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Cost-Effectiveness of Genotype-Guided and Dual Antiplatelet Therapies in Acute Coronary Syndrome

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Background: The choice of antiplatelet therapy after acute coronary syndrome (ACS) is complicated: Ticagrelor and prasugrel are novel alternatives to clopidogrel, patients with some genotypes may not respond to clopidogrel, and low-cost generic formulations of clopidogrel are available.

Objective: To determine the most cost-effective strategy for dual antiplatelet therapy after percutaneous coronary intervention for ACS.

Design: Decision-analytic model.

Data Sources: Published literature, Medicare claims, and life tables.

Target Population: Patients having percutaneous coronary intervention for ACS.

Time Horizon: Lifetime.

Perspective: Societal.

Intervention: Five strategies were examined: generic clopidogrel, prasugrel, ticagrelor, and genotyping for polymorphisms of CYP2C19 with carriers of loss-of-function alleles receiving either ticagrelor (genotyping with ticagrelor) or prasugrel (genotyping with prasugrel) and noncarriers receiving clopidogrel.

Outcome Measures: Direct medical costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs).

Results of Base-Case Analysis: The clopidogrel strategy produced $179 301 in costs and 9.428 QALYs. Genotyping with prasugrel was superior to prasugrel alone, with an ICER of $35 800 per QALY relative to clopidogrel. Genotyping with ticagrelor was more effective than genotyping with prasugrel ($30 200 per QALY relative to clopidogrel). Ticagrelor was the most effective strategy ($52 600 per QALY relative to genotyping with ticagrelor).

Results of Sensitivity Analysis: Stronger associations between genotype and thrombotic outcomes rendered ticagrelor substantially less cost-effective ($104 800 per QALY). Genotyping with prasugrel was the preferred therapy among patients who could not tolerate ticagrelor.

Limitation: No randomized trials have directly compared genotyping strategies or prasugrel with ticagrelor.

Conclusion: Genotype-guided personalization may improve the cost-effectiveness of prasugrel and ticagrelor after percutaneous coronary intervention for ACS, but ticagrelor for all patients may be an economically reasonable alternative in some settings.

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Dual antiplatelet therapy combining aspirin with a second agent is the mainstay of therapy after acute coronary syndrome (ACS), particularly among patients who receive a percutaneous coronary intervention (PCI) (1). Antiplatelet agents reduce thrombotic events, such as myocardial infarction (MI) and stent thrombosis, but increase risk for bleeding (2). Approximately one half of the 1.1 million ACS events in the United States every year are treated with a PCI, making the choice of antiplatelet therapy a common and important clinical decision (3, 4).

Clopidogrel has been the standard of care after PCI for nearly a decade (5). Until recently, it was the second-largest drug in terms of sales, and much of the $12 billion spent on it each year was for use after ACS (6). However, many patients receiving clopidogrel and aspirin have recurrent cardiovascular events (7, 8), and on-treatment platelet inhibition varies considerably (9, 10). Patients who carry a loss-of-function polymorphism of CYP2C19 (a key enzyme involved in the hepatic activation of clopidogrel) achieve less platelet inhibition with clopidogrel and have more thrombotic events (11–13) and less bleeding. However, carriers of gain-of-function alleles of the CYP2C19 enzyme achieve greater platelet inhibition with clopidogrel and have fewer thrombotic events and more bleeding (14, 15).

Two new drugs, prasugrel and ticagrelor, are approved for use in patients having PCI for ACS (16–19). The greater antiplatelet activity of these agents reduces the rate of MI and cardiovascular death compared with clopidogrel. However, prasugrel increases fatal bleeding so that its net effect on mortality rates is neutral (16, 17). Ticagrelor is dosed twice daily and causes mild to moderate dyspnea in some patients (18, 19), which may adversely affect adherence. Both agents are expensive, particularly when compared with generic formulations of clopidogrel that are now available.

Further, commercial availability of genetic testing may allow clinicians to personalize antiplatelet therapy so that

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Supplement

Context

Several options for antiplatelet therapy after percutaneous coronary intervention for acute coronary syndrome are available.

Contribution

This cost-effectiveness analysis compared drug-only strategies (generic clopidogrel, prasugrel, or ticagrelor) and genotype-guided strategies targeting ticagrelor or prasugrel. Ticagrelor was the most cost-effective strategy. The genotyping-with-prasugrel strategy was superior to giving all patients prasugrel. The genotyping-with-ticagrelor strategy was clinically superior but more expensive than clopidogrel.

Caution

No randomized trials have directly compared genotyping strategies or prasugrel with ticagrelor.

Implication

Genotype-guided personalization of antiplatelet therapy could improve cost-effectiveness in some situations, but ticagrelor for all without genotyping also seems reasonable.

—The Editors

the new, more expensive drugs could be selectively prescribed to patients most likely to benefit (11, 12, 20, 21). These recent developments have altered the therapeutic landscape, highlighting the need for a comprehensive evaluation of alternative strategies for dual antiplatelet therapy. There are no head-to-head clinical trials of ticagrelor with prasugrel and no prospective studies of genotype-based treatment decisions. In this article, we present a simulation that addresses uncertainties about the role of genotyping and identifies the most cost-effective strategies for dual antiplatelet therapy after PCI for ACS.

METHODS

We developed a discrete-state Markov model to compare 5 strategies of dual antiplatelet therapy (22).

Drug-Only Strategies

Drug-only strategies were generic clopidogrel, prasugrel, or ticagrelor. We assumed that generic clopidogrel had the same efficacy as the proprietary formulation. On the basis of the results of TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction), we assumed that prasugrel led to fewer cardiovascular deaths but more fatal bleeding compared with clopidogrel (16, 17). On the basis of the PLATO (Platelet Inhibition and Patient Outcomes) study, we assumed that ticagrelor reduced cardiovascular deaths without a corresponding increase in fatal bleeding (18, 19) and that some patients had dyspnea and bradyarrhythmias while on treatment (23, 24). We did not distinguish between patients who presented with or without ST-segment elevations because this feature did not modify the effect of prasugrel or ticagrelor on the primary end point in either TRITON-TIMI 38 or PLATO (16, 18).

Genotype-Guided Strategies

We modeled the genotype-guided regimens on the basis of the recently published guidelines of the Clinical Pharmacogenetics Implementation Consortium (25) (**Table 1** of the **Supplement**, available at www.annals.org). In the 2 genotype-guided strategies, we assumed that carriers of 1 or 2 loss-of-function alleles would receive prasugrel (genotyping-with-prasugrel strategy) or ticagrelor (genotyping-with-ticagrelor strategy), whereas patients with 2 gain-of-function alleles, 1 gain-of-function allele and 1 wild-type allele, or 2 wild-type alleles would be treated with clopidogrel. Because 1 gain-of-function allele does not completely compensate for 1 loss-of-function allele (25), such persons would receive prasugrel or ticagrelor after genotyping. We did not evaluate strategies using tests of platelet reactivity or clopidogrel dose-escalation because their clinical relevance was unclear (26, 27).

The base case was a hypothetical cohort of 100 000 patients aged 65 years with ACS who had PCI with 1 or more drug-eluting stents. All patients received dual antiplatelet therapy with 1 of the previously mentioned agents and aspirin for 12 months after the last PCI or MI and low-dose aspirin daily thereafter unless contraindicated. We assumed the societal perspective (28), considering all direct and induced medical costs and relevant clinical outcomes. Utilities and costs were assigned to each clinical event in 1-month cycles and discounted at 3% annually (29). We conducted extensive deterministic, probabilistic, and scenario-based sensitivity analyses to account for uncertainty in the input variables. We adhered to the recommendations of the Panel on Cost-Effectiveness in Health and Medicine (30).

We reported results in 2011 U.S. dollars, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs) (30). For each ICER evaluation, the comparator was the strategy that produced the next-most QALYs, excluding strategies that cost more (strictly dominated) or had a greater ICER (dominated by extension). Because of the inherent challenges of indirect comparisons between the 2 drugs, we did tiered comparisons: We first compared the drug-only strategies (to distinguish the drug effect from the effect of genetic testing), then we examined the effect of genotyping on prasugrel and ticagrelor separately; finally, we did a global comparison across all 5 strategies. Where required, we applied a willingness-to-pay threshold of $50 000 per QALY.

Modeling was done using TreeAge Pro 2009 (TreeAge Software, Williamstown, Massachusetts) and Excel 2007 (Microsoft, Redmond, Washington), and statistical analy-

ses were done using Stata, version 11 (StataCorp, College Station, Texas).

Model Structure

After the initial PCI, patients were at risk for stent thrombosis, nonfatal MI (unrelated to stent thrombosis), percutaneous or surgical revascularization, intracranial and extracranial bleeding, and death of cardiovascular and noncardiovascular causes (**Figure 1** of the **Supplement**). Three additional states were modeled: Post-MI (patients who had an MI after entering the model had an increased risk for future MIs and cardiovascular death); intracranial bleed; and a "steady state," into which all patients entered after a coronary artery bypass graft or 4 years after their initial PCI, whichever was sooner. The steady state accounted for age-specific medical costs and QALYs without tracking individual clinical events.

Model Inputs

Details can be found in the **Appendix Table** (available at www.annals.org). For patients in the clopidogrel group, we estimated the incidence and management of major coronary events from trials (8, 16, 18, 19, 31–37), observational data (4, 38–54), U.S. life tables (55), U.S. Food and Drug Administration publications (56), Medicare claims data (57, 58), clinical guidelines (5, 59–61), and other publications (48, 62). Event rates in the other groups were estimated using rate ratios relative to patients on clopidogrel (16–19, 33–35). Long-term survival of patients with ACS was estimated using Medicare claims data from 2002 to 2006 (**Figure 2** of the **Supplement**) (57, 58). See the **Supplement** for additional information.

We estimated the prevalence of loss-of-function polymorphisms from published studies (25, 34, 63–65). Although some studies showed that loss-of-function carriers had a greater rate of thrombotic events than noncarriers when treated with clopidogrel (66), 2 recent reviews estimated different degrees of association between carrier states and thrombotic events. In a collaborative, random-effects model meta-analysis of 9 studies including 9685 patients (91% of whom had a PCI), Mega and colleagues (12) found that carriers of 1 or 2 CYP2C19 loss-of-function alleles had a hazard ratio of 1.57 for thrombotic events (95% CI, 1.13 to 2.16) relative to noncarriers. In a fixed-effects model meta-analysis of 42 016 patients from 32 clopidogrel trials that were not limited to patients with PCI, Holmes and colleagues (67) found that carriers of loss-of-function alleles had a relative risk of 1.18 (CI, 1.09 to 1.28) for thrombotic events relative to noncarriers. In light of this uncertainty in the ability of loss-of-function alleles to discriminate between high- and low-risk patients, we modeled 2 scenarios (66). In the base-case or low-discrimination scenario, we modeled conservative correlations as seen by Holmes and colleagues among all patients treated with clopidogrel, including patients who had not had PCI (67). In a sensitivity analysis, we modeled a high-discrimination scenario on the basis of the associations seen by Mega and colleagues (12) in the cohort of patients treated with clopidogrel after PCI. In both cases, we assumed that carriers of loss-of-function alleles had a lower risk for bleeding than noncarriers (67).

Carriers of gain-of-function alleles achieved a greater degree of platelet inhibition than patients with wild-type alleles treated with clopidogrel, which translated into fewer thrombotic events and increased bleeding (14, 15). Because some evaluations suggested that this correlation may be partly due to linkage disequilibrium with loss-of-function alleles, we conducted a sensitivity analysis that assumed no correlation between gain-of-function alleles and outcomes (25). We assumed that genotyping was 100% sensitive and 99.3% specific in detecting CYP2C19 alleles (21) but varied these assumptions in sensitivity analyses. The pharmacologic effects of ticagrelor and prasugrel are unaffected by genotype (34, 35, 68, 69), so the model assumed that carriers and noncarriers have similar outcomes when treated with 1 of these drugs.

Quality-of-Life Estimates

We estimated age-specific quality of life (70), which we also adjusted for adverse clinical events or invasive procedures (71–76). We assumed that patients who had an MI or stent thrombosis had a 12% permanent quality-of-life decrement relative to their age-matched counterparts (77), patients who had a nonfatal intracranial hemorrhage had a 61% permanent quality-of-life decrement (78), and patients with ticagrelor-associated dyspnea had a quality-of-life decrement equal to that of patients with a history of angina (79).

Costs

We included direct medical costs (such as inpatient admissions, procedures, outpatient visits, and drugs) and induced costs (such as cost of procedural complications) but not indirect costs (such as lost wages and caregiver costs). We estimated acute event costs from Medicare reimbursement rates, the Nationwide Inpatient Sample, and the published literature (74, 80–82). We estimated age-specific costs of outpatient and total medical care from the Agency for Healthcare Research and Quality's Medical Expenditure Panel Survey (83). All costs were converted to 2011 dollars using the U.S. gross domestic product deflator (84).

We assumed a base-case cost of $30 per month for generic clopidogrel and included the current average wholesale price of the proprietary formulation ($218 per month) in the sensitivity analyses (82). We assumed the costs of prasugrel and ticagrelor to equal their average wholesale price ($220 and $261 per month for prasugrel and ticagrelor, respectively) (82). We estimated the cost of genotyping from a survey of retail prices of commercially available tests but included the estimated unit cost of point-of-care tests in the range tested in sensitivity analyses.

Table 1. **Incremental Cost-Effectiveness of Strategies for Dual Antiplatelet Therapy After Percutaneous Coronary Intervention for Acute Coronary Syndrome***

Strategy	Costs, $		Outcomes				Incremental Costs, $	Incremental QALYs, *n*	ICER, $/QALY†
	Study Drug and Genotyping	Total	Cardiovascular Death, %‡	Fatal Bleed, %‡	Life Years, *n*	QALYs, *n*			
Drug-only therapy									
Generic clopidogrel	366	179 301	9.87	0.45	11.41	9.428	–	–	–
Prasugrel	2687	181 546	9.38	0.95	11.43	9.446	2244	0.018	Dominated§
Ticagrelor	2978	183 531	9.15	0.43	11.54	9.533	4230§	0.105§	40 270§
Low-discrimination scenario									
Generic clopidogrel	366	179 301	9.87	0.45	11.41	9.428	–	–	–
Prasugrel	2687	181 546	9.38	0.95	11.43	9.446	2244	0.018	Dominated‖
Genotyping with prasugrel¶	1269	180 470	9.49	0.61	11.45	9.461	1169‖	0.033‖	Dominated**
Genotyping with ticagrelor††	1352	181 040	9.44	0.45	11.48	9.486	1739**	0.058**	30 200**
Ticagrelor	2978	183 531	9.15	0.43	11.54	9.533	2491	0.047	52 600
High-discrimination scenario									
Generic clopidogrel	366	179 301	9.87	0.45	11.41	9.429	–	–	–
Prasugrel	2687	181 546	9.38	0.95	11.43	9.446	2244	0.018	Dominated††
Genotyping with prasugrel¶	1269	180 819	9.22	0.62	11.48	9.488	1518††	0.059††	Dominated‡‡
Genotyping with ticagrelor§§	1353	181 390	9.17	0.45	11.51	9.513	2089‡‡	0.084‡‡	24 700‡‡
Ticagrelor	2978	183 531	9.15	0.43	11.54	9.533	2141	0.020	104 800

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.
* Costs are expressed in 2011 U.S. dollars. Costs, QALYs, and life expectancy are discounted at 3% a year.
† Incremental cost-effectiveness for each strategy was measured relative to the next-best strategy that had not been eliminated by dominance and was rounded to the closest $100 to reflect the precision in the model.
‡ Proportion of patients who die of a cardiovascular cause or fatal bleed in the first 4 y after index percutaneous coronary intervention.
§ The ICER of prasugrel relative to clopidogrel ($124 400/QALY) was greater than the ICER of ticagrelor, relative to prasugrel ($22 800/QALY). Prasugrel was therefore eliminated from the comparison by the principle of extended dominance, and ticagrelor was compared directly with clopidogrel.
‖ In the genotyping with prasugrel strategy, carriers of 1 or 2 loss-of-function polymorphisms in CYP2C19 were treated with prasugrel; the others received generic clopidogrel.
¶ In the low-discrimination scenario, prasugrel cost $1076 more than the genotyping-with-prasugrel strategy and produced 0.015 fewer QALYs. It was therefore eliminated from the evaluation (strictly dominated), and genotyping with prasugrel was compared with clopidogrel.
** In the low-discrimination scenario, the ICER of genotyping with prasugrel relative to clopidogrel ($35 800/QALY) was less favorable than the ICER of genotyping with ticagrelor relative to genotyping with prasugrel ($22 800/QALY). Therefore, genotyping with prasugrel was eliminated from the comparison by the principle of extended dominance, and genotyping with ticagrelor was compared directly with clopidogrel.
†† In the high-discrimination scenario, prasugrel cost $727 more than genotyping with prasugrel and produced 0.042 fewer QALYs. Prasugrel was therefore eliminated from the evaluation (strictly dominated), and genotyping with prasugrel was compared with clopidogrel.
‡‡ In the high-discrimination scenario, the ICER of genotyping with prasugrel relative to clopidogrel ($25 600/QALY) was less favorable than the ICER of genotyping with ticagrelor relative to genotyping with prasugrel ($22 800/QALY). Therefore, genotyping with prasugrel was eliminated from the comparison by the principle of extended dominance, and genotyping with ticagrelor was compared directly with clopidogrel.
§§ In the genotyping-with-ticagrelor strategy, carriers of 1 or 2 loss-of-function polymorphisms in CYP2C19 were treated with ticagrelor; the others received generic clopidogrel.

Role of the Funding Source

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RESULTS

The estimated model outcomes compared well with the experience of Medicare enrollees from 2002 to 2005. Mortality rates in the clopidogrel group of the model were similar to the mortality rates among 65-year old Medicare patients at 1 year (4.6% vs. 4.6%) and 5 years (17.3% vs. 17.4%). Patients aged 65 years having PCI for ACS who were treated with 12 months of clopidogrel and aspirin were projected to have a life expectancy of 11.4 life-years (15.2 undiscounted life-years), with $179 301 in costs and 9.428 QALYs over their lifetimes (**Table 1**).

Clinical Events and Cost-Effectiveness

Drug-Only Strategies

Both prasugrel and ticagrelor reduced thrombotic events relative to clopidogrel, but patients receiving prasugrel had substantially greater fatal bleeding (**Table 2** of the **Supplement**). As a result, prasugrel was relatively expensive, with an ICER of $124 400 per QALY relative to clopidogrel, whereas ticagrelor had a lower ICER of $22 800 per QALY relative to prasugrel. Thus, prasugrel was eliminated by extended dominance, and ticagrelor had an ICER of $40 300 per QALY relative to clopidogrel.

All Strategies

In the base case, we assumed that loss-of-function alleles were only modestly correlated with thrombotic out-

comes (12). When all 5 strategies were considered in order of increasing QALYs gained and compared incrementally (**Table 1** and **Figure 1**), the prasugrel strategy was more expensive and had worse outcomes than genotyping with prasugrel and was therefore eliminated ("dominated"). Next, the ICER for genotyping with prasugrel relative to clopidogrel ($35 800 per QALY) was less favorable than the ICER for genotyping with ticagrelor relative to genotyping with prasugrel ($22 800 per QALY); genotyping with prasugrel was therefore inside the "cost-effectiveness frontier" and was eliminated (**Figure 1**). Genotyping with ticagrelor was therefore compared directly with clopidogrel (the next-best, nondominated strategy) and yielded an ICER of $30 200 per QALY. The ticagrelor-for-all strategy produced the highest QALYs but was also the most expensive with a less favorable ICER ($52 600 per QALY relative to genotyping with ticagrelor).

Sensitivity Analyses

High-Discrimination Scenario

Assuming stronger associations between loss-of-function genotype and thrombotic outcomes greatly increased the cost-effectiveness of genotyping-based strategies (**Table 1** and **Figure 1**) (12). In this setting, genotyping with ticagrelor was the most cost-effective strategy, with an ICER of $24 700 per QALY. Treating all patients with ticagrelor produced 0.02 additional QALYs but was economically unattractive, with an ICER of $104 800 per QALY relative to genotyping with ticagrelor.

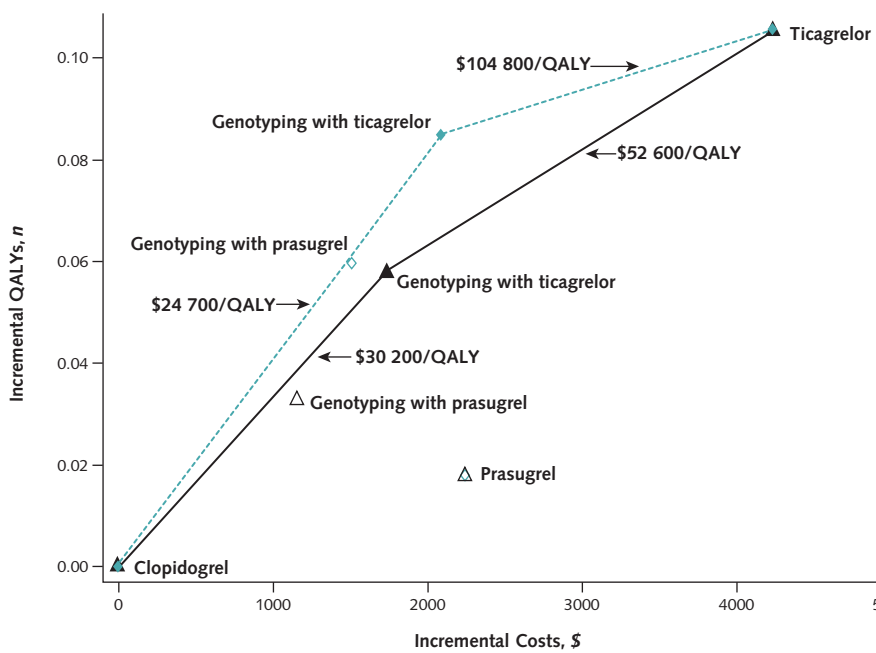
Efficacy and Safety Variables

The cost-effectiveness of genotyping with ticagrelor was sensitive to modest changes in assumptions about the efficacy and safety of ticagrelor relative to clopidogrel and the association between thrombotic events in loss-of-function carriers relative to noncarriers (**Table 3** of the **Supplement** and **Appendix Figures 1** and **2**, available at www.annals.org). For instance, if the rate of cardiovascular death among patients treated on ticagrelor decreased by 1.3% or the rate of fatal bleeding by 38.0%, treating all patients with ticagrelor became the most cost-effective strategy. In contrast, in the high-discrimination scenario, the optimal strategy—genotyping with ticagrelor—was robust to wide variations in underlying assumptions (**Table 3** of the **Supplement**).

Ticagrelor-Associated Dyspnea

The choice of optimal therapy was sensitive to the decrement in the patient's quality of life from ticagrelor-associated dyspnea (**Figure 3** of the **Supplement**). A utility decrement of greater than 0.049 (≥6% of baseline quality of life at the age of 65 years) made genotyping with prasugrel the most cost-effective therapy.

Figure 1. **Cost-effectiveness plane.**



Results of the base-case analysis are presented on the cost-effectiveness plane, with clopidogrel at the origin. The lines indicate the cost-effectiveness frontier, and the slope of the frontier that connects 2 strategies is the incremental cost-effectiveness ratio (in 2011 U.S. dollars per QALY). Both low- (*solid line*) and high-discrimination scenarios (*dashed line*) are shown; strategies that are inside the corresponding frontier (*hollow markers*) are eliminated by strict or extended dominance.

Allelic Frequency

The population frequency of loss-of-function alleles varied substantially by race and ethnicity, and it was considerably greater in South Asia (35%), East Asia (40%), and Oceania (76%) than in Europe (16%) or Africa (16%) (25). As the proportion of carriers 1 or 2 loss-of-function alleles increased, both genotyping with ticagrelor and ticagrelor became increasingly cost-effective (**Appendix Figure 3**, available at www.annals.org). Treating all patients with ticagrelor was the most cost-effective therapy when loss-of-function carriers constituted more than 52.7% of the population. In contrast, increasing population frequency of the gain-of-function allele did not materially affect the cost-effectiveness of genotyping but made the ticagrelor-for-all strategy less cost-effective (**Figure 4** of the **Supplement**).

Accuracy of Genetic Testing

The ICER for ticagrelor relative to genotyping with ticagrelor was affected by the accuracy of genotyping (**Figure 5** of the **Supplement**), and declining accuracy favored treating all patients with ticagrelor independent of genotype. For instance, if the sensitivity and specificity of the test were 95% (instead of the base case of 100% sensitivity and 99.3% specificity), the ICER for ticagrelor would decrease to $51 500 per QALY and the ICER for genotyping with ticagrelor would increase to $31 500 per QALY.

Cost of Genetic Testing

In the low-discrimination scenario, it was cost-effective to treat all patients with ticagrelor regardless of genotype if genetic testing cost more than $358 per patient (**Figure 6** of the **Supplement**). In the high-discrimination scenario, genotyping with ticagrelor was the most cost-effective strategy until the cost of genetic testing exceeded $1355.

Drug Costs

The choice of optimal antiplatelet therapy was sensitive to the difference in the monthly cost of ticagrelor and clopidogrel: Smaller differences in cost made both ticagrelor and genotyping with ticagrelor more cost-effective (**Figure 7** of the **Supplement**). In the low-discrimination scenario, treating all patients with ticagrelor was the most cost-effective strategy when the difference in monthly cost of ticagrelor and clopidogrel decreased from a base case of $231 to $215, either because ticagrelor was less expensive or clopidogrel was more expensive than the base case. In the high-discrimination scenario, the difference had to decrease to $93 or less to make ticagrelor cost-effective at a threshold of $50 000 per QALY.

Duration of Dual Antiplatelet Therapy

The absolute cardiovascular risk was greatest in the first year after PCI, whereas bleeding risk and drug costs persisted for the entire duration of antiplatelet therapy. Therefore, dual antiplatelet therapy became less economically attractive as the duration of treatment increased from 12 to 36 months. The genotyping-with-ticagrelor strategy remained the most cost-effective alternative for dual antiplatelet therapy after PCI for ACS, with an ICER less than $50 000 per QALY (**Figure 8** of the **Supplement**).

Probabilistic Sensitivity Analysis

We performed 10 000 microsimulations where all input variables were varied simultaneously along prespecified distributions. In the low-discrimination scenario, genotyping with ticagrelor was the preferred strategy in 39% of the simulations and ticagrelor in 42% of the simulations (**Figure 2**). In the high-discrimination scenario, the preferred strategy was genotyping with ticagrelor in 63% of the simulations, ticagrelor in 19%, and genotyping with prasugrel in 13% (**Figure 2**). Ticagrelor was the preferred strategy in more than 50% of simulations at thresholds greater than $54 500 per QALY in the low-discrimination scenario and $98 000 per QALY in the high-discrimination scenario.

Scenario Analyses

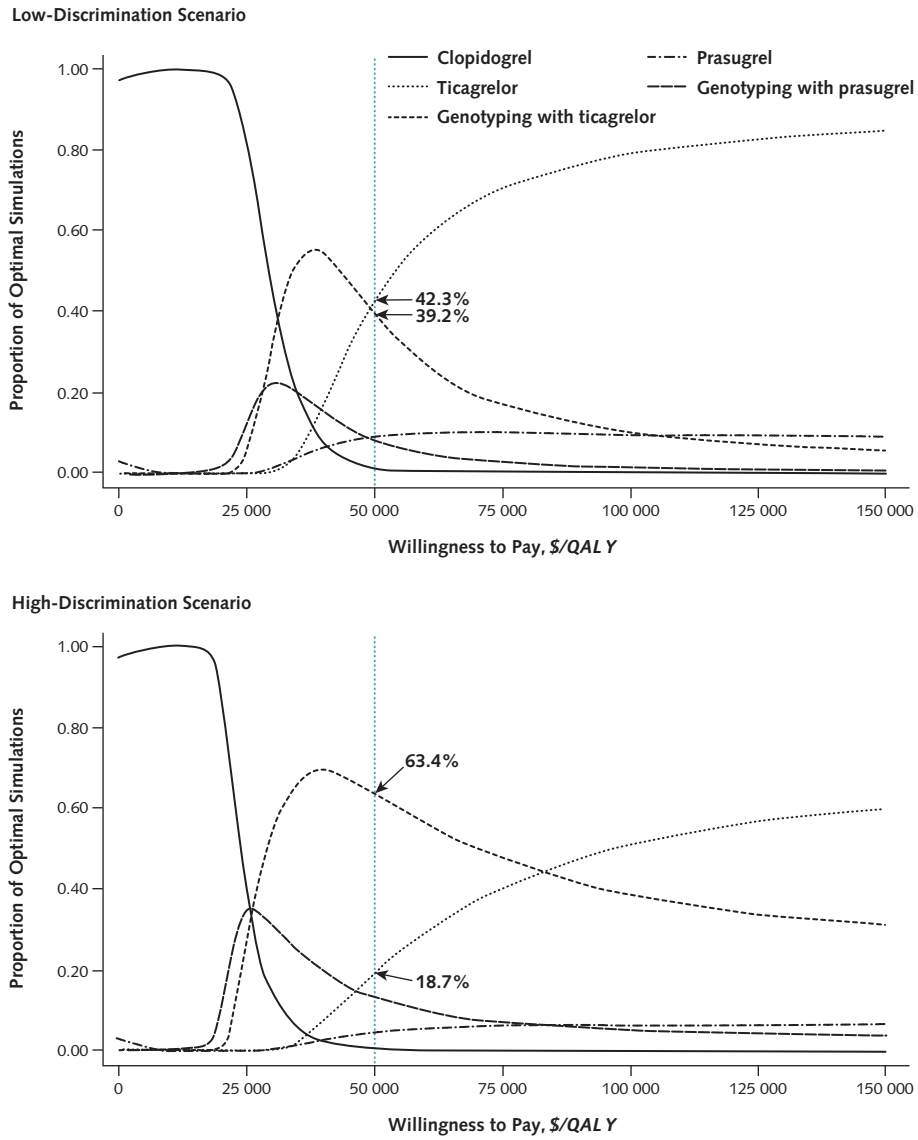
The optimal strategies for dual antiplatelet therapy under different clinical scenarios in which ticagrelor or prasugrel may not be indicated (for example, among patients with a history of a transient ischemic attack) are presented in **Table 2**. Additional sensitivity analyses are presented in **Tables 4** to **7** and **Figures 9** to **13** of the **Supplement**.

DISCUSSION

Nearly 500 000 patients in the United States face the choice of dual antiplatelet therapy after PCI for ACS every year. This choice has substantial clinical and economic implications and entails a marked difference in drug costs as well as a tradeoff between thrombotic events and major bleeding. Our analysis suggests that genotype-guided personalization of therapy may improve the cost-effectiveness of the newer, more expensive antiplatelet agents. The targeted use of prasugrel in carriers of CYP2C19 loss-of-function alleles consistently decreased costs and improved outcomes relative to treating all patients with prasugrel, making genotyping before treatment with prasugrel the clinically and economically superior strategy. The selective use of ticagrelor in CYP2C19 loss-of-function carriers and clopidogrel in noncarriers was the most cost-effective strategy when genotyping discriminates well between patients at high and low risk for thrombotic events (that is, where there is a strong association between genotype and clinical outcomes). If genotype were only modestly predictive of thrombotic outcomes, ticagrelor for all patients independent of genotype would be the most cost-effective strategy for dual antiplatelet therapy after PCI for ACS.

Genotype-guided therapy aims to reduce costs and improve outcomes by targeting the use of the more expensive

Figure 2. **Probabilistic sensitivity analysis.**



Results of the probabilistic sensitivity analysis are illustrated as acceptability curves, which plot the proportion of simulations in which a certain strategy is "optimal" (or most cost-effective) against the amount one is willing to pay per QALY gained. In the low-discrimination scenario, genotyping with ticagrelor is the preferred strategy in 42.3% of the simulations at a willingness-to-pay threshold of $50 000/QALY (*green vertical line*) and ticagrelor is the preferred strategy in 32% of the simulations, reflecting the underlying uncertainty. Greater thresholds make ticagrelor more economically attractive. In the high-discrimination scenario, which assumes stronger associations between loss-of-function genotype and the rate of thrombotic events, genotyping with ticagrelor is the optimal strategy in 63.4% of the simulations at a threshold of $50 000/QALY. QALY = quality-adjusted life-year.

drugs to patients most likely to benefit from them. Contrary to concerns that cost-effectiveness considerations encourage a "1-size-fits-all" approach (85) or "stymie progress in personalized medicine" (86), models such as ours that estimate clinically meaningful outcomes among genetic subgroups of patients can help clarify the potential value of individualized therapeutics (87). Further, sensitivity analyses help quantify the effect of uncertainty on clinical and policy-level decision making and identify the knowledge gaps that should be addressed in future research. Our study highlights that a well-designed cost-effectiveness analysis can both support and guide innovation in personalized medicine (87).

Our results suggest 4 key considerations in the choice of antiplatelet therapy after PCI for ACS. First, clinicians should consider genotyping all patients before using prasugrel because targeted use of prasugrel therapy among loss-of-function carriers seems to reduce costs and improve clinical outcomes. Second, clinicians should be cognizant of the effect of ticagrelor-associated dyspnea on the pa-

Table 2. **Optimal Strategy for Dual Antiplatelet Therapy Under Different Clinical Scenarios**

Scenario	Most Effective Therapy	Most Cost-Effective Therapy*
Patient unable to tolerate ticagrelor†		
Generic clopidogrel available	Genotyping with prasugrel‡	Genotyping with prasugrel
No clopidogrel generics	Genotyping with prasugrel	Genotyping with prasugrel
Genotyping unavailable	Prasugrel	Clopidogrel
Patient with a history of TIA or stroke	Clopidogrel	Clopidogrel
Patient with a history of TIA or ischemic stroke§		
Generic clopidogrel available	Ticagrelor	Genotyping with ticagrelor‖
No clopidogrel generics	Ticagrelor	Ticagrelor
Genotyping unavailable	Ticagrelor	Ticagrelor
Ticagrelor not tolerated	Clopidogrel	Clopidogrel

TIA = transient ischemic attack.
* Cost-effectiveness threshold was $50 000 per quality-adjusted life year.
† Ticagrelor is contraindicated in patients with a history of hemorrhagic stroke. In a small group of patients, ticagrelor produces a syndrome of subjective dyspnea that may last several months. In some patients, this may be severe enough to result in discontinuation of the medication.
‡ In the genotyping-with-prasugrel strategy, patients with 1 or 2 loss-of-function polymorphisms in CYP2C19 were treated with prasugrel; the others received clopidogrel.
§ Prasugrel is contraindicated in patients with a history of stroke or transient ischemic attack. Caution is also advised for patients weighing less than 60 kg and those who are aged ≥75 y.
‖ In the genotyping-with-ticagrelor strategy, patients with 1 or 2 loss-of-function polymorphisms in CYP2C19 were treated with ticagrelor; the others received clopidogrel. If a threshold of $50 000 per quality-adjusted life-year was assumed, then ticagrelor was the most cost-effective therapy if the monthly price difference between ticagrelor and clopidogrel was less than $215/mo (low-discrimination scenario) or $93/mo (high-discrimination scenario).

tient's quality of life. Among patients with a moderate to severe decrement in quality of life due to ticagrelor-associated dyspnea (≥6% reduction in on-treatment quality of life relative to baseline), genotyping with prasugrel is the most cost-effective strategy (that is, loss-of-function carriers should receive prasugrel, and noncarriers should receive clopidogrel). Third, genotype-guided antiplatelet therapy may be less attractive in populations or regions with a high prevalence of loss-of-function alleles, where treating all patients with ticagrelor may be the most cost-effective strategy. Future research should specifically examine the role of genotyping among patients with ancestry in South and East Asia and Oceania, in whom the population frequency of loss-of-function alleles is considerably greater than among patients with European, American, or African ancestry (25). Fourth, genotyping may be less economically attractive in health care markets where the monthly cost of ticagrelor is closer to the monthly cost of generic clopidogrel because the cost-effectiveness of genotyping is sensitive to cost differences between the drugs. Treating all patients with ticagrelor independent of genotype becomes the most cost-effective strategy when the difference in monthly cost of ticagrelor and clopidogrel is less than $215.

There are several limitations to this study. Estimated differences in outcomes between various CYP2C19 genotypes are largely based on post hoc analyses of randomized trials. Systematic reviews of the literature have yielded variable results depending upon studies included, definition of end points, and statistical models used. We address this uncertainty by presenting both a low-discrimination scenario that assumes a modest ability to discriminate between high- and low-risk patients on the basis of genotype, as well as a high-discrimination scenario, which assumes a stronger association between genotype and thrombotic outcomes. Future randomized trials of genotype-tailored strategies, either alone or in combination with phenotype-based strategies (for example, based on the measurement of on-treatment platelet reactivity), should help further clarify the role of personalization in optimizing antiplatelet therapy after PCI (88).

Estimates of the efficacy and safety of prasugrel and ticagrelor are based on only 1 large, randomized, clinical trial of each drug versus clopidogrel (16, 18). The indirect comparison of ticagrelor with prasugrel inherent in the structure of the model is limited by structural differences in the design and execution of the PLATO and TRITON-TIMI 38 clinical trials, as well as any clinical differences in the patients enrolled in these trials. Although a definitive, large, randomized, clinical trial comparing various strategies for dual antiplatelet therapy among real-world patients would be ideal, the prohibitive logistics of such a trial argue for comparative effectiveness studies of ticagrelor and prasugrel on the basis of a large, observational study or pragmatic clinical trial. Until either is done, models such as ours that incorporate a wide range of sensitivity analyses facilitate a systematic synthesis of published data. To alleviate confounding arising from interstudy variations, we used data from previously published trials and observational analyses to model baseline event rates in the clopidogrel group and used rate ratios from TRITON-TIMI 38 and PLATO to model event rates among patients on prasugrel and ticagrelor, respectively.

A post hoc analysis of patients receiving prasugrel in TRITON-TIMI 38 (16) found an increase in bleeding among patients with a history of stroke or transient ischemic attack; prasugrel is contraindicated in this subgroup. It is possible that prasugrel compares more favorably with clopidogrel in patients without a history of stroke or transient ischemic attack than indicated by the full-trial estimates used in this model. A subgroup analysis of patients receiving ticagrelor in PLATO found that patients recruited in North America had worse outcomes than patients from other geographic regions. This may represent a chance finding, a dose-dependent interaction with aspirin, or a real discrepancy arising from international differences in treatment algorithms (89). In line with the U.S. Food and Drug Administration approval of the drug, we as-

sumed that the clinical outcomes seen in PLATO can be achieved in U.S. patients on low-dose aspirin therapy, but this will need to be confirmed in future studies. Short-term clinical trials may not adequately define all potential safety concerns with a drug (23, 90, 91). Pursuant to the "life-cycle approach" to drug safety recommended by the Institute of Medicine (92), our analysis should be updated when safety and efficacy data from phase 4 trials or registries become available.

Our results are broadly concordant with previously published analyses that have found genotyping-based personalization of antiplatelet therapy to be cost-effective in other health systems (93, 94) but are more conservative than those reported by the trialists themselves (95–98). For instance, the investigators of TRITON-TIMI 38 concluded that treating patients with prasugrel after PCI for ACS was cost-effective at $50 000 per life-year gained, largely because of a substantially greater gain in life expectancy with prasugrel treatment in their model than seen in our analysis (96). This is probably the result of key methodological differences between the 2 studies—for instance, the trialists estimated life expectancy from a data set of patients who underwent angioplasty in Saskatchewan, Canada, between 1985 and 1995 (before the widespread adoption of intracoronary stenting) (96), whereas we based our estimate on U.S. Medicare beneficiaries who had a PCI for ACS between 2002 and 2005. Nevertheless, the results of our sensitivity analyses underscore the need to accurately define the long-term effect of newer antiplatelet agents on mortality rates, which would define their relative cost-effectiveness in the real world.

Based on currently available evidence, genotyping patients having PCI for ACS, followed by the targeted use of ticagrelor in carriers of loss-of-function CYP2C19 alleles and clopidogrel in noncarriers is economically attractive compared with treating all patients with the newer agents or clopidogrel. However, ticagrelor for all patients independent of genotype may be an economically reasonable alternative in some populations and settings. Future studies should directly compare prasugrel with ticagrelor, assess the effect of ticagrelor-associated dyspnea on quality of life, and prospectively establish the role of personalization of antiplatelet therapy after PCI for ACS.

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Appendix Table. Summary of Key Model Variables

Variable	Point Estimate	Range	Reference
Baseline events*			
Stent thrombosis while receiving clopidogrel and aspirin			38–46, 72
Rate per person of early (days 1–30) stent thrombosis	0.0150	0.010–0.020	
Rate per person of late (days 31–365) stent thrombosis	0.0060	0.003–0.009	
Annual rate per person of very late (beyond 365 d) stent thrombosis	0.0022	0.001–0.003	
Duration of very late stent thrombosis, *y*	4	2–5	72
Case fatality from stent thrombosis, %	20	15–30	72
Annual rate per person of bleeds while receiving clopidogrel and aspirin			
Non–CABG-related bleeding			8, 16, 18, 31, 50
Extracranial (TIMI major and nonfatal)	0.0230	0.015–0.070	
Intracranial (TIMI major and nonfatal)	0.0015	0.001–0.002	
TIMI minor	0.0200	0.010–0.060	
Fatal	0.0015	0.001–0.003	
CABG-related TIMI major bleeding	0.0220	0.013–0.031	8, 32
Annual rate per person for nonfatal MI, on clopidogrel and aspirin, excluding definite and probable stent thrombosis	0.0350	0.013–0.097	16–19, 57, 58, 62, 72
Management of each episode of nonfatal MI, %			4, 72
PCI	55	45–65	
CABG	08	04–12	
Medical management	37	23–51	
Annual rate per person of nonurgent revascularization			
Year 1 after initial PCI for ACS	0.10	0.05–0.15	57, 58
Beyond year 1 after initial PCI for ACS	0.03	0.02–0.04	57, 58
Surgical revascularization (CABG vs. PCI), %	25	15–35	4, 49, 57, 58
Rate per person of all-cause mortality after initial PCI	Age-specific		55, 57, 58
Deaths due to cardiovascular causes, year 1 after PCI for ACS, %	80	72–88	8, 16, 18
Deaths due to cardiovascular causes, beyond year 1 after PCI for ACS, %	67	60–73	51
Procedural complications, %			
Periprocedural death due to PCI	0.12	0.10–1.00	72
Periprocedural death due to CABG	2.10	1.00–10.00	72
Rate ratios†			
Cardiovascular mortality, relative to clopidogrel and aspirin			
Aspirin monotherapy	1.08	0.94–1.24	8
Ticagrelor and aspirin	0.79	0.69–0.91	18, 19
Prasugrel and aspirin	0.89	0.70–1.12	16, 17
Noncardiovascular, unrelated to bleeding, relative to clopidogrel and aspirin			
Aspirin monotherapy	1.00	0.90–1.10	Assumed
Ticagrelor and aspirin	0.63	0.39–1.03	18, 19
Prasugrel and aspirin	0.81	0.51–1.27	16, 17
Nonfatal MI, relative to clopidogrel and aspirin			
Aspirin monotherapy	1.29	1.12–1.48	8
Ticagrelor and aspirin	0.84	0.75–0.95	18, 19
Prasugrel and aspirin	0.76	0.67–0.85	16, 17
Stent thrombosis, relative to clopidogrel and aspirin			
Aspirin monotherapy	1.29	1.12–1.48	8
Ticagrelor and aspirin	0.75	0.59–0.95	18, 19
Prasugrel and aspirin	0.48	0.36–0.64	16, 17
Nonfatal extracranial TIMI major bleeds, relative to clopidogrel and aspirin			
Aspirin monotherapy	0.72	0.60–1.00	8, 31, 62
Ticagrelor and aspirin	1.30	1.05–1.61	18, 19
Prasugrel and aspirin	1.22	0.93–1.6	16, 17
Nonfatal intracranial TIMI major bleeds, relative to clopidogrel and aspirin			
Aspirin monotherapy	0.71	0.23–2.23	8, 31, 62
Ticagrelor and aspirin	1.15	0.55–2.41	18, 19
Prasugrel and aspirin	0.83	0.36–1.92	16, 17
Nonfatal extracranial TIMI minor bleeds, relative to clopidogrel and aspirin			
Aspirin monotherapy	0.47	0.39–0.57	8, 31, 62
Ticagrelor and aspirin	1.07	0.91–1.26	18, 19
Prasugrel and aspirin	1.16	0.91–1.49	16, 17
Fatal bleeds, relative to clopidogrel and aspirin			
Aspirin monotherapy	1.35	0.62–2.95	8, 31, 62
Ticagrelor and aspirin	0.87	0.48–1.59	18, 19
Prasugrel and aspirin	4.19	1.58–11.11	16, 17
CABG-related TIMI major bleeds, relative to clopidogrel and aspirin			
Aspirin monotherapy	1.08	0.61–1.91	8, 31, 32
Ticagrelor and aspirin	1.08	0.85–1.36	33
Prasugrel and aspirin	4.73	1.90–11.82	16, 17

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Appendix Table—**Continued**

Variable	Point Estimate	Range	Reference
Genetic testing			
Clinical events among carriers of loss-of-function alleles treated with clopidogrel, relative to noncarriers treated with clopidogrel			
Stent thrombosis			
Low-discrimination scenario	1.75	1.50–2.03	67
High-discrimination scenario	2.81	1.81–4.37	12
MI			
Low-discrimination scenario	1.48	1.05–2.07	67
High-discrimination scenario	1.45	1.09–1.92	12
Mortality			
All-cause, low-discrimination scenario‡	1.28	0.95–1.73	67
Cardiovascular, high-discrimination scenario	1.84	1.03–3.28	12
Bleeding	0.84	0.75–1.00	11, 34, 67, 69
Clinical events among carriers of gain-of-function alleles treated with clopidogrel, relative to patients with wild-type alleles treated with clopidogrel			
Thrombotic events	0.75	0.66–1.00	14, 15
Bleeding	1.26	1.00–1.50	14, 15
Other key transition probabilities			
Duration of dual antiplatelet therapy, time since last PCI or ACS, whichever is later, *mo*	12	12–48	5, 59–61
Duration of aspirin monotherapy after completion of dual antiplatelet therapy, *mo*	For life	–	5, 59–61
Genotype composition of the cohort, %			25, 34, 63–65
Carriers of 1 or 2 loss-of-function and no gain-of-function alleles	21	0.15–0.40	
Carriers of 1 or 2 gain-of-function and no loss-of-function alleles	33	0.10–0.40	
Carriers of 1 gain-of-function and 1 loss-of-function allele	7	0.05–0.09	
Accuracy of genetic testing, %			
Sensitivity	100	95–100	21
Specificity	99.3	95–100	21
Quality-of-life estimates (utilities)			
Baseline values	Age-specific	–	70
Disutility tolls			
Bleeding			62, 63, 72–75
Intracranial	0.61	0.4–0.8	
Extracranial	0.2 for 14 d	7–21 d	
Minor	0.2 for 2 d	0–7 d	
CABG-related bleed	0.5 for 7 d	3–14 d	
Revascularization			72,75
CABG	0.5 for 14 d	7–21 d	
PCI	0.5 for 7 d	3–14 d	
Nonfatal MI	0.13 for 1 m, then 0.12	0.05–0.25, then 0.07–0.16	70, 72, 75, 77
Ticagrelor-related dyspnea			79
Mild	0.071	0.018–0.124	
Moderate	0.102	0.043–0.161	
Severe	0.338	0.150–0.526	
Syncope or bradyarrhythmia	0.24 for 3 d	1–7 d	76
Costs, $§			
Monthly medical costs			
Clopidogrel	30	4–200	82
Prasugrel	220	150–300	82
Ticagrelor	261	150–300	82
Aspirin	4	2–10	Assumed
Costs of acute care			
Nonfatal extracranial hemorrhage	10 120	5060–20 240	80, 84
Nonfatal intracranial hemorrhage	20 740	10 370–41 480	80, 84
TIMI minor bleed	79	40–158	81, 84
Fatal bleed	17 920	8960–35 840	80, 84
CABG-related bleed	35 570	17 790–71 140	80, 84
Fatal MI	24 540	12 270–49 080	80, 84
Nonfatal MI, PCI	27 840	13 920–55 680	80, 84
Nonfatal MI, medical management	17 200	8600–34 400	80, 84
Hospitalization for syncope	11 467	5734–22 934	80, 84
Admission to observation unit	4877	2439–9754	80, 84

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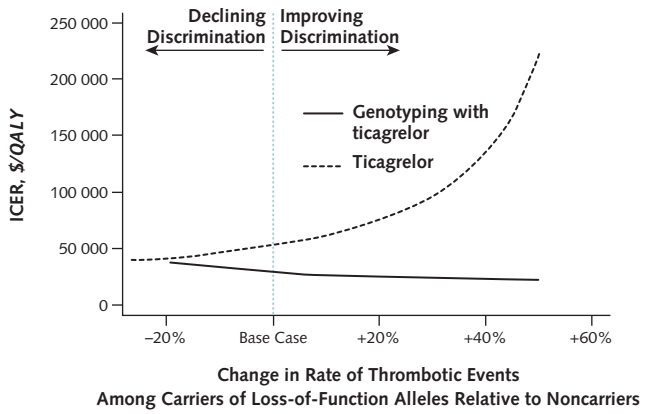
Appendix Table—**Continued**

Variable	Point Estimate	Range	Reference
Inpatient cardiovascular death	27 630	13 820–55 260	80, 84
Inpatient noncardiovascular death	24 630	12 320–49 260	80, 84
CYP2C19 genetic test	235	100–700	Market research
Revascularization			
Elective PCI	20 670	10 340–41 340	80, 84
Elective CABG	50 560	25 280–101 120	80, 84
CABG after MI	67 720	33 860–135 440	80, 84
Annual discount rate, %	3	0–5	29

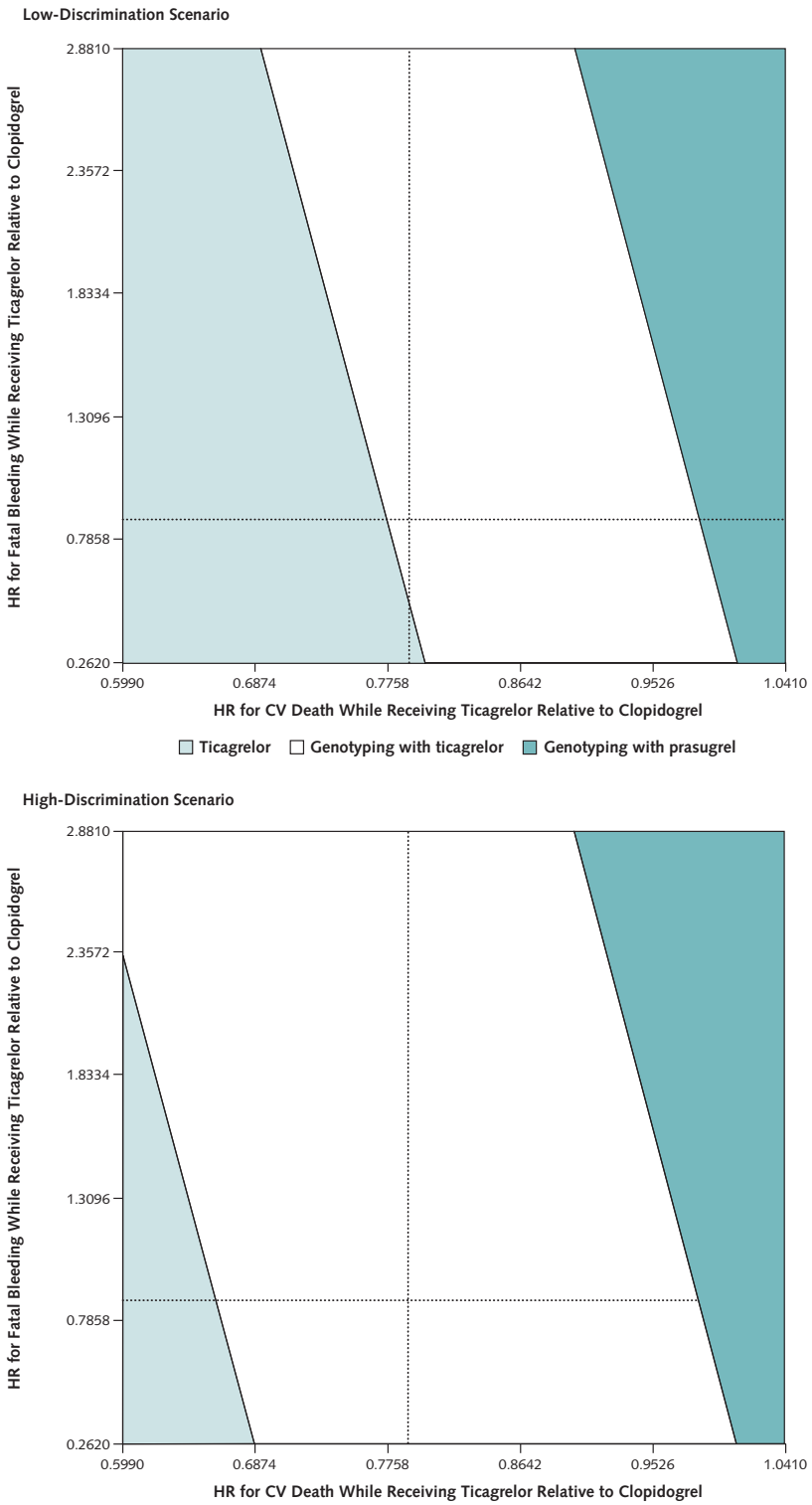
ACS = acute coronary syndrome; CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = thrombolysis in myocardial infarction.
* Rates are per person-year unless otherwise specified.
† Hazard ratios and CIs were used if reported; if they were not reported, point estimate and CI for rate ratios were estimated from reported events.
‡ In the low-discrimination scenario, the rate of cardiovascular mortality among patients treated with clopidogrel was estimated within the model on the basis of all-cause mortality and the proportion of all deaths attributable to cardiovascular causes.
§ In 2011 U.S. dollars.

Appendix Figure 1. **Sensitivity analysis on the association between genotype and clinical outcomes.**



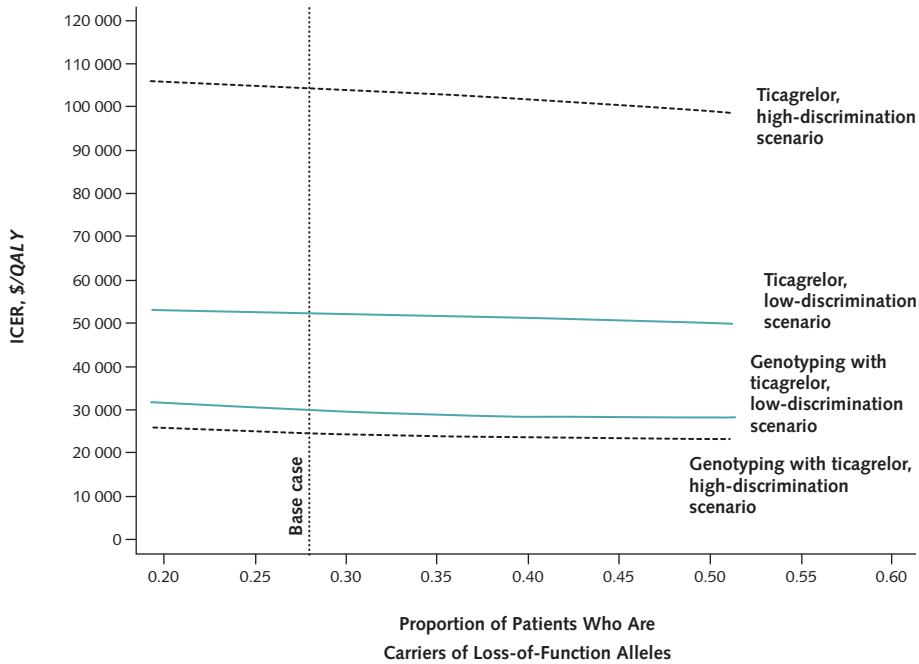
The value of genotyping depends on its ability to discriminate between patients at high and low risk for thrombotic events. In this analysis, the base case assumes a low-discrimination scenario: that carriers of loss-of-function alleles are at modestly greater risk for thrombotic events than noncarriers. The ICER of genotyping with ticagrelor is measured relative to clopidogrel, and the ICER for ticagrelor is measured relative to genotyping with ticagrelor. As the discrimination of the test is dialed up (moving rightward on the *x*-axis), carriers have more thrombotic events and fewer bleeding events relative to noncarriers. This results in improved outcomes associated with genotyping, making genotyping with ticagrelor more cost-effective and treating all patients with ticagrelor independent of genotype less cost-effective. As a point of reference, the rate ratio for cardiovascular death (carriers to noncarriers) was 35% greater in the high-discrimination scenario than in the base case. ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Appendix Figure 2. **Tradeoff between bleeding and thrombosis.**



In 2-way sensitivity analyses, we simultaneously varied the rate of cardiovascular death and fatal bleeding among patients receiving ticagrelor (relative to patients receiving clopidogrel), holding constant the event rates among patients receiving prasugrel. In the low-discrimination scenario and at a willingness-to-pay threshold of $50 000/quality-adjusted life-year, genotyping with ticagrelor was the most cost-effective strategy at baseline (*dotted lines*), but relatively small improvements in the efficacy or safety of ticagrelor (e.g., 1.3% decrease in cardiovascular mortality rates) made treating all patients with ticagrelor the most cost-effective option. In the high-discrimination scenario, genotyping with ticagrelor was robust to large changes in the efficacy and safety of ticagrelor. CV = cardiovascular; HR = hazard ratio.

Appendix Figure 3. **Effect of population frequency of CYP2C19 loss-of-function polymorphisms.**



As the population frequency of CYP2C19 loss-of-function polymorphisms increases, treating all patients receiving a percutaneous coronary intervention for acute coronary syndrome with ticagrelor (independent of genotyping) becomes more cost-effective. At a threshold of $50 000/QALY, ticagrelor is the most cost-effective strategy when carriers constitute 52.7% or more of the population. ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.