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Efficacy and Safety of Ticagrelor Over Time in Patients With Prior MI in PEGASUS-TIMI 54

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ABSTRACT

BACKGROUND Ticagrelor reduces ischemic risk in patients with prior myocardial infarction (MI). It remains unclear whether ischemic risk and the benefits of prolonged $P2Y_{12}$ inhibition in this population remain consistent over time.

OBJECTIVES The study sought to investigate the pattern of ischemic risk over time and whether the efficacy and safety of ticagrelor were similar early and late after randomization.

METHODS The PEGASUS-TIMI (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 randomized patients with prior MI (median 1.7 years prior) to ticagrelor 90 mg, ticagrelor 60 mg, or placebo on a background of aspirin. The rates of cardiovascular (CV) death, MI, and stroke as well as TIMI major bleeding were analyzed at yearly landmarks (years 1, 2, and 3).

RESULTS A total of 21,162 patients were randomized and followed for 33 months (median), with 28% of patients ≥5 years from MI at trial conclusion. The risk of CV death, MI, or stroke in the placebo arm remained roughly constant over the trial at an ~3% annualized rate. The benefit of ticagrelor 60 mg was consistent at each subsequent landmark (year 1 hazard ratio [HR]: 0.82; 95% confidence interval [CI]: 0.67 to 0.99; year 2 HR: 0.90; 95% CI: 0.74 to 1.11; and year 3 HR: 0.79; 95% CI: 0.62 to 1.00). TIMI major bleeding was increased with ticagrelor 60 mg at each landmark, but with the greatest hazard in the first year (year 1 HR: 3.22; year 2 HR: 2.07; year 3 HR: 1.65).

CONCLUSIONS Patients with a history of MI remain at persistent high risk for CVD, MI, and stroke as late as 5 years after MI. The efficacy of low-dose ticagrelor is consistent over time with a trend toward less excess bleeding. (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin [PEGASUS]; NCT01225562) (J Am Coll Cardiol 2017;70:1368–75) © 2017 by the American College of Cardiology Foundation.

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The occurrence of spontaneous myocardial infarction (MI) caused by plaque rupture and thrombosis identifies an underlying disease state associated with heightened long-term atherothrombotic risk. Observational data have demonstrated that patients with a history of MI, even more than 1 year prior, are at long-term risk of cardiovascular (CV) complications (1,2). Therefore, preventive therapies that are initiated in the acute setting have the potential to provide ongoing benefit if continued long term.

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The data that support the long-term utilization of such therapies are derived from clinical trials of variable durations. Although clinical benefits and bleeding rates are observed only for the duration of the trial, a consistent pattern of efficacy and safety over time in a chronic disease state generally supports long-term therapy. As an example, the data supporting lifelong aspirin in patients experiencing an MI are generally derived from trials with a mean duration of approximately 2 years (3,4).

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 demonstrated that ticagrelor 60 mg twice daily or 90 mg twice daily as long-term secondary prevention reduced ischemic risk in patients with a history of MI at least 1 year before the onset of treatment (5). Although no statistical heterogeneity was seen in key subgroups, for the approved ticagrelor 60-mg dose, patients randomized within 2 years of MI appeared to derive greater benefit (hazard ratio [HR]: 0.77) relative to patients randomized >2 years from MI (HR: 0.96). Therefore, some have questioned whether the risk of adverse CV events and benefit of ticagrelor are the same at various times after the occurrence of MI. We investigated whether the ischemic risk in patients enrolled in the PEGASUS-TIMI 54 trial was consistent over time from randomization in the trial as

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
CV = cardiovascular
HR = hazard ratio
IQR = interquartile range
MI = myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

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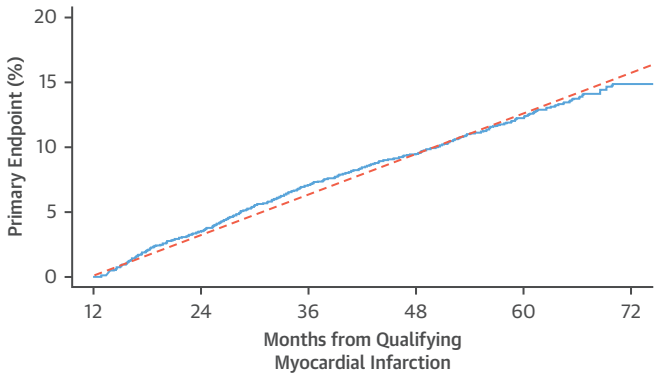
FIGURE 1 Primary Endpoint: Placebo Cohort



Patients were to be randomized at least 1 year from qualifying index myocardial infarction (MI), and therefore no events within the first year from MI were observed; events rose steadily in the placebo group after the first year. Estimates are based on left-truncated analysis. **Solid line** shows the observed relationship; **dashed line** shows a linear relationship.

well as from the index MI. We then evaluated whether the efficacy and safety of ticagrelor was consistent after accounting for factors such as the time when $P2Y_{12}$ inhibition was stopped before randomization. In addition, because high-risk patients may experience multiple events over the long term, we performed an analysis of total events prevented. Although both doses reduced ischemic risk with a similar magnitude of benefit, the 60-mg dose was better tolerated and offered a more attractive benefit-risk profile, leading to approval in the United States and Europe for long-term prevention. We therefore evaluated both doses but with a specific focus on the approved 60-mg dose.

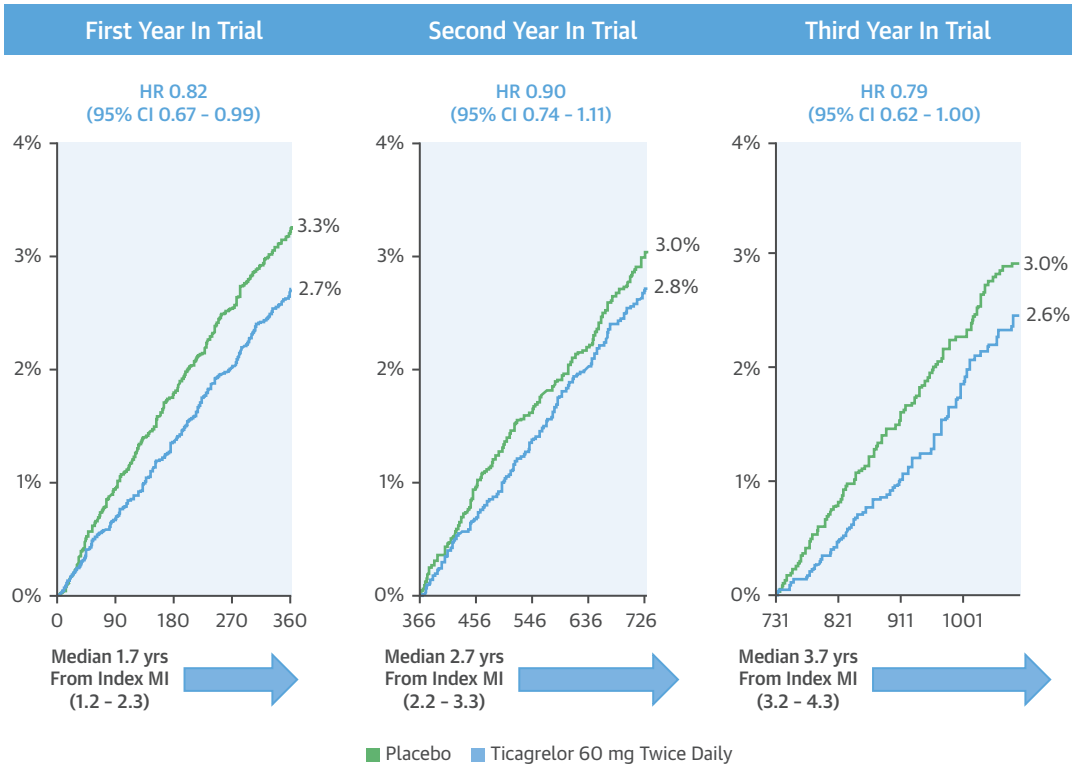
METHODS

STUDY POPULATION. The PEGASUS-TIMI 54 trial randomized patients with prior MI to ticagrelor 60 mg twice daily, ticagrelor 90 mg twice daily, or placebo, all on a background of low-dose aspirin. The protocol was approved by the relevant ethics committee at each participating site. Written informed consent was obtained from all participating patients. The trial design (6) and primary results have been published (5). Enrolled patients were at least 50 years of age and with a spontaneous MI occurring 1 to 3 years before enrollment and at least 1 of the following additional high-risk features: ≥65 years of age, diabetes mellitus requiring medication, a second prior spontaneous MI, multivessel coronary artery disease, or chronic renal dysfunction, defined as a creatinine clearance <60 ml/min as estimated by the Cockroft-Gault equation. Patients were ineligible if there was planned use of a $P2Y_{12}$ receptor antagonist or anticoagulant therapy during the study period; if they had a bleeding disorder, a history of intracranial bleeding, a central nervous system tumor, or an intracranial vascular abnormality; or if they experienced gastrointestinal bleeding within the previous 6 months or major surgery within the previous month.

ENDPOINTS. The primary efficacy endpoint for the PEGASUS-TIMI 54 trial was the composite of CV death, MI, or stroke, and the primary safety endpoint was Thrombolysis In Myocardial Infarction (TIMI) major bleeding. Additional efficacy endpoints included the individual components of the composite primary endpoint as well as coronary heart disease-related death. Other safety endpoints included TIMI minor bleeding, intracranial hemorrhage, and fatal bleeding. All potential events were adjudicated by a clinical events committee, which was blinded to treatment allocation.

STATISTICAL ANALYSIS. Cumulative event rates at 3 years following randomization were calculated by the Kaplan-Meier method. To determine the consistency of risk over time from the index MI, failure rates were also estimated using a Kaplan-Meier product limit estimator with time of origin as the date of the qualifying MI with risk set calculation accounting for left truncation based on the literature (7,8). HRs and 95% confidence intervals (CIs) were generated using a Cox proportional hazards model and all reported p values are 2-sided. Efficacy analyses were performed on an intention-to-treat basis. Safety analyses included all patients who received at least 1 dose of study drug and "on treatment," meaning only events

CENTRAL ILLUSTRATION **Long-Term Effects of Ticagrelor in Patients With Prior MI**



Bonaca, M.P. et al. J Am Coll Cardiol. 2017;70(11):1368–75.

Although ticagrelor reduced ischemic risk in patients with prior myocardial infarction (MI), the consistency of its longer-term effects is unknown. In analyzing the rates of cardiovascular death, MI, and stroke (the primary endpoint) at yearly landmarks 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, efficacy of ticagrelor 60 mg remained consistent over time with a trend toward less excess bleeding (safety endpoint). CI = confidence interval; HR = hazard ratio.

occurring on treatment or within 7 days of the last dose of study drug were counted. This was considered conservative as counting events in patients who prematurely discontinued the study drug could underestimate the bleeding risk of ticagrelor, particularly at later time points.

To evaluate whether the efficacy and safety of ticagrelor were consistent over time, landmark analyses were performed at yearly intervals from randomization in patients who were alive and event free at the start of the landmark period. Additional sensitivity analyses explored efficacy over time in patients stratified based on the time from qualifying MI to randomization and the timing of discontinuation of $P2Y_{12}$ inhibitor therapy before randomization as previously reported (9). Finally, an analysis of efficacy and safety was performed counting all events including recurrent events. This was done using both a negative binomial model (modified Poisson model) counting total events with exposure time included in the model. A sensitivity analysis used the Wei-Lin-Weissfeld model, which extends the survival models based on the Cox proportional hazards including the first 3 events for any subject. All analyses described above were pre-specified before database closure. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

RESULTS

A total of 21,162 patients were randomized to placebo (n = 7,067), ticagrelor 60 mg twice daily (n = 7,045), or ticagrelor 90 mg twice daily (n = 7,050). At randomization, the median time from the most recent MI was 1.7 years, with 61% occurring between 1 and 2 years (Online Figure 1). Median follow-up was

TABLE 1 Efficacy Outcomes

Year From Randomization	Placebo	Ticagrelor 60 mg	HR (95% CI)
First year*	7,067	7,045	
Primary endpoint	3.33	2.73	0.82 (0.67-0.99)
CV death	0.83	0.77	0.93 (0.65-1.35)
CHD death	0.56	0.53	0.95 (0.61-1.49)
MI	2.10	1.71	0.81 (0.64-1.03)
Stroke	0.69	0.50	0.73 (0.47-1.13)
Second year†	6,750	6,779	
Primary endpoint	3.05	2.78	0.90 (0.74-1.11)
CV death	1.21	1.26	1.02 (0.76-1.39)
CHD death	0.82	0.76	0.91 (0.62-1.33)
MI	1.80	1.50	0.83 (0.63-1.08)
Stroke	0.62	0.46	0.73 (0.46-1.17)
Third year‡	5,751	5,789	
Primary endpoint	3.00	2.63	0.79 (0.62-1.00)
CV death	1.39	0.91	0.52 (0.35-0.77)
CHD disease death	0.71	0.49	0.50 (0.29-0.86)
MI	1.50	1.50	0.93 (0.67-1.29)
Stroke	0.65	0.52	0.78 (0.47-1.31)

Values are n or Kaplan-Meier %, unless otherwise indicated. *Median from MI 1.7 years (interquartile range [IQR]: 1.2 to 2.3 years). †Median from MI 2.7 years (IQR: 2.2 to 3.3 years). ‡Median from MI 3.7 years (IQR: 3.2 to 4.3 years).

CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction.

2.7 (interquartile ratio [IQR]: 2.3 to 3.0) years so that at the conclusion of the trial, the median time from index MI was 4.5 (IQR: 3.8 to 5.1) years and 28% of patients were ≥5 years from their index event (Online Figure 1).

The risk of the primary endpoint in patients randomized to placebo when evaluated based on time from MI demonstrated a linear pattern of risk (**Figure 1**). No inflection point or plateau suggesting decreased risk was observed at any duration from MI.

EARLY AND LATE EFFICACY OF TICAGRELOR. The efficacy of ticagrelor 60 mg was similar over each sequential year of follow-up with the start of the first time period a median 1.7 years from the qualifying MI, increasing 1 year each for the second and third years of the trial (**Central Illustration**). The start of these time periods corresponded to a median of 1.7 (IQR: 1.2 to 2.3) years, 2.7 (IQR: 2.2 to 3.3) years, and 3.7 (IQR: 3.2 to 4.3) years from the qualifying MI. Reductions in the primary endpoint over the same landmark periods were similarly consistent for ticagrelor 90 mg (Online Table 1).

The efficacy of ticagrelor 60 mg in each serial landmark was also similar for the components of the primary endpoint (**Table 1**). Specifically, at the latest landmark, starting 2 years post-randomization, when patients were a median of >3 years from qualifying MI, the efficacy of ticagrelor 60 mg remained consistent for CV death (HR: 0.52; 95% CI: 0.35 to 0.77), coronary heart disease death (HR: 0.50; 95% CI: 0.29 to 0.86), MI (HR 0.93; 95% CI: 0.67 to 1.29), and stroke (HR: 0.78; 95% CI: 0.47 to 1.31). Results were similar for ticagrelor 90 mg (Online Table 1).

TICAGRELOR EFFICACY STRATIFIED BY TIME. When stratifying patients based on the time from MI at randomization (<2 years vs. ≥2 years), there tended to be greater benefit for ticagrelor 60 mg for the primary endpoint in patients <2 years from MI (HR: 0.77; 95% CI: 0.66 to 0.90) relative to those 2 or more years from MI (HR: 0.96; 95% CI: 0.79 to 1.17; p = 0.09 for interaction) with a reduction in CV mortality in those <2 years (HR: 0.68; 95% CI: 0.53 to 0.89) but not in those ≥2 years from MI (HR: 1.12; 95% CI: 0.81 to 1.54; p = 0.019 for interaction) (Online Table 2). Results for the 90-mg dose for these subgroups were similar (Online Table 3).

Because time from last dose of $P2Y_{12}$ inhibition at randomization is related to time from MI and has been shown to modify the efficacy of ticagrelor (9), the time from MI subgroups were further stratified by last dose of $P2Y_{12}$ inhibitor as previously reported (<30 days vs. ≥30 days) (Online Table 4). Patients within 2 years of qualifying MI appeared to have similar benefits with ticagrelor 60 mg for the primary endpoint regardless of time from last dose of $P2Y_{12}$ inhibitor (<30 days HR: 0.73; 95% CI: 0.57 to 0.92; ≥30 days HR: 0.81; 95% CI: 0.64 to 1.02) (Online Table 4). Similarly, patients ≥2 years from MI at randomization that were continued on $P2Y_{12}$ inhibitor (last dose <30 days) derived consistent benefit for the primary endpoint (HR: 0.83; 95% CI: 0.56 to 1.24). However, those patients who ≥2 years from MI and had survived event free off $P2Y_{12}$ inhibition (last dose ≥30 days) did not appear to benefit from ticagrelor (HR: 1.06; 95% CI: 0.81 to 1.37) (Online Table 4); of note, though, the test for heterogeneity did not meet nominal statistical significance for these subgroups (p = 0.20 for interaction for ticagrelor 60 mg and p = 0.16 for interaction for ticagrelor 90 mg). Results were similar for these subgroups with the ticagrelor 90-mg dose (Online Table 4).

EARLY AND LATE SAFETY OF TICAGRELOR. In patients randomized to placebo, rates of TIMI major bleeding appeared consistent over time (year 1: 0.27%; year 2: 0.42%; year 3: 0.37%). Online Figure 2 shows Kaplan-Meier rates for bleeding in the placebo arm, based on left-truncated analysis. Ticagrelor 60 mg increased TIMI major bleeding with the greatest hazard in the first year of treatment relative to years 2 and 3 (**Table 2**). Similar to the overall trial results, there was no significant increase in fatal bleeding or intracranial hemorrhage with ticagrelor

60 mg early or late (**Table 2**). Rates of bleeding with ticagrelor 90 mg generally tended to be higher than with ticagrelor 60 mg (Online Table 5).

RECURRENT EVENTS. Overall, 1,830 primary efficacy events occurred during follow-up, including 1,558 first events, 214 second events, 43 third events, and 15 with fourth, fifth, or sixth events (Online Figure 3). Total primary efficacy events were reduced 17% with ticagrelor 60 mg versus placebo (4.34 vs. 5.18; incidence-rate ratio: 0.83; 95% CI: 0.72 to 0.95; p = 0.006) and 17% with ticagrelor 90 mg versus placebo (incidence-rate ratio: 0.83; 95% CI: 0.73 to 0.95; p = 0.007). Use of the Wei-Lin-Weissfeld model demonstrated a consistent pattern of benefit with ticagrelor for 1, 2, and 3 or more ischemic events (Online Figure 4). Of the 300 primary safety events, there were 296 first events, 3 second events, 1 third event, and none with more than 3 events. The 4 recurrent safety events had no significant impact on the risk of bleeding with ticagrelor. For every 1,000 patients treated for 3 years, ticagrelor 60 mg twice daily would prevent 18 primary endpoint events, including 6 CV deaths, 9 MIs, and 5 strokes at the cost of 9 TIMI major bleeds but no intracranial hemorrhages or fatal bleeding events (**Figure 2**).

TABLE 2 Safety Outcomes

Year From Randomization	Placebo	Ticagrelor 60 mg	HR (95% CI)
First year	6,996	6,958	
TIMI major	0.27	0.86	3.22 (1.86–5.57)
TIMI major or minor	0.38	1.30	3.48 (2.20–5.50)
TIMI minor	0.11	0.44	4.10 (1.79–9.42)
Intracranial hemorrhage	0.10	0.15	1.61 (0.57–4.53)
Fatal bleeding	0.03	0.11	3.24 (0.65–16.06)
Second year	5,987	5,461	
TIMI major	0.42	0.86	2.07 (1.25–3.43)
TIMI major or minor	0.55	1.13	2.10 (1.35–3.27)
TIMI minor	0.13	0.29	2.36 (0.96–5.78)
Intracranial hemorrhage	0.18	0.18	0.99 (0.40–2.44)
Fatal bleeding	0.13	0.04	0.31 (0.07–1.51)
Third year	4,938	4,447	
TIMI major	0.37	0.60	1.65 (0.84–3.24)
TIMI major or minor	0.50	1.03	2.02 (1.14–3.58)
TIMI minor	0.13	0.45	3.56 (1.16–10.92)
Intracranial hemorrhage	0.20	0.28	1.57 (0.60–4.11)
Fatal bleeding	0.11	0.11	1.09 (0.22–5.40)

Values are n or Kaplan-Meier %, unless otherwise indicated.
TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in **Table 1**.

DISCUSSION

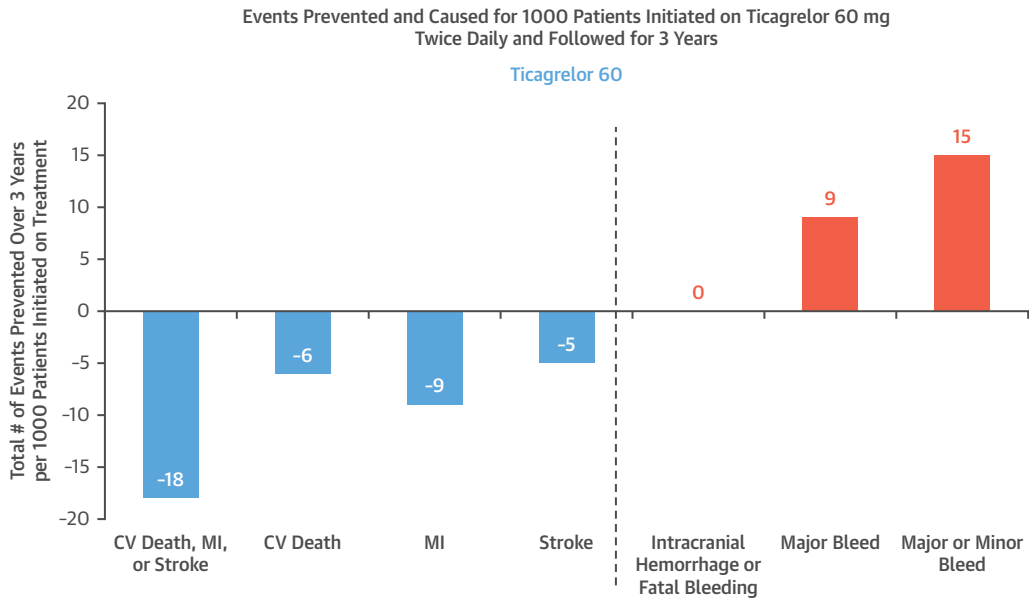
This analysis demonstrated 3 major findings. First, the risk of ischemic events in patients who have experienced an MI continues for several years without evidence of decreasing risk more than 5 years from the qualifying MI. Second, the benefits of ticagrelor for secondary prevention are consistent both early and late after MI and do not attenuate with time, although the safety profile may improve over time. Third, the benefit of intensive secondary prevention is greater when accounting for total rather than just first events.

Long-term ischemic risk after MI has been observed in registries and subgroups of prior trials (1,10,11). The PEGASUS-TIMI 54 trial, however, is the first trial to prospectively study the natural history of patients with a history of spontaneous MI at least 1 year before enrollment who received high rates of indicated secondary prevention therapies, including aspirin, statins, and beta-blockers. This pattern, which is similar to that seen in atrial fibrillation, suggests an ongoing disease state rather than residual risk related to the index event (12). Ongoing ischemic risk was present even at the conclusion of the trial when patients were a median of 4.7 years beyond their index MI and 28% were ≥5 years from their MI.

The benefits of ticagrelor were consistent both early and late. The consistency of late benefit built on the observations from PLATO (Study of Platelet Inhibition and Patient Outcomes) study, where the benefit of ticagrelor relative to clopidogrel was the same in the short term (days 0 to 30) and intermediate term (days 31 to 360); however, whether benefit continued late (beyond 1 year) was previously unknown (13). Overall, the PEGASUS-TIMI 54 trial demonstrated continued benefit with intensive antiplatelet therapy. Efficacy was maintained without attenuation over the duration of the trial. These data covered a period of time well beyond the 2-year data used to justify recommendations for lifetime use of aspirin in MI patients (3). Overall, these findings further supported continued long-term ticagrelor in patients who tolerate therapy for the first 12 months after MI and did not suggest late waning in efficacy that would support subsequent withdrawal.

Observations that the apparent efficacy of ticagrelor was less in patients >2 years from index MI at randomization are partially confounded by the interaction with $P2Y_{12}$ inhibitor use. We have previously described a significant interaction between the efficacy of long-term ticagrelor in the PEGASUS-TIMI 54 trial and time from last dose of $P2Y_{12}$ inhibitor before randomization (9). Specifically, patients who have been event free while on aspirin monotherapy for a protracted time are by definition a low-risk "survivor" cohort. When stratified by time from MI at 2 years in those continuing on $P2Y_{12}$ inhibition or restarting after a brief interruption, there is consistent efficacy of ticagrelor regardless of time from MI.

FIGURE 2 Total Events Prevented and Caused



Per 1,000 patients initiated on ticagrelor 60 mg twice daily and followed for 3 years, cardiovascular (CV) events would be reduced but at the potential detriment of additional bleeding events. MI = myocardial infarction.

This benefit was consistent in those who were randomized more than 2 years from MI, an observation further supported by the landmark analysis in the current paper.

In terms of assessing the overall clinical impact of long-term ticagrelor, recurrent events must be considered. When looking at all ischemic events, the benefit of ticagrelor was consistent for first and recurrent events with a 17% reduction in total events for the primary endpoint. When considering total primary endpoint events prevented relative to major bleeds caused, for 1,000 patients initiated on ticagrelor 60 mg, 18 primary endpoint events would be prevented versus an increase in 9 major bleeds but with no intracranial or fatal bleeds. These data may support clinician decision making in evaluating the risk-benefit ratio of long-term ticagrelor in patients with prior MI.

STUDY LIMITATIONS. Landmark analyses begin observation at a time after randomization and in patients who have not yet had an event; therefore, randomization may not be maintained. It should be noted, however, that 96% and 82% of the total cohort remained at the 1- and 2-year landmarks, respectively. In addition, baseline characteristics by randomization group remained similar at both landmarks (Online Tables 6 and 7 [1 year and 2 years, respectively]). Likewise, safety analyses by definition are in patients still on study drugs and, therefore, select for a cohort who has tolerated therapy; thus, the trend for a diminished bleeding risk over time likely reflects selection of patients who have maintained therapy without intolerable bleeding. Nonetheless, such information is useful to clinicians as they periodically re-evaluate whether to further continue dual antiplatelet therapy in a patient and balance ischemic and bleeding risk.

CONCLUSIONS

Patients with prior MI more than 1 year from their event remain at long-term risk of recurrent atherothrombotic events with no indication of waning risk, even more than 5 years from the event. Ticagrelor reduced ischemic risk in patients with prior MI, with consistent efficacy both early and late and with a trend toward lesser excess in bleeding over time. These data support consideration of prolonged therapy in patients who continue to tolerate the drug.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Therapy with ticagrelor after MI reduces ischemic risk but increases the risk of bleeding, and these effects are consistent over about 3 years, supporting long-term use of ticagrelor for secondary prevention in high-risk MI survivors rather than a fixed duration of therapy following an index event or procedure.

TRANSLATIONAL OUTLOOK: Comparative trials are needed to clarify the optimum long-term antithrombotic strategy for survivors of acute MI.

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KEY WORDS cardiovascular death, ischemic risk, myocardial infarction, $P2Y_{12}$ inhibition, secondary prevention, stroke

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