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Economic Analysis of Ticagrelor Therapy From a U.S. Perspective

Results From the PLATO Study

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ABSTRACT

BACKGROUND Based on results of the PLATO (Platelet Inhibition and Patient Outcomes) trial comparing ticagrelor with clopidogrel therapy, the U.S. Food and Drug Administration approved ticagrelor in 2011 for reducing thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) with the proviso that it be taken with low-dose aspirin.

OBJECTIVES This study sought to assess the cost and cost effectiveness of ticagrelor therapy relative to clopidogrel in treating ACS patients from the perspective of the U.S. health care system.

METHODS We estimated within-trial resource use and costs using U.S. low-dose aspirin patients in PLATO (n = 547). Quality-adjusted life expectancy was estimated using the total PLATO population (n = 18,624), combined with baseline risk and long-term survival data from an external ACS patient cohort. Study drugs were valued at current costs. Cost effectiveness was assessed, as was the sensitivity of results to sampling and methodological uncertainties.

RESULTS One year of ticagrelor therapy, relative to that of generic clopidogrel, cost $29,665/quality-adjusted life-year gained, with 99% of bootstrap estimates falling under a $100,000 willingness-to-pay threshold. Results were robust to extensive sensitivity analyses, including variations in clopidogrel cost, exclusion of costs in extended years of life, and a recalibrated estimate of survival reflecting a lower underlying mortality risk in the United States.

CONCLUSIONS For PLATO-eligible ACS patients, a U.S. perspective comparison of the current standard of dual antiplatelet therapy of aspirin with clopidogrel versus aspirin plus ticagrelor showed that the ticagrelor regimen increased life expectancy at an incremental cost well within accepted benchmarks of good value for money. (A Comparison of Ticagrelor [AZD6140] and Clopidogrel in Patients With Acute Coronary Syndrome [PLATO]; NCT00391872) (J Am Coll Cardiol 2015;65:465–76) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CI = 95% confidence interval

FDA = U.S. Food and Drug Administration

ICER = incremental cost-effectiveness ratio

MI = myocardial infarction

PCI = percutaneous coronary intervention

QALY = quality-adjusted life-year

STEMI = ST-segment elevation myocardial infarction

Dual antiplatelet therapy (DAPT) with aspirin and an adenosine diphosphate receptor $P2Y_{12}$ inhibitor is currently recommended for patients with acute coronary syndrome (ACS) to reduce risk of myocardial infarction (MI) and death (1,2). Although clopidogrel is the drug most commonly used with aspirin for this purpose, significant variability in its antiplatelet effects along with the irreversibility of its action on the platelet have prompted searches for an alternative second antiplatelet agent. The PLATO (Platelet Inhibition and Patient Outcomes) trial reported that the combination of ticagrelor, a newer $P2Y_{12}$ inhibitor, and aspirin was superior to clopidogrel plus aspirin in preventing death and MI (3). Based on these results, the U.S. Food and Drug Administration (FDA) approved ticagrelor in 2011 for use in ACS patients in combination with low-dose aspirin.

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Novel therapeutic innovations face intense scrutiny regarding not only their safety and clinical effectiveness but also their value (the balance between incremental societal costs to provide the care and its incremental health benefits). Our study's objective was to use detailed patient-level clinical and resource use data collected in PLATO to evaluate the costs and cost effectiveness of ticagrelor relative to clopidogrel in treating patients with ACS from the perspective of the U.S. health care system.

METHODS

PLATO. The PLATO study enrolled 18,624 subjects with ACS in 43 countries in a randomized, double-blind clinical trial conducted between October 2006 and February 2009 (3,4). Patients received a loading dose of study drug, followed by up to 1 year of maintenance therapy (ticagrelor, 90 mg twice/day; clopidogrel, 75 mg daily). Compared with clopidogrel, ticagrelor significantly reduced the primary endpoint of vascular death, MI, or stroke (9.8% vs. 11.7%; hazard ratio [HR]: 0.84; $p < 0.001$), as well as other secondary endpoints including all-cause death (4.5% vs. 5.9%; HR: 0.78; $p < 0.001$), with no increase in major bleeding (11.6% vs. 11.2%; HR: 1.04; $p = 0.43$).

Pre-specified exploratory analyses identified significant interaction between geographic region and treatment, with a ticagrelor-clopidogrel HR for the primary endpoint of 1.25 for North America compared to ratios of 0.80 to 0.86 in other regions ($p = 0.05$ for interaction). The North American effect appeared to be driven by U.S. results (HR: 1.27; $p = 0.01$ for interaction) (5). In extensive post hoc analyses, only maintenance aspirin dose emerged as a potential effect modifier: with high-dose aspirin, used primarily in the United States, primary event rates were higher in patients treated with ticagrelor than in those treated with clopidogrel (6). Although chance cannot be ruled out as a source of the region-treatment interaction, FDA approval of ticagrelor included a boxed warning that maintenance aspirin doses exceeding 100 mg/day might reduce effectiveness and should be avoided (7,8).

PLATO U.S. ECONOMIC ANALYSIS. This prospectively designed cost-effectiveness analysis includes a within-trial comparison of resource use and associated costs, as well as a long-term cost-effectiveness analysis. Original plans were to base cost estimates on U.S. PLATO patients and effectiveness on the overall trial experience. This split approach was based on the premise that U.S. resource use patterns would differ considerably from those in other countries, but effectiveness of therapy would not be regionally dependent (9). Consistent with FDA approval, we modified our approach to assume ticagrelor would be prescribed in the context of low-dose aspirin therapy.

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Because <40% of U.S. patients received low-dose aspirin and costs based on total U.S. sample might not reflect the FDA-approved therapy, we estimated within-trial costs using the low-dose aspirin U.S. cohort. As planned, we based effectiveness on the overall trial, in which low-dose aspirin therapy was predominant. Although U.S. patients had higher baseline risk than those enrolled elsewhere, use of overall effectiveness in the U.S. analysis was supported by the near absence of risk factor-treatment interactions (2 of 31 risk factors) (3). Because mortality rates with clopidogrel therapy were lower in the U.S. subset than in the rest of the PLATO population, we also developed recalibrated models to address the possibility of reduced absolute benefits in the United States. Inputs to the cost-effectiveness analysis are described below and summarized in Online Table 1.

WITHIN-TRIAL RESOURCE USE. Resource use data for major components of health care were collected on the case report form and included dates of admission and discharge for all hospitalizations; days in intensive care (follow-up hospitalizations only); and details regarding major procedures, therapies, and diagnostic tests, including percutaneous coronary revascularization (PCI), cardiac surgeries, coronary angiography, noninvasive cardiac imaging, and transfusions. Intensity of care during the index hospitalization was not recorded; we assumed patients were treated in the coronary care unit (CCU) for the first 2 days of their stay and in the cardiology ward thereafter. For follow-up hospitalizations, procedure and diagnosis information was used to assign the intensive care days, as recorded in the case report form, to specific hospital units (thoracic intensive care, CCU, or intensive care unit).

ESTIMATION OF COSTS. Duration of treatment with study drug was obtained from the case report form. Study drug costs were based on the National Average Drug Acquisition Cost (ticagrelor = $7.88/day; clopidogrel = $0.11/day) (10). The analysis excluded concomitant drug costs because days on concomitant medications were similar between treatment groups.

Because cost data were not collected in PLATO, external cost weights were required to value health care services collected on the case report form. We developed cost weights for hospital services using detailed, patient-level cost accounting data for patients with coronary disease hospitalized at Duke University Medical Center from 2006 through 2008. A generalized linear model for hospitalization cost was specified with an identity link and a gamma distribution function (11). Independent variables included major resources collected in PLATO, along with variables to capture major procedures not collected in the trial. Unit costs are presented in Online Table 2.

The cost of physician services for resources tracked in PLATO, including daily hospital care, procedures, and tests were based on the Medicare fee schedule (12). Each identified service was mapped to the corresponding current procedural terminology code, and North Carolina rates were applied.

Within-trial patient-level costs were calculated by applying cost weights to resources consumed during the study period by U.S. low-dose patients. Productivity losses and informal care costs were not collected in PLATO and were excluded. Costs were updated to 2013 using the general medical and surgical hospital component of the producer price index (13). Because PLATO was an event-driven trial, individual follow-up times varied. To account for differential follow-up, 12-month costs were estimated using inverse probability weighting methods that account for administrative censoring (14).

We conservatively assumed that nonfatal events prevented by ticagrelor would not reduce cost or mortality beyond trial follow-up. Because there are no known factors that would differentially increase the cost of care after ticagrelor discontinuation, treatment-related costs beyond trial follow-up were limited to background costs in years of life gained with therapy. An estimate of average annual health care expenditures, including inpatient care, outpatient services, and medications, was developed using 2008 Medical Expenditure Panel Survey data for patients reporting coronary heart disease, angina, or MI (15).

ESTIMATING SURVIVAL AND HEALTH-RELATED QUALITY OF LIFE. Projections of survival following an intervention require assumptions regarding long-term treatment benefits. For our base case, we assumed that ticagrelor therapy was discontinued after 1 year with no additional reduction in mortality risk after cessation of therapy. To model life expectancy, we used a 2-stage approach that relied on within-trial experience for the 1-year treatment phase and used external data to extrapolate beyond treatment (16). The external dataset selected for extrapolation was the U.S. cohort from PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) (17), an international trial that enrolled non-ST-segment elevation ACS patients. Vital status at 10-year follow-up was ascertained for 79% of U.S. patients (n = 2,773) by using the National Death Index.

Survival through 1 year of treatment was estimated using a conventional time-based Cox proportional

TABLE 1 Baseline Characteristics for the U.S. Cohort by Maintenance Aspirin Dose and Treatment*

	U.S. Cohort			U.S. Low-Dose Cohort		
	High-Dose Aspirin (n = 866)	Low-Dose Aspirin (n = 547)	p Value†	Ticagrelor Group (n = 284)	Clopidogrel Group (n = 263)	p Value‡
Age, yrs	60 (52–69)	62 (54–71)	<0.001	62 (55–70)	63 (54–72)	0.35
Female	26.1	32.9	0.006	33.1	32.7	0.92
Body mass index, kg/m^2	29 (26–33)	29 (26–34)	0.53	29 (26–34)	29 (26–34)	0.97
Race			0.71			0.63
White	89.2	89.6		91.2	87.8	
Black	10.1	9.1		7.8	10.7	
Asian	0.5	0.9		0.7	1.1	
Other	0.4	0.4		0.4	0.4	
Baseline clinical history						
Prior MI	27.6	27.1	0.81	27.5	26.6	0.82
Prior PCI	30.3	28.0	0.35	28.2	27.8	0.91
Prior CABG	15.7	18.3	0.21	19.4	17.1	0.50
CHF	6.4	9.3	0.04	7.8	11.0	0.19
Hypertension	68.0	75.3	0.003	74.7	76.1	0.70
Dyslipidemia	69.3	65.5	0.13	65.9	65.0	0.84
Nonhemorrhagic stroke	3.6	3.3	0.77	3.5	3.0	0.75
PAD	8.4	10.4	0.21	10.6	10.3	0.91
Chronic renal disease	5.1	7.1	0.11	7.4	6.8	0.80
Diabetes	33.1	34.0	0.72	34.9	33.1	0.66
History of dyspnea	26.1	24.3	0.45	23.9	24.7	0.83
COPD	13.1	11.9	0.52	12.0	11.8	0.95
Smoking			0.20			0.61
Nonsmoker	28.9	30.4		29.6	31.2	
Ex-smoker	32.8	36.0		34.9	37.3	
Habitual smoker	38.3	33.6		35.6	31.6	
Index ACS diagnosis			0.02			0.78
STEMI	17.5	13.0		13.7	12.2	
NSTEMI	65.4	70.2		68.3	72.2	
Unstable angina	9.3	11.3		12.3	10.3	
Other/missing	7.9	5.5		5.6	5.3	
Procedures during study						
Planned invasive treatment	95.8	90.1	<0.001	90.5	89.7	0.77
PCI	69.3	62.5	0.009	63.0	62.0	0.80
CABG	14.2	12.4	0.34	12.0	12.9	0.73
Study drug						
Time from event to study drug, h	16.5 (8.3–23.0)	17.1 (9.3–22.9)	0.36	16.6 (8.3–22.1)	17.6 (10.6–23.2)	0.13
Time taking drug, days	265 (51–363)	303 (182–366)	<0.001	298 (177–366)	329 (189–365)	0.57
Compliant	61.2	62.7	0.57	62.7	62.7	0.99
Premature discontinuation	32.9	25.8	0.004	27.8	23.6	0.26

Values are median (25th-75th percentiles) or %. *Hours from event to study drug and days taking the drug regimen in the high-dose U.S. group have 7% missing data; all other variables have <1% missing data. †High-dose versus low-dose aspirin. ‡Ticagrelor group versus clopidogrel group.

ACS = acute coronary syndrome; CABG = coronary artery bypass graft surgery; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

hazards model with adjustment for baseline covariates and stratification by treatment. Survival beyond 1 year was estimated using an age-based survival model, which treats the hazard of death as a function of age rather than time to take full advantage of the patient years of follow-up (21,136 patient years). The time-based and age-based models were combined to estimate patient-specific lifetime survival curves. Life expectancies, calculated as the area under individual survival curves, were averaged to obtain a mean predicated life expectancy by treatment.

In PLATO, observed mortality in the clopidogrel arm was lower in the U.S. subset than in the rest of

the trial population (3.6% vs. 6.1%, respectively) (5). Although other international studies of ACS populations have not found U.S. mortality rates to be 40% lower than elsewhere (18,19), effectiveness estimates based on the overall trial might exaggerate the underlying U.S. mortality risk, thereby inflating predicted absolute gains in survival associated with ticagrelor treatment. Therefore, we performed an alternative set of analyses in which underlying mortality risk was recalibrated to reflect the lower observed rate of death among U.S. clopidogrel patients.

The EuroQol five dimensional health state classification instrument (EQ-5D) was collected in PLATO as a measure of health-related quality of life (QOL) at baseline and regular follow-up intervals in countries with official EQ-5D translations (92% of enrolled patients). No differences between treatments in EQ-5D scores were observed (20). We estimated an age-dependent QOL adjustment factor for patients living with ACS using the last complete EQ-5D assessment for each patient, valued with U.S. preference weights (21,22).

STATISTICAL ANALYSES. Baseline characteristics of the U.S. low-dose aspirin maintenance cohort were compared with those of the high-dose cohort to determine whether, with the exception of aspirin dose, the low-dose subset represented U.S. patients. Within-trial resource use (index and follow-up) was summarized using descriptive statistics and compared by treatment group using Pearson chi-square test for proportions and Mann-Whitney *U* test for continuous variables. Cumulative 1-year costs, estimated using inverse probability weighting methods, were compared between treatments using the normal approximation, with standard errors estimated using a bootstrap approach (described below). Because the distribution of within-trial costs in the U.S. low-dose cohort had a positive skew with a few extreme outliers whose reproducibility could not be determined, outliers exceeding the 99th percentile were replaced with the 99th percentile value (Winsorized) in primary analyses.

Incremental cost-effectiveness ratios (ICERs) were calculated as the between group difference in mean lifetime costs divided by the between group difference in mean quality-adjusted life expectancy. In light of considerable uncertainty surrounding the small cost offset favoring ticagrelor found in the U.S. low-dose subset, we excluded within-trial health care costs from the base case cost-effectiveness analysis. The base case, estimated using the overall sample, included a generic clopidogrel cost of $0.11 per day; health care costs in years of life gained with ticagrelor; persistence beyond trial follow-up of within-trial gains in survival; and a discount rate of 3% for costs and survival. Sensitivity analyses assessed the effect of methodological assumptions on results. Assuming no within-trial cost offset, we examined the effects of varying average clopidogrel cost ($0/day to $6/day), excluding costs in years of life gained, removing the QOL adjustment, varying the discount rate (0% and 6%), and restricting the time horizon over which survival benefits could accrue (within-trial and 5 years). Cost effectiveness in subgroups of interest was also explored. We then incorporated within-trial costs using the U.S. low-dose cohort and assessed their effect on cost effectiveness. Scenarios included variations in the externally derived cost weights (50% and 150% of base values) and inclusion of all observed cost data (without Winsorizing outliers). Combinations of these sensitivity analyses were examined to assess the effect of changing several key parameters simultaneously. All analyses were repeated after recalibrating survival using observed within-trial experience of the U.S. clopidogrel cohort.

For each scenario, sampling uncertainty was characterized using nonparametric bootstrap techniques, resampling 1,000 times with replacement. In scenarios using U.S. low-dose costs, the joint distribution of costs and effects was preserved to the extent possible by stratifying bootstrap sampling by region (U.S. low-dose vs. rest of world) and then combining the 2 subsamples to create an overall sample for each bootstrap repetition. Confidence intervals were calculated for differences in cost and effects using the

TABLE 2 Within-Trial Use of Resources for U.S. Low-Dose Cohort*

Parameter	Ticagrelor Group (n = 284)	Clopidogrel Group (n = 263)	Difference†	p Value
Index				
Days‡	3.95 ± 3.28 (2,3,4)	4.10 ± 3.52 (2,3,4)	−0.15	0.59
PCI	60.6%	59.7%	0.9%	0.84
CABG	10.6%	11.0%	−0.4%	0.86
Follow-up				
Hospitalizations	0.59 ± 0.99 (0,0,1)	0.60 ± 0.95 (0,0,1)	−0.01	0.47
Ward days	2.26 ± 4.88 (0,0,2)	2.69 ± 6.82 (0,0,3)	−0.43	0.43
Intensive care§	0.34 ± 1.49 (0,0,0)	0.34 ± 1.59 (0,0,0)	0	0.80
CCU days	0.19 ± 0.84 (0,0,0)	0.22 ± 1.39 (0,0,0)	−0.03	0.98
ICU days	0.15 ± 1.04 (0,0,0)	0.12 ± 0.66 (0,0,0)	+0.03	0.99
PCI	12.7%	10.7%	2.0%	0.46
CABG	1.4%	1.9%	−0.5%	0.65

Values are mean ± SD, %, or mean ± SD (25th, 50th, 75th percentiles). *Observed data in PLATO (6 to 12 months of follow-up). †Ticagrelor group minus clopidogrel group. ‡For costing purposes, the first 2 days were assumed to be in the CCU, with the remainder in the cardiology ward. §Intensive care days were assigned to CCU or ICU based on final discharge diagnoses and procedures.

CCU = coronary care unit; ICU = intensive care unit; other abbreviations as shown in Table 1.

TABLE 3 Cumulative 1-Year Within-Trial Costs for U.S. Low-Dose Cohort*

Cost	Ticagrelor Group (n = 284)	Clopidogrel Group (n = 263)	Difference (95% CI)†	p Value
Medical costs (observed)	29,223 (26,655–31,790)	30,716 (27,155–34,277)	−1,493 (−5,884 to 2,897)	0.50
Medical costs (Winsorized)	29,191 (26,648–31,735)	29,907 (26,999–32,815)	−716 (−4,579 to 3,147)	0.72
Study drug	2,204 (2,072–2,336)	32 (30–34)	2,172 (2,040 to 2,304)	<0.001
Total (Winsorized)	31,395 (28,848–33,942)	29,939 (27,031–32,847)	1456 (−2410 to 5,322)	0.46

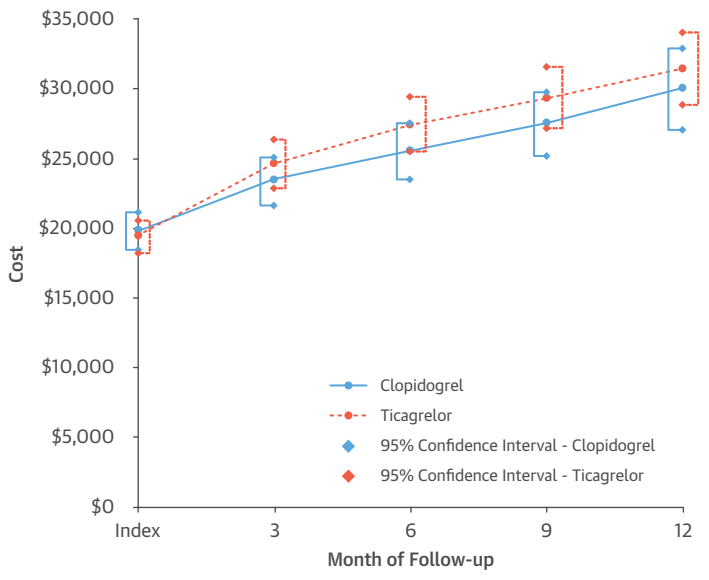
Values are mean (95% confidence interval). *One-year estimates were derived using inverse probability weighting. †Ticagrelor group minus clopidogrel group.

normal approximation, with standard errors estimated from the bootstrap. Incremental cost effectiveness was examined graphically on the cost-effectiveness plane and summarized using cost-effectiveness acceptability curves (23). All costs were expressed in 2013 dollars. Analyses were performed using SAS version 9.3 software (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS. A comparison of baseline characteristics of U.S. and non-U.S. patients enrolled in PLATO has been published (5). Compared to the non-U.S. cohort, U.S. patients had a less favorable risk profile, with higher rates of diabetes (33% vs. 24%, respectively), chronic obstructive pulmonary disease (13% vs. 5%, respectively), previous MI (27% vs. 20%, respectively), dyslipidemia (68% vs. 45%, respectively), non-ST-segment elevation myocardial infarction (NSTEMI) presentation (67% vs. 41%, respectively), and previous revascularization (29% vs. 12% PCI, respectively; 17% vs. 5% bypass surgery, respectively; all $p < 0.001$). However, within the U.S. cohort, characteristics of patients receiving low-dose aspirin were very similar to those receiving high-dose aspirin (Table 1). Minor differences included a higher proportion of females and higher rates of NSTEMI presentation, congestive heart failure, and hypertension in low-dose aspirin patients. Within the low-dose U.S. cohort, baseline risk was balanced between treatments (Table 1).

FIGURE 1 1-Year Cumulative Within-Trial Costs



Incorporating study drug and Winsorized health care costs, treatment groups are compared through 1 year of treatment for the U.S. low-dose aspirin cohort. **Brackets** are confidence intervals.

WITHIN-TRIAL CONSUMPTION AND COST OF MEDICAL RESOURCES. Resource use during the index hospitalization in the ticagrelor arm was similar to that in the clopidogrel arm, with an average length of stay of 3.95 versus 4.10 days, respectively, and ~70% of patients undergoing revascularization (Table 2). The average number of readmissions did not differ by treatment (0.59 vs. 0.60, respectively). Although the number of nonintensive care days during follow-up was slightly lower in the ticagrelor group (mean = 2.26 vs. 2.69, respectively; $p = 0.43$), days in intensive care and revascularizations were similar (Table 2) (detailed resource use counts are shown in Online Table 2). The small differences in length of stay led to slightly lower but statistically similar cumulative costs at 1 year (Table 3) (Winsorized difference = −$716, 95% confidence interval [CI]: −$4,579 to $3,147; $p = 0.72$). When antiplatelet therapy costs were included, cumulative within-trial costs were slightly higher with ticagrelor ($31,395 vs. $29,939, respectively; $p = 0.46$) (Figure 1).

LIFE EXPECTANCY AND QOL. The lifetime extrapolation model yielded undiscounted life expectancy estimates of 16.60 (95% CI: 16.47 to 16.73) and 16.38 (95% CI: 16.25 to 16.52) years in the ticagrelor and clopidogrel groups, respectively. After discounting

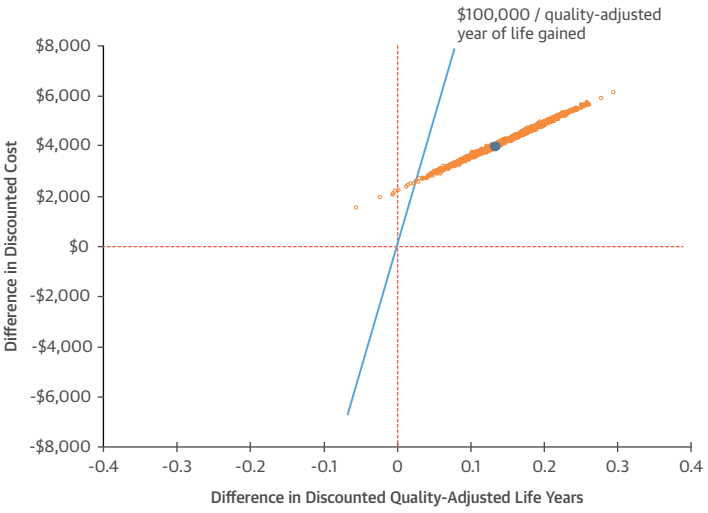
at 3% annually, average life expectancy with ticagrelor exceeded that with clopidogrel by 0.16 years (95% CI: 0.05 to 0.27; p = 0.004; ticagrelor = 12.06, clopidogrel = 11.90). QOL as measured by patients' last EQ-5D score averaged 0.886 (n = 15,713). EQ-5D scores decreased with age (mean values by age group were <45 = 0.930; 45 to 54 years = 0.907; 55 to 64 years = 0.900; 65 to 75 years = 0.876; 75 to 84 years = 0.836; and ≥85 years = 0.799). Adjusting survival for QOL reduced gains to 0.137 years (95% CI: 0.038 to 0.236; p = 0.007; ticagrelor = 10.44, clopidogrel = 10.30) (Online Table 3).

LIFETIME COSTS AND COST EFFECTIVENESS. Based on 2008 Medical Expenditure Panel Survey data, total annual medical expenditures for patients with coronary disease (inpatient, outpatient, and medications) averaged $12,376. Projected lifetime costs (excluding study drug) averaged $1,863 more with ticagrelor than clopidogrel ($137,279 vs. $135,417; p = 0.006). Incorporating the incremental cost of study drug ($2,195) yielded a total incremental lifetime cost of $4,058 for ticagrelor compared to clopidogrel.

Under base case assumptions, ticagrelor's additional cost, relative to generic clopidogrel, was $29,665/quality-adjusted year of life (QALY) gained with a 98.7% likelihood of being cost effective at a willingness-to-pay threshold of $100,000 (Online Table 3). Variation in life expectancy and related chronic medical costs, along with minor variation in days taking study drug, created some uncertainty around this estimate (**Figure 2**). Cost effectiveness of ticagrelor improved slightly when the QOL adjustment was removed (ICER = $25,457/life-year gained) and when the annual cost of medical care beyond the trial was excluded (ICER = $16,050/QALY gained) (**Figure 3**). Increasing the average cost of clopidogrel toward the proprietary cost ($6/day) improved the cost-effectiveness profile of ticagrelor, with the ICER falling to $17,288 and a 99% likelihood of meeting a $100,000 threshold (Online Table 3). Varying the discount rate within accepted ranges (0% and 6%) caused minimal changes to cost effectiveness (**Figure 3**). When the lifetime horizon was limited to 5 years, the ICER increased to $58,049 but met a $100,000 threshold with near certainty (Online Table 3). Only in the most extreme scenario, which assumed that reductions in mortality observed in PLATO did not produce additional life expectancy beyond 1 year, was ticagrelor unlikely to be cost effective (ICER = $268,881/QALY gained). Cost effectiveness was reasonably consistent in subgroups examined, in keeping with the absence of interactions between treatment and baseline risk (**Table 4**) (3). ICERs varied with differences among subgroups in absolute within-trial mortality risk and life expectancy projections.

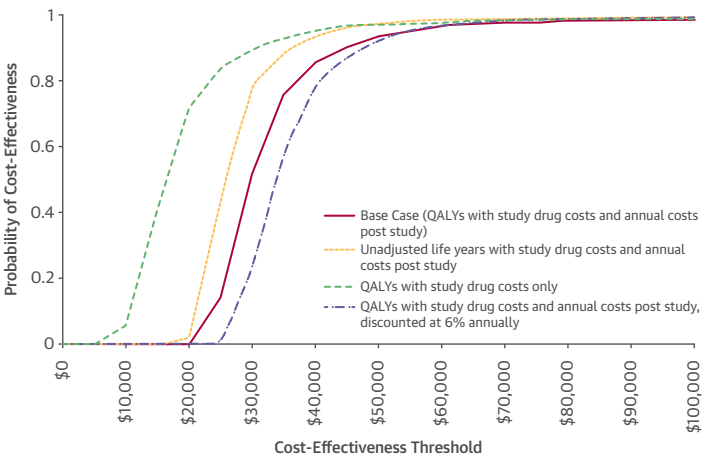
Incorporating within-trial costs in the analysis reduced incremental cost to $3,319 but increased uncertainty considerably (**Figure 4**), with little net effect on the likelihood of meeting a $100,000

FIGURE 2 Distribution of Lifetime Incremental Cost and Effectiveness: Base Case



Base scenario includes study drug costs, annual post-study costs, and quality-adjusted life years. Point estimate is represented by **solid blue circle**. Differences = ticagrelor minus clopidogrel.

FIGURE 3 Cost-Effectiveness Acceptability Curves Excluding Within-Trial Cost Offset



Scenarios illustrate effects of varying estimates of cost and life years on cost effectiveness of ticagrelor versus clopidogrel, assuming no within-trial cost offset.

TABLE 4 Lifetime Cost and Cost Effectiveness in Overall Cohort by Subgroup*

Subgroup	Sample Size T	Sample Size C	QALYs† T	QALYs† C	Difference in QALYs (95% CI)‡	Cost† T	Cost† C	Difference in Cost (95% CI)‡	ICER	ICER <$100,000§
Diabetes										
Yes	2,326	2,336	8.2	8.1	0.11 (−0.06 to 0.27)	$108,007	$104,587	$3,420 ($1,181 to $5,659)	$32,145	83.5
No	6,999	6,952	11.2	11.0	0.14 (0.03 to 0.25)	$149,948	$145,821	$4,127 ($2,690 to $5,563)	$30,189	97.3
ACS type										
STEMI	3,496	3,530	11.5	11.4	0.09 (−0.07 to 0.24)	$153,558	$150,019	$3,539 ($1,522 to $5,556)	$40,816	79.2
NSTEMI	4,005	3,950	9.8	9.6	0.17 (0.02 to 0.31)	$130,572	$126,187	$4,385 ($2,427 to $6,342)	$26,245	97.3
Treatment plan										
Invasive	6,732	6,676	10.9	10.7	0.16 (0.05 to 0.27)	$145,261	$140,947	$4,314 ($2,826 to $5,802)	$27,331	98.7
Medical	2,601	2,615	9.3	9.3	0.07 (−0.12 to 0.25)	$124,612	$121,411	$3,201 ($734 to $5,668)	$47,068	67.9
Age, yrs										
<65	5,311	5,334	12.5	12.4	0.09 (0.01 to 0.18)	$166,345	$162,808	$3,537 ($2,333 to $4,741)	$37,236	92.8
65–74	2,626	2,475	8.7	8.5	0.18 (0.08 to 0.28)	$117,849	$113,221	$4,628 ($3,117 to $6,140)	$25,721	99.8
≥75	1,396	1,482	5.7	5.6	0.15 (0.04 to 0.27)	$78,139	$74,096	$4,043 ($2,297 to $5,789)	$26,274	98.9

*Subgroup analyses mirror the base case and exclude within-trial health care costs. †Mean values. ‡Mean differences of ticagrelor group minus clopidogrel group. §Percentage of 1,000 bootstrap samples. C = clopidogrel; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; T = ticagrelor; other abbreviations as in Table 1.

threshold (Figure 5). Similarly, increasing (or decreasing) unit costs and associated cost offset reduced (or increased) both the ICER estimate and its precision, leaving the likelihood of satisfying a $100,000 threshold virtually unchanged (Figure 5). When Winsorized values were replaced by observed costs, the within-trial offset increased 50% to $1,494, reducing incremental cost to $2,541 and improving the ICER to $18,576/QALY gained, with a 98% likelihood of satisfying a willingness-to-pay threshold of $100,000 (Figure 5).

FIGURE 4 Distribution of Lifetime Incremental Cost and Effectiveness, Including Within-Trial Cost Offset

Winsorized within-trial health care costs are added to the base scenario. Point estimate is represented by **solid blue circle**; differences = ticagrelor minus clopidogrel.

To address concerns that the clinical effect achievable in the United States may be overestimated by the overall PLATO result, we repeated our analysis after recalibrating survival projections to reflect the lower mortality observed in the U.S. clopidogrel group. In that scenario, the incremental benefit fell from 0.14 to 0.10 QALYs, resulting in an ICER of $36,507 and a 92% likelihood of meeting a $100,000 threshold (Figure 6). When the within-trial cost offset was incorporated, or costs in additional years of life were excluded, the estimated ICER improved considerably, although the likelihood of satisfying a willingness-to-pay threshold of $100,000 fell with inclusion of the cost offset due to the underlying uncertainty (Figure 6). Results of all sensitivity analyses are presented in Online Table 3 and summarized in the Central Illustration.

DISCUSSION

Our analysis suggests that relative to the established DAPT regimen of clopidogrel plus aspirin, ticagrelor plus low-dose aspirin increases life expectancy in ACS patients at an additional cost that compares favorably with accepted benchmarks for U.S. medical interventions. These findings rest entirely on the mortality reduction observed in PLATO. In keeping with the FDA approval of ticagrelor, we have assumed that the relative reduction in mortality risk observed in PLATO can be obtained in the United States in the context of low-dose aspirin therapy. Rejection of this premise (and

acceptance of the observed lack of treatment effect in the small U.S. subgroup) would render the issue of cost effectiveness moot.

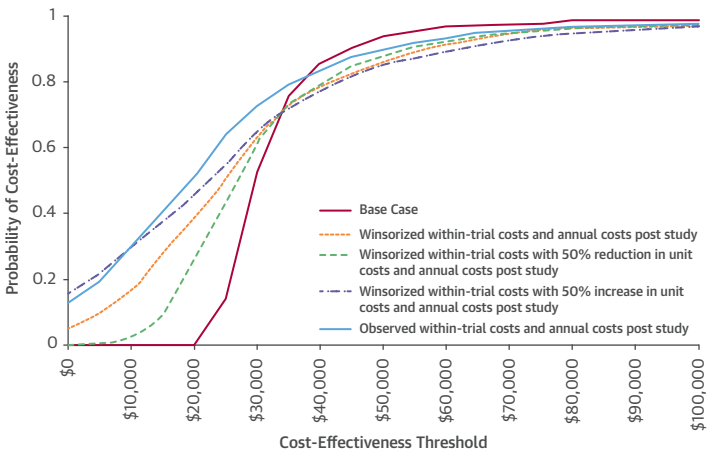
Our primary results are based on a conservative scenario that included: 1) no mortality benefit from reductions in nonfatal MI beyond that observed in PLATO; 2) no reduction in health care costs during treatment with ticagrelor; 3) a comprehensive estimate of costs in years of life gained with ticagrelor; and 4) use of generic clopidogrel only. Relaxing these assumptions improved the value of ticagrelor. Ticagrelor therapy remained cost effective after recalibrating the underlying mortality risk to reflect the U.S. PLATO clopidogrel cohort's experience. Only when the time horizon over which benefits and costs accrued was limited to the short term did the cost effectiveness of ticagrelor appear unlikely.

Economic analyses of PLATO data from a European perspective have estimated cost-effectiveness ratios for ticagrelor (versus clopidogrel) in the range of $4,000 to $6,000/QALY gained (24,25). These more favorable findings stem primarily from the lower incremental cost of ticagrelor in Europe (30% of U.S. costs), substantially lower estimates of medical costs after trial follow-up, and the small but significant reduction in intensive care days observed with ticagrelor among non-U.S. PLATO patients. A recent literature-based decision analysis from a U.S. perspective of DAPT after PCI in ACS patients estimated an ICER for ticagrelor (relative to clopidogrel) of $40,270/QALY gained (26).

An alternative thienopyridine, prasugrel, was reported to be a dominant strategy relative to clopidogrel in an ACS PCI population, with a cost offset of $221 and incremental life expectancy of 0.102 years (27). However, when availability of generic clopidogrel was assumed ($1/day) and costs in extended years of life included, the ICER rose to $14,655/life-year gained (2005 dollars). In contrast to our study, these estimates were predicated on extrapolating survival benefits from nonfatal events avoided during treatment. However, results of the 2 studies are not directly comparable given differences in the target population and higher underlying mortality rates in PLATO (5.9% vs. 3.2% in the clopidogrel arm) (28).

Although our analyses showed ticagrelor to be a cost-effective treatment relative to clopidogrel in the U.S. setting (**Central Illustration**), the financial impact on pharmacy budgets of widespread adoption of the new therapy at the current price could still be substantial. Furthermore, in the current fragmented, multi-payer environment, those funding the medication may differ from those who recoup any potential cost offsets.

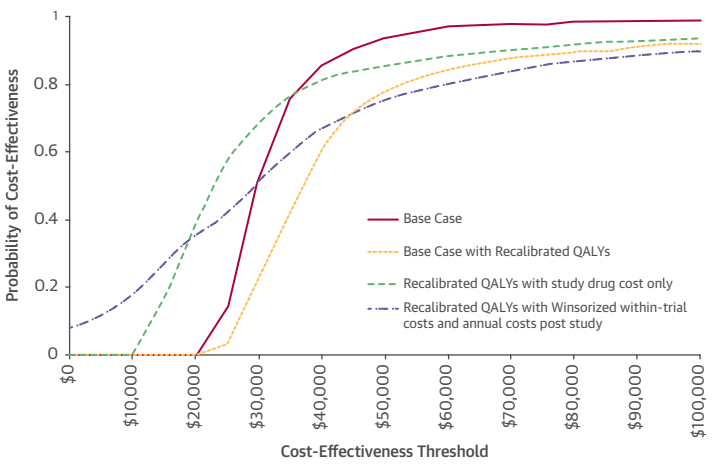
FIGURE 5 Cost-Effectiveness Acceptability Curves Including Within-Trial Cost Offset



Scenarios illustrate effects of varying estimates of within-trial costs on cost effectiveness of ticagrelor versus clopidogrel for scenarios that include within-trial cost offset. Effectiveness measure is quality-adjusted life-years.

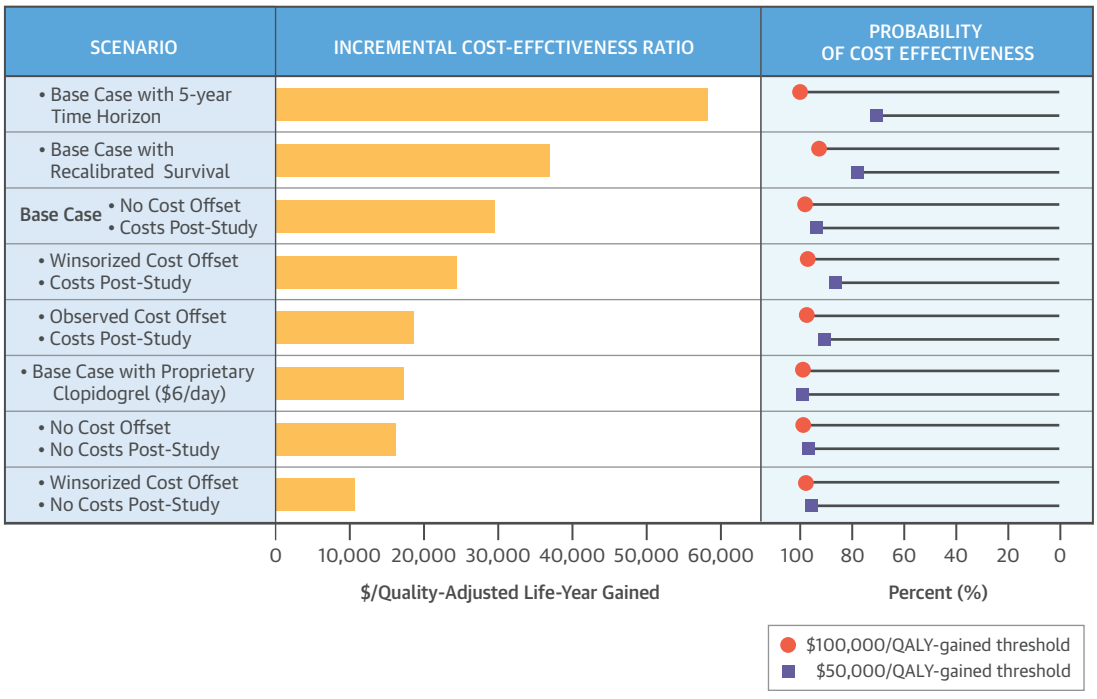
STUDY LIMITATIONS. First, lower U.S. enrollment than anticipated, together with an unexpected region-treatment interaction and consequent FDA recommendation to use ticagrelor only with low-dose aspirin, produced a small sample size with which to estimate U.S. resource use and costs. Given the

FIGURE 6 Cost-Effectiveness Acceptability Curves: Recalibrated Effectiveness



Scenarios illustrate effects of varying estimates of cost on cost effectiveness with recalibrated survival.

CENTRAL ILLUSTRATION **U.S. Economic Analysis of Ticagrelor Therapy in Patients With Acute Coronary Syndrome**



Cowper, P.A. et al. J Am Coll Cardiol. 2015; 65(5):465–76.

The incremental cost-effectiveness ratio (ICER) and probability of meeting willingness-to-pay thresholds of $50,000 and $100,000/quality-adjusted life-year are shown for the base case and for key alternative scenarios. Scenarios are ordered by ICER. Cost offset refers to within-trial costs.

significant differences observed in resource use between the United States and elsewhere (hospital days of 6.8 vs. 12.7, respectively; overall trial resource use is shown in Online Table 4), we felt that dealing with sampling uncertainty was preferable to estimating cost with resource use inconsistent with U.S. practice patterns. Second, use of a trial subset to estimate incremental cost in analyses that incorporated within-trial costs limited the extent to which the joint distribution between costs and effects was reflected in the cost-effectiveness results. Third, to the extent that the underlying U.S. mortality rate is less than that in the PLATO clopidogrel cohort, absolute benefits attainable in the United States may have been overestimated. However, cost effectiveness was maintained when underlying mortality risk was recalibrated. Fourth, because empirical cost data were not collected in PLATO, an analysis from the U.S. perspective required that health services be valued with externally derived unit costs. Although unit cost estimates were based on experience at one institution, they were estimated using actual cost data (not reimbursement or charges) and were internally consistent. Overall conclusions were unchanged with wide variations in unit costs. Fifth, evaluating an intervention's cost effectiveness requires extrapolation of survival beyond trial follow-up. Although our survival models were developed using an ACS dataset that excluded those presenting with STEMI, patients with a history of MI were included, resulting in a broad mix of ACS patients upon which to base long-term projections. Our estimates of life expectancy are similar to those developed independently for a European economic evaluation of ticagrelor (24). Sixth, as with most trial-based economic evaluations of new therapies, little information was available regarding long-term efficacy and cost. We assumed therapy would be discontinued at 12 months, but that treatment-related survival advantages achieved during the first year would

persist. Only when the time horizon was limited to the short term was the cost effectiveness of ticagrelor jeopardized. Seventh, analyses of cost effectiveness in patient subgroups were not designed a priori and should be considered exploratory. Finally, while prasugrel is now a relevant treatment alternative for ACS patients, it was beyond this paper's scope to assess ticagrelor's cost effectiveness relative to this new therapeutic option.

CONCLUSIONS

Ticagrelor therapy for PLATO-eligible ACS patients, in combination with low-dose aspirin, is economically attractive relative to clopidogrel from the perspective of the U.S. health care system under a wide range of assumptions regarding health care costs and mortality benefit.

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PERSPECTIVES

COMPETENCY IN SYSTEMS-BASED PRACTICE: In patients hospitalized with ACS, treatment with ticagrelor plus low-dose aspirin for 1 year, instead of clopidogrel and aspirin, improved life expectancy at an additional cost that falls within accepted benchmarks for value in the U.S. health care system.

TRANSLATIONAL OUTLOOK: Collection of economic data as part of long-term follow-up of ACS patients managed with dual antiplatelet therapy in community practice in the United States could enhance understanding of the relative value of alternative treatment options.

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KEY WORDS acute coronary syndrome(s), antiplatelet therapy, clopidogrel, cost effectiveness, ticagrelor

APPENDIX For supplemental tables, please see the online version of this article.