrel. The dotted line depicts the base-case monthly drug costs (ticagrelor = $261, clopidogrel = $30, difference = $231). In the low-discrimination scenario (broken orange lines), the ICER for ticagrelor drops below $50,000/QALY when the monthly price difference between ticagrelor and clopidogrel is less than $215. In the high-discrimination scenario (solid blue line), this occurs when the monthly price difference between ticagrelor and clopidogrel is less than $93.

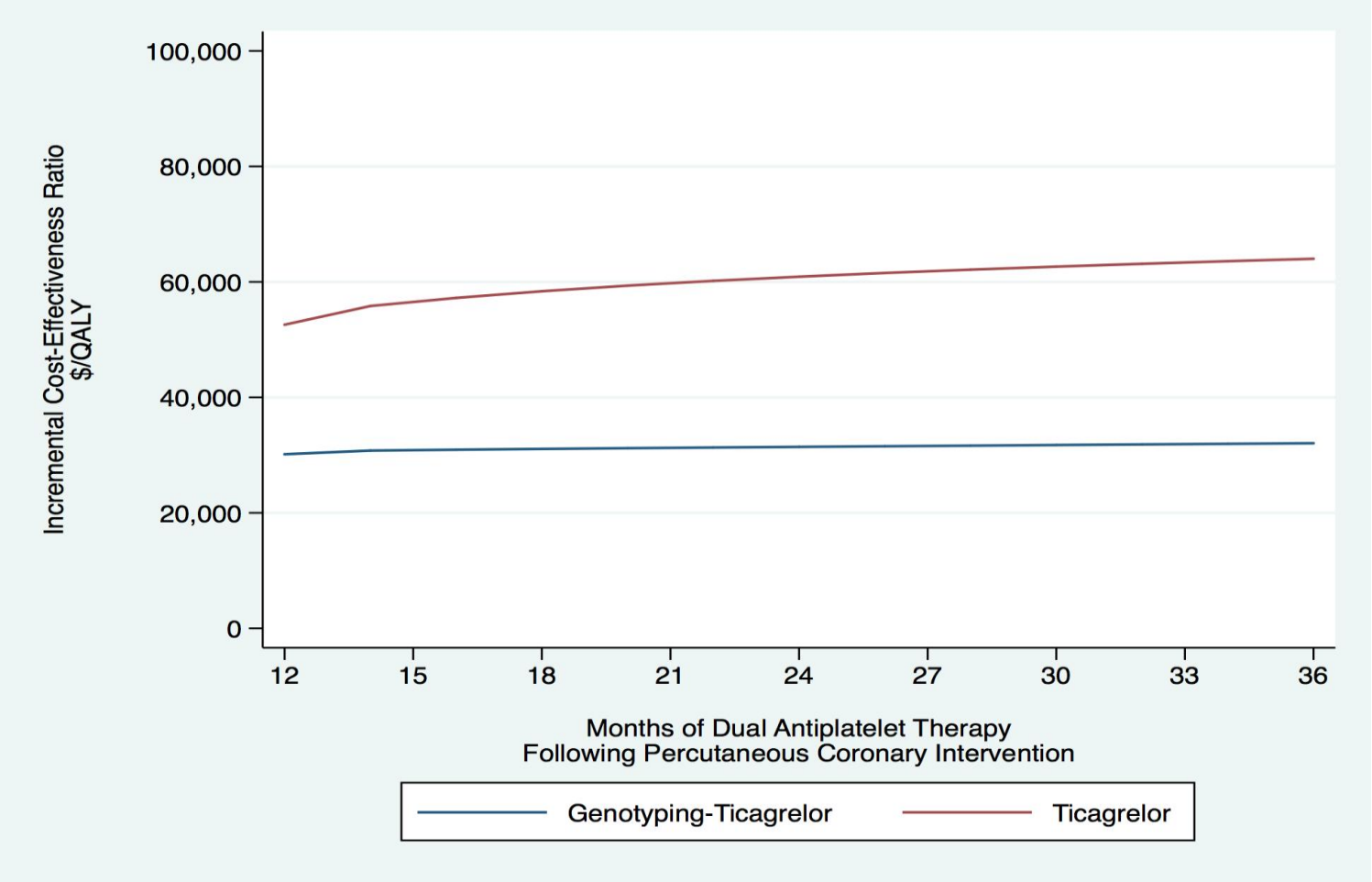


Duration of Antiplatelet Therapy

In the model, treatment time horizon for the second antiplatelet agent is 12 months, which is consistent with ACC/AHA recommendations for at least one year of dual antiplatelet therapy following DES PCI for ACS for patients who are not at high bleeding risk (2011 PCI guidelines, Level I Class B) (99). However, the guidelines note that "continuation of clopidogrel, prasugrel, or ticagrelor beyond 12 months may be considered in patients undergoing placement of DES," which

is a Level IIB Class C recommendation (99). We therefore examined the change in cost-effectiveness of each of the strategies with increasing duration of antiplatelet therapy (Supplement Figure 8). In this exploratory analysis, we assumed that antiplatelet agents produced similar relative reductions in the hazard of cardiovascular death, MI, and stent thrombosis in months 13-36 as in months 1-12. However, the absolute cardiovascular risk was greatest in the first year after PCI, whereas bleeding risk and drug costs remained relatively constant over time beyond the first year. Therefore dual antiplatelet therapy (both genotyping–ticagrelor relative to clopidogrel and ticagrelor relative to genotyping–ticagrelor) was less economically attractive with increasing duration of therapy (from 12 to 36 months). Genotyping–ticagrelor strategy remained the most cost-effective alternative for dual antiplatelet therapy after PCI for ACS, with an ICER less than $50,000/QALY. This analysis made the simplifying assumption that the rate of premature discontinuation of antiplatelet medications in months 24-36 was similar to that observed during months 13-24 in the recently published PARIS registry (100). Examining the impact of increasing persistence over time was beyond the scope of this manuscript.

Supplement Figure 8. Duration of Antiplatelet Therapy (Exploratory Analysis).



Death from "Other Causes": The Case of Noncardiovascular, Non-Bleeding-Related Mortality

Next, we examined the effect of assuming that neither prasugrel nor ticagrelor affect mortality other than that related to cardiovascular disease or bleeding. When cause-specific mortality is classified as cardiovascular, bleeding and "other" (referring to noncardiovascular deaths unrelated to bleeding), we note that in both PLATO and TRITON-TIMI38, the treatment arm (patients receiving ticagrelor or prasugrel respectively) had fewer deaths in this third category compared with patients on clopidogrel. Although it is possible that the treatment had some previously undescribed or off-target pharmacological action by which it reduced noncardiovascular mortality, it is also plausible that this observation may have resulted from misclassification of the cause of death (if some cardiovascular deaths were misclassified as noncardiovascular, a drug that reduces cardiovascular mortality may also be seen to reduce noncardiovascular mortality), or from a chance finding. We therefore studied a scenario where we assumed that neither prasugrel nor ticagrelor affected noncardiovascular mortality unrelated to bleeding (Supplement Table 4). Under these circumstances, genotyping–ticagrelor is the most cost-effective strategy under both low- and high-discrimination scenarios (at a threshold of $50,000/QALY). Thus we conclude that the incremental cost-effectiveness of ticagrelor is sensitive to the underlying assumption regarding its effect on noncardiovascular mortality.

Supplement Table 4. Scenario Analysis: Assuming That Neither Prasugrel nor Ticagrelor Affect Noncardiovascular Mortality Other Than Through Their Effect on Bleeding.[*]

Strategy	Total Lifetime Cost, *$*	QALYs, *n*	Incremental Costs, *$*	Incremental QALYs, *n*	Incremental cost-effectiveness, *$/QALY*[†]
Low-Discrimination Scenario					
Generic Clopidogrel	179,301	9.428	-	-	-
Prasugrel	181,299	9.431	-	-	Eliminated by strict dominance[‖]
Genotyping–Prasugrel[‡]	180,399	9.457	-	-	Eliminated by extended dominance[‖]
Genotyping–Ticagrelor[§]	180,908	9.478	1,606[¶]	0.049[¶]	32,500[¶]
Ticagrelor	183,069	9.505	2,162	0.027	80,500
High-Discrimination Scenario					
Generic Clopidogrel	179,301	9.428	-	-	-
Prasugrel	181,299	9.431	-	-	Eliminated by strict dominance[‖]
Genotyping–Prasugrel[‡]	180,748	9.483	-	-	Eliminated by extended dominance[‖]
Genotyping–Ticagrelor[§]	181,257	9.505	1,948[¶]	0.076[¶]	25,700[¶]
Ticagrelor	183,069	9.505	-	-	Eliminated by strict dominance[‖]

Abbreviation: LOF, loss-of-function; QALY, quality-adjusted life year.

[*] Numbers may not appear to tally exactly because of rounding. Costs are measured in 2011 U.S. dollars. Cost, QALYs and life expectancy discounted at 3% a year.

[†] Incremental cost-effectiveness for each strategy, expressed as an incremental cost-effectiveness ratio relative to the next best strategy that is not eliminated by strict or extended dominance, rounded to the closest $100 to reflect the precision in the model.

[‡] In the genotyping–prasugrel strategy, carriers of one or two loss-of-function polymorphisms in CYP2C19 were treated with prasugrel; others received generic clopidogrel.

[§] In the genotyping–ticagrelor strategy, carriers of one or two loss-of-function polymorphisms in CYP2C19 were treated with ticagrelor; others received generic clopidogrel.

‖ When a strategy costs more but produces fewer QALYs than a comparator (in this case prasugrel vs. genotyping–prasugrel in both scenarios, and ticagrelor vs. genotyping–ticagrelor in the high-discrimination scenario), it is a clinically and economically inferior strategy, and, in economics parlance, is eliminated from consideration by "strict dominance".

‖ A strategy is said to be eliminated by "extended dominance" if the costs and benefits can be improved by a mixed strategy of two other alternatives. In this case, genotyping–prasugrel is eliminated by a combination of clopidogrel and genotyping–ticagrelor.

¶ The cost-effectiveness of genotyping–ticagrelor is measured relative to clopidogrel because prasugrel is eliminated by strict dominance and genotyping–prasugrel by extended dominance.

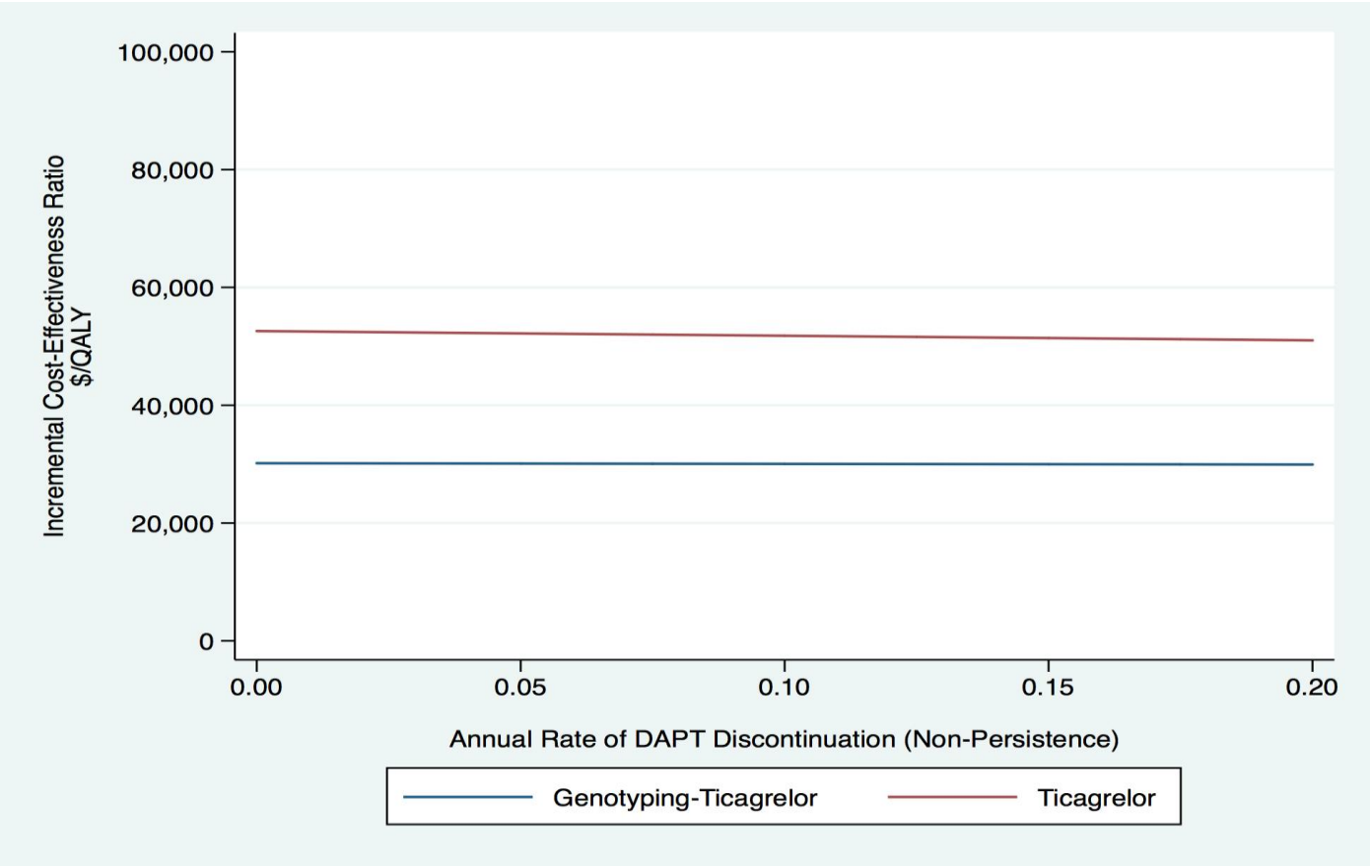
Adherence and Persistence

As with all drugs, real world effectiveness of the newer antiplatelet agents is a function of adherence (defined as percentage of prescribed pills taken) and persistence (defined as taking the pills for the prescribed duration).

Hazard ratios obtained from randomized trials incorporate some non-adherence observed during the trial, but adherence in the real world may be substantially lower. Although adherence is predictive of pharmacokinetic parameters such as serum drug concentrations, it is unclear whether it has a linear correlation with outcomes. Of note, there are no data systematically correlating adherence to ticagrelor or prasugrel with clinically relevant outcomes, and circumstantial evidence suggests that the association between drug dose, platelet inhibition and clinical outcomes may not be linear. For instance, although ticagrelor is a reversible drug requiring twice daily dosing, patients who stop taking the drug several days prior to CABG still have a small increased risk of bleeding, suggesting a longer duration of clinical effect than implied by drug pharmacokinetics (101). It is plausible that occasionally missing a dose may have no effect on outcomes until a threshold of non-adherence is reached. Nevertheless, if we assume a linear correlation with outcomes, 100% adherence to all medications (as compared with the base-case of 93.1% adherence to ticagrelor in months 2 through 12 of therapy) did not materially alter the results. the proportion of patients with dyspnea requiring discontinuation the proportion of patients with dyspnea requiring discontinuation the proportion of patients with dyspnea requiring discontinuation An extensive analysis varying both the magnitude and shape of the association between adherence and outcomes is beyond the scope of this manuscript.

Persistence, defined as taking the therapy for the duration it has been prescribed, is also a relevant consideration. Two-year results from the recently published PARIS registry suggest that patients frequently prematurely discontinue dual antiplatelet therapy (which the investigators differentiated from disruption of therapy due to adverse events or planned surgery) (100). However, this premature discontinuation of therapy is likely similar with all three drugs, so that the *incremental* cost-effectiveness of the strategies remains largely unchanged (Supplement Figure 9). In the absence of real-world data on persistence and its impact on outcomes with the newer antiplatelet agents, this analysis should be considered exploratory.

Supplement Figure 9: Persistence With Dual Antiplatelet Therapy (Exploratory Analysis).



Carrier Status

Finally, as an illustrative exercise, we explored the impact of carrier status on cost-effectiveness of each of the three drug strategies (Supplement Table 5). This provides mechanistic insight into the results of the cost-effectiveness analysis. Consider a comparison of a drug-only strategy with the genotype-based strategy for the same drug, e.g., prasugrel vs. genotyping–prasugrel. In both cases, carriers of loss-of-function alleles receive prasugrel (assuming that the genotyping test is perfectly sensitive and specific), so that the comparison between the prasugrel and genotyping–prasugrel depends on whether loss-of-function noncarriers (wild-type and gain-of-function carriers) do better on prasugrel - in which case the prasugrel strategy is the preferred strategy, or whether loss-of-function noncarriers do better on clopidogrel - in which case the genotyping-prasugrel is the preferred strategy. Supplement Table 5 helps reinforce the point: relative to noncarriers on clopidogrel, noncarriers receiving prasugrel have worse outcomes and incur greater costs. This explains why, in the base-case, genotyping–prasugrel is preferred over prasugrel (in effectiveness as well as cost-effectiveness). In contrast, noncarriers have better outcomes with ticagrelor relative to clopidogrel, although this comes at a relatively large cost, making universal treatment with ticagrelor more effective but also more expensive.

Supplement Table 5. Cost-Effectiveness of Drug Therapies by Carrier Status.[*]

	Low-Discrimination Scenario[†]			High-Discrimination Scenario[†]		
Strategy	**Total Lifetime Cost**	**QALYs**	**Incremental Cost-Effectiveness**	**Total Lifetime Cost**	**QALYs**	**Incremental Cost-Effectiveness**
Carriers of CYP2C19 Loss-of-Function Polymorphisms						
Generic Clopidogrel	$178,267	9.330	-	$177,032	9.234	-
Prasugrel	$181,546	9.446	Eliminated by extended dominance	$181,546	9.446	21,300
Ticagrelor	$183,531	9.533	25,800	$183,531	9.533	22,800
Carriers of CYP2C19 Gain-of-Function Polymorphisms						
Generic Clopidogrel	$180,425	9.519	-	$180,842	9.551	-
Prasugrel	$181,546	9.446	Eliminated by strict dominance	$181,546	9.446	Eliminated by strict dominance
Ticagrelor	$183,531	9.533	222,600	$183,531	9.533	Eliminated by strict dominance
Noncarriers of CYP2C19 Gain-of-Function or Loss-of-Function Polymorphisms ("Wild Type")						
Generic Clopidogrel	$179,093	9.422	-	$179,646	9.465	-
Prasugrel	$181,546	9.446	Eliminated by extended dominance	$181,546	9.446	Eliminated by strict dominance
Ticagrelor	$183,531	9.533	22,800	$183,531	9.533	56,600

QALY = quality-adjusted life year.

[*] Numbers may not appear to tally exactly because of rounding. Costs are measured in 2011 U.S. dollars. Cost, QALYs and life expectancy discounted at 3% a year. Note that because one gain-of-function allele cannot compensate completely for one loss-of-function allele, patients with one gain-of-function allele and one loss-of-function allele ("unknown metabolizers") are treated similar to carriers of loss-of-function polymorphisms.

[†] Incremental cost-effectiveness for each strategy, expressed as an incremental cost-effectiveness ratio relative to the next best strategy, rounded to the closest $100 to reflect the precision in the model.

6. Single-Drug Therapies

These sensitivity analyses separately examine the role of genotyping with prasugrel and ticagrelor.

A. Prasugrel-based therapies.

In the base-case, we assumed that loss-of-function genotype was only modestly correlated with thrombotic outcomes after PCI for ACS (low-discrimination scenario) (67). Among prasugrel-based therapies, genotype–guided treatment generated greater QALYs than treating all patients with prasugrel and also cost less (Table 1). Genotyping-prasugrel was therefore clinically and economically superior, with an ICER of $35,800/QALY relative to clopidogrel.

One-Way Sensitivity Analyses

Among prasugrel-based therapies, genotyping–prasugrel was clinically and economically superior to prasugrel (i.e., genotyping–prasugrel produced more QALYs at lower costs than prasugrel), and this result was robust to large one-way variations in the input parameters under both low- and high-discrimination scenarios (Supplement Table 6).

Two-Way Sensitivity Analysis

In a two-way sensitivity analysis, we varied the rate ratios for bleeding and cardiovascular mortality on prasugrel relative to clopidogrel (higher ratios imply more frequent adverse events on prasugrel), while holding the corresponding rate ratios for ticagrelor constant at their base-case estimate (Supplement Figure 10). We assumed a willingness-to-pay threshold of $50,000/QALY. The broken lines represent the base-case value. Genotyping-prasugrel is the most cost-effective strategy in the base-case in the low- and high-discrimination scenarios. However the result is more robust to uncertainty in the efficacy or safety of prasugrel in the high-discrimination scenario (as seen by distance to the threshold, Panel B). For prasugrel to be the most cost-effective strategy at $50,000/QALY, it would have to lower bleeds as well as thrombotic events relative to clopidogrel.

Probabilistic Sensitivity Analyses

In probabilistic sensitivity analyses we varied all input parameters using pre-specified distributions, but restricted the comparison to clopidogrel, prasugrel, and genotyping–prasugrel (Supplement Figure 11). In the low-discrimination scenario (Panel A), genotyping-prasugrel produced more QALYs than prasugrel in 59% of the simulations, and cost less than prasugrel genotyping-prasugrel cost less than prasugrel in 90% of the simulations. Overall, genotyping-prasugrel was the more cost-effective alternative at a threshold of $50,000/QALY in 86% of the simulations.

In the high discrimination scenario (Panel B), genotyping-prasugrel produced more QALYs than prasugrel in 76% of the simulations, and cost less than prasugrel in 80% of the simulations. Overall, genotyping-prasugrel was the more cost-effective alternative in 94% of the simulations.

Supplement Table 6. Results of One-Way Sensitivity Analyses Across Prasugrel-Based Strategies. Variables that affect the choice of the most cost-effective strategy for dual antiplatelet therapy after percutaneous coronary intervention for acute coronary syndrome at a willingness-to-pay threshold of $50,000/QALY under low- and high-discrimination scenarios .*

Variable	Base Case	Low-Discrimination Scenario Most cost-effective strategy: Genotyping–Prasugrel†		High-Discrimination Scenario Most cost-effective strategy: Genotyping–Prasugrel†	
		Threshold for most cost-effective strategy	Optimal Dual Antiplatelet Therapy When Threshold is Crossed	Threshold for most cost-effective strategy	Optimal Dual Antiplatelet Therapy When Threshold is Crossed
Rate ratio for cardiovascular death, prasugrel relative to clopidogrel	0.89	> 1.02‡	Clopidogrel	< 0.58 > 1.29	Prasugrel Clopidogrel
Rate ratio for noncardiovascular death unrelated to bleeding, prasugrel relative to clopidogrel	0.81	-	-	-	-
Rate ratio for fatal bleeding, prasugrel relative to clopidogrel	4.19	> 7.29	Clopidogrel	> 13.87	Clopidogrel
Rate ratio for nonfatal intracranial bleeding, prasugrel relative to clopidogrel	0.83	-	-	-	-
Rate ratio for nonfatal myocardial infarction, prasugrel relative to clopidogrel	0.76	-	-	-	-
Rate ratio for stent thrombosis, prasugrel relative to clopidogrel	0.48	-	-	-	-
Rate ratio for cardiovascular death, LOF carriers relative to noncarriers§	-	< 1.16	Clopidogrel	< 1.09	Clopidogrel
Proportion of the population that carriers the LOF polymorphisms	28%	-	-	-	-
Difference in monthly cost of prasugrel and generic clopidogrel	$189	> $323	Clopidogrel	-	-
Specificity of genetic testing	99.3%	< 77%	Clopidogrel	< 56%	Clopidogrel
Cost of genetic testing	$235	> $700	Clopidogrel	> $1,680	Clopidogrel
Discount factor	3%	-	-	-	-

LOF = loss-of-function; QALY = quality-adjusted life year.

* This table presents results of one-way sensitivity analyses comparing generic clopidogrel, prasugrel, and genotyping–prasugrel strategies for dual antiplatelet therapy and reports the threshold values of the input parameters where the choice of optimal therapy changes at a willingness-to-pay threshold of $50,000/QALY. The low-discrimination scenario assumes weak associations between LOF carrier status and thrombotic events (67), whereas the high-discrimination scenario assumes stronger associations between LOF genotype and thrombotic events (25). Note that for several key parameters, e.g., drug costs or costs of genetic testing, we tested ranges beyond those pre-specified in the Appendix Table in order to identify thresholds where the optimal choice of therapy switches.

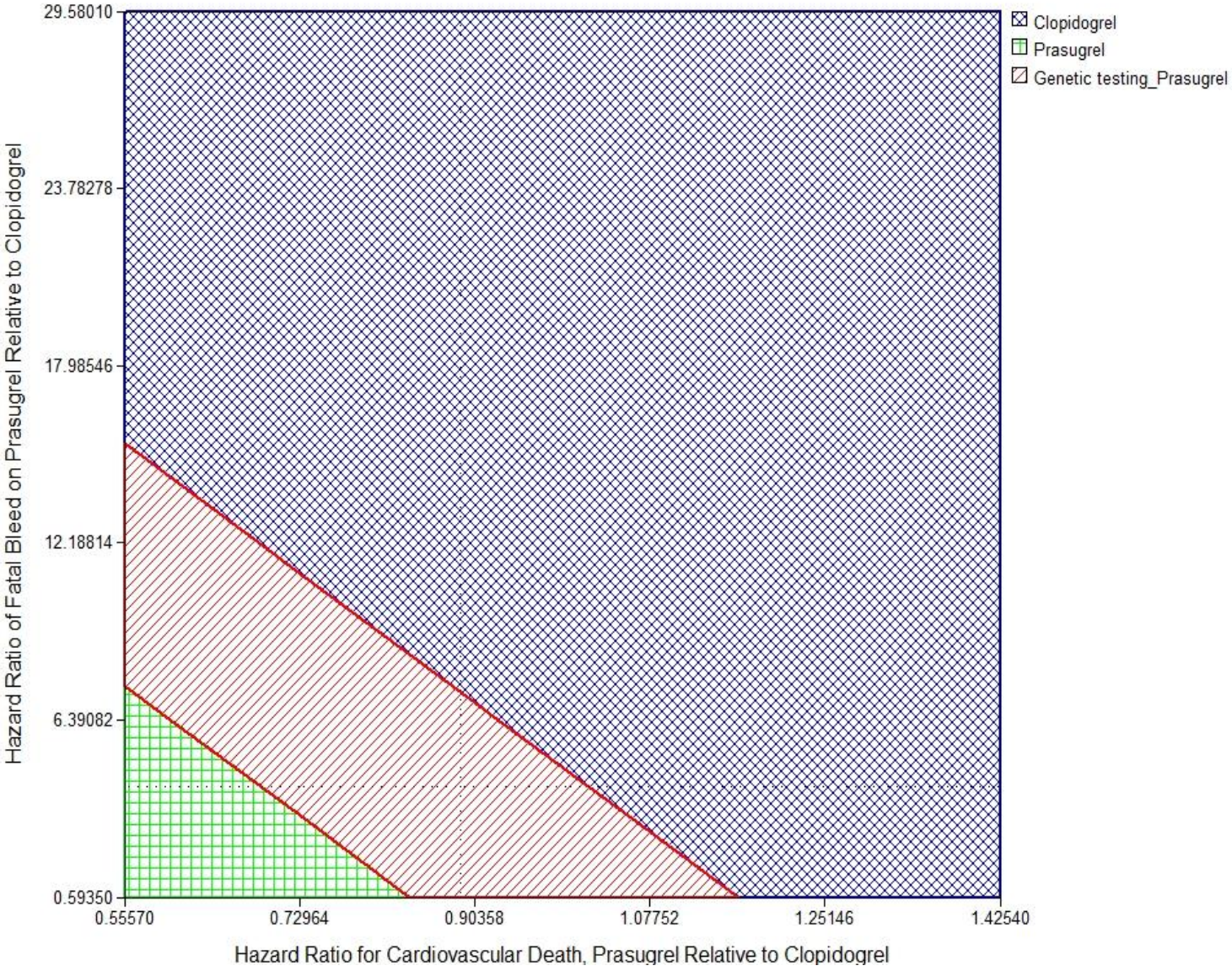
† In the Genotyping–Ticagrelor strategy, patients with one or two LOF polymorphisms in CYP2C19 were treated with ticagrelor; all others received generic clopidogrel.

‡ This can be interpreted as follows: at a willingness-to-pay threshold of $50,000/QALY, genotyping–prasugrel is the most cost-effective strategy in the base-case, but if the rate ratio for cardiovascular death on prasugrel relative to clopidogrel were greater than 1.02 (for reference, base-case 0.89; 95% confidence interval: 0.7-1.12), the most cost-effective strategy would be to give all patients clopidogrel.

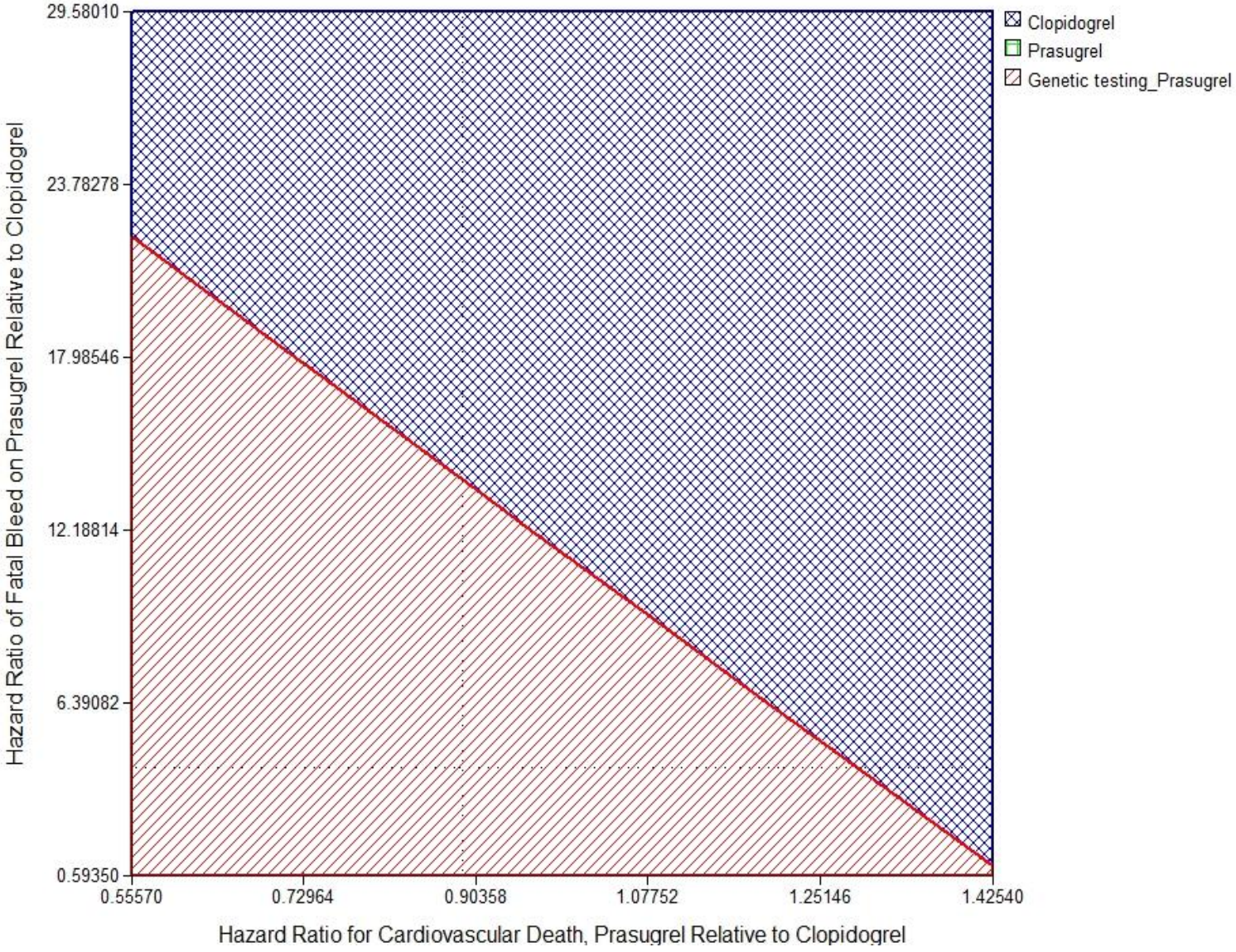
§ The base-case rate ratio for cardiovascular death among carriers of LOF alleles relative to noncarriers was 1.37 in the low-discrimination scenario (estimated in the model from the rate ratio for death from all causes reported by Holmes, et al.); and 1.84 in the high-discrimination scenario.

Supplement Figure 10. The Trade-Off Between Bleeding and Thrombosis. Two Way Sensitivity Analyses: Prasugrel-Based Therapies. Broken lines indicate the base-case assumptions. QALY, quality-adjusted life year. See text for details. Willingness-to-pay Threshold = $50,000/QALY.

A. Low-Discrimination Scenario

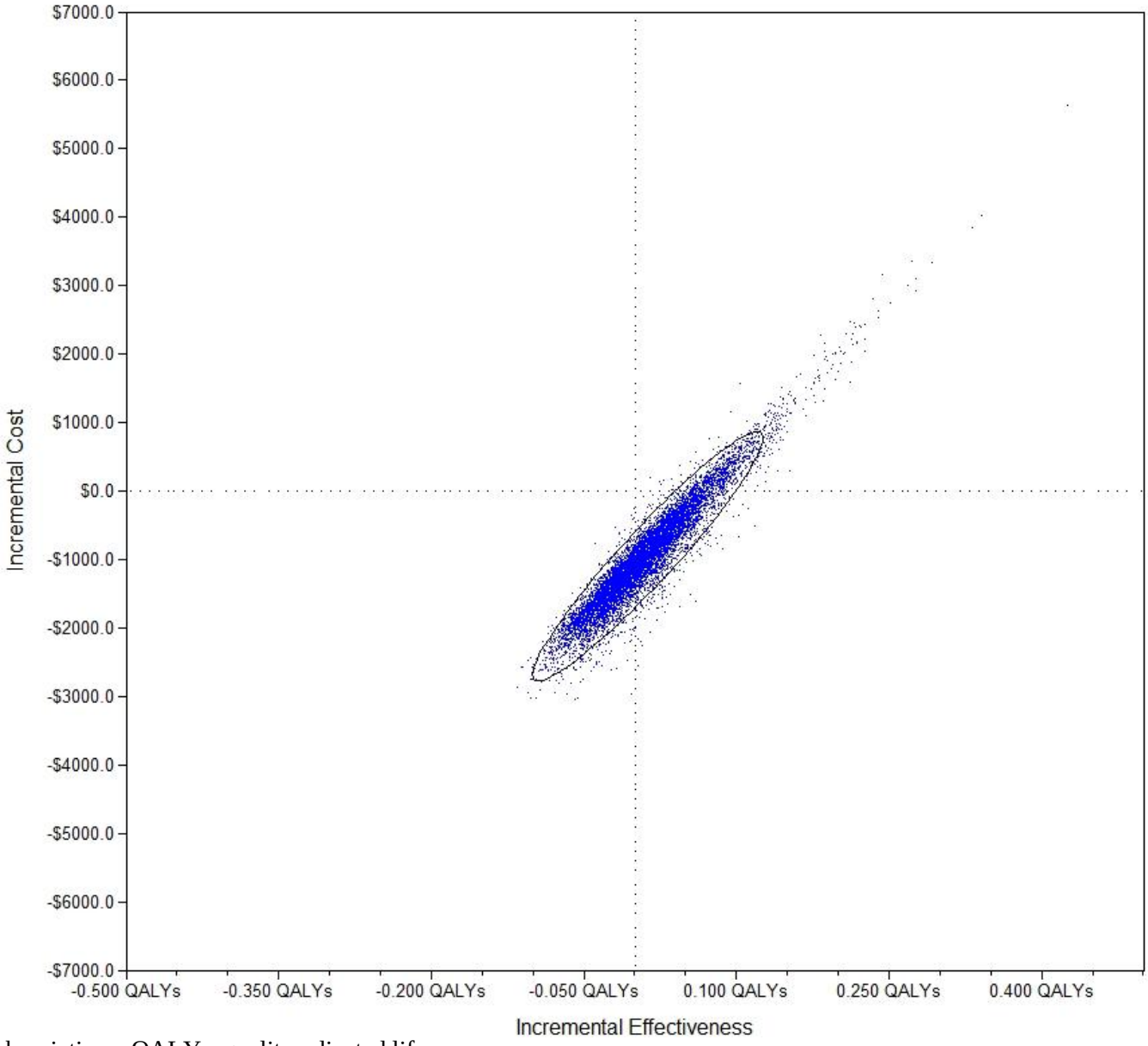


B . High-Discrimination Scenario



Supplement Figure 11. Probabilistic Sensitivity Analysis Comparing Genotyping–Prasugrel With Prasugrel

A. Low-Discrimination Scenario:

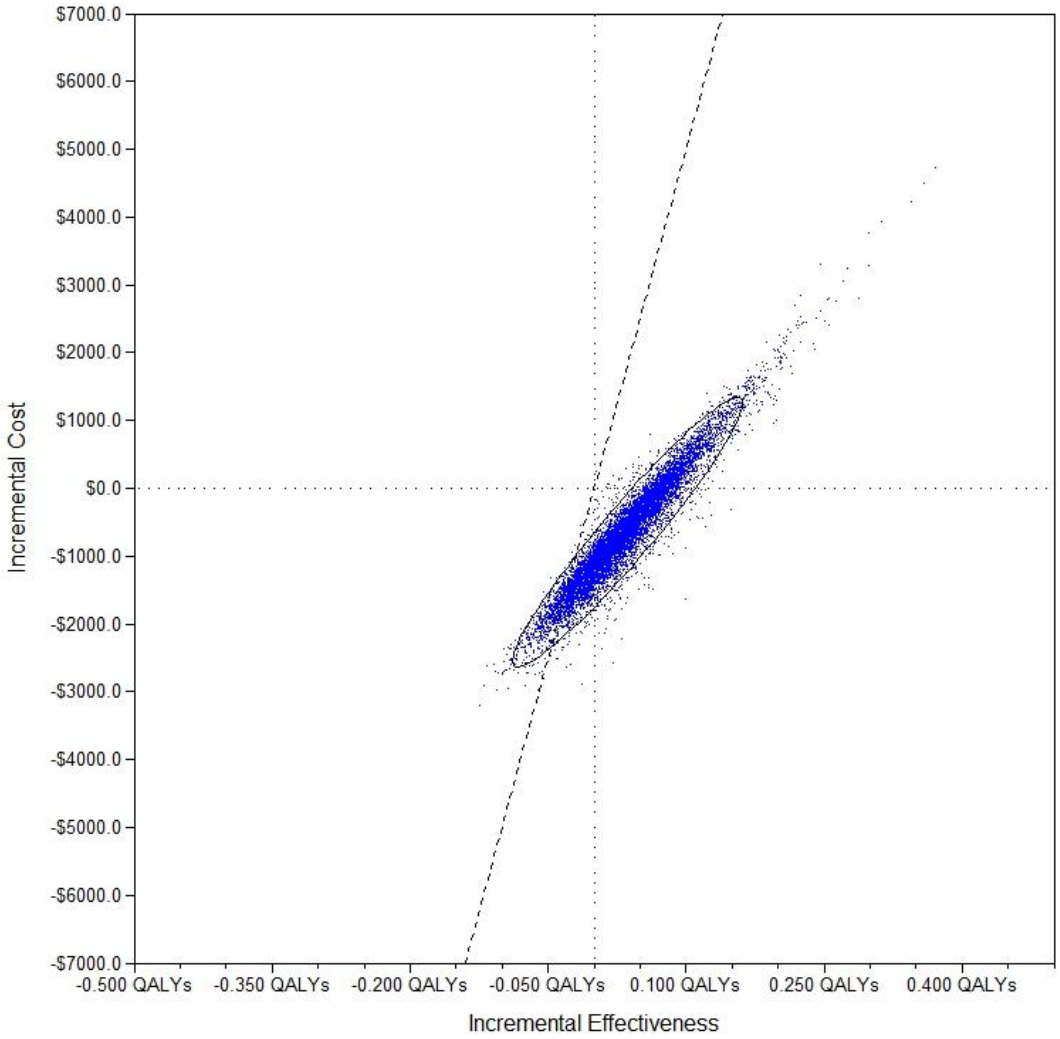


Abbreviations: QALYs, quality-adjusted life years.

This cost-effectiveness scatter plot depicts the results of 10,000 probabilistic simulations through the model in the low-discrimination scenario. Genotyping-prasugrel produced more QALYs than prasugrel in 59% of the simulations (data points to the right of the y-axis), and cost less than prasugrel genotyping-prasugrel cost less than prasugrel in 90% of the simulations (data points below the x-axis). Overall, genotyping-prasugrel was the more cost-effective alternative at a threshold of

$50,000/QALY in 86% of the simulations. The dashed line represents an incremental cost-effectiveness threshold of $50,000/QALY, and the ellipse represents the 95% confidence interval of the joint distribution of incremental costs and QALYs.

B. High-Discrimination Scenario:



Abbreviations: QALYs, quality-adjusted life years.

This cost-effectiveness scatter plot depicts the results of 10,000 probabilistic simulations through the model in the high-discrimination scenario. Genotyping-prasugrel produced more QALYs than prasugrel in 76% of the simulations (data points to the right of the y-axis), and cost less than prasugrel in 80% of the simulations, (data points below the x-axis). Overall, genotyping-prasugrel was the more cost-effective alternative in 94% of the simulations. The dashed line represents an incremental cost-effectiveness threshold of $50,000/QALY, and the ellipse represents the 95% confidence interval of the joint distribution of incremental costs and QALYs.

B. Ticagrelor-based Therapies.

In the base-case, we assumed that loss-of-function genotype was only modestly correlated with thrombotic outcomes after PCI for ACS (low-discrimination scenario) (67). Among ticagrelor-based therapies, genotype-guided treatment generated lower costs than giving all patients ticagrelor, but also produced fewer QALYs. The ICER for genotyping–ticagrelor was $30,200/QALY relative to clopidogrel, whereas the ICER for ticagrelor was $52,600/QALY relative to genotyping–ticagrelor.

One-Way Sensitivity Analyses

Among ticagrelor-based therapies, although genotyping–ticagrelor was the most cost-effective strategy at a threshold of $50,000/QALY, the choice of optimal therapy in the low-discrimination scenario was sensitive to modest variations in the cost, effectiveness, and bleeding-risk associated with ticagrelor, relative to generic clopidogrel (Supplement Table 7).

Two-Way Sensitivity Analysis

In a two-way sensitivity analysis, we varied the rate ratios for cardiovascular mortality and fatal bleeding for ticagrelor, holding the rate ratios for prasugrel constant at the base-case (Supplement Figure 12). In the low-discrimination scenario (Panel A), genotyping–ticagrelor is the most cost-effective therapy, but its cost-effectiveness is sensitive to the underlying assumptions of safety and efficacy, as noted by the proximity of the base-case to the threshold where ticagrelor becomes the most cost-effective therapy.

Probabilistic Sensitivity Analyses

In probabilistic sensitivity analyses we conducted 10,000 simulations, while simultaneously varying all input parameters along pre-specified distributions, but restricted the comparison to clopidogrel, ticagrelor, and genotyping–ticagrelor (Supplement Figure 13). In the low-discrimination scenario (Panel A), ticagrelor produced more QALYs than genotyping-ticagrelor in 97% of the simulations, but was more expensive than genotyping-ticagrelor in 100% of the simulations. At a willingness-to-pay threshold of $50,000/QALY, genotyping-ticagrelor was the more cost-effective strategy in 53% of the simulations, and ticagrelor was the more cost-effective alternative in remaining 47%. In the high discrimination scenario (Supplement Figure 13, Panel B), ticagrelor produced more QALYs than genotyping-ticagrelor in 77% of the simulation , but cost more than genotyping-ticagrelor in 100% of the simulations. At a willingness-to-pay threshold of $50,000/QALY, genotyping-ticagrelor was the more cost-effective strategy in 80% of the simulations, and ticagrelor was the more cost-effective strategy in the remainder .

The dashed line represents an incremental cost-effectiveness threshold of $50,000/QALY, and the ellipse represents the 95% confidence interval of the joint distribution of incremental costs and QALYs.

Supplement Table 7. Results of One-Way Sensitivity Analyses Across Ticagrelor-Based Strategies. Variables that affect the choice of the most cost-effective strategy for dual antiplatelet therapy after percutaneous coronary intervention for acute coronary syndrome at a willingness-to-pay threshold of $50,000/QALY under low- and high-discrimination scenarios .*

Variable	Base-Case	Low-Discrimination Scenario Most cost-effective strategy: Genotyping– Ticagrelor†		High-Discrimination Scenario Most cost-effective strategy: Genotyping– Ticagrelor	
		Threshold for most cost-effective strategy	Optimal Dual Antiplatelet Therapy When Threshold is Crossed	Threshold for most cost-effective strategy	Optimal Dual Antiplatelet Therapy When Threshold is Crossed
Rate ratio for cardiovascular death, ticagrelor relative to clopidogrel	0.79	<0.78	Ticagrelor‡	< 0.66	Ticagrelor
Rate ratio for noncardiovascular death unrelated to bleeding, ticagrelor relative to clopidogrel	0.63	<0.57	Ticagrelor	-	-
Rate ratio for fatal bleeding, ticagrelor relative to clopidogrel	0.87	<0.54	Ticagrelor	-	-
Rate ratio for nonfatal intracranial bleeding, ticagrelor relative to clopidogrel	1.15	<0.97	Ticagrelor	-	-
Rate ratio for nonfatal myocardial infarction, ticagrelor relative to clopidogrel	0.84	-	-	-	-
Rate ratio for stent thrombosis, ticagrelor relative to clopidogrel	0.75	-	-	-	-
Rate ratio for cardiovascular death, LOF carriers relative to LOF noncarriers§	-	< 1.32	Ticagrelor	< 1.26	Ticagrelor
Rate ratio for non-fatal myocardial infarction, LOF carriers relative to LOF noncarriers‖	-	<1.09	Ticagrelor	-	-
Proportion of the population that carriers the CYP2C19 loss of function polymorphism	28%	>52.7%	Ticagrelor	> 86.8%	Ticagrelor
Difference in monthly cost of ticagrelor and generic clopidogrel	$231	< 215	Ticagrelor	< $93	Ticagrelor
Sensitivity of Genetic Test for CYP2C19 polymorphisms		<90%	Ticagrelor	<51%	Ticagrelor
Cost of Genetic Testing	$235	>358	Ticagrelor	-	-
Discount factor	3%	<2.1%¶	Ticagrelor	-	-

Abbreviations: LOF, loss-of-function, QALY, quality-adjusted life year.

* This table presents results of one-way sensitivity analyses comparing generic clopidogrel, ticagrelor and genotyping–ticagrelor strategies, and reports the threshold values of the input parameters where the choice of optimal therapy changes at a willingness-to-pay threshold of $50,000/QALY. The low-discrimination scenario assumes weak associations between LOF carrier status and thrombotic events (67), whereas the high-discrimination scenario assumes stronger associations between LOF genotype and

thrombotic events (25). Note that for several key parameters, e.g., drug costs or costs of genetic testing, we tested ranges beyond those pre-specified in the Appendix Table in order to identify thresholds where the optimal choice of therapy switches.

† In the Genotyping–Ticagrelor strategy, patients with one or two LOF polymorphisms in CYP2C19 were treated with ticagrelor; all others received generic clopidogrel.

‡ This can be interpreted as follows: Assuming that all input parameters are at their base-case values, genotyping-ticagrelor is the most cost-effective strategy at a threshold of $50,000/QALY, but if ticagrelor were more effective at reducing cardiovascular mortality (rate ratio for cardiovascular death on ticagrelor relative to clopidogrel <0.78; for reference, the base-case is 0.79, 95% confidence interval: 0.69-0.91), ticagrelor would become the most cost-effective therapy.

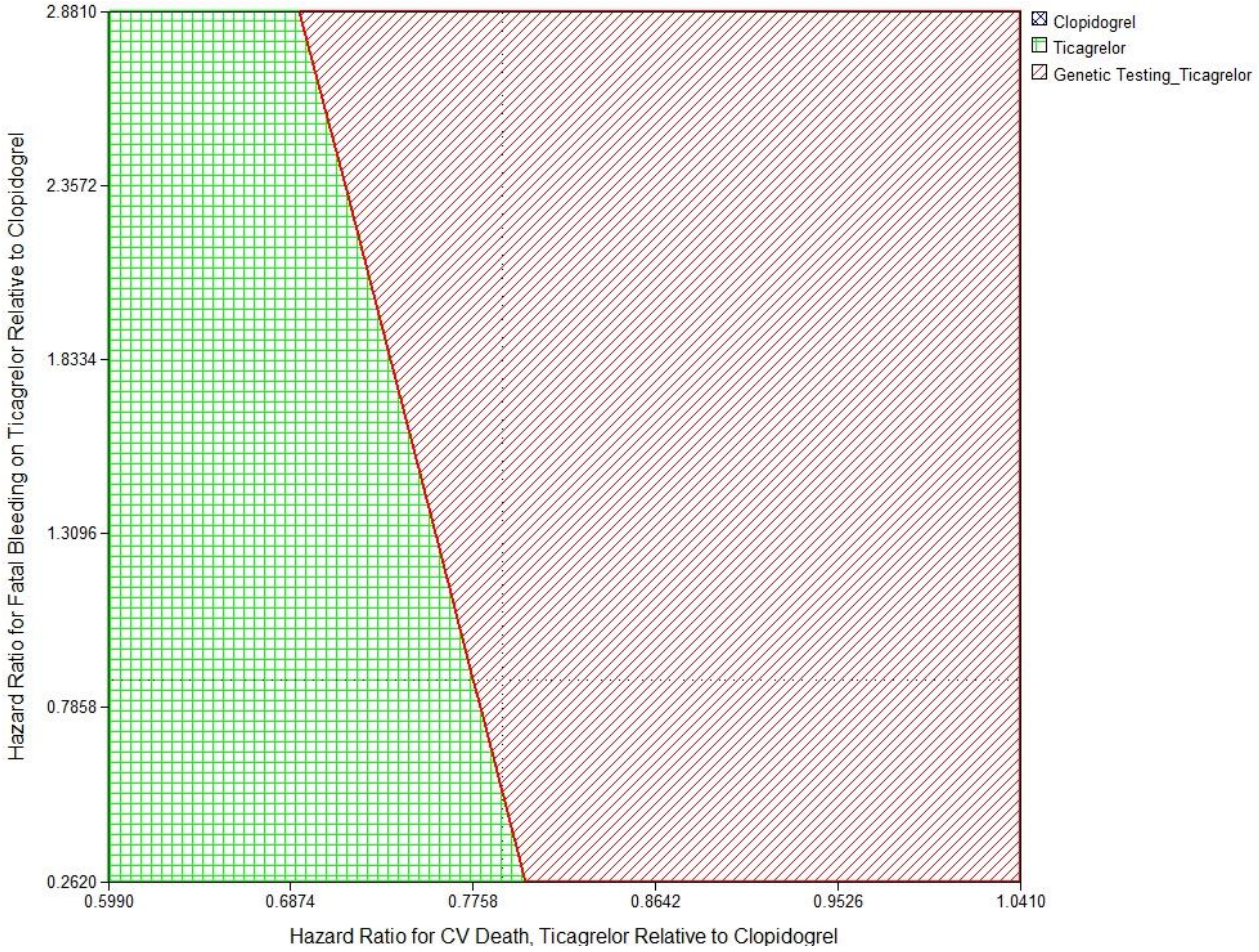
§ The base-case rate ratio for cardiovascular death among carriers of LOF alleles relative to noncarriers was 1.37 in the low-discrimination scenario (estimated in the model from the rate ratio for death from all causes reported by Holmes, et al.); and 1.84 in the high-discrimination scenario.

‖ The base-case rate ratio for non-fatal myocardial infarction among carriers of LOF alleles relative to noncarriers was 1.48 in the low-discrimination scenario and 1.45 in the high-discrimination scenario.

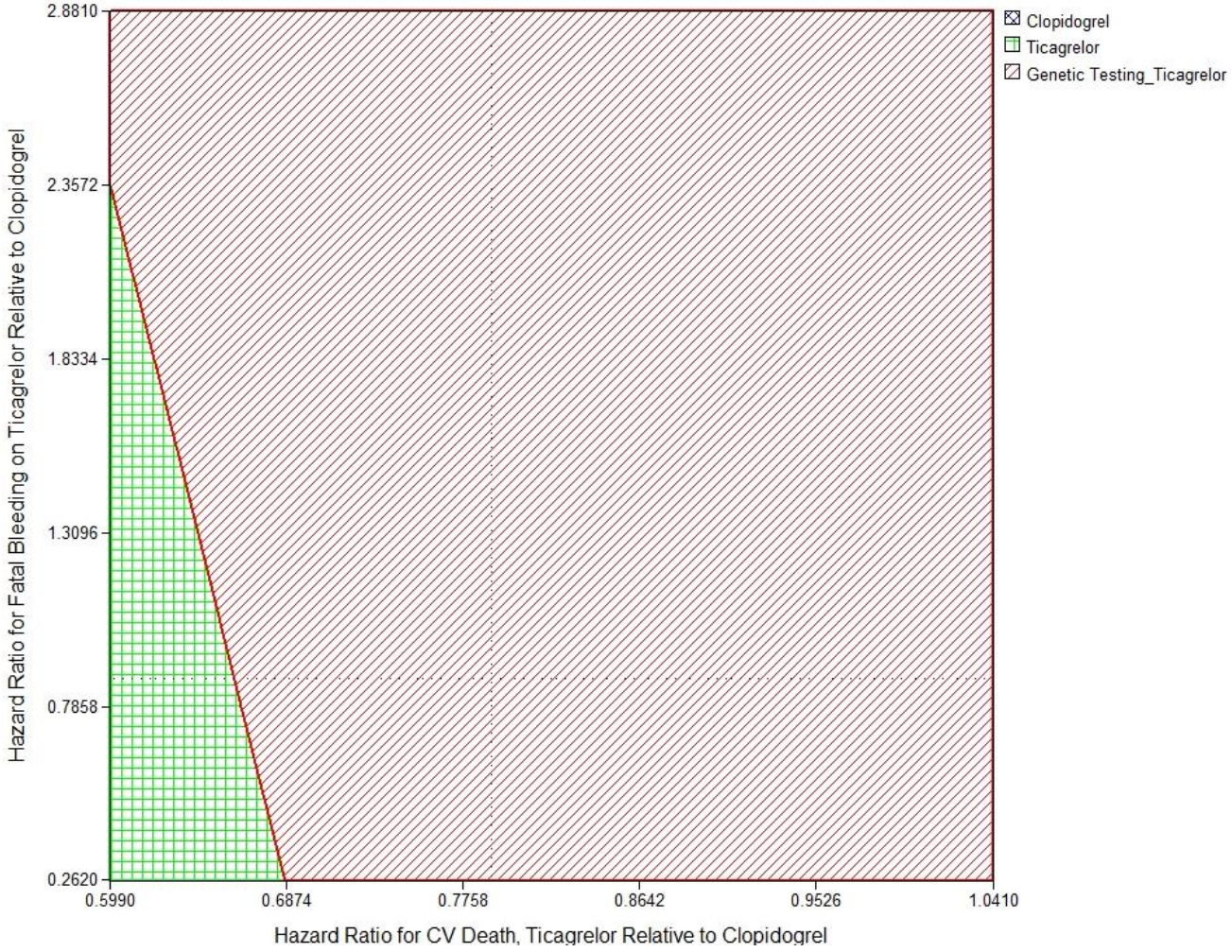
¶ This can be interpreted as follows: if the discount rate for costs and outcomes were less than 2.1% a year, ticagrelor would become the most cost-effective strategy at $50,000/QALY. The intuition is that lower discount rates make it more attractive to invest in a more expensive drug like ticagrelor, where the costs are incurred upfront (in the first year after coronary revascularization) whereas the benefits accrue over the patients' lifetime.

Supplement Figure 12. The Trade-Off Between Bleeding and Thrombosis. Ticagrelor-Based Therapies. Broken lines indicate the base-case assumptions. QALY, quality-adjusted life year. Willingness-to-pay Threshold = $50,000/QALY.

A. Low-Discrimination Scenario.

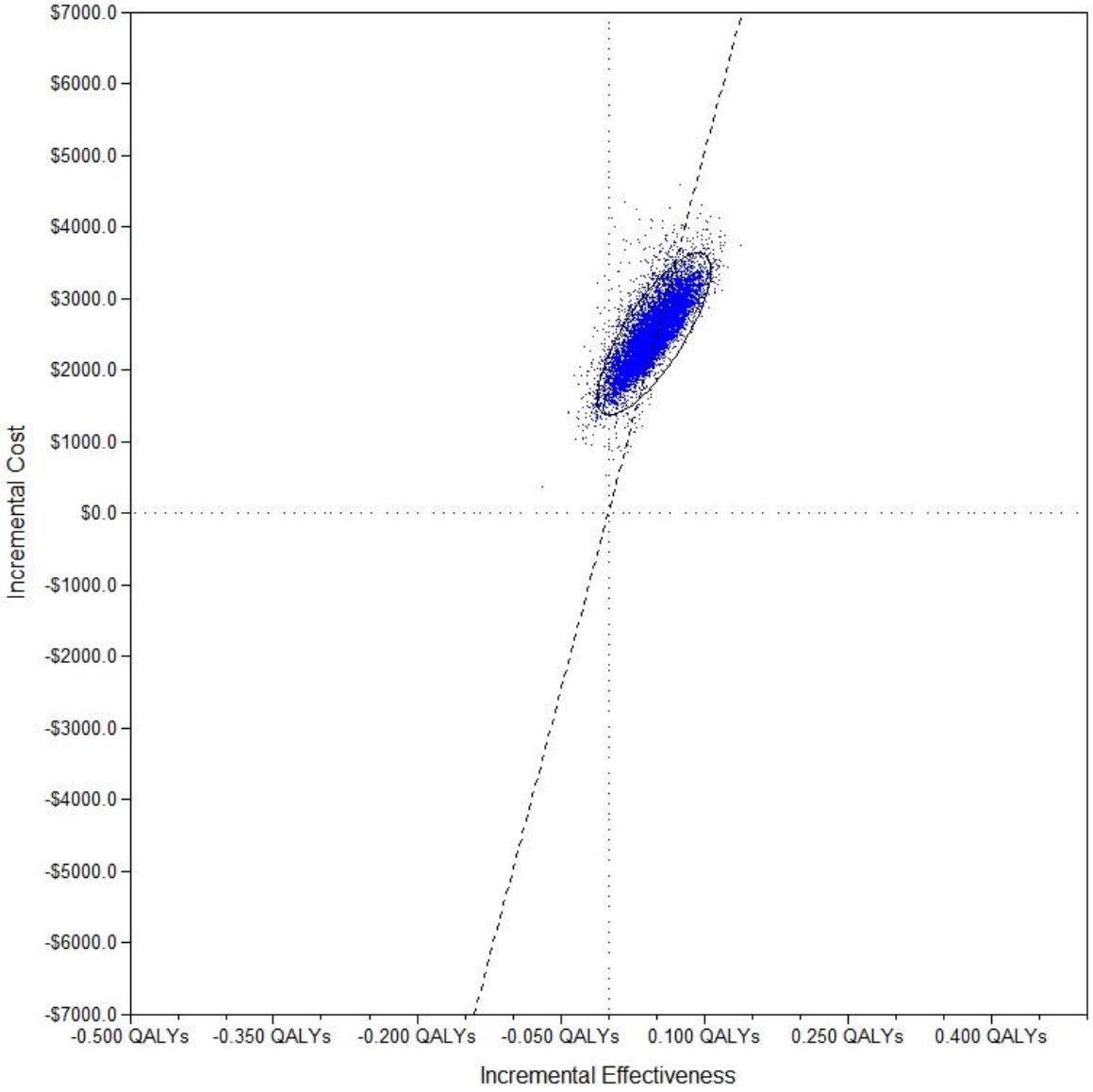


B. High-Discrimination Scenario



Supplement Figure 13. Probabilistic Sensitivity Analysis Comparing Ticagrelor With Genotyping–Ticagrelor.

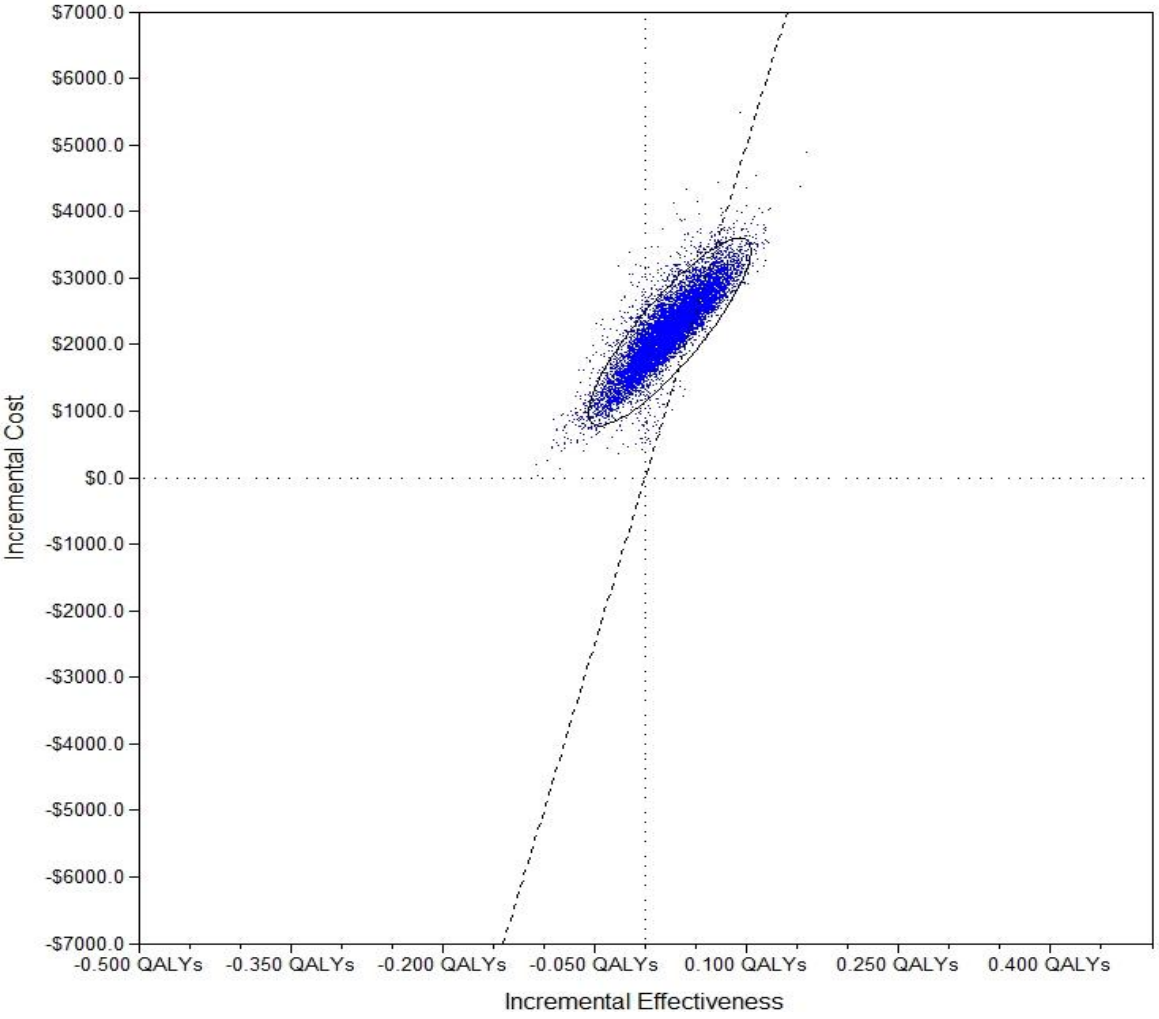
A. Low-Discrimination Scenario:



Abbreviations: QALYs, quality-adjusted life years.

This cost-effectiveness scatter plot depicts the results of 10,000 probabilistic simulations through the model in the low-discrimination scenario. Ticagrelor produced more QALYs than genotyping-ticagrelor in 97% of the simulations (data points to the right of the y-axis), and cost more than genotyping-ticagrelor in 100% of the simulations (data points above the x-axis). At a willingness-to-pay threshold of $50,000/QALY, genotyping-ticagrelor was the more cost-effective strategy in 53% of the simulations, and ticagrelor was the more cost-effective alternative in 47% of the simulations. The dashed line represents an incremental cost-effectiveness threshold of $50,000/QALY, and the ellipse represents the 95% confidence interval of the joint distribution of incremental costs and QALYs.

B. High-Discrimination Scenario:



Abbreviations: QALYs, quality-adjusted life years.

This cost-effectiveness scatter plot depicts the results of 10,000 probabilistic simulations through the model in the high-discrimination scenario. Ticagrelor produced more QALYs than genotyping-ticagrelor in 77% of the simulations (data points to the right of the y-axis), and cost more than genotyping-ticagrelor in 100% of the simulations (data points above the x-axis). At a willingness-to-pay threshold of $50,000/QALY, genotyping-ticagrelor was the more cost-effective strategy in 80% of the simulations, and ticagrelor was the more cost-effective strategy in 20%. The dashed line represents an incremental cost-effectiveness threshold of $50,000/QALY, and the ellipse represents the 95% confidence interval of the joint distribution of incremental costs and QALYs.

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