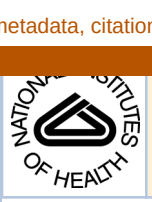

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Ticagrelor versus genotype-driven antiplatelet therapy for secondary prevention after acute coronary syndrome: a cost-effectiveness analysis

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Abstract

Background—Clopidogrel's effectiveness is likely reduced significantly for prevention of thrombotic events after acute coronary syndrome (ACS) in patients exhibiting a decreased ability to metabolize clopidogrel into its active form. A genetic mutation responsible for this reduced effectiveness is detectable by genotyping. Ticagrelor is not dependent on gene-based metabolic activation and demonstrated greater clinical efficacy than clopidogrel in a recent secondary prevention trial. In 2011, clopidogrel will lose its patent protection and likely will be substantially less expensive than ticagrelor.

Objective—To determine the cost-effectiveness of ticagrelor compared with a genotype-driven selection of antiplatelet agents.

Methods—A hybrid decision tree/Markov model was used to estimate the 5-year medical costs (in 2009 US$) and outcomes for a cohort of ACS patients enrolled in Medicare receiving either genotype-driven or ticagrelor-only treatment. Outcomes included life years and quality-adjusted life years (QALYs) gained. Data comparing the clinical performance of ticagrelor and clopidogrel were derived from the Platelet Inhibition and Patient Outcomes trial.

Results—The incremental cost-effectiveness ratio (ICER) for universal ticagrelor was $10,059 per QALY compared to genotype-driven treatment, and was most sensitive to the price of ticagrelor and the hazard ratio for death for ticagrelor compared with clopidogrel. The ICER remained below $50,000 per QALY until a monthly ticagrelor price of $693 or a 0.93 hazard ratio for death for ticagrelor relative to clopidogrel. In probabilistic analyses, universal ticagrelor was below $50,000 per QALY in 97.7% of simulations.

Conclusion—Prescribing ticagrelor universally increases quality-adjusted life years for ACS patients at a cost below a typically accepted threshold.

Keywords

acute coronary syndrome; clopidogrel; ticagrelor; cost-benefit analysis; secondary prevention

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Introduction

Current American and European guidelines recommend dual antiplatelet therapy with aspirin and clopidogrel for at least one month and optimally one year for all acute coronary syndrome (ACS) patients to reduce the risk of recurrent thrombotic events [1-4]. Clinical trials indicate that when added to aspirin following ACS, clopidogrel is effective at reducing the risk of repeat ischemic episodes, heart failure, and revascularization procedures [5-7]. Although it remains part of the current recommended treatment after ACS, clopidogrel has substantial limitations. Because it irreversibly inactivates platelets its effect is not eliminated until the patient replaces his/her platelet supply. Clopidogrel administration has been associated with increased bleeding following coronary artery bypass surgery (CABG), and the current American guidelines currently recommend a five-day waiting period prior to elective surgical procedures due to this complication [8-12]. The frequent need for emergent CABG in the ACS population has led to controversy about the safety of the procedure in the setting of clopidogrel exposure [13]. A more important limitation of clopidogrel is that in some patients it may fail to inactivate platelets when given at therapeutic doses [14]. Extensive genetic analyses targeting both the $P2Y_{12}$ receptor and the enzymes that metabolize clopidogrel into its active form have been conducted [15-26]. Attention has focused on mutations in the gene encoding CYP2C19 (a P450 hepatic enzyme), which have been shown to reduce clopidogrel's effectiveness both in vitro and in healthy volunteers [16,20,25]. Observational clinical studies have shown that patients with a CYP2C19*2 mutation have approximately a 50% higher likelihood of adverse cardiac outcomes than patients without such mutation, but only when patients are treated with clopidogrel [27-31]. This result strongly suggests that the mutation's effects are mediated through its effects on clopidogrel activation. These mutations are very common; with estimates of the prevalence of at least a single copy of the mutation ranging from 20% in white populations to 50% in some Asian groups [27,32].

Trial results for ticagrelor, a novel antiplatelet agent, have been promising. Among patients admitted with ACS, administering 90 mg ticagrelor twice daily reduced both rates of recurrent cardiac events and all-cause mortality without increasing the risk of major bleeding compared to standard dose clopidogrel [33]. Furthermore, ticagrelor is not dependent on metabolic activation and its mechanism of action is reversible, giving a faster elimination of effect upon withdrawal [34]. The platelet inhibition levels of clopidogrel patients after five days of withdrawal have been observed in ticagrelor patients just three days post withdrawal [35]. However, ticagrelor is associated with an increased risk of minor bleeding compared to clopidogrel [33].

The patent on the branded formulation of clopidogrel, Plavix™, is scheduled to expire in 2011; consequently, the cost of generic clopidogrel, currently $131 per month at retail prices in the United States, is likely to fall substantially [36]. Given its expected low cost in the near future, clopidogrel will likely continue to be a feasible option for antiplatelet therapy, particularly for patients without a decreased ability to metabolize clopidogrel in to its active form. Therefore, providers will likely have a choice in treatment options for choosing antiplatelet therapy for ACS. We developed a cost-effectiveness study comparing two likely strategies for treating ACS: 1) a genotype-driven treatment, in which providers test for CYP2C19*2 mutations that limit clopidogrel's effectiveness and prescribe clopidogrel in their absence and ticagrelor in their presence, and 2) universally prescribe ticagrelor. This analysis was conducted from the viewpoint of Medicare, as patients of age 65 and older experience over half of all ACS cases [37]. Although economic evaluations have been used to determine clopidogrel's role in secondary prevention after ACS [38,39], to the best of our knowledge no studies have been published to date evaluating the cost-effectiveness of ticagrelor versus clopidogrel. Private payers and integrated health delivery systems will need

to weigh the inexpensive pharmaceutical costs of a genotype-based strategy centered on generic clopidogrel against the incremental clinical benefits of ticagrelor.

Methods

Model Cohort

In order to capture relatively small monthly rates of events, we developed our model with a population of 100,000 Medicare beneficiaries of age 66 or older hospitalized for ACS. We used 66 as the starting age of the cohort to allow for one year of claims data to apply exclusion criteria in the process of generating mortality and repeat myocardial infarction (MI) hazard rates. The analysis population differs somewhat from the Platelet Inhibition and Patient Outcomes (PLATO) trial cohort, which included adults hospitalized with any form of ACS, with the exception of ST-elevation myocardial infarction (STEMI) treated by fibrinolysis [40]. Because our model hazard rate ratios are derived from the PLATO study our model is most applicable to patients who meet the study's criteria, which including having no contraindication for clopidogrel, need for anticoagulation therapy, use of a CYP3A inhibitor, dialysis dependence, thrombocytopenia, or anemia. Our model population was older than the median PLATO participant (mean age 79 vs. 62); No heterogeneity in treatment response by age was observed in the PLATO cohort [33].

Model Structure

We used a hybrid decision tree/Markov model to analyze the cost-effectiveness of genotype-driven antiplatelet therapy for ACS. As presented in the decision tree in Figure 1, our model allowed providers two choices for ACS treatment: 1) genotype-driven treatment, and 2) universal ticagrelor. For genotype-driven treatment each patient is tested for CYP2C19*2 mutations and prescribed clopidogrel in their absence and ticagrelor in the presence of any CYP2C19*2 mutation. We created a Markov model to estimate the outcomes for each treatment option using one-month cycles as presented in Figure 2. The Markov model included events that were shown to have statistically and clinically significant differences between ticagrelor and clopidogrel in the PLATO study, which included MI, dyspnea, and all-cause mortality [33]. Although overall rates of major or minor bleeding were not significantly different between ticagrelor and clopidogrel patients in the PLATO study we accounted for major or minor bleeding in the model because the rates of bleeding were significantly different for major bleeding not related to CABG and for fatal intracranial bleeding [33]. Because the effectiveness of ticagrelor is independent of the CYP2C19*2 mutation, we assumed ticagrelor response to be the same for patients of all genotypes [41].

Two general Markov states are used in the model: 1) post-ACS event, and 2) dead. During each month's cycle a patient was at risk for MI, bleeding, dyspnea, or death due to any cause. All events were assumed to be independent of one another. Quality-adjusted life years (QALYs) were accumulated during each cycle and were adjusted for time since last ACS event. Adjustments for bleeding and dyspnea were made only in the month that the complication occurred. Medical costs were experienced during the month of the event and subsequent care costs, excluding those for recurrent MI and bleeding, were incurred in the month of an ACS-event and lasted until the lesser of 12 months or death. We assumed patients were prescribed antiplatelet medication for the first 12 months after the initial ACS event and after any subsequent MI. We allowed rates of all-cause mortality, MI, and bleeding to be equal between the two treatment options beyond the 12 months of antiplatelet therapy; thus survival of the two treatment options converge over time. Patients had no risk of dyspnea in either treatment strategy when not undergoing antiplatelet therapy. All costs and outcomes were discounted at an annual rate of 3%, with sensitivity analysis performed for rates of 0 to 5% [42].

Model Probabilities

The probabilities, hazard rates, and hazard rate ratios used to calculate transitions probabilities incorporated into the decision model are listed in Table 1 and Supplementary Table 1 available at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH14i4_Crespin-Rossi.asp. The probability of CYP2C19*2 mutation was obtained by weighting ethnicity-specific estimates by the ethnic composition of the Medicare program; because ethnicity was categorized as White, Black, Hispanic, and other, all patients identified as other were assumed to be Asian [43-47]. The utility/usefulness of historical estimates of long term survival after ACS are limited by recent reductions in mortality due to improvements in ACS care and in risk factors [48]. We responded by generating novel hazard rates for mortality, repeat myocardial infarction, and bleeding risk in a contemporary cohort of Medicare beneficiaries. We identified all Medicare patients of ages 66 and older admitted to a hospital with an International Classification of Diseases, 9th edition, Clinical Modification (ICD-9-CM) diagnosis code for ACS, either myocardial infarction (410.xx) or unstable angina (411.1), between January 1, 2003, and October 15, 2004, and divided the cohort into five-year age intervals. We used inpatient claims data from the 2003-2007 Medicare Provider and Analysis File as well as Medicare Denominator files to evaluate patients for up to five years after ACS admission, using censoring to account for patients with shorter follow-up durations. This claims-based analysis received approval from the Institutional Review Board at the University of North Carolina at Chapel Hill. Because MI is a transitory state, its risk was modeled using a repeated risk framework [49]. The Supplementary Appendix (found at; http://www.ispor.org/Publications/value/ViHsupplementary/ViH14i4_Crespin-Rossi.asp) describes the methodology used to develop our hazard rate estimates in more detail. The PLATO trial did not individualize therapy based on genotype, so it likely underestimates the performance of clopidogrel in a genotype-directed strategy because some patients with CYP2C19*2 mutations would have been randomized to receive clopidogrel. We assumed these patients received no benefit from clopidogrel and used data from the Clopidogrel in Unstable Angina to Prevent Recurrent Events trial [5] (which compared clopidogrel with placebo) to adjust the hazard rates according to Equation 1.

$$\text{Rate}_{Adj}=\text{Rate}_{Unadj}/\left(P(wild\quad type)+P(mutation)*Risk_{Placebo}/Risk_{Clopidogrel}\right) \qquad \text{(Eq 1)}$$

In all cases, when probabilities were adjusted to change cycle length they were first converted to instantaneous rates [50]. Ranges were calculated as 95% confidence intervals to reflect the degree of uncertainty in the source data [5,33,42-47,51-65].

Analytical Perspective

This analysis was conducted from the perspective of Medicare, which is the primary health insurance provider for virtually all US citizens ages 65 and older [66]. Although patient cost sharing is not explicitly included within the model, the range provided for the costs of the antiplatelet medications indirectly allows for substantial pharmaceutical copayments. Until recently this perspective would have excluded most outpatient prescription medications, but the advent of Medicare Prescription Drug Plans (PDPs) has meant that such costs are now within Medicare's scope. Costs were included only if they directly relate to the provision of medical services and thus accrue to the Medicare budget. We assume reimbursements based on traditional Medicare Parts A and B and do not account for differences in reimbursement resulting from enrollment in Medicare Advantage or private, fee-for-service plans.

Cost Estimates

Table 1 presents the costs for each resource used after ACS diagnosis. All costs are in 2009 US dollars and were inflated using the Medical Care Component of the Consumer Price Index when necessary [67,68]. Genotype tests to determine whether a patient has CYP2C19*2 mutations, although not yet widely available throughout the either North American or European settings, recently have been offered for the first time in the United States [69]. Initial reports place the price of the test at approximately $200, which represents the complete cost to the payer for the laboratory service and not simply the marginal cost of processing the test [54]. We assumed that the genotyping assay utilizes a buccal swab rather than blood for DNA collection, which can be self-administered and thus we excluded costs for obtaining a sample. This assumption underestimates the cost of the genotype-driven treatment if some institutions utilize blood testing. We assumed each patient received this test one time, simultaneously with their index ACS diagnosis, and that the test had both 100% sensitivity and specificity. These assumptions likely bias our results in favor of the genotype-driven therapy.

Pricing data are not currently available for ticagrelor or generic clopidogrel. We assumed the price of a one-month's supply (i.e. 30 75-mg tablets) of generic clopidogrel to be $30. This estimate is consistent with the projected price used in a previous cost-effectiveness analysis of prasugrel versus clopidogrel [70]. We assumed the price of ticagrelor to be the same as the net wholesale price of prasugrel. Prasugrel's manufacturers, Eli Lilly & Co and Daiichi Sankyo Co, have initially priced the drug at approximately $164 for a one-month supply of 30 10-mg tablets [71].

We searched both the Cost-Effectiveness Analysis (CEA) Registry at Tufts University and the National Institute of Health's PubMed database for MI and bleeding hospitalization costs for Medicare patients. The direct medical costs of MI and bleeding events were assumed to be the same for both treatment options. We used event costs of $18,390 for non-fatal MI and $16,093 for fatal MI, derived from the frequency of Medicare diagnosis-related group hospital payments in the Agency for Healthcare Research and Quality's nationwide inpatient sample [62]. For the purposes of costing and health-related quality of life (HRQOL) adjustment, we assumed that all cases of bleeding were gastrointestinal (GI) bleeding. The base-cost for bleeding was estimated to be $7491 [55,56,58]. This estimate is equivalent to the same bleeding cost used by Schleinitz et al.'s cost-effectiviness analysis of clopidogrel versus placebo. We then obtained subsequent care costs for all ACS patients, excluding those costs for recurrent MI, that were derived from frequency of acute care procedures present in the nationwide inpatient sample and using costs from the Medicare physician fee schedule [62]. We then excluded bleeding costs to estimate subsequent ACS care costs of $356 per month. We attributed no direct medical costs for dyspnea as we assumed dyspnea to be untreated in our sample; although more patients discontinued ticagrelor due to dyspnea than did clopidogrel (0.9% vs. 0.1%), we viewed the absolute number as small enough to justify not modeling as part of this analysis.

Outcomes

We reported outcomes in terms of QALYs and life years gained. The cohort's baseline utility values were obtained from a nationally representative survey of non-institutionalized Americans utilizing the EQ-5D instrument [59]. We obtained baseline utility values of 0.86 for 66-74-year-olds and 0.84 for 75-95-year-olds and then used their average value (0.85) as our baseline utility value. We searched the CEA Registry to locate utility weightings for each outcome state within the model, limiting results to reports on American patient populations published since 1998 [72]. From this literature we derived HRQOL multiplicative adjustments of 0.87 in the first year post-MI and 0.91 in subsequent years.

ACS includes unstable angina, which is not a form of MI; however, European evidence suggests that unstable angina causes an equivalent reduction in HRQOL [73]. Because of the unclear external validity of this measure we enlarged the standard errors of our estimates; our range included all point estimates listed within the CEA registry for myocardial infarction without other comorbidities specified. GI bleed was estimated to have a utility toll equivalent to one quality-adjusted life-week. We therefore used a monthly HRQOL adjustment of 0.75, the equivalent of 1 week's utility. We assumed in the absence of additional information that the dyspnea experienced by the trial subjects is mild, as only 8% of subjects who experienced dyspnea during the PLATO trial stopped taking ticagrelor for that reason. Thus, we assumed that the dyspnea experienced by trial subjects is, at worst, equivalent to Global Initiative for Chronic Obstructive Lung Disease stage I disease, which corresponds to a mild decline in respiratory function as measured by spirometry [74]. Chronic obstructive pulmonary disease was selected over asthma because of the more episodic nature of the latter condition. Using this information we derived an estimated HRQOL adjustment of 0.93 from the relevant literature. As is customary, we assigned death a utility weight of 0 [42].

Sensitivity Analyses

To determine the sensitivity of our model to uncertainty within the input variables, we conducted one-way analysis by varying parameters individually and reporting the resulting incremental cost-effectiveness ratios (ICERs). Because of the large number of input parameters included, only parameters that altered the ICER by more than $1500 are reported. We also varied the model length and discount rate to determine whether the analytic horizon affected the base-case results. Because some patients may receive treatment for periods longer than 12 months, we also simulated 15- and 24-month therapy durations. Threshold analysis was conducted to determine both the cost-effective threshold for the price of ticagrelor and the hazard rate ratio for mortality between ticagrelor and clopidogrel. To determine whether the joint uncertainty of model parameters affected the model results, we conducted probabilistic sensitivity analysis using Monte Carlo simulation (1000 iterations). Transition probabilities and the utility of health states were generally modeled using beta distributions, using count data from trials when available and method of moment approximations otherwise [50]. Beta distribution parameters were specified using median, maximum, alpha and beta parameters to ensure sampling distributions were centered at the base-case estimate. Most hazard rates, hazard rate ratios, and costs were modeled using log-normal or normal distributions [50]. Because the costs of genotyping, generic clopidogrel, and ticagrelor have not been established, we modeled these parameters as triangular distributions, with minimum and maximum values pre-specified as 50% and 150% of the point estimate, respectively. All other medical costs were assumed to follow a log-normal distribution. Results from these analyses are presented via both the cost-effectiveness plane and cost-effectiveness acceptability curves. Although an appropriate cost-effectiveness threshold for American health care purchasers remains a subject of debate, we used the typical accepted U.S. threshold of $50,000 per QALY as cost-effective [42,75]. Simulations were conducted in Excel 2007 (Microsoft, Redmond, Washington) using Crystal Ball, Fusion Edition version 11.1.1.3 (Oracle, Redwood City, California). The cost-effectiveness curves were calculated with SAS version 9.2 (SAS Institute, Cary, North Carolina) using the net-benefit framework [50].

Results

Base-Case Results

Providing ticagrelor universally rather than employing genotype-driven treatment produced 0.10 additional QALYs per person at an incremental cost of $1040 per person. The ICER

was $10,059 per QALY for a 5-year time horizon, as compared to a genotype-driven treatment option (Table 2). Because the majority of the cost differential between the two treatments occurs in the first year the ICER reached its maximum after eleven months of therapy (Fig. 3) and was $42,546 per QALY after one year of treatment. We found that the ICER increased for longer durations of therapy. A 15-month duration of therapy resulted in an ICER of $12,334 per QALY and at 24 months the ICER increased to $18,682 per QALY. Similar results were obtained in the analysis of life years gained, as expected given the survival benefit produced by ticagrelor. The ICER for universal ticagrelor was $7539 per life year compared to the genotype-driven treatment over the 5-year period. On average, universal ticagrelor resulted in 0.14 life years gained.

One-way sensitivity analysis results (Table 3) indicate that universal ticagrelor remains a cost-effective intervention across the probable range of each input parameter. The ICER as predicted by our model is most sensitive to the price of ticagrelor ($3,858- $16,260 per QALY) and the hazard rate ratio for death for ticagrelor compared with clopidogrel ($7,594- $21,181 per QALY). Threshold analysis calculations indicate that the monthly price of ticagrelor would need to increase from $164 to $693, or the hazard rate ratio for death relative to clopidogrel increased from 0.78 to 0.93 for the ICER to exceed $50,000 per QALY. Even in the scenario in which clopidogrel becomes a deeply discounted generic (costing $4 for a 30-day supply) ticagrelor retains its cost-effectiveness advantage ($11,927 per QALY). The model was insensitive to changes in the discount rate when varied between 0% and 5% ($9,641- $10,338 per QALY). To determine whether the model was sensitive to systematic changes in mortality risk we modified the baseline mortality risk using a hazard rate ratio from 0.5 to 3.0 and found ticagrelor remained cost-effective across the entire range ($15,954- $6,873 per QALY).

Probabilistic sensitivity analyses demonstrated that universal ticagrelor is a more costly yet more effective intervention than genotype-driven therapeutic selection (Fig. 4). The cost-effectiveness plane illustrates both the magnitude and sign of the incremental benefits and costs of one treatment over another; the slope from the origin to each point indicates the incremental-cost effectiveness ratio for that iteration. In only 1 of 1000 simulations was universal ticagrelor the dominant intervention (less expensive and more effective) and in 12 of 1000 it was the dominated intervention (more expensive and less effective). For 977 of the 1,000 simulations, the estimated ICER was less than the $50,000 per QALY threshold. The cost-effectiveness acceptability curve (Fig. 5) illustrates the probability that an intervention is cost-effective given a policymaker's stated cost-effectiveness threshold (i.e., how much he or she is willing to pay per additional quality-adjusted life year) [76]. In this model, policymakers willing to pay $30,200 or more per QALY would have a 95% chance of being correct in choosing universal ticagrelor (that ticagrelor would in fact be cost effective).

Discussion

In a cohort of ACS patients of age 66 or older enrolled in Medicare, the cost of universally prescribed ticagrelor is $10,059 per QALY compared to a genotype-driven alternative over a 5-year time horizon. On average each patient gains 0.10 QALYs. This cost is well within the $50,000 per QALY threshold typically used for health services research in the United States. In probabilistic sensitivity analysis only 2.2% of simulations produced an ICER greater than $50,000 per QALY. This result signals that ticagrelor's efficacy outweighs generic clopidogrel's likely inexpensive price, even if the patients for whom clopidogrel is not effective are identified and receive ticagrelor instead. In shorter analytic horizons universal ticagrelor is less cost-effective but still within the $50,000 per QALY threshold. This result is not surprising given that all patients receive drug therapy during the first year of treatment

and patients prescribed ticagrelor have substantially higher medication cost than patients prescribed generic clopidogrel. In subsequent years the number of patients receiving medication is considerably reduced (only those patients suffering recurrent MI were assumed to restart dual antiplatelet therapy), decreasing the medication cost differential of the two treatment options. As expected the cost-effectiveness of universal ticagrelor is most sensitive to the hazard rate ratio of death for ticagrelor relative to clopidogrel, as the major benefit of ticagrelor is reduced mortality. The cost-effectiveness of universal ticagrelor likely will be reduced if the magnitude of this benefit is less than that found in the PLATO trial or if the benefits of clopidogrel are greater than have been observed in clinical trials. In our sensitivity analysis the cost-effectiveness of universal ticagrelor increased considerably as the hazard rate ratio approach 1.00 and at 0.93 the ICER surpasses the $50,000 per QALY threshold. Ticagrelor's clinical efficacy allows universal ticagrelor to be cost-effective at prices significantly higher than generic clopidogrel. Universal ticagrelor is less cost-efficient than genotype-driven treatment only when the price of ticagrelor exceeds $693 per month, a price that is unrealistic given clopidogrel and prasugrel's branded price of approximately $150 per month.

This study had several limitations. Most notably, our analysis was based on the efficacy of antiplatelet medication in clinical trials. The ultimate effectiveness of antiplatelet medication likely cannot be determined from clinical trial data alone due to their short duration. Long-term projections should be reviewed with caution as the clinical trial investigated antiplatelet medication in much shorter time intervals. Many of the key inputs to our model were from the PLATO trial, which was 12 months in duration. While we estimated the cost-effectiveness of universal ticagrelor at duration lengths of 15 and 24 months, our estimates may be biased if the effectiveness of ticagrelor differs after 12 months of therapy. Ongoing studies evaluating the efficacy of dual antiplatelet therapy beyond 12 months will have significant implications on the long-term cost effectiveness of clopidogrel and ticagrelor. Due to selection criteria our results may not apply to subpopulations excluded from these trials. Particularly, subgroups of the general ACS population may exhibit different treatment responses that may affect the cost-effectiveness of any treatment option. Adverse events costs may vary within subpopulations due to events that significantly differ between ticagrelor and clopidogrel patients outside of MI, bleeding, and dyspnea. The inclusion of these costs should be considered when estimating the cost-effectiveness of universal ticagrelor for other populations. For example, PLATO patients with a planned invasive treatment strategy were less likely to result in stent thrombosis when given ticagrelor compared to clopidogrel (HR=0.73, 95% CI 0.59-0.92; p-value=0.007) [77]. Secondly, we assumed that recurrent MI and death were independent events. This occurrence is likely unrealistic but was unavoidable in our model because data from the PLATO trial was presented in a manner that did not make it possible to determine how many MIs and deaths were not independent events. Because ticagrelor remained cost effective even if no reduction in MI was included in the model (ICER $10,967 per QALY), we view the impact of this limitation as minor. Lastly, our results cannot be used to determine universal ticagrelor's cost-effectiveness relative to other viable treatment options for secondary prevention after ACS. When making decisions regarding ACS treatment other treatments that could be considered include using prasugrel and a doubled dose (150 milligrams daily) of clopidogrel; although preliminary cost-effectiveness results powered by data from the TRITON-TIMI trial indicate that prasugrel is cost-effective when compared to clopidogrel for patients receiving percutaneous coronary intervention for ACS, a comparison of all proposed treatment strategies would clarify how providers should approach this important clinical problem [78]. Controversy continues to grow about the role of specific genetic mutations, including those within CYP2C19, in affecting outcomes for patients treated with clopidogrel [79,80]. While our results are robust to a broad range of sensitivity assumptions regarding the prevalence of clopidogrel non-response and test characteristics, additional

analyses will be valuable as alternative methods of characterizing clopidogrel response are developed.

Universal ticagrelor is cost-effective in a cohort of Medicare beneficiaries hospitalized for ACS when compared to a genotype-driven alternative. The efficacy of ticagrelor relative to clopidogrel substantially outweighed the higher medication costs associated with ticagrelor. Further research is needed to assess the cost-effectiveness of universal ticagrelor across subpopulations and to compare the cost-effectiveness of ticagrelor to other ACS treatment options. However, if these results are confirmed then they support the prioritization of ticagrelor over generic clopidogrel for Medicare beneficiaries; a policy recommendation complicated by the structure of Medicare. Most Medicare beneficiaries receive medical benefits from the government but outpatient prescription coverage through a government-subsidized private PDP. Because PDPs maximize their profitability by minimizing pharmaceutical expenditures, PDPs create incentives to prefer generic medications through co-payment tier arrangements. Complimenting the incentives to insurers offering PDPs, the use of lower cost generics is supported by members of Congress eager to reduce budgetary pressures [81,82]. Our findings highlight both the importance of evaluating the relative value of health care interventions in light of their cost and the need to develop more nuanced payment models creating incentives for the provision of affordable, high quality care, rather than simply the cheapest option.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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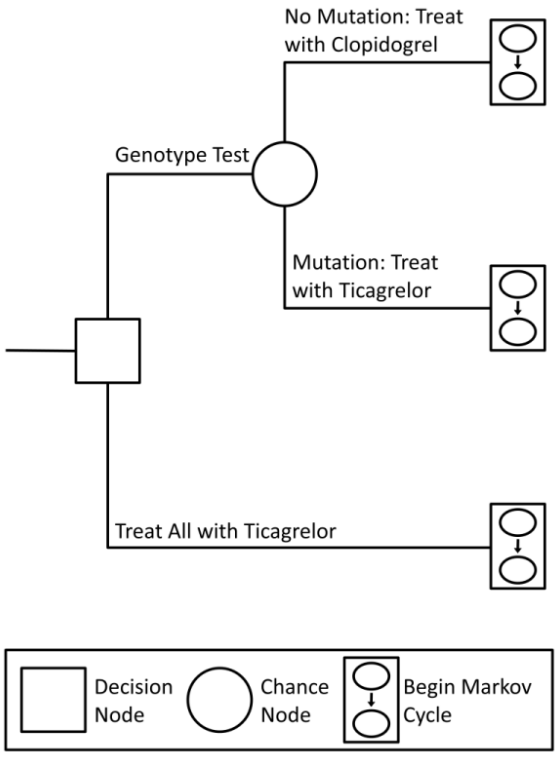

Figure 1.
Decision tree outlining treatment options under comparison. Patients either receive CYP2C19*2 mutation testing and have antiplatelet therapy selected by testing result or receive ticagrelor without genetic testing.

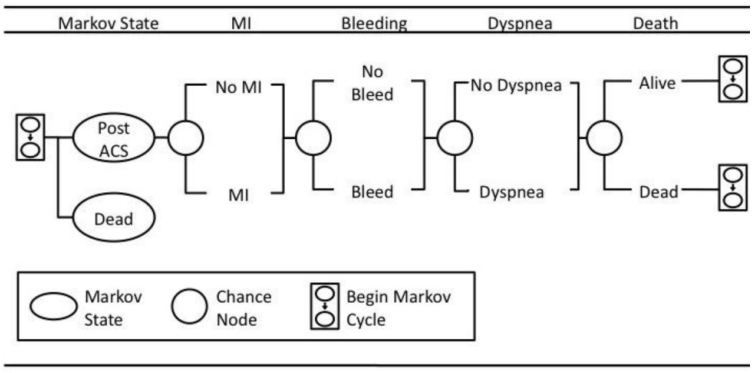

Figure 2.

Markov model. During each month-long cycle, patients may experience repeat myocardial infarction, bleeding, dyspnea, or death. Transition probabilities adjust to reflect patient age and choice of antiplatelet treatment. ACS, Acute Coronary Syndrome; MI, Myocardial Infarction

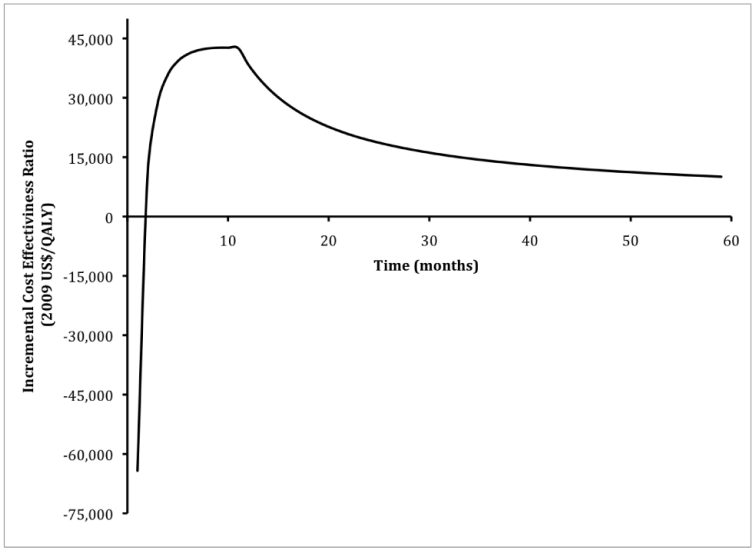

Figure 3.

The incremental cost effectiveness ratio (ICER) calculated as a function of the discounted cumulative costs and outcomes (QALYs) accrued from initiation of therapy up to each time period indicated. Thus, this diagram portrays the effect of different analytical horizons on cost-effectiveness. In this model, the higher monthly cost of ticagrelor during the initial one year of therapy leads to a peak ICER of $42,656 per QALY at 11 months after the initial ACS episode.

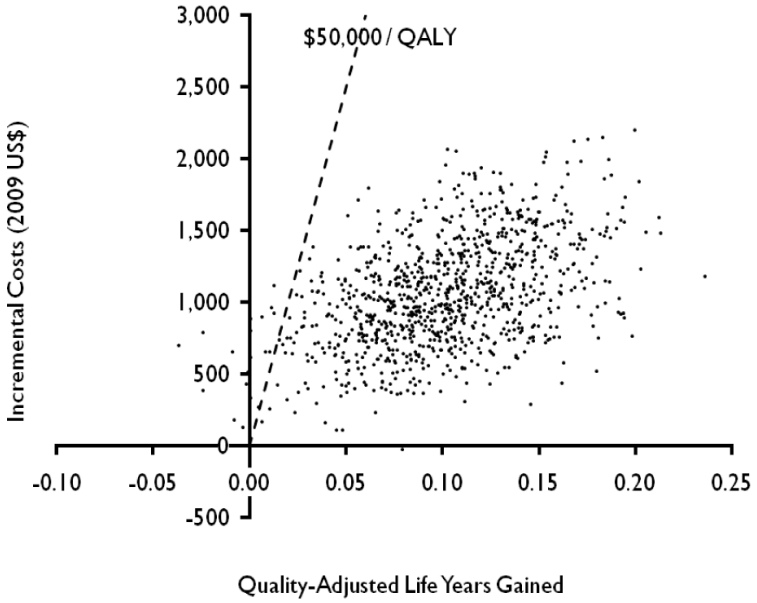

Figure 4.
Incremental cost-effectiveness plane showing Monte Carlo estimates of incremental costs and benefits of using ticagrelor universally for secondary prevention after acute coronary syndrome versus genotype-based selection of clopidogrel or ticagrelor.

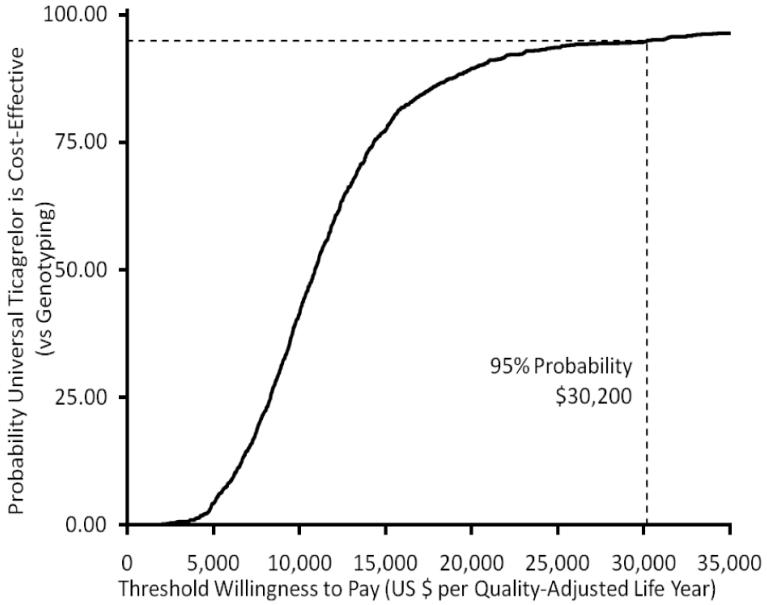

Figure 5.

Cost-effectiveness acceptability curve depicting the probability that using ticagrelor universally for secondary prevention after acute coronary syndrome versus genotype-driven selection of clopidogrel or ticagrelor is cost effective at different cost-effectiveness thresholds. The dashed lines indicate the amount a decision maker should be willing to pay to be 95-percent certain that the decision to use ticagrelor universally is cost-effective ($30,200).

Table 1

Model inputs used in comparison of antiplatelet strategies after Acute Coronary Syndrome.

Parameter	Base Case	Range	Reference
Probability of Mutation	0.2835	(0.1831, 0.3839)	(43-47)
Hazard Rate of Death (by month)			
1	0.2063	(0.2052-0.2075)	This Study
2	0.0474	(0.0468-0.0479)	
3	0.0289	(0.0284-0.0294)	
4	0.0224	(0.0220-0.0228)	
5	0.0185	(0.0181-0.0189)	
6	0.0165	(0.0162-0.0169)	
7-60		See Supplemental Table 1	
Hazard Rate of MI (by month)			
1	0.0273	(0.0269-0.0277)	This Study
2	0.0183	(0.0179-0.0187)	
3	0.0122	(0.0119-0.0125)	
4	0.0103	(0.0100-0.0105)	
5	0.0088	(0.0085-0.0091)	
6	0.0077	(0.0074-0.0079)	
7-60		See Supplemental Table 1	
Hazard Rate of Bleeding (by month)			
1	0.0939	(0.0931-0.0947)	This Study
2	0.0134	(0.0131-0.0137)	
3	0.0098	(0.0095-0.0101)	
4	0.0083	(0.0081-0.0086)	
5	0.0073	(0.0070-0.0075)	
6	0.0069	(0.0067-0.0072)	
7-60		See Supplemental Table 1	
Probability of Dyspnea (monthly)	0.0785	(0.0731,0.0841)	(33)
Hazard Rate Ratios			
Clopidogrel vs. Placebo			
Death	0.91	(0.78, 1.06)	(5)
MI	0.77	(0.67, 0.89)	(5)
Bleeding	1.69	(1.47, 1.94)	(5)
Ticagrelor vs. Clopidogrel			
Death	0.78	(0.68, 0.89)	(33)
MI	0.84	(0.74, 0.95)	(33)
Bleeding	1.11	(1.07, 1.16)	(33)
Dyspnea	1.84	(1.68, 2.02)	(33)
Costs *			
Genotype Test †	$200	($100-$300)	(54)

Parameter	Base Case	Range	Reference
Medication1			
Generic Clopidogrel	$30	($15-$45)	(70)
Ticagrelor	$164	($100-$300)	assumed
ACS Event Costs			
Fatal MI	$16,093	($6,902-$48,999)	(62)
Non-fatal MI	$18,390	($6,040-$42,879)	(62)
Bleeding	$7,491	($2,862-$19,606)	(55, 56, 58)
Subsequent Monthly ACS Care‡	$356	($156-$1,109)	(62)
Baseline Utility Weight	0.85	(0.83-0.87)	(59)
Event-related Utility Tolls			
MI (first year)	0.87	(0.80-0.96)	(60-62)
MI (subsequent years)	0.91	(0.80-0.95)	(60-62)
Death	0	N/A	(42)
GI Bleeding (utility toll during month of event)	0.75	(0.50-1.00)	(61, 63, 64)
Dyspnea (at any time during treatment)	0.93	(0.47-1.00)	(65)

*Cost are expressed in 2009 US Dollars

†One-time cost for all patients in genotyping arm

‡Cost incurred every month for 1-year after ACS event MI, myocardial infarction; ACS, acute coronary syndrome; GI, gastrointestinal

Table 2

Case cost-utility analysis of antiplatelet strategies after acute coronary syndrome

	Cost*	Outcome (QALYs)	Incremental Cost	QALYs Gained	ICER ($ /QALY)
After 1 Year					
Genotype-Driven	$713,983,854	56,603	-	-	-
Universal Ticagrelor	$794,382,109	58,492	$80,398,255	1,890	42,546
After 5 Years					
Genotype-Driven	$943,144,383	217,711	-	-	-
Universal Ticagrelor	$1,047,138,812	228,049	$103,994,429	10,338	10,059

QALY, quality adjusted life-year; ICER, incremental cost-effectiveness ratio

*Cost are expressed in 2009 US Dollars and discounted at 3% per year.

Table 3

One-way sensitivity analysis * comparing universal ticagrelor to genotype-driven therapy

	Input Values			ICER ($ / QALY)		
	Low	**High**	**Base**	**Low**	**High**	**Difference**
HR Ratio: Death (ticagrelor vs. clopidogrel)	0.68	0.89	0.78	7,594	21,181	13,587
Cost: Ticagrelor	$82	$246	$164	3,858	16,260	12,402
HR Ratio: Death (clopidogrel vs. placebo)	0.78	1.06	0.91	15,743	7,951	7,792
Cost: Subsequent Monthly ACS care	$156	$1,109	$354	9,298	12,924	3,626
HR Ratio: MI (ticagrelor vs. clopidogrel)	0.74	0.95	0.84	8,395	11,890	3,495
HR Ratio: MI (clopidogrel vs. placebo)	0.67	0.89	0.77	11,182	8,884	2,298
Cost: Clopidogrel	$15	$45	$30	11,137	8,982	2,154
Cost: Genotype Test	$100	$300	$200	11,027	9,092	1,934
HRQOL Adjustment: Dyspnea	0.47	1.00	0.93	11685	9,851	1,834
	$6,902	$48,99	$18,39	9,461	11,245	1,784
Cost: Non-Fatal MI		9	0			

QALY, quality adjusted life-year; MI, myocardial infarction; HR, Hazard Rate; ICER, Incremental costeffectiveness ratio; HRQOL, health-related quality of life

* Only parameters that altered the ICER by more than $1,500 are reported.