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Cost-Effectiveness of Long-Term Ticagrelor in Patients With Prior Myocardial Infarction

Results From the PEGASUS-TIMI 54 Trial

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ABSTRACT

BACKGROUND In patients with a myocardial infarction (MI) 1 to 3 years earlier, treatment with ticagrelor + low-dose aspirin (ASA) reduces the risk of cardiovascular (CV) death, MI, or stroke compared with low-dose aspirin alone, but at an increased risk of major bleeding.

OBJECTIVES The authors evaluated cost-effectiveness of ticagrelor + low-dose ASA in patients with prior MI within the prior 3 years.

METHODS The authors performed a prospective economic substudy alongside the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis In Myocardial Infarction 54) trial, which randomized 21,162 patients to ASA alone, ticagrelor 60 mg twice daily + low-dose ASA, or ticagrelor 90 mg twice daily + low-dose ASA. Medical resource use data were collected over a median 33-month follow-up. Costs were assessed from the U.S. health care system perspective. In-trial data relating to survival, utility, and costs were combined with lifetime projections to evaluate lifetime cost-effectiveness of the Food and Drug Administration–approved lower-dose ticagrelor regimen (60 mg twice daily).

RESULTS Hospitalization costs were similar for ticagrelor 60 mg and placebo ($2,262 vs. $2,333; 95% confidence interval for difference −$303 to $163; $p = 0.54$); after inclusion of a daily ticagrelor 60 mg cost of $10.52, total costs were higher for ticagrelor ($10,016 vs. $2,333; 95% CI: $7,441 to $7,930; $p < 0.001$). In-trial quality-adjusted life-years (QALYs) were similar (2.28 vs. 2.27; $p = 0.34$). Over a lifetime horizon, ticagrelor was associated with QALY gains of 0.078 and incremental costs of $7,435, yielding an incremental cost-effectiveness ratio (ICER) of $94,917/QALY gained. Several high-risk groups had more favorable ICERs, including patients with >1 prior MI, multivessel disease, diabetes, renal dysfunction (all with ICERs $50,000 to $70,000/QALY gained), patients age <75 years (ICER = $44,779/QALY gained), and patients with peripheral artery disease (ICER = $13,427/QALY gained).

CONCLUSIONS For patients with a history of MI >1 year previously, long-term treatment with ticagrelor 60 mg + low-dose ASA yields a cost-effectiveness ratio suggesting intermediate value based on current guidelines. Ticagrelor appears to provide higher value for patients in several recognized high-risk subgroups. (Prevention of Cardiovascular Events [e.g., Death From Heart or Vascular Disease, Heart Attack, or Stroke] in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin [PEGASUS]; NCT01225562)
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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

ASA = aspirin

CI = confidence interval

CV = cardiovascular

EQ-5D = EuroQOL-5D health status instrument

HR = hazard ratio

ICER = incremental cost-effectiveness ratio

MI = myocardial infarction

MS-DRG = Medicare Severity Diagnosis Related Group

PAD = peripheral artery disease

PCI = percutaneous coronary intervention

QALY = quality-adjusted life-year

Despite treatment with multiple evidence-based therapies (1–3), patients with a history of myocardial infarction (MI) remain at long-term elevated risk for ischemic events that are associated with reduced long-term survival (4,5) and substantial health care costs (6). Numerous studies have demonstrated the benefit of dual antiplatelet therapy for the prevention of ischemic cardiovascular (CV) events in the first year after an MI (7–9), and cost-effectiveness studies carried out alongside pivotal trials have demonstrated the economic value of dual antiplatelet therapy during this time period (5,10–12).

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More recently, several studies have demonstrated the benefit of extended dual antiplatelet therapy beyond 1 year in patients with a prior MI (13–15). In the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) trial, treatment with ticagrelor at doses of both 60 mg and 90 mg twice daily in addition to low-dose aspirin (ASA) was shown to reduce the risk of the primary efficacy endpoint of CV death, MI or stroke compared with low-dose ASA alone (13). Although both ticagrelor doses reduced the rate of the primary composite efficacy endpoint to a similar extent, the rates of both bleeding and dyspnea, and associated discontinuation of ticagrelor, were lower with the 60-mg dose. As a result, the 60-mg dose was approved by the U.S. Food and Drug Administration for the long-term prevention of ischemic events in patients with a history of myocardial infarction. Whether ticagrelor 60 mg twice daily provides meaningful health benefits at an acceptable cost is unknown, and is critically important for health policy, given the relatively large population who might be candidates for this therapy. We therefore performed a prospective health economic evaluation alongside the PEGASUS-TIMI 54 trial to examine the

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cost-effectiveness of ticagrelor 60 mg twice daily versus placebo from the perspective of the U.S. health care system.

METHODS

The PEGASUS-TIMI 54 trial was a randomized, double-blind, placebo-controlled trial of patients from 31 countries who had a spontaneous myocardial infarction 1 to 3 years before enrollment, and were at least 50 years of age with at least 1 additional characteristic putting them at high risk of a major ischemic event (16,17). Patients were assigned in a 1:1:1 ratio to ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily, or placebo, and followed for a median of 33 months. This economic analysis was restricted to the Food and Drug Administration-approved lower-dose ticagrelor regimen (60 mg twice daily, hereafter referred to as ticagrelor).

HEALTH CARE RESOURCE USE AND COSTS. Resource utilization data relating to hospitalizations were collected prospectively for all patients in the PEGASUS-TIMI 54 trial. Each hospitalization for a CV, bleeding, or pulmonary condition was assigned a U.S. Medicare Severity Diagnosis Related Group (MS-DRG) on the basis of diagnoses, major clinical events and complications, and procedures performed; all assignments were based on computer algorithms in combination with review by a team of clinicians/coders who were blinded to treatment assignment. Each hospitalization was then assigned a cost based on average Medicare payments for the specific MS-DRG. Physician costs associated with hospital care (e.g., daily care, procedures) were estimated as 20% of hospital costs.

Ticagrelor was assigned a cost of $10.52 per day, based on the wholesale acquisition cost in the United States; this cost was assigned based on actual daily study drug exposure reported at each follow-up assessment. Utilization of other CV medications was similar for ticagrelor and placebo; costs of nonstudy drug medications were therefore excluded from the analysis. All costs were assessed in constant-year U.S. dollars on the basis of 2014 CMS reimbursement rates inflated to 2016 using the medical care component of the Consumer Price Index and current costs for study medications at the time of the analysis.

QUALITY OF LIFE. The EuroQOL health status instrument (EQ-5D) was used to assess quality of life for each study patient at baseline, 8, 12, 18, 24, 30, and 36 months after randomization. Health utility weights (range 0 to 1, higher = better health) were obtained from the EQ-5D data using an algorithm developed from the U.S. population (18).

TABLE 1 Baseline Characteristics for the Economic Study Population

	Ticagrelor (n = 7,040)	Placebo (n = 7,067)	p Value
Sociodemographic characteristics			
Age, yrs	65.6 ± 8.4	65.9 ± 8.3	0.073
Male	5,380 (76.4)	5,350 (75.7)	0.318
White race	6,073 (86.3)	6,124 (86.7)	0.496
Enrolling country			
United States	861 (12.2)	872 (12.3)	0.843
Rest of world	6,179 (87.8)	6,195 (87.7)	
Clinical characteristics			
Hypertension	5,457 (77.5)	5,484 (77.6)	0.915
Hypercholesterolemia	5,378 (76.4)	5,451 (77.1)	0.304
Current smoker	1,205 (17.1)	1,143 (16.2)	0.132
Diabetes mellitus	2,308 (32.8)	2,257 (31.9)	0.282
Multivessel coronary artery disease	4,186 (59.5)	4,213 (59.6)	0.851
History of PCI	5,871 (83.4)	5,835 (82.6)	0.190
>1 previous myocardial infarction	1,166 (16.6)	1,188 (16.8)	0.692
Peripheral vascular disease	367 (5.2)	404 (5.7)	0.188
Years since myocardial infarction	1.71	1.72	0.254

Values are mean ± SD, n (%), or median.
PCI = percutaneous coronary intervention.

STATISTICAL ANALYSIS: IN-TRIAL ANALYSIS. For the purposes of the economic analysis, patients were categorized according to their assigned treatment. Categorical data are reported as frequencies, and continuous data are reported as mean ± SD. Discrete variables were compared using the Fisher exact test. Normally distributed continuous variables were compared using the Student *t* test, and non-normally distributed data were compared using the Wilcoxon rank sum test. Hospitalization rates were compared using Poisson regression models. Three-year clinical event rates were calculated using the Kaplan-Meier method, and hazard ratios and associated 95% confidence intervals (CIs) were obtained using Cox proportional hazards regression. Cost data are reported as both mean and median values, and CIs

TABLE 2 Primary Clinical Efficacy and Safety Endpoints for the Economic Study Population

	Kaplan-Meier Rates at 36 Months, %				
	Ticagrelor	Placebo	HR	95% CI	p Value
CV death, MI, stroke	7.8	9.0	0.84	0.74–0.95	0.004
CV death	2.9	3.4	0.83	0.68–1.01	0.07
MI	4.5	5.2	0.84	0.72–0.98	0.03
Stroke	1.5	1.9	0.75	0.57–0.98	0.03
TIMI major bleeding	2.3	1.1	2.32	1.68–3.21	<0.001

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; TIMI = Thrombosis In Myocardial Infarction.

TABLE 3 Follow-Up Hospitalizations and Costs

Reason for Hospitalization	Frequency		Cost per Patient per Year ($)		
	Ticagrelor, n	Placebo, n	Ticagrelor	Placebo	Overall Δ*
Cardiac					
Acute MI	108	133	25.13	31.17	Δ cardiac costs −$35.65 (−$123.14 to $53.41)
AICD lead/generator procedures	1	0	2.57	0.00	
Angina	137	150	17.78	19.21	
Arrhythmia	152	116	22.29	16.69	
Atherosclerosis	24	39	4.06	6.58	
CABG	62	65	80.61	95.92	
Cardiac arrest	6	6	0.87	1.03	
Cardiac cath without acute MI	233	261	71.40	81.47	
Chest pain	119	105	15.19	14.19	
Defibrillator implant	26	22	42.51	34.80	
Heart failure/shock	146	130	31.90	29.75	
Hypertension	26	25	4.58	4.51	
Major CV procedures	7	3	8.00	2.98	
Other circulatory diagnoses	15	16	3.03	3.47	
Pacemaker replacement/revision	37	28	21.99	16.68	
PCI, BMS	69	70	58.42	58.02	
PCI, DES	279	283	234.78	250.41	
Permanent pacemaker implant	1	1	0.46	0.55	
PTCA	64	90	56.76	74.01	
Syncope	36	32	7.83	6.13	
Valve disorders	6	8	1.63	2.09	
Valve procedures	9	6	15.89	13.68	
Peripheral vascular					
Amputation	1	1	0.29	0.37	Δ peripheral vascular costs −$14.23 (−$28.87 to $0.01)
Peripheral angioplasty/stenting	24	50	12.81	27.61	
Peripheral vascular disorders	52	53	11.51	11.88	
Pulmonary embolism	13	11	4.17	3.15	
Cerebrovascular					
Carotid endarterectomy	9	8	2.39	2.39	Δ cerebrovascular costs −$6.72 (−$-6.15 to $4.43)
Carotid stent	0	1	0.00	0.44	
ICH/stroke	95	116	24.36	27.91	
Ischemic stroke	1	0	0.59	0.00	
Nonspecific CV disorders	6	5	1.16	1.30	
Nonspecific CVA	4	6	1.14	1.49	
Stroke-related procedure	1	1	0.69	0.70	
TIA	21	36	4.11	6.93	
Non-ICH bleeding					
Bleed (typically GI) related anemia	2	1	0.52	0.25	Δ non-ICH bleeding costs $19.56 ($10.77 to $28.83)
Epistasis	12	0	2.61	0.00	
GI hemorrhage	117	64	28.32	14.73	
Hematoma	1	1	0.19	0.27	
Hematuria	15	2	3.21	0.36	
Hyphema	3	3	0.67	0.54	
Menorrhagia	1	2	0.12	0.25	
Spontaneous bleeding gums	1	0	0.19	0.00	
Spontaneous skin bleed/thrombocytopenia	1	1	0.86	0.73	

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for the differences in costs between treatment groups were obtained via bootstrapping (500 replicates) (19).

Quality-adjusted life expectancy during the trial period was estimated for each patient as the time-weighted average of his or her utility value, using the midpoint between assessments as the transition between health states. For the calculation of quality-adjusted life-years (QALYs), missing utility values for patients known to have been alive at follow-up time points were estimated using multiple imputation, with baseline patient characteristics, previous utility

TABLE 3 Continued

Reason for Hospitalization	Frequency		Cost per Patient per Year ($)		
	Ticagrelor, n	Placebo, n	Ticagrelor	Placebo	Overall Δ*
Pulmonary					
Bronchitis/asthma	2	5	0.32	0.79	Δ pulmonary costs $0.25 (−$7.69 to $8.72)
Chest/respiratory system procedures	2	3	0.71	1.77	
COPD	5	5	1.57	1.05	
Interstitial lung disease	3	2	0.65	0.72	
Other respiratory	2	4	1.73	2.26	
Pleural effusion	5	12	1.05	2.73	
Pneumothorax	6	7	1.11	1.27	
Pulmonary edema	7	8	3.44	2.91	
Respiratory signs/symptoms	20	12	4.44	2.27	
Simple pneumonia & pleurisy	8	8	2.46	1.47	
Total hospitalization costs			845.07	881.88	−$36.79
95% CI for the cost difference					(−$127.97 to $58.70)

*Ticagrelor − placebo.

AICD = automated implantable cardioverter-defibrillator; BMS = bare-metal stent; cath = catheterization; CABG = coronary artery bypass grafting; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; DES = drug-eluting stent; GI = gastrointestinal; ICH = intracranial hemorrhage; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; TIA = transient ischemic attack; other abbreviations as in Table 2.

values, and previous in-trial clinical events informing the imputation.

LIFETIME COST-EFFECTIVENESS. The cost-effectiveness of treatment for a median of 33 months with ticagrelor 60 mg versus placebo was assessed over a lifetime horizon from a modified societal perspective using both QALYs and life-years as measures of health benefit; the study protocol specified that the analysis based on QALYs would be considered the primary analysis, consistent with current U.S. guidelines (20). This analysis was based on a combination of observed data up to the common study end date, from which in-trial costs, life-years, and QALYs were estimated, and lifetime projections of patient-level costs, life expectancy, and quality-adjusted life expectancy obtained from a Markov disease-simulation model. In this model, each surviving patient was assumed to face a monthly risk of death, with estimates of this risk based upon age-, sex-, and race-matched risks of death obtained from U.S. life tables. Because of the sensitivity of estimates of the incremental life-years and QALYs gained to small differences in age and sex between the treatment groups, all projections were adjusted for differences between treatment groups in the age and sex of patients alive at the end of the trial.

In the base case analysis, for patients alive at the end of the trial who experienced an MI, stroke, or major bleed during the trial period, additional multiplicative factors were applied to the mortality probabilities in order to reflect the increased long-term hazard of death associated with these events. For patients who experienced an MI, this multiplier was based on the hazard ratio (HR) from a time-varying covariate Cox regression model examining the impact of having survived an in-trial MI for 30 days on longer-term survival during the course of the trial, adjusting for baseline factors (age, sex, race, >1 MI before enrollment, diabetes). Analogous models were developed for nonfatal stroke and major bleed.

Patient-level costs and utility weights applied to each projected year of life beyond the trial observation period were derived from regression models developed from the in-trial data (Online Tables 1 and 2). All projected life years, QALYs, and costs were discounted at 3% annually on the basis of time from randomization. Uncertainty in the joint distribution of lifetime costs, life-years, and QALYs for each treatment group was estimated by the bootstrap method. Sensitivity analyses examined the impact of alternative assumptions about the prognostic impact

TABLE 4 EQ-5D-Derived Utility Scores Over Time

Time Point	Ticagrelor	Placebo	p Value*
Baseline	0.880 ± 0.1323 (7,040)	0.880 ± 0.138 (7,067)	0.800
8 months	0.883 ± 0.135 (6,967)	0.882 ± 0.135 (6,988)	0.876
12 months	0.885 ± 0.132 (6,925)	0.884 ± 0.135 (6,940)	0.945
18 months	0.885 ± 0.130 (6,856)	0.885 ± 0.135 (6,855)	0.846
24 months	0.884 ± 0.133 (6,512)	0.884 ± 0.134 (6,541)	0.527
30 months	0.881 ± 0.135 (5,595)	0.881 ± 0.138 (5,667)	0.739
36 months	0.886 ± 0.134 (3,765)	0.884 ± 0.141 (3,883)	0.638

Values are mean ± SD (n). *p Value from analysis of covariance, adjusting for baseline utility.

EQ-5D = EuroQOL health status instrument.

TABLE 5 Lifetime Cost-Effectiveness Results for Base Case and Sensitivity Analyses

	Cost with TIC, $	Cost with Placebo, $	Δ Cost ($) (95% CI)	QALYs With TIC	QALYs With Placebo	Δ QALYs With T60 (95%CI)	ICER ($/QALY)	% Dominant	% Dominated	% <$50K	% $50K-$150K	% <$150K
Base case												
Long-term impact of nonfatal stroke/MI/major bleeding on survival (and utility), 3% discount	15,976	8,541	7,435 (7,137 to 7,670)	11.408	11.330	0.078 (0.001 to 0.149)	94,917	0.0	2.0	3.2	75.8	79.0
Sensitivity analyses												
No impact of nonfatal stroke or MI or Major bleeding on survival	16,233	8,822	7,410 (7,110 to 7,718)	11.579	11.497	0.082 (0.015 to 0.153)	90,090	0	1.0	3.8	79.2	83
No impact of nonfatal bleeding	16,008	8,552	7,455 (7,157 to 7,697)	11.454	11.347	0.1063 (0.029 to 0.182)	70,107	0.0	0.4	14.0	78.8	92.8
No discounting	19,277	11,669	7,608 (7,301 to 7,892)	16.005	15.876	0.130 (0.017 to 0.239)	58,538	0.0	1.4	37.2	55.0	92.2
Cost per life-year gained (no utility adjustment)	15,976	8,541	7,435 (7,137 to 7,670)	13.107	13.047	0.060 (−0.018 to 0.135)	123,612	0.0	7.2	0.8	60.4	61.2

ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life-years; TIC = ticagrelor; other abbreviations as in Table 2.

of in-trial events, discount rate, and ticagrelor costs on the results, and the base case analysis was repeated for clinically relevant pre-specified subgroups defined according to the presence/absence of the following high-risk characteristics: >1 prior MI, diabetes, multivessel disease, age ≥75 years, peripheral artery disease (PAD), and renal dysfunction at baseline (estimated glomerular filtration rate <60 ml/min/1.73 m^2 vs. ≥60 ml/min/1.73 m^2). In addition the analysis was carried out separately for patients with $P2Y_{12}$ discontinuation <1 month versus ≥1 month before randomization, and for patients enrolled at U.S. versus non-U.S. sites. All analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

PATIENT POPULATION AND CLINICAL OUTCOMES. A total of 7,045 and 7,067 patients were randomized to 60-mg ticagrelor and placebo, respectively (17). Five patients in the ticagrelor arm withdrew from the study on the day of randomization and were excluded from the economic study population. Mean [median] follow-up time was similar for the 2 treatment groups (placebo 975 [1,017] days; ticagrelor 977 [1,017] days). Baseline characteristics for patients in the economic study population are summarized in Table 1. There were no significant differences in any observed characteristics between the ticagrelor and placebo groups. Mean age was 66 years, 76% were male, 17% had >1 prior MI, and the median time since the qualifying MI was 1.7 years. A total of 1,733 patients (12%) were enrolled in the United States.

Results for the primary clinical efficacy and safety endpoints for the economic study population are summarized in Table 2. Compared with placebo, over the 33-month median treatment duration, ticagrelor was associated with a significant reduction in the risk of CV death, MI, or stroke (HR: 0.84; 95% CI: 0.74 to 0.95; p = 0.004), driven by similar relative reductions in the risk of each of the component endpoints: MI (HR: 0.84; 95% CI: 0.72 to 0.98; p = 0.03), stroke (HR: 0.75; 95% CI: 0.57 to 0.98; p = 0.03), CV death (HR: 0.83; 95% CI: 0.68 to 1.01; p = 0.07). There was a significant increase in the risk of TIMI major bleeding with ticagrelor (HR: 2.32; 95% CI: 1.68 to 3.21; p < 0.01).

RESOURCE UTILIZATION AND COSTS. Rates of rehospitalization within broad categories and specific MS-DRGs are summarized in Table 3. Over the 33-month treatment period, there was no difference between treatment groups in the rates of hospitalization either overall or within pre-specified categories (cardiac, peripheral vascular, cerebrovascular, and pulmonary) other than nonintracranial bleeding, for which costs were significantly higher with ticagrelor by $20 (95% CI: $11 to $29). Overall hospitalization costs were thus similar for the 2 treatment groups ($37 per patient per year lower with ticagrelor; 95% CI for difference: −$128 to $59; p = 0.41). Examination of the specific indications for hospitalization demonstrates that there were modest reductions in costs related to cardiac, peripheral vascular, and cerebrovascular disease. These savings were offset by higher costs due to bleeding, however. Costs associated with pulmonary-related hospitalizations were virtually identical for the 2 treatment groups.

Total hospitalization costs over the follow-up period were $2,262 per patient for ticagrelor versus $2,333 for placebo (95% CI for difference: −$303 to $163; p = 0.54); after inclusion of the cost of ticagrelor, total costs were higher for ticagrelor ($10,016 vs. $2,333; 95% CI for difference: $7,441 to $,7930; p < 0.001).

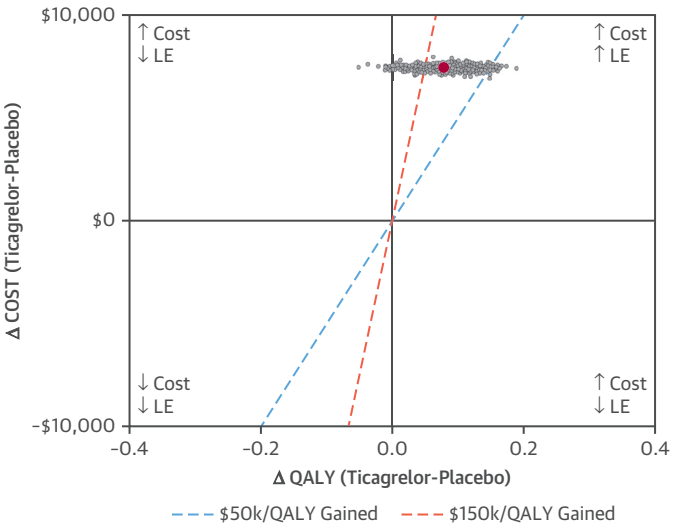
UTILITY WEIGHTS AND QALYs. EQ-5D-derived utility scores obtained at baseline and each follow-up assessment are summarized in Table 4. Mean baseline utility was 0.88 for both treatment groups, and remained stable throughout follow-up with no significant difference between groups at any time point. Cumulative QALYs over the trial period were similar for the ticagrelor and placebo groups (2.28 vs. 2.27; p = 0.34).

ESTIMATED PROGNOSTIC IMPACT OF NONFATAL EVENTS ON SURVIVAL. The estimated HRs for the impact of nonfatal MI, nonfatal stroke, and nonfatal major bleed events on survival within the trial were 2.8 (95% CI: 2.1 to 3.6), 3.4 (95% CI: 2.2 to 5.1), and 3.3 (95% CI: 2.2 to 4.9), respectively.

COST-EFFECTIVENESS. Lifetime cost-effectiveness results for the base case and sensitivity analyses are summarized in Table 5. For the base case analysis, which incorporated the estimated long-term impact of nonfatal MI, stroke, and major bleeding events on projected survival, ticagrelor was associated with lifetime incremental costs of $7,435 (95% CI: $7,137 to $7,670) and an increase in overall quality-adjusted life expectancy of 0.078 QALYs (95% CI: 0.001 to 0.149). The resulting incremental cost-effectiveness ratio (ICER) for ticagrelor versus placebo was $94,917/QALY gained, with 3.2% of bootstrap replicates below a societal willingness to pay threshold of $50,000/QALY gained and 79% below a threshold of $150,000/QALY gained (Figures 1 and 2, Table 5, row 1). In a sensitivity analysis that excluded the prognostic impact of nonfatal MI, stroke, and major bleed, the ICER was $90,090/QALY gained. When we excluded the estimated impact of a TIMI major bleed on long-term survival (while retaining the impact of nonfatal MI and stroke), the estimated ICER was $70,107/QALY gained. When outcomes were assessed in life years, ticagrelor was associated with a gain in life expectancy of 0.060 years and an associated ICER of $123,612/life-year gained (Table 5, Central Illustration). Not surprisingly, the cost effectiveness was sensitive to the acquisition cost of ticagrelor (Figure 2). At a price of $5.62/day, the ICER was $50,000/QALY gained.

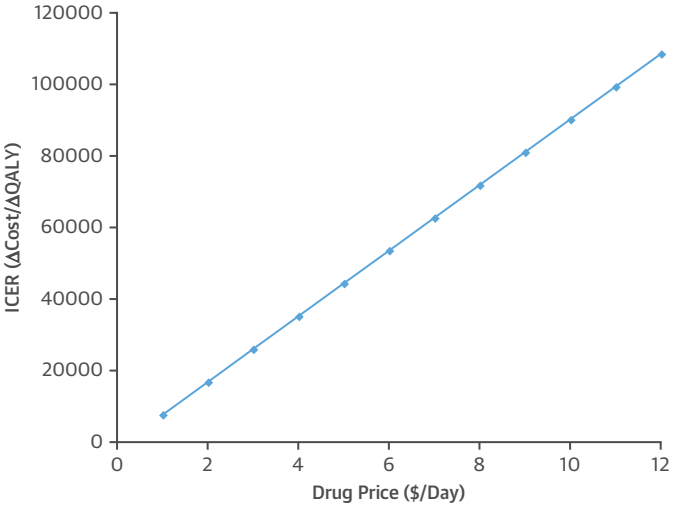
SUBGROUP ANALYSES. Results from subgroup analyses are summarized in Table 6. The ICER for

FIGURE 1 Joint Distribution of Projected Lifetime Incremental Costs and Quality-Adjusted Life Expectancy



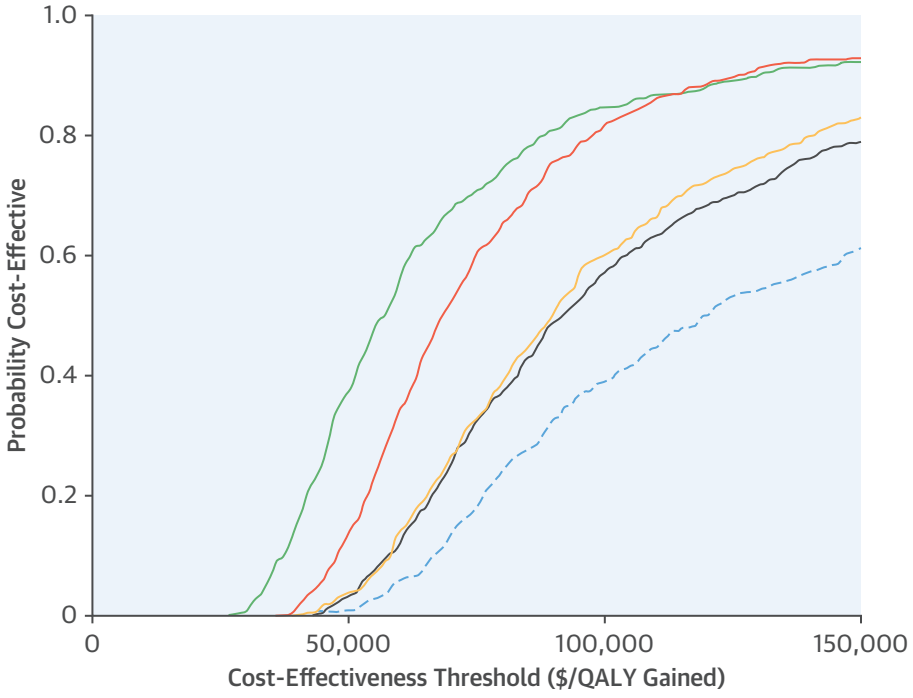
Joint distribution of projected lifetime incremental costs and quality-adjusted life expectancy for ticagrelor versus placebo is based on bootstrap replication of the PEGASUS-TIMI 54 trial population. The **red circle** represents the estimated mean values (incremental cost = $7,435, incremental QALYs = 0.078). The **dashed orange and blue lines** represent $150,000/QALY and $50,000/QALY cost-effectiveness thresholds. LE = life expectancy; PEGASUS-TIMI 54 = Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54; QALY = quality-adjust life-year.

FIGURE 2 ICER for Ticagrelor Versus Placebo as a Function of the Price of Ticagrelor



ICER = incremental cost-effectiveness ratio; QALY = quality-adjust life-year.

CENTRAL ILLUSTRATION **Cost-Effectiveness of Ticagrelor in Patients With Prior MI**



Magnuson, E.A. et al. J Am Coll Cardiol. 2017;70(5):527–38.

Cost-effectiveness acceptability curve of ticagrelor versus placebo, for the base case **(black line)** and sensitivity analyses: cost/life-year gained **(blue)**; no discounting **(green)**; no long-term impact of nonfatal MI, stroke, or major bleed on survival **(yellow)**; excluding estimated impact of TIMI major bleed on survival, including estimated impact of nonfatal MI and stroke **(orange)**. The probability that ticagrelor is cost-effective is calculated as the proportion of bootstrap-derived estimates falling below a given cost-effectiveness threshold, and is plotted across a range of possible cost-effectiveness thresholds. MI = myocardial infarction; QALY = quality-adjust life-year; TIMI = Thrombolysis In Myocardial Infarction.

ticagrelor versus placebo was <$50,000 for patients with PAD and for patients age <75 years at baseline, and between $50,000 and $60,000 for patients with diabetes or renal dysfunction (estimated glomerular filtration rate >60 ml/min/1.73 m^2), patients who were randomized within 30 days of $P2Y_{12}$ inhibitor withdrawal, and patients enrolled at U.S. sites. For patients with multivessel coronary artery disease and for patients with >1 prior MI, the ICER was <$70,000. For patients age ≥75 years, there was a predicted decrease in QALYs with ticagrelor in conjunction with an increase in costs, rendering ticagrelor a dominated treatment strategy.

DISCUSSION

The PEGASUS-TIMI 54 trial is the first study to demonstrate that dual antiplatelet therapy with ticagrelor + low-dose ASA results in improved CV outcomes compared with low-dose ASA alone for patients who are >1 year post MI. Results from this prospectively designed economic study carried out alongside the PEGASUS-TIMI 54 trial reveal that ticagrelor at a dose of 60 mg twice daily for up to 3 years in conjunction with low-dose ASA is associated with an increase in quality-adjusted life expectancy of 0.078 years (discounted), compared with ASA alone. These benefits are largely due to the combined impact of the absolute reduction in CV (and all-cause) mortality observed during the trial and the observed and projected impact of nonfatal MI and stroke events on long-term mortality and quality of life. Using the wholesale acquisition cost for ticagrelor of $10.52/day (assuming no manufacturer discounts or rebates) and discounting future costs and QALYs at 3% annually, we estimated that the lifetime ICER for ticagrelor versus placebo was $94,917/QALY gained—results that were robust in sensitivity analyses over a range of alternative assumptions. According to current American College of

TABLE 6 Lifetime Cost-Effectiveness Results for Subgroups

	Cost With TIC, $	Cost With Placebo, $	Δ Cost ($) (95% CI)	QALYs With TIC	QALYs With Placebo	Δ QALYs With TIC (95% CI)	ICER ($/QALY)	% Dominant	% Dominated	Prob. <$50K	Prob. < $150K
>1 prior MI	19,618	12,396	7,222 (6,362 to 8,000)	10.910	10.806	0.104 (−0.117 to 0.346)	69,537	0	17.0	40.0	69.6
1 prior MI	15,253	7,759	7,495 (7,202 to 7,767)	11.507	11.437	0.071 (−0.006 to 0.155)	106,366	0	3.8	2.8	70.0
Diabetes	17,287	9,969	7,317 (6,798 to 7,880)	11.496	11.351	0.145 (−0.005 to 0.304)	50,325	0	2.8	50.0	89.0
No diabetes	15,342	7,871	7,470 (7,179 to 7,771)	11.370	11.316	0.054 (−0.025 to 0.139)	137,384	0	10.2	1.4	53.4
Multivessel CAD	17,503	10,198	7,304 (6,938 to 7,734)	11.950	11.840	0.110 (0.009 to 0.199)	66,386	0	1.0	26.4	87.2
No multivessel CAD	13,715	6,079	7,636 (7,269 to 8,008)	10.608	10.576	0.033 (−0.097 to 0.161)	234,708	0	33.2	3.2	34.0
Age ≥75 yrs	12,318	5,452	6,866 (6,254 to 7,444)	6.847	6.865	−0.018 (−0.201 to 0.178)	dominated	0	59.0	5.6	23.8
Age <75 yrs	16,616	9,034	7,582 (7,273 to 7,919)	12.211	12.042	0.169 (0.049 to 0.281)	44,779	0	0.4	61.6	97.6
With PAD	23,566	16,435	7,130 (5,550 to 8,838)	10.184	9.653	0.531 (0.128 to 0.921)	13,427	0	0.8	97.0	99.0
No PAD	15,565	8,057	7,508 (7,230 to 7,766)	11.476	11.432	0.044 (−0.032 to 0.125)	169,772	0	13.4	0.2	44.4
$P2Y_{12}$ discontinued <1 month	16,795	9,402	7,393 (6,824 to 7,846)	11.6548	11.513	0.142 (0.018 to 0.271)	52,167	0	0.8	47.6	93.2
$P2Y_{12}$ discontinued ≥1 month	15,815	8,348	7,466 (7,101 to 7,862)	11.4111	11.391	0.021 (−0.084 to 0.123)	362,173	0	32.8	1.4	26.0
eGFR <60 ml/min/1.73 m^2	14,828	8,360	6,468 (5,870 to 7,051)	9.5573	9.434	0.123 (−0.062 to 0.312)	52,492	0	10.4	50.4	79.8
eGFR ≥60 ml/min/1.73 m^2	16,352	8,593	7,759 (7,464 to 8,103)	11.9501	11.909	0.041 (−0.039 to 0.122)	187,235	0	14.4	0.6	40.8
U.S.	17,320	10,397	6,923 (5,978 to 7,822)	11.4845	11.363	0.121 (−0.089 to 0.332)	57,004	0	13.4	46.0	76.2
Non-U.S.	15,789	8,281	7,508 (7,216 to 7,823)	11.3978	11.326	0.072 (−0.007 to 0.150)	103,988	0	4.4	2.6	69.2

CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; PAD = peripheral artery disease; other abbreviations as in Tables 2 and 5.

Cardiology/American Heart Association guidelines, ICERs <$50,000/QALY gained suggest high-value, ICERs between $50,000 and $150,000/QALY gained suggest intermediate-value, and ICERs >$150,000/QALY gained suggest low-value treatment strategies (21). The results of our patient-level economic study, therefore, suggest that ticagrelor + low-dose ASA provides intermediate value relative to ASA alone for patients who are >1 year post-MI.

Subgroup analyses revealed some heterogeneity in ICER estimates such that long-term ticagrelor yielded ICERs in the "high-value" (<$50,000/QALY gained) range for patients with PAD (22) and patients <75 years of age, and ICERs between $50,000 and $70,000 for several other well-recognized higher-risk subgroups (patients with >1 prior MI, multivessel coronary artery disease, renal dysfunction [23], diabetes [24], or patients who had discontinued $P2Y_{12}$ inhibition within 30 days of randomization [25]). These findings suggest that targeting of the use of long-term ticagrelor to patients with PAD or patients <75 years of age would be an economically attractive approach to secondary coronary prevention and would provide value similar to many other widely accepted therapies, such as ICD implantation for primary prevention of sudden death in patients with coronary artery disease and depressed left ventricular function (26). For most other subgroups, long-term ticagrelor provides intermediate value, similar to other therapies that are commonly used in practice, such as transcatheter aortic valve replacement for patients with severe aortic stenosis and high surgical risk (27,28).

On the other hand, results for patients age ≥75 years showed prolonged ticagrelor to be a dominated strategy, due to both higher costs and lower QALYs relative to placebo. These results reflect the combination of modest efficacy, increased bleeding risk, and competing mortality risks from other conditions in the elderly population. Although subgroup analyses are typically considered hypothesis generating when interpreting clinical trial results, measures of absolute incremental costs and effectiveness, which drive cost-effectiveness results, are directly impacted by baseline risk and are thereby more likely to be

considered meaningful than relative risk estimates from clinical trials. Indeed, when supported by appropriate uncertainty analyses and consistent with underlying pathophysiology, subgroup estimates of cost-effectiveness are frequently considered to be valid considerations for guideline development and healthcare policy (29).

COMPARISON WITH PREVIOUS STUDIES. The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial was the first randomized trial to establish the efficacy of dual antiplatelet therapy, specifically clopidogrel plus ASA, versus ASA alone, for up to 12 months in patients with acute coronary syndromes (ACS) (9). Cost-effectiveness analyses carried out alongside the CURE trial yielded favorable ICERs (<$10,000 per life-year gained), both for the overall ACS patient population (5) and for the subset of patients who underwent percutaneous coronary intervention (PCI) (11). More recently the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38) trial and the PLATO (Platelet Inhibition and Patient Outcomes) trial have demonstrated the efficacy and cost-effectiveness (ICERS <$20,000 per QALY or life-year gained) of 2 second-generation $P2Y_{12}$ inhibitors, prasugrel and ticagrelor, versus clopidogrel in patients with ACS also treated with ASA (7,8,30). The favorable ICERs in these trials reflect the high event rates in the first year after ACS, which lead to both substantial reductions in prognostically important events and substantial cost offsets. In addition, most of these earlier analyses did not consider the prognostic impact of major bleeding events on long-term survival.

The optimal duration of dual antiplatelet therapy following an ACS event is uncertain, however, and depends upon the delicate balance of ischemic event versus bleeding risk, that may shift over time after ACS. The CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial was the first prospective randomized trial to examine the potential efficacy of dual antiplatelet therapy in nonacute patients at elevated risk of CV events. The CHARISMA trial enrolled a broad population of patients including those with established coronary, cerebrovascular or peripheral arterial disease and patients without established vascular disease but with 3 or more risk factors for CV events. Although there was no benefit of clopidogrel for the overall CHARISMA population, there was benefit in the subgroup of patients with established CV disease (which included patients with a prior MI) (31,32). A cost-effectiveness analysis for this subgroup yielded an ICER <$50,000 per QALY gained, although these results should be viewed with caution given the neutral results for the overall trial (4).

Generalizability of results from this cost-effectiveness evaluation of ticagrelor to other $P2Y_{12}$ inhibitors is not straightforward. The projected QALY gains with ticagrelor in our analysis were largely driven by a trend toward reduced mortality (specifically, a reduction in CV death and null effect on non-CV death) observed in the PEGASUS-TIMI 54 trial. By contrast, in the DAPT (Dual Antiplatelet Therapy) trial, treatment with prolonged clopidogrel or prasugrel was associated with increased non-CV and all-cause mortality, suggesting that the results from the PEGASUS-TIMI 54 trial may not extend to other $P2Y_{12}$ inhibitors (33–35). It is important to note that increased mortality was not observed with prolonged thienopyridine therapy in the post-MI subgroup of the DAPT trial (36).

IMPLICATIONS FOR TREATMENT DURATION. Our analysis assumed no further treatment costs or benefits beyond the 33-month median time frame of the trial, an approach commonly used when evaluating cost-effectiveness using patient-level data from a clinical trial (5,12,37). Whether our results can be extrapolated to more prolonged treatment scenarios depends upon the extent to which the observed absolute differences in costs, clinical benefits, and side effects of ticagrelor therapy continue with more prolonged therapy; if so, the ICER for additional years of therapy would be similar to that obtained herein.

Patients were enrolled in the PEGASUS-TIMI 54 trial at a median of 1.7 years following a qualifying MI. Compared with patients with stable ischemic heart disease, patients with MI have heightened platelet activation that may persist for years following an MI (2,38), and stable patients with a history of MI have an elevated predisposition for atherothrombotic events for years following an MI (1,39). A meta-analysis of data from randomized trials examining long-term dual antiplatelet therapy for secondary prevention in the subgroup of patients with previous MI, including the CHARISMA, DAPT, PEGASUS-TIMI 54 and 3 trials, specifically focused on ACS patients treated with PCI showed reduced atherothrombotic risk with extended dual antiplatelet therapy regardless of whether patients underwent PCI (15). It was thereby suggested that the mechanism of long-term CV benefit with extended therapy in prior MI patients is an extension of the benefits seen following the early post-MI treatment period and different from the time delineated prevention of stent thrombosis post-PCI.

STUDY LIMITATIONS. Although this study derives considerable strength from its prospective design and the use of patient-level data from the PEGASUS-TIMI 54 trial, our findings should be interpreted in light of the following limitations. This analysis is predicated on the assumption that the benefits and risks of ticagrelor in the overall U.S. population of post-MI patients are similar to those observed in the PEGASUS-TIMI 54 trial. Patients with a prior gastrointestinal bleed, who would be expected to be at higher risk for a subsequent gastrointestinal bleed if treated with ticagrelor versus placebo, were excluded from the PEGASUS-TIMI 54 trial. The results of this study should not be extrapolated to patients at higher risk of bleeding or lower risk of ischemic events, because such patients were not enrolled in the PEGASUS-TIMI 54 trial. Moreover, health care cost data were not collected directly from the patients in the trial, and the application of U.S. MS-DRG–based Medicare reimbursement rates to hospitalizations from the multinational trial population does not fully account for the possibility of differences in treatment practices and resource use between countries or health care systems. It is nonetheless reassuring that the clinical outcomes of the PEGASUS-TIMI 54 trial were consistent across geographic regions (13), and the ICER for ticagrelor versus placebo approaches the high-value range based on data from the subset of patients enrolled at U.S. sites.

Our analysis considered costs associated with hospitalizations and study drug; resource use relating to outpatient care was not collected in the PEGASUS-TIMI 54 trial, and costs associated with outpatient care were therefore not included. Exclusion of outpatient care costs may have biased the results in favor of ticagrelor if outpatient costs are actually higher in the ticagrelor arm owing to higher rates of bleeding complications and dyspnea. On the other hand, it is possible that the higher rates of nonfatal MI and especially stroke in the placebo arm could have led to greater outpatient resource utilization related to chronic and institutional care, and this would have biased the results against ticagrelor. In addition, the price of ticagrelor included in the analysis is the wholesale acquisition cost, which does not take into account manufacturer discounts or rebates. As of this writing, the daily national average drug acquisition cost of ticagrelor 60 mg listed at by the Center for Medicare & Medicaid Services is $10.65, virtually identical to the cost used in our analysis (40). Finally, the need for lifetime projections required several assumptions about the impact of ticagrelor versus placebo on long-term survival, health care costs, and quality of life. To the greatest extent possible, we used empirical data from the trial to inform these assumptions and examined the impact of plausible alternatives in sensitivity analyses.

CONCLUSIONS

For patients with a history of MI >1 year previously, treatment with ticagrelor + low-dose ASA versus ASA alone yields a cost-effectiveness ratio suggesting intermediate value based on current guidelines. Ticagrelor appears to provide greater value for higher-risk subgroups including patients <75 years of age or those with >1 prior MI, multivessel disease, diabetes, baseline renal dysfunction, or PAD, or patients who discontinued $P2Y_{12}$ <1 month before baseline.

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PERSPECTIVES

COMPETENCY IN SYSTEMS-BASED PRACTICE: Compared with aspirin alone, addition of ticagrelor in patients with a history of MI >1 year previously is associated with a cost-effectiveness ratio suggesting intermediate value. Ticagrelor has greater value for higher-risk patients, including those <75 years of age with multivessel disease or multiple prior infarcts, diabetes, renal dysfunction, peripheral artery disease, or those who recently interrupted $P2Y_{12}$ inhibitor therapy.

TRANSLATIONAL OUTLOOK: Analysis of longer-term economic and health outcome data is necessary to determine whether differences in the cost, benefit, and side effects of ticagrelor therapy are sustained over more prolonged treatment periods.

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