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Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction

Marc P. Bonaca, M.D., M.P.H., Deepak L. Bhatt, M.D., M.P.H., Marc Cohen, M.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., Eva C. Jensen, M.D., Ph.D., Giulia Magnani, M.D., Sameer Bansilal, M.D., M. Polly Fish, B.A., Kyungah Im, Ph.D., Olof Bengtsson, Ph.Lic., Ton Oude Ophuis, M.D., Ph.D., Andrzej Budaj, M.D., Ph.D., Pierre Theroux, M.D., Mikhail Ruda, M.D., Christian Hamm, M.D., Shinya Goto, M.D., Jindrich Spinar, M.D., José Carlos Nicolau, M.D., Ph.D., Robert G. Kiss, M.D., Ph.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Peter Held, M.D., Ph.D., Eugene Braunwald, M.D., and Marc S. Sabatine, M.D., M.P.H., for the PEGASUS-TIMI 54 Steering Committee and Investigators*

ABSTRACT

BACKGROUND

The potential benefit of dual antiplatelet therapy beyond 1 year after a myocardial infarction has not been established. We investigated the efficacy and safety of ticagrelor, a $P2Y_{12}$ receptor antagonist with established efficacy after an acute coronary syndrome, in this context.

METHODS

We randomly assigned, in a double-blind 1:1:1 fashion, 21,162 patients who had had a myocardial infarction 1 to 3 years earlier to ticagrelor at a dose of 90 mg twice daily, ticagrelor at a dose of 60 mg twice daily, or placebo. All the patients were to receive low-dose aspirin and were followed for a median of 33 months. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. The primary safety end point was Thrombolysis in Myocardial Infarction (TIMI) major bleeding.

RESULTS

The two ticagrelor doses each reduced, as compared with placebo, the rate of the primary efficacy end point, with Kaplan–Meier rates at 3 years of 7.85% in the group that received 90 mg of ticagrelor twice daily, 7.77% in the group that received 60 mg of ticagrelor twice daily, and 9.04% in the placebo group (hazard ratio for 90 mg of ticagrelor vs. placebo, 0.85; 95% confidence interval [CI], 0.75 to 0.96; P=0.008; hazard ratio for 60 mg of ticagrelor vs. placebo, 0.84; 95% CI, 0.74 to 0.95; P=0.004). Rates of TIMI major bleeding were higher with ticagrelor (2.60% with 90 mg and 2.30% with 60 mg) than with placebo (1.06%) (P<0.001 for each dose vs. placebo); the rates of intracranial hemorrhage or fatal bleeding in the three groups were 0.63%, 0.71%, and 0.60%, respectively.

CONCLUSIONS

In patients with a myocardial infarction more than 1 year previously, treatment with ticagrelor significantly reduced the risk of cardiovascular death, myocardial infarction, or stroke and increased the risk of major bleeding. (Funded by AstraZeneca; PEGASUS-TIMI 54 ClinicalTrials.gov number, NCT01225562.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Bonaca at the TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at mbonaca@partners.org.

*A complete list of investigators in the 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 (PEGASUS-TIMI 54) trial is provided in the Supplementary Appendix, available at NEJM.org.

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Myocardial infarction is a global problem.[1] In the United States alone, nearly 8 million people have a history of myocardial infarction.[2] Patients who have had a myocardial infarction are at heightened risk for recurrent ischemic events,[3-5] which suggests that this population may derive particular benefit from intensive secondary prevention.

A key element in the pathobiology of cardiovascular ischemic events is the activated platelet.[6] Aspirin reduces the risk of ischemic events both among patients who present with an acute coronary syndrome and in secondary prevention for patients with a history of myocardial infarction.[7] The addition of a $P2Y_{12}$ receptor antagonist to aspirin has been shown to reduce further the risk of ischemic events in this population in the first year after an acute coronary syndrome.[8-11] The role of $P2Y_{12}$ receptor antagonists in long-term secondary prevention after myocardial infarction, however, has not been established. Practice guidelines in the United States and Europe currently recommend treatment with a $P2Y_{12}$ receptor antagonist for up to 1 year after a myocardial infarction.[12-15]

Ticagrelor is a potent, reversibly binding, direct-acting $P2Y_{12}$ receptor antagonist.[16] When added to aspirin for 1 year after an acute coronary syndrome, ticagrelor at a dose of 90 mg twice daily reduced the rate of major adverse cardiovascular events including cardiovascular death, as compared with clopidogrel at a dose of 75 mg once daily.[11] Building on these observations, we designed the 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 (PEGASUS-TIMI 54) trial to test the hypothesis that long-term therapy with ticagrelor added to low-dose aspirin reduces the risk of major adverse cardiovascular events among stable patients with a history of myocardial infarction. Furthermore, the PEGASUS-TIMI 54 trial evaluated two doses of ticagrelor therapy: 90 mg twice daily, which has been studied previously in acute coronary syndromes,[11] and 60 mg twice daily, which was selected to provide slightly less, but still consistent, platelet inhibition.

Methods

Study Design and Oversight

In this randomized, double-blind, placebo-controlled clinical trial,[17] patients underwent randomization at 1161 sites in 31 countries (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial was designed as a collaboration among the Thrombolysis in Myocardial Infarction (TIMI) Study Group, the executive and steering committees, and AstraZeneca, the trial sponsor (see the Supplementary Appendix). The protocol was approved by the relevant ethics committee at each participating site.

The raw database was provided to the TIMI Study Group, which conducted all the data analyses independently of the sponsor. The first draft of the manuscript was written by the first and last authors, and all the coauthors participated in subsequent revisions of the manuscript. The authors from the TIMI Study Group assume responsibility for the accuracy and completeness of the data and all the analyses, as well as for the fidelity of this report to the trial protocol (available at NEJM.org).

Study Population

Eligible patients had had a spontaneous myocardial infarction 1 to 3 years before enrollment, were at least 50 years of age, and had one of the following additional high-risk features: age of 65 years or older, diabetes mellitus requiring medication, a second prior spontaneous myocardial infarction, multivessel coronary artery disease, or chronic renal dysfunction, defined as an estimated creatinine clearance of less than 60 ml per minute. Patients were ineligible if there was planned use of a $P2Y_{12}$ receptor antagonist, dipyridamole, cilostazol, or anticoagulant therapy during the study period; if they had a bleeding disorder or a history of an ischemic stroke or intracranial bleeding, a central nervous system tumor, or an intracranial vascular abnormality; or if they had had gastrointestinal bleeding within the previous 6 months or major surgery within the previous 30 days. Full eligibility criteria are provided in the Supplementary Appendix.[17] Written informed consent was obtained from all the patients.

Randomization and Study Treatment

Eligible patients were randomly assigned, in a 1:1:1 ratio within each study site, to receive ticagrelor orally at a dose of 90 mg twice daily, ticagrelor orally at a dose of 60 mg twice daily, or placebo. Randomization was performed with the use of a central computerized telephone or Web-based system, and assignment was double-blinded. A modified study-drug option (blinded, double-dummy

ticagrelor or clopidogrel) was provided to investigators for use if a patient had an indication for $P2Y_{12}$-receptor blockade (see the Supplementary Appendix).[17] Patients planning to undergo elective major noncardiovascular procedures were advised to stop the study treatment 5 days before the procedure and resume it when it was deemed appropriate by the treating physician. All the patients were to take aspirin at a dose of 75 to 150 mg daily.

END POINTS

The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. Secondary end points were cardiovascular death and death from any cause. Prespecified exploratory efficacy end points included the composite of death from coronary heart disease, myocardial infarction, or stroke; the individual components of the composite end points; and the additional end points of urgent coronary revascularization, hospitalization for unstable angina, and transient ischemic attack. The primary safety end point was TIMI major bleeding. Other safety end points included intracranial hemorrhage and fatal bleeding. Definitions of the end points are provided in the Supplementary Appendix.[17] A central clinical-events committee, whose members were unaware of the treatment assignments, adjudicated all efficacy end points and bleeding episodes.

STATISTICAL ANALYSIS

We estimated that a total of 1360 primary endpoint events would be required in order to provide the study with approximately 90% power to detect a 20% reduction in relative risk with the 90-mg dose of ticagrelor and approximately 83% power to detect a 19% reduction in relative risk with the 60-mg dose of ticagrelor, when each dose was compared individually with placebo (see the Methods section in the Supplementary Appendix). The primary efficacy analysis was conducted on an intention-to-treat basis, with each dose compared with placebo, as a time-to-event analysis from randomization to the first occurrence of any element of the primary composite end point (cardiovascular death, myocardial infarction, or stroke).

The analysis of secondary end points proceeded in a hierarchical fashion, starting with cardiovascular death and then death from any cause; the additional end points listed above were evaluated on an exploratory basis. An exploratory analysis of the combined results observed with the two ticagrelor doses, as compared with placebo, was prespecified.

Safety analyses included all the patients who underwent randomization and received at least one dose of study drug. These analyses included all the events occurring after receipt of the first dose and within 7 days after receipt of the last dose of study drug.

To control the overall type I error, alpha was apportioned to the comparison of each ticagrelor dose with placebo (with the use of a correlation of 0.5 between the test statistics), and a Haybittle–Peto approach was used to take into account an interim analysis of efficacy that was performed by the independent data monitoring committee, resulting in a significance level of 0.026 being considered to indicate statistical significance in the final analyses. Event probabilities are expressed as Kaplan–Meier estimates of cumulative incidence at 36 months. Hazard ratios and 95% confidence intervals were generated with the use of a Cox proportional-hazards model, and all reported P values are two-sided.

RESULTS

STUDY PATIENTS, STUDY DRUG, AND FOLLOW-UP

A total of 21,162 patients underwent randomization from October 2010 through May 2013 (Fig. S1 in the Supplementary Appendix). The characteristics at baseline are shown in Table 1. The median time from the qualifying myocardial infarction to randomization was 1.7 years (interquartile range, 1.2 to 2.3); 53.6% of the qualifying events were ST-segment elevation myocardial infarctions. A total of 83.0% of the patients had a history of percutaneous coronary intervention, and 59.4% had multivessel coronary artery disease. Nearly all the patients (99.9%) received aspirin, which was given at a dose between 75 mg and 100 mg in 97.3% of patients.

A total of 20,942 patients (99.0%) received at least one dose of study drug. The proportions of patients in each group who discontinued treatment prematurely over the duration of the trial were 32.0% in the group that received 90 mg of ticagrelor twice daily, 28.7% in the group that received 60 mg of ticagrelor twice daily, and 21.4% in the placebo group (P<0.001 for the comparison of each ticagrelor dose vs. placebo). The majority of premature discontinuations in

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Ticagrelor, 90 mg (N=7050)	Ticagrelor, 60 mg (N=7045)	Placebo (N=7067)
Age — yr	65.4±8.4	65.2±8.4	65.4±8.3
Female sex — no. (%)	1682 (23.9)	1661 (23.6)	1717 (24.3)
White race — no. (%)†	6126 (86.9)	6077 (86.3)	6124 (86.7)
Weight — kg	82.0±16.7	82.0±17.0	81.8±16.6
Hypertension — no. (%)	5462 (77.5)	5461 (77.5)	5484 (77.6)
Hypercholesterolemia — no. (%)	5410 (76.7)	5380 (76.4)	5451 (77.1)
Current smoker — no. (%)	1187 (16.8)	1206 (17.1)	1143 (16.2)
Diabetes mellitus — no. (%)	2241 (31.8)	2308 (32.8)	2257 (31.9)
Multivessel coronary artery disease — no./total no. (%)	4155/7049 (58.9)	4190/7042 (59.5)	4213/7067 (59.6)
History of PCI — no./total no. (%)‡	5852/7049 (83.0)	5879/7044 (83.5)	5837/7066 (82.6)
>1 Prior myocardial infarction — no. (%)	1143 (16.2)	1168 (16.6)	1188 (16.8)
Peripheral-artery disease — no. (%)	371 (5.3)	368 (5.2)	404 (5.7)
Estimated glomerular filtration rate <60 ml/min/1.73 m^2 — no./total no. (%)§	1653/6958 (23.8)	1547/6955 (22.2)	1649/6985 (23.6)
Qualifying event¶			
Years since myocardial infarction			
Median	1.7	1.7	1.7
Interquartile range	1.2–2.3	1.2–2.3	1.2–2.3
Type of myocardial infarction — no. (%)			
STEMI	3763/7043 (53.4)	3757/7035 (53.4)	3809/7057 (54.0)
NSTEMI	2898/7043 (41.1)	2842/7035 (40.4)	2843/7057 (40.3)
Unknown type	382/7043 (5.4)	436/7035 (6.2)	405/7057 (5.7)
Medication at enrollment — no. (%)			
Aspirin at any dose	7039 (99.8)	7036 (99.9)	7057 (99.9)
Statin	6526 (92.6)	6495 (92.2)	6583 (93.2)
Beta-blocker	5812 (82.4)	5796 (82.3)	5878 (83.2)
ACE inhibitor or ARB	5702 (80.9)	5631 (79.9)	5697 (80.6)

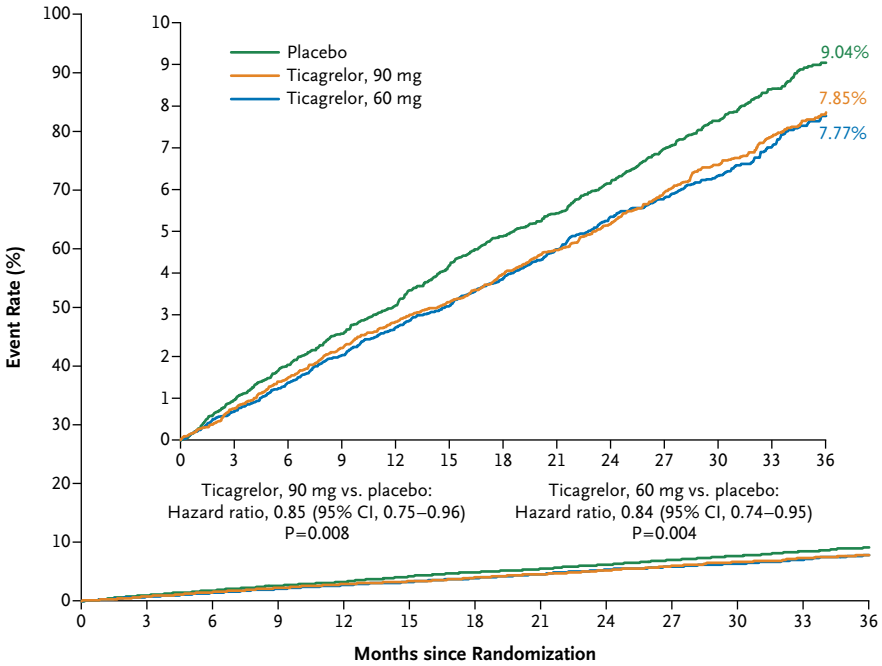
* Plus–minus values are means ±SD. Study drugs were administered twice daily. P>0.05 for all comparisons. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, NSTEMI non–ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.
† Race was self-reported.
‡ A total of 96.5% of PCIs involved stenting.
§ The estimated glomerular filtration rate was calculated with the use of the Modification of Diet in Renal Disease equation.
¶ Patients for whom it could not be verified that they had had a myocardial infarction were excluded from the denominator (7 patients in the 90-mg group, 10 in the 60-mg group, and 10 in the placebo group) as well as from the calculation for the median years since the myocardial infarction.

the two ticagrelor groups were due to adverse events (Fig. S1 in the Supplementary Appendix).

The median duration of follow-up was 33 months (interquartile range, 28 to 37), resulting in 56,004 patient-years of follow-up. Ascertainment of the primary end point was complete for 99.2% of the potential patient-years of follow-up.

EFFICACY

The two ticagrelor doses each significantly reduced, as compared with placebo, the rate of the primary composite end point of cardiovascular death, myocardial infarction, or stroke. Kaplan–Meier rates at 3 years were 7.85% in the group that received 90 mg of ticagrelor twice daily, 7.77% in the group that received 60 mg of ti-



No. at Risk

Placebo	7067	6979	6892	6823	6761	6681	6508	6236	5876	5157	4343	3360	2028
Ticagrelor, 90 mg	7050	6973	6899	6827	6769	6719	6550	6272	5921	5243	4401	3368	2038
Ticagrelor, 60 mg	7045	6969	6905	6842	6784	6733	6557	6270	5904	5222	4424	3392	2055

Figure 1. Kaplan–Meier Rates of Cardiovascular Death, Myocardial Infarction, and Stroke through 3 Years, According to Study Group.

Study drugs were administered twice daily. The inset shows the same data on an enlarged y axis.

cagrelor twice daily, and 9.04% in the placebo group (hazard ratio for 90 mg of ticagrelor vs. placebo, 0.85; 95% confidence interval [CI], 0.75 to 0.96; P=0.008; hazard ratio for 60 mg of ticagrelor vs. placebo, 0.84; 95% CI, 0.74 to 0.95; P=0.004) (Fig. 1). There was a trend with ticagrelor toward a reduction in the rate of cardiovascular death alone, but this effect was not significant (Table 2). Therefore, on the basis of the prespecified hierarchical testing procedure, the assessment of all the other efficacy end points was considered to be exploratory.

In the exploratory analyses, there was a significant reduction, as compared with placebo, in the rate of myocardial infarction with both the 90-mg dose and the 60-mg dose of ticagrelor and a significant reduction, as compared with placebo, in the rate of stroke with the 60-mg dose. Pooled analyses combining the two ticagrelor dose groups are shown in Figure 2. The two ticagrelor doses each significantly reduced the rate of composite end point of death from coronary heart disease, myocardial infarction, or stroke (Table 2). The rate of death from any cause did not differ significantly with either ticagrelor dose, as compared with placebo (Table 2). There were also no significant differences in the rates of urgent revascularization, hospitalization for unstable angina, or transient ischemic attack; these events each occurred in less than 1.2% of the patients overall and are shown in Table S1 in the Supplementary Appendix. We estimate that, for every 10,000 patients who began treatment (i.e., in an intention-to-treat analysis), 40 primary end-point events per year would be prevented with ticagrelor at a dose of 90 mg twice daily and 42 primary end-point events per year would be prevented with ticagrelor at a dose of 60 mg twice daily (see the Supplementary Appendix).

There was no apparent heterogeneity in the efficacy of ticagrelor at either dose with respect

Table 2. Efficacy End Points as 3-Year Kaplan–Meier Estimates.

End Point	Ticagrelor, 90 mg (N=7050)	Ticagrelor, 60 mg (N=7045)	Placebo (N=7067)	Ticagrelor, 90 mg vs. Placebo		Ticagrelor, 60 mg vs. Placebo	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Cardiovascular death, myocardial infarction, or stroke	493 (7.85)	487 (7.77)	578 (9.04)	0.85 (0.75–0.96)	0.008	0.84 (0.74–0.95)	0.004
Death from coronary heart disease, myocardial infarction, or stroke	438 (6.99)	445 (7.09)	535 (8.33)	0.82 (0.72–0.93)	0.002	0.83 (0.73–0.94)	0.003
Cardiovascular death or myocardial infarction	424 (6.79)	422 (6.77)	497 (7.81)	0.85 (0.75–0.97)	0.01	0.85 (0.74–0.96)	0.01
Death from coronary heart disease or myocardial infarction	350 (5.59)	360 (5.75)	429 (6.68)	0.81 (0.71–0.94)	0.004	0.84 (0.73–0.96)	0.01
Cardiovascular death	182 (2.94)	174 (2.86)	210 (3.39)	0.87 (0.71–1.06)	0.15	0.83 (0.68–1.01)	0.07
Death from coronary heart disease	97 (1.53)	106 (1.72)	132 (2.08)	0.73 (0.56–0.95)	0.02	0.80 (0.62–1.04)	0.09
Myocardial infarction	275 (4.40)	285 (4.53)	338 (5.25)	0.81 (0.69–0.95)	0.01	0.84 (0.72–0.98)	0.03
Stroke							
Any	100 (1.61)	91 (1.47)	122 (1.94)	0.82 (0.63–1.07)	0.14	0.75 (0.57–0.98)	0.03
Ischemic	88 (1.41)	78 (1.28)	103 (1.65)	0.85 (0.64–1.14)	0.28	0.76 (0.56–1.02)	0.06
Death from any cause	326 (5.15)	289 (4.69)	326 (5.16)	1.00 (0.86–1.16)	0.99	0.89 (0.76–1.04)	0.14

to the risk of the primary composite end point across major subgroups. These subgroups included age, sex, race, weight, type of index myocardial infarction, time from qualifying myocardial infarction to randomization, history of percutaneous coronary intervention, presence or absence of diabetes, presence or absence of multivessel coronary disease, presence or absence of chronic kidney disease, aspirin dose, and geographic region (Fig. S2 in the Supplementary Appendix).

SAFETY

The rate of the primary safety end point of TIMI major bleeding was higher with the two ticagrelor doses than with placebo. Kaplan–Meier rates at 3 years were 2.60% in the group that received 90 mg of ticagrelor twice daily, 2.30% in the group that received 60 mg of ticagrelor twice daily, and 1.06% in the placebo group (hazard ratio for 90 mg of ticagrelor vs. placebo, 2.69; 95% CI, 1.96 to 3.70; P<0.001; hazard ratio for 60 mg of ticagrelor vs. placebo, 2.32; 95% CI, 1.68 to 3.21; P<0.001) (Table 3), with no apparent heterogeneity among major subgroups (Fig. S3 in the Supplementary Appendix). The rates of TIMI minor bleeding, bleeding leading to transfusion, and bleeding leading to discontinuation of the study drug were also significantly higher with ticagrelor than with placebo (Table 3). The rates of fatal bleeding or nonfatal intracranial hemorrhage did not differ significantly between either ticagrelor dose group and placebo (Table 3). We estimate that, for every 10,000 patients who began treatment (i.e., in an intention-to-treat analysis), 41 TIMI major bleeding events per year would be caused with ticagrelor at a twice-daily dose of 90 mg and 31 TIMI major bleeding events per year would be caused with ticagrelor at a twice-daily dose of 60 mg (see the Supplementary Appendix).

Dyspnea was more frequent with the two ticagrelor doses, with 3-year event rates of 18.93% in the group that received 90 mg of ticagrelor twice daily, 15.84% in the group that received 60 mg of ticagrelor twice daily, and 6.38% in the placebo group (P<0.001 for each ticagrelor dose vs. placebo) (Table 3). The majority of episodes with ticagrelor were either mild (58.1%) or moderate (36.9%) in severity. The rates of dyspnea leading to discontinuation of the study drug were 6.5% in the group that received 90 mg of ticagrelor twice daily, 4.55% in the group that

End Point	Ticagrelor	Placebo	Hazard Ratio (95% CI)	P Value
	3-yr Kaplan–Meier event rate (%)			
Cardiovascular death, myocardial infarction, or stroke				
Ticagrelor, 90 mg	7.85	9.04	0.85 (0.75–0.96)	0.008
Ticagrelor, 60 mg	7.77	9.04	0.84 (0.74–0.95)	0.004
Ticagrelor pooled	7.81	9.04	0.84 (0.76–0.94)	0.001
Cardiovascular death				
Ticagrelor, 90 mg	2.94	3.39	0.87 (0.71–1.06)	0.15
Ticagrelor, 60 mg	2.86	3.39	0.83 (0.68–1.01)	0.07
Ticagrelor pooled	2.90	3.39	0.85 (0.71–1.00)	0.06
Myocardial infarction				
Ticagrelor, 90 mg	4.40	5.25	0.81 (0.69–0.95)	0.01
Ticagrelor, 60 mg	4.53	5.25	0.84 (0.72–0.98)	0.03
Ticagrelor pooled	4.47	5.25	0.83 (0.72–0.95)	0.005
Stroke				
Ticagrelor, 90 mg	1.61	1.94	0.82 (0.63–1.07)	0.14
Ticagrelor, 60 mg	1.47	1.94	0.75 (0.57–0.98)	0.03
Ticagrelor pooled	1.54	1.94	0.78 (0.62–0.98)	0.03

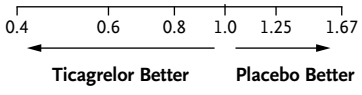


Figure 2. Hazard Ratios and Rates of the Primary End Point and Individual Components for Each Dose of Ticagrelor and for the Two Doses Pooled.

The squares and circles reflect the point estimates for the ticagrelor 90-mg group and the ticagrelor 60-mg group, respectively, as compared with placebo. The horizontal lines indicate 95% confidence intervals. The diamonds indicate both the point estimate (center of diamond) and the 95% confidence interval (width) for the two doses pooled versus placebo.

received 60 mg of ticagrelor twice daily, and 0.79% in the placebo group (P<0.001 for each ticagrelor dose vs. placebo) (Table 3). There were no notable differences between either ticagrelor dose group and placebo in the rates of renal or bradyarrhythmic adverse events; however, adverse events of gout were significantly more frequent with ticagrelor than with placebo (Table 3). Rates of overall adverse events, serious adverse events, and noncardiovascular causes of death are listed in Table S2 in the Supplementary Appendix.

DISCUSSION

Patients who have had a myocardial infarction remain at heightened risk for ischemic events over the long term.[3-5] In the PEGASUS-TIMI 54 trial, the addition of the $P2Y_{12}$ receptor antagonist ticagrelor to low-dose aspirin in patients 1 to 3 years after a myocardial infarction significantly reduced the risk of cardiovascular death, myocardial infarction, or stroke. The benefit of ticagrelor was consistent in major clinical subgroups and according to geographic region, and it continued to accrue over time, with a median of 33 months of follow-up.

Current practice guidelines recommend treatment with $P2Y_{12}$ receptor antagonists for 1 year after a myocardial infarction.[12-15] Post hoc landmark analyses from other studies have suggested a benefit to a longer duration of more-intensive antiplatelet therapy.[11,18-21] However, a dedicated trial of long-term prevention with clopidogrel on a background of aspirin in a broad population of patients with atherosclerotic disease or risk factors did not show a significant benefit.[22] A subsequent analysis specifically examining the subgroup of patients with prior myocardial infarction suggested a reduction in ischemic risk,[23] but this analysis was post hoc. The results of the present trial provide prospectively defined evidence affirming the hypothesis that long-term, intensive platelet inhibition with ticagrelor reduces ischemic events in patients with prior myocardial infarction.

Addressing a related but distinct question, the Dual Antiplatelet Therapy (DAPT) trial recently showed a reduction in nonfatal ischemic events with the continuation of a $P2Y_{12}$-receptor blocker on a background of aspirin for more than 12 months after coronary stenting.[24] Two notable differences between the trial designs are

Table 3. Safety End Points as 3-Year Kaplan–Meier Estimates.*

End Point	Ticagrelor, 90 mg (N=6988)	Ticagrelor, 60 mg (N=6958)	Placebo (N=6996)	Ticagrelor, 90 mg vs. Placebo		Ticagrelor, 60 mg vs. Placebo	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Bleeding							
TIMI major bleeding	127 (2.60)	115 (2.30)	54 (1.06)	2.69 (1.96–3.70)	<0.001	2.32 (1.68–3.21)	<0.001
TIMI minor bleeding	66 (1.31)	55 (1.18)	18 (0.36)	4.15 (2.47–7.00)	<0.001	3.31 (1.94–5.63)	<0.001
Bleeding requiring transfusion	122 (2.43)	105 (2.09)	37 (0.72)	3.75 (2.59–5.42)	<0.001	3.08 (2.12–4.48)	<0.001
Bleeding leading to study-drug discontinuation	453 (7.81)	354 (6.15)	86 (1.50)	5.79 (4.60–7.29)	<0.001	4.40 (3.48–5.57)	<0.001
Fatal bleeding or nonfatal intracranial hemorrhage	32 (0.63)	33 (0.71)	30 (0.60)	1.22 (0.74–2.01)	0.43	1.20 (0.73–1.97)	0.47
Intracranial hemorrhage	29 (0.56)	28 (0.61)	23 (0.47)	1.44 (0.83–2.49)	0.19	1.33 (0.77–2.31)	0.31
Hemorrhagic stroke	4 (0.07)	8 (0.19)	9 (0.19)	0.51 (0.16–1.64)	0.26	0.97 (0.37–2.51)	0.94
Fatal bleeding	6 (0.11)	11 (0.25)	12 (0.26)	0.58 (0.22–1.54)	0.27	1.00 (0.44–2.27)	1.00
Other adverse event							
Dyspnea	1205 (18.93)	987 (15.84)	383 (6.38)	3.55 (3.16–3.98)	<0.001	2.81 (2.50–3.17)	<0.001
Event leading to study-drug discontinuation	430 (6.50)	297 (4.55)	51 (0.79)	8.89 (6.65–11.88)	<0.001	6.06 (4.50–8.15)	<0.001
Serious adverse event	22 (0.41)	23 (0.45)	9 (0.15)	2.68 (1.24–5.83)	0.01	2.70 (1.25–5.84)	0.01
Renal event	166 (3.30)	173 (3.43)	161 (2.89)	1.17 (0.94–1.46)	0.15	1.17 (0.94–1.45)	0.15
Bradyarrhythmia	107 (2.04)	121 (2.32)	106 (1.98)	1.15 (0.88–1.50)	0.31	1.24 (0.96–1.61)	0.10
Gout	115 (2.28)	101 (1.97)	74 (1.51)	1.77 (1.32–2.37)	<0.001	1.48 (1.10–2.00)	0.01

* TIMI denotes Thrombolysis in Myocardial Infarction.

that DAPT randomly assigned patients to continuing versus stopping a $P2Y_{12}$-receptor blockade after 12 months of therapy and that DAPT included only patients who had not had clinically significant bleeding and were able to keep taking a $P2Y_{12}$-receptor antagonist, which would tend to minimize their bleeding complications. In PEGASUS-TIMI 54, by comparison, most patients began treatment with ticagrelor after an interruption in dual antiplatelet therapy, since most patients were enrolled close to 2 years after myocardial infarction, and patients were not necessarily excluded from the trial if they had had an intervening bleeding episode or cardiovascular event (except a recurrent myocardial infarction). Nonetheless, broadly speaking, the two trials showed that prolonged $P2Y_{12}$-receptor blockade reduced the rate of ischemic events and increased the rate of bleeding events among patients with coronary disease.

Ticagrelor significantly increased the rate of bleeding, including TIMI major bleeding, bleeding leading to transfusion, and bleeding leading to discontinuation of the study drug. The rates of bleeding leading to severe or irreversible harm (i.e., fatal bleeding or nonfatal intracranial hemorrhage) were less than 1% over a 3-year period in all three groups in this trial. However, the study protocol excluded patients with recent bleeding, prior stroke, or the need for oral anticoagulant therapy. Therefore, the safety profile of long-term ticagrelor that we observed should not be generalized to other populations at heightened risk for bleeding.

The two ticagrelor doses also caused dyspnea, which occurred early after the initiation of treatment and contributed to significantly higher rates of discontinuation of the study drug, as compared with placebo. The rates of drug discontinuation because of dyspnea observed with ticagrelor

in this trial were higher than those observed in the Study of Platelet Inhibition and Patient Outcomes (PLATO).[11] However, that trial enrolled patients with acute coronary syndromes in whom transient dyspnea is frequently associated with their acute illness, in contrast to the stable patients in the current trial, in whom the onset of dyspnea would be more surprising and hence would be more likely to lead to discontinuation.

The two ticagrelor doses were associated with a similar magnitude of efficacy in the intention-to-treat analysis. However, the rates of bleeding and dyspnea were numerically lower with the 60-mg dose of ticagrelor than with the 90-mg dose, resulting in a lower rate of discontinuation of the study drug and a better safety profile with the 60-mg dose. Thus, in general, the 60-mg dose may offer a more attractive benefit–risk profile, although these differences were not significant. The two ticagrelor doses were studied on a background of low-dose aspirin, as is recommended for patients with stable ischemic heart disease.[25,26]

In conclusion, the addition of ticagrelor, at a dose of 90 mg twice daily or 60 mg twice daily, to low-dose aspirin reduced the risk of cardiovascular death, myocardial infarction, or stroke and increased in the risk of TIMI major bleeding among patients who had had a myocardial infarction 1 to 3 years earlier.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

The authors' affiliations are as follows: the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston (M.P.B., D.L.B., G.M., M.P.F., K.I., S.A.M., S.D.W., E.B., M.S.S.); the Cardiovascular Division, Department of Medicine, Newark Beth Israel Medical Center, Rutgers–New Jersey Medical School, Newark (M.C.); French Alliance for Cardiovascular Trials, Département Hospitalo-Universitaire Fibrosis, Inflammation, Remodeling, Hôpital Bichat, Assistance Publique–Hôpitaux de Paris, INSERM Unité 1148, and Université Paris–Diderot, Sorbonne Paris Cité — all in Paris (P.G.S.); National Heart and Lung Institute, Royal Brompton Hospital, Imperial College, London (P.G.S.), and Department of Cardiovascular Science, University of Sheffield, Sheffield, United Kingdom (R.F.S.); AstraZeneca, Mölndal, Sweden (E.C.J., O.B., P.H.); Icahn School of Medicine at Mount Sinai, New York (S.B.); Canisius–Wilhelmina Hospital, Nijmegen, the Netherlands (T.O.O.); Postgraduate Medical School, Grochowski Hospital, Warsaw, Poland (A.B.); Montreal Heart Institute, Université de Montréal, Montreal (P.T.); Cardiology Research Center, Moscow (M.R.); Kerckhoff Heart Center, Bad Nauheim, and University of Giessen, Giessen — both in Germany (C.H.); Department of Medicine (Cardiology), Tokai University School of Medicine, Isehara, Japan (S.G.); University Hospital, Jihlavska, Brno, Czech Republic (J.S.); Heart Institute (InCor)–University of São Paulo Medical School, São Paulo (J.C.N.); and the Department of Cardiology, Military Hospital, Budapest, Hungary (R.G.K.).

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