Original Investigation

Long-term Tolerability of Ticagrelor for the Secondary Prevention of Major Adverse Cardiovascular Events
A Secondary Analysis of the PEGASUS-TIMI 54 Trial

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IMPORTANCE In the PEGASUS-TIMI 54 trial, treatment with ticagrelor reduced the incidence of cardiovascular death, myocardial infarction, or stroke by 15% to 16% among stable patients compared with placebo. However, more patients prematurely discontinued treatment with ticagrelor than with placebo.

OBJECTIVE To investigate the reasons and timing of discontinuation of treatment with ticagrelor among stable patients prior myocardial infarction.

DESIGN, SETTING, AND PARTICIPANTS In the PEGASUS-TIMI 54 trial, 21 162 stable outpatients with prior myocardial infarction were randomly assigned to 90 mg of ticagrelor twice daily, 60 mg of ticagrelor twice daily, or placebo, with all of the patients receiving a low dose of aspirin. These participants were followed up for a median of 33 months (study start date: October 2010; completion date: December 2014). Discontinuation of treatment was evaluated by treatment arm, cause, and timing. This analysis was initiated in May 2015.

MAIN OUTCOME AND MEASURE Discontinuation of treatment.

RESULTS Over 33 months, 32%, 29%, and 21% of patients receiving 90 mg of ticagrelor, 60 mg of ticagrelor, and placebo, respectively, discontinued treatment ($P < .001$). Discontinuation of treatment due to an adverse event occurred in 19%, 16%, and 9% of patients, respectively ($P < .001$). The most frequent adverse events leading to discontinuation of treatment were bleeding (with Kaplan-Meier event rates of 7.8%, 6.2%, and 1.5% of patients, respectively; $P < .001$) and dyspnea (6.5%, 4.6%, and 0.8% of patients, respectively; $P < .001$). Eighty-six percent of bleeding events that led to the discontinuation of treatment with ticagrelor were nonmajor, and 86% of adverse events due to dyspnea that led to discontinuation of treatment with ticagrelor were mild or moderate in severity. The discontinuation rates are annualized for patients who received 90 mg of ticagrelor twice daily (hazard ratio [HR], 2.00 [95% CI, 1.84-2.16] for the first year; HR, 1.12 [95% CI, 1.00-1.26] for the second and third years) and patients who received 60 mg of ticagrelor twice daily (HR, 1.59 [95% CI, 1.46-1.73] for the first year; HR, 1.18 [95% CI, 1.06-1.32] for the second and third years) compared with patients who received placebo.

CONCLUSIONS AND RELEVANCE When initiated among stable patients with prior myocardial infarction, discontinuation of treatment with ticagrelor was driven primarily by nonserious adverse events occurring primarily early after randomization. For patients completing 1 year of treatment, the subsequent discontinuation rate was low. These data demonstrate how adverse events considered "nonserious" by traditional trial criteria may have an effect on quality of life and, thus, may precipitate the discontinuation of treatments and underscore the need for patient education and counseling on the timing and nature of adverse effects with the aim of improving adherence when appropriate.

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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, it was found that long-term treatment with ticagrelor reduced the risk of major adverse cardiovascular events among stable outpatients with a history of myocardial infarction.[1] Enrollment in the trial started in 2010, contemporaneous with its approval in Europe and 1 year before its approval in the United States, and patients were required to have had their myocardial infarction more than 1 year ago. Therefore, few patients (<1%) had been treated with ticagrelor for their qualifying myocardial infarction, and the majority of patients were newly exposed to ticagrelor as stable outpatients at randomization.[2]

However, incorporation of the result of the PEGASUS-TIMI 54 trial into practice would most likely be in the form of continuing treatment with ticagrelor for patients beyond the current recommended 12 months after their myocardial infarction, rather than initiating de novo among patients who had already discontinued their treatment with a $P2Y_{12}$ inhibitor. To that end, initiation of ticagrelor in the setting of an acute coronary syndrome has already been shown to be generally well tolerated, with adverse effects leading to treatment discontinuation in 7.4% of patients receiving ticagrelor vs 6.0% of patients receiving clopidogrel.[3]

More broadly, the tolerability of long-term antithrombotic therapy in stable populations may have an important effect on treatment adherence. The traditional regulatory categorization of adverse events as "serious" or "nonserious" is typically based on objective criteria such as the need for hospitalization; however, it is possible that nonserious adverse events could have important practical sequelae and, specifically, may disproportionately drive premature treatment discontinuation.

We therefore investigated the rates, reasons, and timing of treatment discontinuation in the PEGASUS-TIMI 54 trial. We hypothesized that adverse events leading to treatment discontinuation would occur relatively early in the study and that the difference in the rates of treatment discontinuation between treatment arms would be attenuated over time. Moreover, we hypothesized that the majority of adverse events leading to treatment discontinuation would be nonsevere. Finally, we explored the effect of treatment with ticagrelor on ischemic and bleeding events occurring in patients while receiving the treatment during the trial.

Key Points

Question Why do patients receiving ticagrelor discontinue treatment at a higher rate than those receiving placebo?

Findings In this secondary analysis, for stable outpatients, discontinuation of ticagrelor occurred early and was driven by nonserious adverse events, including dyspnea and nonmajor bleeding. For patients who completed 1 year of treatment, subsequent rates of discontinuation were lower.

Meaning Adverse events traditionally considered "nonserious" may affect quality of life and precipitate the discontinuation of treatment.

Methods

Study Population

In the PEGASUS-TIMI 54 trial, 21 162 patients with a history of a spontaneous myocardial infarction and 1 additional high-risk feature were randomly assigned to receive 90 mg of ticagrelor orally twice daily, 60 mg of ticagrelor orally twice daily, or placebo for the duration of the trial. Full inclusion and exclusion criteria have been published previously.[2] Stable patients were recruited a median of 1.7 years (interquartile range, 1.2-2.3 years) from their qualifying myocardial infarction. All patients were to receive aspirin at a low dose of 75 to 150 mg daily. Patients with known hemorrhagic diathesis or a coagulation disorder, a history of an ischemic stroke or previous intracranial bleeding at any time, gastrointestinal bleeding within the past 6 months, or major surgery within 30 days were excluded. This study was approved by the corresponding health authorities and ethics board or institutional review boards for all participating study sites, and the patients provided written informed consent to participate in the trial.

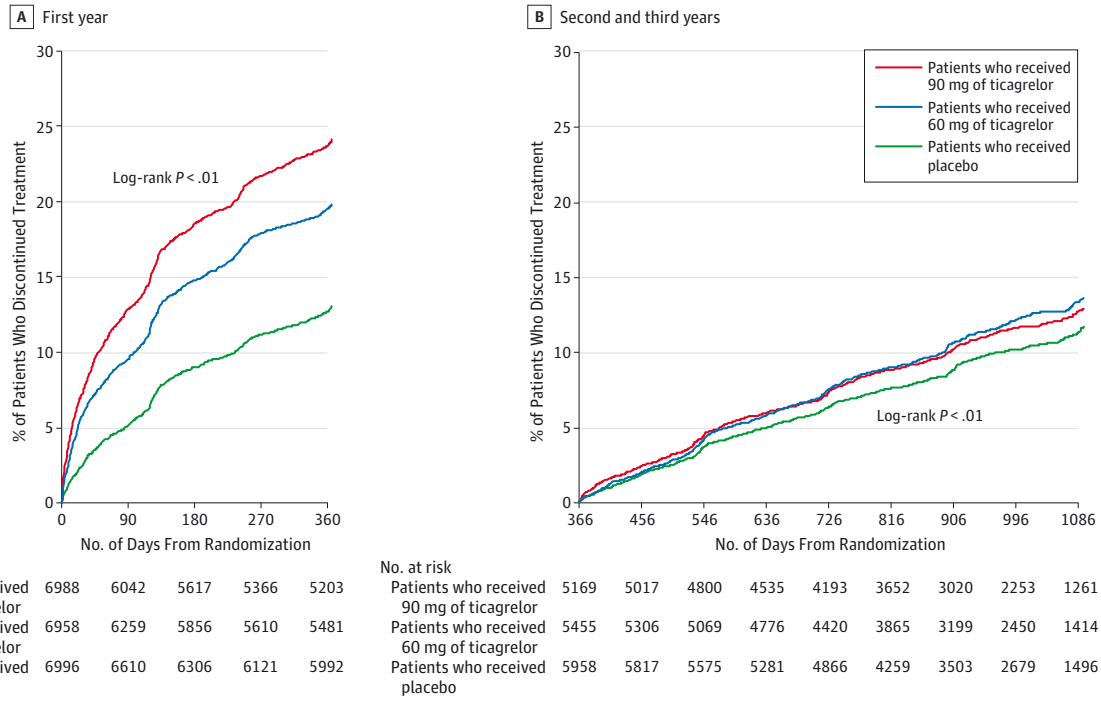
End Points

The prespecified primary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. Additional efficacy end points included the individual components of the composite, as well as coronary heart disease–related death and all-cause mortality. The primary safety end point was TIMI major bleeding; other safety end points included other categories of TIMI bleeding (eAppendix in the Supplement).[2] All potential bleeding and efficacy events were adjudicated by a clinical events committee, which was blinded to treatment allocation. Data on additional safety events such as dyspnea were collected through standard reporting of adverse events, including the study site's indication of the severity of symptoms. A subset of adverse events were identified as "serious" by study sites based on criteria outlined in the protocol and consistent with standard regulatory definitions (eg, fatal, life-threatening, leading to hospitalization, and otherwise medically important). Data on treatment discontinuation was collected by each study site, including the dates of, as well as the reasons for, treatment discontinuation. Treatment discontinuation for adverse event was defined as stopping treatment for a safety event and excluded discontinuation in the setting of an efficacy event. All patients were to be followed up for the duration of the study for efficacy and safety of treatment regardless of whether they continued treatment. Among patients who were randomly assigned 60 or 90 mg of ticagrelor, pill counts were to be performed at each visit, and "adherence" was predefined as taking at least 80% of expected pills over the course of the study.

Statistical Methods

Patients were categorized by whether they continued treatment until the end of the trial or prematurely discontinued

Figure 1. Drug Discontinuation for Any Reason by Treatment



No. at risk					
Patients who received 90 mg of ticagrelor	6988	6042	5617	5366	5203
Patients who received 60 mg of ticagrelor	6958	6259	5856	5610	5481
Patients who received placebo	6996	6610	6306	6121	5992

No. at risk									
Patients who received 90 mg of ticagrelor	5169	5017	4800	4535	4193	3652	3020	2253	1261
Patients who received 60 mg of ticagrelor	5455	5306	5069	4776	4420	3865	3199	2450	1414
Patients who received placebo	5958	5817	5575	5281	4866	4259	3503	2679	1496

The annualized rate of discontinuation was 7.2% for patients who received 90 mg of ticagrelor twice daily, 7.5% for patients who received 60 mg of ticagrelor twice daily, and 6.4% for patients who received placebo within the first year (A) and as a 1-year landmark for the subsequent 2 years (B).

treatment prior to the end of the trial. Baseline characteristics among groups were compared using the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. The rates of and the reasons for treatment discontinuation were compared between treatment groups overall and as a landmark starting at 1 year for patients who continued treatment through the first year of the trial. Additional analyses were performed comparing by treatment arm the categories of bleeding and the levels of severity of dyspnea that led to treatment discontinuation.

The efficacy and safety of ticagrelor relative to placebo was compared including events that occurred while receiving treatment or within 7 days of the last dose. Additional sensitivity analyses were performed that also included all adverse events through 30 days from the last dose, as well as including all adverse events occurring in patients who discontinued treatment because of bleeding. To adjust for differences between patients who discontinued treatment and patients who continued treatment, a propensity score for discontinuation was created by applying a forward selection algorithm to candidate variables that significantly differed between such patients on univariate analysis. This score was used to perform an adjusted analysis of efficacy by treatment arm. Cumulative event rates were calculated by the complement of Kaplan-Meier survival estimates. Log-rank *P* values are also reported, when applicable. Hazard ratios and 95% CIs were generated using a Cox proportional hazards model, and all reported *P* values are 2-sided. The assumption of proportional hazards was tested by including time-dependent covariates in the model and scaled Schoenfeld residual plots. The validity of the linearity assumption was visually examined by use of Martingale residual plots. Analyses were performed using SAS software version 9.3 (SAS Institute Inc).

Results

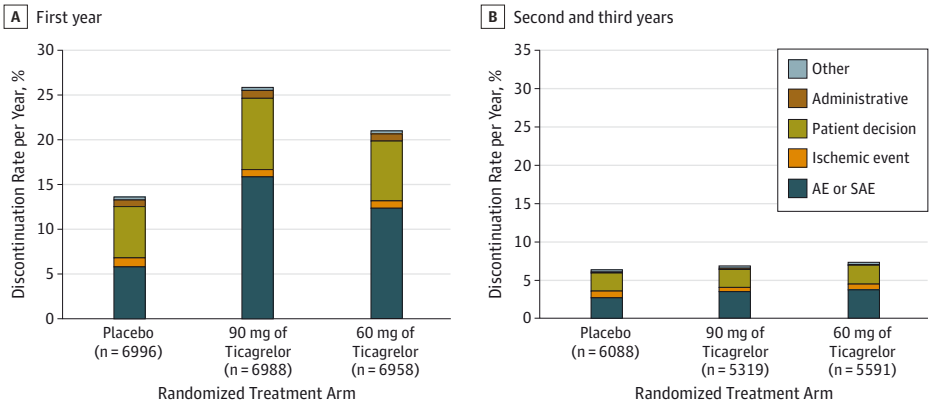
Baseline Characteristics

A total of 21 162 patients were randomly assigned to 1 of 3 treatment arms and were followed up for a median of 33 months, with 20 942 receiving at least 1 dose of treatment drug (ticagrelor or placebo). A total of 5728 patients (27.4%) discontinued treatment over the trial period. Baseline characteristics stratified by whether treatment was continued throughout follow-up or prematurely discontinued are shown in eTable 1 in the Supplement. Of note, patients who prematurely discontinued treatment were older by 2 years, more likely to be female and have renal dysfunction, were more distant in time from their last dose of a $P2Y_{12}$ inhibitor at the time of randomization, and were more likely to have a history of spontaneous bleeding compared with those who continued treatment. The baseline characteristics of the patients who continued treatment over the duration of the trial were generally balanced among the treatment arms (eTable 2 in the Supplement).

Drug Discontinuation by Treatment Arm

The drug discontinuation rate was significantly higher for both ticagrelor treatment arms (32% of patients who received 90 mg

Figure 2. Distribution of Reasons for Drug Discontinuation by Treatment Arm



The discontinuation rates are annualized for patients who received 90 mg of ticagrelor twice daily (hazard ratio [HR], 2.00 [95% CI, 1.84-2.16] for the first year [A]; HR, 1.12 [95% CI, 1.00-1.26] for the second and third years [B]) and patients who received 60 mg of ticagrelor twice daily (HR, 1.59 [95% CI, 1.46-1.73] for the first year [A]; HR, 1.18 [95% CI, 1.06-1.32] for the second and third years [B]) compared with patients who received placebo. AE indicates adverse event; SAE, severe adverse event.

Table. Data on Bleeding and Dyspnea Leading to Discontinuation

Adverse Event	Patients, No. (%)		
	Placebo (n = 6996)	90 mg of Ticagrelor Twice Daily (n = 6988)	60 mg of Ticagrelor Twice Daily (n = 6958)
Dyspnea leading to discontinuation (n = 778)			
Patients, Total No. (%)[a]	51 (0.8)	430 (6.5)	297 (4.6)
Distribution of serious adverse events among patients who discontinued treatment			
Serious adverse event	2 (4)	8 (2)	11 (4)
Nonserious adverse event	49 (96)	422 (98)	286 (96)
Severe	7 (14)	56 (13)	25 (8)
Moderate	27 (53)	244 (57)	176 (59)
Mild	15 (29)	122 (28)	85 (29)
Bleeding leading to discontinuation (n = 893)			
Patients, Total No. (%)[a]	86 (1.5)	453 (7.8)	354 (6.2)
Distribution of TIMI Bleeding Classification among patients who discontinued treatment			
Major	26 (30)	59 (13)	52 (15)
Minor	3 (3)	23 (5)	15 (4)
Requiring medical attention	43 (50)	277 (61)	221 (62)
Minimal	14 (16)	94 (21)	66 (19)

Abbreviation: TIMI, Thrombolysis in Myocardial Infarction.

[a] Kaplan-Meier event rate.

of ticagrelor twice daily and 29% of patients who received 60 mg of ticagrelor twice daily) relative to placebo (21% of patients). This difference was most marked in the first year after randomization, and particularly in the first 90 days, with discontinuation rates at 1 year of 24.1%, 19.8%, and 13.1% in the 90-mg, 60-mg, and placebo arms, respectively (**Figure 1**). When evaluated as a landmark analysis starting 1 year after randomization among patients who had tolerated treatment for the first year, the annualized rates of discontinuation were far lower in all 3 treatment arms at 7.2%, 7.5%, and 6.4%, respectively (Figure 1).

Reasons for Drug Discontinuation by Treatment Arm

Overall, the percentage of patients who discontinued treatment owing to the patient's decision or administrative reasons (eg, site closure) was balanced among treatment groups and was approximately 10.2% to 11.4%. The rate of drug discontinuation due to an adverse event, however, was highest in the treatment arm receiving 90 mg of ticagrelor (19%), followed by the treatment arm receiving 60 mg of ticagrelor (16%), both of which were significantly higher than that in the placebo arm (9%) ($P < .001$ for each dose of ticagrelor relative to placebo; eTable 3 in the Supplement). Differences in the rates of drug discontinuation due to adverse events by treatment arm were most marked within the first year from randomization compared with those who tolerated treatment for the first year (**Figure 2**). For patients who had completed 1 year of treatment, the subsequent annualized rates of discontinuation due to an adverse event were 3.4%, 3.7%, and 2.6%, respectively.

The median time to an adverse event that led to discontinuation of treatment was shorter for patients who were receiving ticagrelor (55 days for those who were receiving a 90-mg dose and 103 days for those who were receiving a 60-mg dose) than for patients who were receiving placebo (189 days).

The most common adverse events (serious and nonserious) leading to discontinuation of treatment are listed in eTable 3 in the Supplement. Of these, the most frequent adverse events leading to discontinuation of 90 mg of ticagrelor, 60 mg of ticagrelor, and placebo were bleeding (with rates of 7.8%, 6.2%, and 1.5%, respectively) and dyspnea (with rates of 6.5%, 4.6%, and 0.8%, respectively) ($P < .001$ for comparisons of each dose of ticagrelor compared with placebo) (**Table**). The majority of patients who discontinued treatment with ticagrelor owing to dyspnea or bleeding did so early after randomization (**Figure 3**). Of those who discontinued treatment because of dyspnea, the median times were 8 and 11 days in the 90- and 60-mg arms, respectively. Of those that discontinued treatment because of bleeding, the median times were 86 and 156 days in the 90- and 60-mg arms, respectively.

Types and Severity of Adverse Events Leading to Drug Discontinuation

The majority of adverse events leading to discontinuation of treatment were nonserious with proportions of 80%, 76%, and 63% in the 90-mg, 60-mg, and placebo arms, respectively. Bleeding leading to drug discontinuation in the ticagrelor arms was nonmajor in 86% of cases (Table). Dyspnea leading to discontinuation in the ticagrelor arms was mild or moderate in 86% of cases (Table).

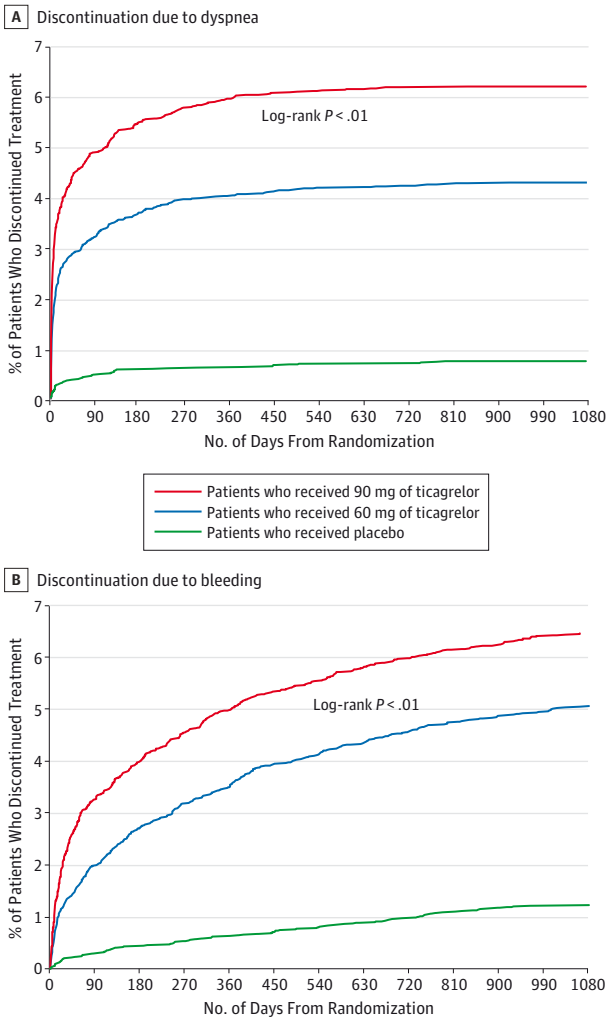
Treatment Adherence

For the patients in the trial, assessment of adherence using pill counts revealed that the percentage of patients who were adherent (predefined as taking at least 80% of expected tablets) was greater than 80% for all treatment arms but was slightly lower for each ticagrelor arm (83% for both doses) relative to the placebo arm (86%) ($P < .001$ for each dose of ticagrelor vs placebo).

Efficacy and Safety of Ticagrelor

While receiving treatment, patients had significantly lower rates of the primary end-point composite of cardiovascular death, myocardial infarction, or stroke with 90 mg of ticagrelor (6.6%; hazard ratio, 0.79 [95% CI, 0.68-0.91]; $P < .001$) and 60 mg of ticagrelor (6.8%; hazard ratio, 0.78 [95% CI, 0.68-0.90]; $P < .001$) than with placebo (8.4%), with consistent reductions in each of the elements of the primary end point relative to placebo (**Figure 4**; eFigure and eTable 4 in the Supplement). Various sensitivity analyses, including a propensity score–adjusted model accounting for baseline differences between patients who prematurely discontinued treatment and patients who did not, yielded similar results (eTables 5-7 in the Supplement). As previously noted, both ticagrelor doses increased bleeding with rates of TIMI major bleeding of 2.60% in the 90-mg arm, 2.30% in the 60-mg arm, and 1.06% in the placebo arm.

Figure 3. Drug Discontinuation Due to Dyspnea (A) or Bleeding (B) Over Time by Treatment Arm



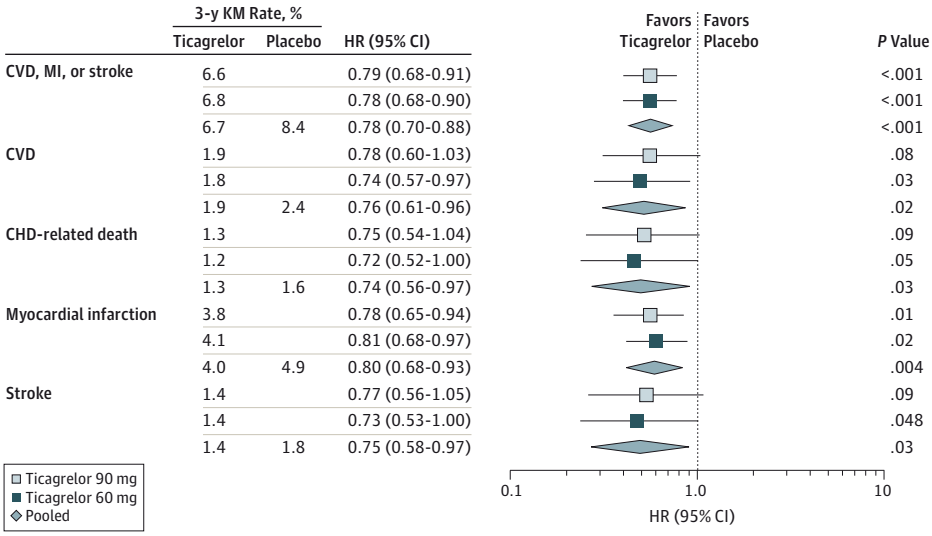
The median time to discontinuation was 8 days for patients who received 90 mg of ticagrelor twice daily (n = 6998), 11 days for patients who received 60 mg of ticagrelor twice daily (n = 6958), and 53 days for patients who received placebo (n = 6669). The proportions are the number of patients who discontinued over time divided by the number of patients who received treatment (safety cohort).

Discussion

When initiated in stable outpatients for secondary prevention, treatment with ticagrelor compared with placebo resulted in more patients discontinuing treatment, primarily owing to adverse events that did not meet the regulatory definition of "serious." The most frequent adverse events driving discontinuation were symptoms of dyspnea and bleeding; however, these adverse events occurred early in the course of treatment, and the majority of cases of bleeding were nonmajor, whereas the majority of cases of dyspnea were mild or moderate in severity. Among patients who completed 1 year of treatment, subsequent rates of discontinuation were low.

By way of comparison, in the PLATO (Platelet Inhibition and Patient Outcomes) trial, in which the median duration of exposure to study drug was 277 days, dyspnea occurred more frequently with ticagrelor than with clopidogrel (13.8% vs 7.8%; $P < .001$), and treatment discontinuation due to dyspnea was infrequent (0.9% vs 0.1%, $P < .001$).[3] In contrast, in the present study, in which the duration of exposure to study drug was

Figure 4. Efficacy of Ticagrelor



The risk of cardiovascular death (CVD), myocardial infarction (MI), stroke, or all-cause mortality with 90 mg of ticagrelor twice daily, 60 mg of ticagrelor twice daily, or both doses pooled for 20 942 patients who received at least 1 dose of study drug and including events within 7 days of the last dose of study drug. CHD indicates coronary heart disease; HR, hazard ratio; and KM, Kaplan-Meier.

more than 3 times as long, the discontinuation rate was 6.5% for 90 mg of ticagrelor, 4.6% for 60 mg of ticagrelor, and 0.8% for placebo. Similarly, in phase 2 studies including stable patients with atherosclerosis, dyspnea occurred in 10% of patients who received either 50 or 100 mg of ticagrelor over 28 days of exposure.[4] Reasons for the differences may be that dyspnea is not uncommon in the setting of acute coronary syndromes, whereas it would be unexpected in stable outpatients and hence would be more likely to lead to the discontinuation of treatment. To that end, the absolute excess rate of dyspnea was about 5% to 6% in both the PLATO and PEGASUS-TIMI 54 trials. The excess discontinuation of ticagrelor due to dyspnea generally occurred early, typically within days of exposure, and was generally in response to dyspnea symptoms that were nonserious and characterized as mild or moderate in severity. Although extensive evaluation of the dyspnea induced by ticagrelor has shown no associated cardiovascular or pulmonary harm, a significant proportion of patients still discontinued treatment in response to their mild or moderate symptoms.

Similarly to dyspnea, the vast majority of bleeding events that prompted discontinuation of ticagrelor were classified as nonmajor. This observation illustrates that even bleeding events such as bruising and epistaxes, which are typically categorized as "nonmajor" by trial definitions, may affect patients and have important unintended consequences in terms of leading to some form of unscheduled medical attention (eg, evaluation of bleeding with or without any intervention) and the discontinuation of antithrombotic therapies. It also should be acknowledged that patients who have nonmajor bleeding episodes may be at greater risk for major bleeding. More broadly, the results of our analyses underscore that the adverse effects of a drug, in this case dyspnea and bleeding, regardless of their clinical severity, transience, or long-term implications, can have an immediate effect on quality of life and compliance. Therefore, it is important to always have a careful discussion with patients regarding the potential adverse effects of therapies, so that they may carefully weigh these symptoms against the potential benefits of continued therapy and thereby make the best possible choices.[5]

The importance of nonserious adverse events in impacting treatment continuation is further supported by the observation that treatment adherence was lower for patients who received ticagrelor than for patients who received placebo. Because of the blinded nature of the trial, this difference in adherence is most likely explained by tolerability, highlighting that patients may make decisions about treatment without telling their physician or acknowledging adverse events. It is also notable that 784 patients who were randomly assigned to placebo discontinued owing to an adverse event that was attributed to the treatment. This finding also serves as a reminder that adverse events not causally related to the study drug frequently occur even in stable populations such as the patients enrolled in the PEGASUS-TIMI 54 trial. These observations are similar to those from other studies of antithrombotic drugs in stable populations, such as the blinded CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial,[6] in which the permanent discontinuation rate was higher for patients who received clopidogrel than for patients who received placebo (20.4% vs 18.2%; $P < .001$), driven in part by discontinuation not only for bleeding (125 vs 56 patients) but also for "other reasons" (386 vs 319 patients) and patient request (672 vs 627 patients). These data highlight the complex challenge that tolerability presents for long-term secondary preventive strategies and particularly for antithrombotic therapies that cause bleeding. While strategies attempting to link pharmacodynamic testing and outcomes as a potential mechanism for tailoring therapy have been investigated, to date, those strategies have not been successful in outcomes studies.[7,8]

In this evaluation, we performed an exploratory analysis of the efficacy of ticagrelor while receiving the study drug. The

PEGASUS-TIMI 54 trial included patients both close to and remote from their last dose of a $P2Y_{12}$ antagonist and did not include a "run-in" period to assess tolerability. In addition, very few patients had been exposed to ticagrelor previously. This is in contrast to the design of the Dual Antiplatelet Therapy study,[9] which randomly assigned patients who were tolerating and compliant with 1 year of $P2Y_{12}$ inhibition to either continue or discontinue the same agent or have it withdrawn. To that end, in the PEGASUS-TIMI 54 trial, the patients who had completed 1 year of treatment had low rates of drug discontinuation beyond a year. This observation may be useful in clinical practice in illustrating that those patients tolerating ticagrelor at 1 year from their myocardial infarction are more likely to tolerate continued therapy relative to reinitiation of therapy in those patients who are distant from their last exposure. The robust risk reduction with ticagrelor in ischemic events occurring while receiving treatment was similar to that observed in studies of the continuation of treatment for patients tolerating therapy and suggests that efforts to improve medication adherence could improve outcomes.[5,10]

There are limitations to the present analysis. Patients in a randomized, placebo-controlled, clinical trial may be more likely to discontinue treatment for even mild adverse events than patients receiving open-label therapy who anticipate a benefit from the treatment. Therefore, rates of drug discontinuation due to dyspnea or minor bleeding may be overestimated in the present analysis. In addition, ticagrelor was not available in most participating countries when the PEGASUS-TIMI 54 trial began enrollment, and clinicians had little clinical experience with its tolerability profile. It is possible that, in current clinical practice, physicians are more familiar with the benign and usually transient nature of dyspnea caused by ticagrelor and, therefore, more likely to encourage patients to continue treatment. Adverse events identified through standard reporting may be less accurately identified; however, dedicated case-report form pages were used for selected adverse events (eg, bleeding). On-treatment analyses for efficacy may overestimate the magnitude of benefit, whereas intention-to-treat analyses may underestimate the magnitude of benefit, especially when there are early differences in treatment adherence due to mild or moderate adverse effects that are less likely to dissuade use as much in clinical practice with patient counseling.

Conclusions

When treatment was initiated in stable patients with prior myocardial infarction, the rate of treatment discontinuation was significantly higher for patients who received ticagrelor than for patients who received placebo, particularly early after initiation. This early discontinuation of treatment was primarily driven by nonserious adverse events, including mild to moderate dyspnea and nonmajor bleeding, illustrating the practical importance of such events. Among patients who completed 1 year of treatment, the subsequent rates of discontinuation were low. Moreover, for patients receiving the study drug, there was a substantial benefit to ticagrelor. These data underscore the need for patient counseling when initiating treatment with ticagrelor, to optimize shared decision making and, when appropriate, maximize adherence and improve clinical efficacy.

ARTICLE INFORMATION

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Author Contributions: Drs Bonaca and Sabatine had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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