ORIGINAL ARTICLE

Ticagrelor in Patients with Stable Coronary Disease and Diabetes

P.G. Steg, D.L. Bhatt, T. Simon, K. Fox, S.R. Mehta, R.A. Harrington, C. Held, M. Andersson, A. Himmelmann, W. Ridderstråle, M. Leonsson-Zachrisson, Y. Liu, G. Opolski, D. Zateyshchikov, J. Ge, J.C. Nicolau, R. Corbalán, J.H. Cornel, P. Widimský, and L.A. Leiter, for the THEMIS Steering Committee and Investigators*

ABSTRACT

BACKGROUND

Patients with stable coronary artery disease and diabetes mellitus who have not had a myocardial infarction or stroke are at high risk for cardiovascular events. Whether adding ticagrelor to aspirin improves outcomes in this population is unclear.

METHODS

In this randomized, double-blind trial, we assigned patients who were 50 years of age or older and who had stable coronary artery disease and type 2 diabetes mellitus to receive either ticagrelor plus aspirin or placebo plus aspirin. Patients with previous myocardial infarction or stroke were excluded. The primary efficacy outcome was a composite of cardiovascular death, myocardial infarction, or stroke. The primary safety outcome was major bleeding as defined by the Thrombolysis in Myocardial Infarction (TIMI) criteria.

RESULTS

A total of 19,220 patients underwent randomization. The median follow-up was 39.9 months. Permanent treatment discontinuation was more frequent with ticagrelor than placebo (34.5% vs. 25.4%). The incidence of ischemic cardiovascular events (the primary efficacy outcome) was lower in the ticagrelor group than in the placebo group (7.7% vs. 8.5%; hazard ratio, 0.90; 95% confidence interval [CI], 0.81 to 0.99; P=0.04), whereas the incidence of TIMI major bleeding was higher (2.2% vs. 1.0%; hazard ratio, 2.32; 95% CI, 1.82 to 2.94; P<0.001), as was the incidence of intracranial hemorrhage (0.7% vs. 0.5%; hazard ratio, 1.71; 95% CI, 1.18 to 2.48; P=0.005). There was no significant difference in the incidence of fatal bleeding (0.2% vs. 0.1%; hazard ratio, 1.90; 95% CI, 0.87 to 4.15; P=0.11). The incidence of an exploratory composite outcome of irreversible harm (death from any cause, myocardial infarction, stroke, fatal bleeding, or intracranial hemorrhage) was similar in the ticagrelor group and the placebo group (10.1% vs. 10.8%; hazard ratio, 0.93; 95% CI, 0.86 to 1.02).

CONCLUSIONS

In patients with stable coronary artery disease and diabetes without a history of myocardial infarction or stroke, those who received ticagrelor plus aspirin had a lower incidence of ischemic cardiovascular events but a higher incidence of major bleeding than those who received placebo plus aspirin. (Funded by AstraZeneca; THEMIS ClinicalTrials.gov number, NCT01991795.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Steg at the Department of Cardiology, Hôpital Bichat, 46 rue Henri Huchard, 75018 Paris, France, or at gabriel.steg@aphp.fr; or to Dr. Bhatt at Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, 75 Francis St., Boston, MA 02115, or at dlbhattmd@post.harvard.edu.

*A list of THEMIS investigators and committee members is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Steg and Bhatt contributed equally to this article.

This article was published on September 1, 2019, at NEJM.org.

DOI: 10.1056/NEJMoa1908077

Patients with both coronary artery disease and type 2 diabetes mellitus are at high risk for cardiovascular events.[1-4] Platelet-mediated thrombosis is a major mechanism contributing to ischemic events, and the higher risk among patients with diabetes is due in part to increased platelet activation.[5] Therefore, aspirin alone, the standard therapy in this population, may not provide fully effective antithrombotic protection. Ticagrelor, a reversible antagonist of the platelet $P2Y_{12}$ receptor, has been shown to provide more consistent platelet inhibition than aspirin or clopidogrel.[6] Ticagrelor has also been shown to provide protection against cardiovascular events when added to aspirin in patients with acute coronary syndromes[7] and in high-risk patients with previous myocardial infarction.[8] The relative benefit of ticagrelor in these patients has been consistent regardless of the presence of diabetes. However, since patients with diabetes are at high baseline risk, they have had a large absolute benefit from the addition of ticagrelor to aspirin.[9,10]

Whether patients with stable coronary artery disease and diabetes who do not have a history of myocardial infarction or stroke also derive benefit from dual antiplatelet therapy with ticagrelor plus aspirin is unclear. The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study (THEMIS) was designed to test the efficacy and safety of ticagrelor, as compared with placebo, in addition to aspirin in this population.

Methods

Trial Design and Conduct

The design of this randomized, double-blind trial has been published previously.[11] The protocol is available with the full text of this article at NEJM.org. AstraZeneca funded the trial, which was designed and overseen by an academic executive committee. All the trial centers obtained ethical approval according to local regulations. Site selection was conducted jointly by the national lead investigators and representatives of AstraZeneca, who performed site monitoring and supervision and handled the collection, storage, and analysis of the data. The Baim Clinical Research Institute independently validated all the data that are reported, with funding from AstraZeneca. All the authors contributed to the writing of the manuscript and made the decision to submit the manuscript for publication. The authors vouch for the completeness and accuracy of the data and the analyses and for the fidelity of the trial to the protocol.

Trial Population

The trial population consisted of patients who were 50 years of age or older and who had stable coronary artery disease and type 2 diabetes mellitus. The presence of stable coronary artery disease was determined by any one of the following mutually nonexclusive criteria: a history of previous percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG) or documentation of angiographic stenosis of at least 50% in at least one coronary artery. The presence of type 2 diabetes mellitus was determined by the receipt of an antihyperglycemic medication for at least 6 months. Patients with known history of myocardial infarction or stroke were excluded, as were patients who were receiving dual antiplatelet therapy. Details regarding the inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org. All the patients provided written informed consent.

Randomization and Treatment Groups

Eligible patients were randomly assigned in a 1:1 ratio to the ticagrelor group or the placebo group by means of an interactive voice-response or Web-response system. Randomization codes were generated in blocks of constant size. The trial-group assignment was conducted in a double-blind manner.

Patients were initially assigned to receive ticagrelor at a dose of 90 mg twice daily or matching placebo. During the trial, in view of the results of 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,[8,10,12,13] the protocol was amended and the dose of ticagrelor was reduced to 60 mg twice daily.[11] After May 11, 2015, patients who were already enrolled in the trial were switched to the 60-mg twice-daily dose of ticagrelor or placebo, and newly enrolled patients were randomly assigned to receive the

same reduced dose. All the patients also received low-dose aspirin (75 to 150 mg) unless such administration was contraindicated or was associated with unacceptable side effects.

TRIAL OUTCOMES

The primary efficacy outcome was a composite of cardiovascular death, myocardial infarction, or stroke. Secondary efficacy outcomes were tested hierarchically according to the following sequence: cardiovascular death, myocardial infarction, ischemic stroke, and death from any cause. The primary safety outcome was major bleeding, which was defined according to the TIMI classification. An exploratory outcome of net irreversible harm was prespecified as a composite of death from any cause, myocardial infarction, stroke, fatal bleeding, or intracranial hemorrhage. An academic clinical events committee adjudicated all deaths, potential ischemic and bleeding events, and peripheral-artery ischemic events in a blinded manner. The definitions of all trial outcomes are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The primary efficacy outcome was tested at a two-sided 4.96% significance level after adjustment for an interim efficacy analysis with a familywise error rate of 5%. We estimated that the annual event rate in the placebo group would be 2.5%. We determined that the occurrence of 1385 primary outcome events would provide the trial with a power of 90%, assuming a 16% lower risk of a primary outcome event in the ticagrelor group than in the placebo group.[11] This calculation resulted in an estimated sample size of 19,000 patients in the combined groups with a mean follow-up time of 40 months.

Efficacy analyses were performed in the modified intention-to-treat population, which included all the patients who had undergone randomization after the exclusion of those who had been enrolled at a site that was closed before unblinding. Safety analyses were performed in the safety analysis set, which included all the patients who had received at least one dose of ticagrelor or placebo, with patients evaluated according to the one they actually received. The safety analyses were performed with data from the on-treatment period, which was defined as the time from randomization to 7 days after last dose of study drug was administered. Given the proportion of patients who permanently discontinued therapy, sensitivity analyses of the primary efficacy end point were performed as on-treatment analyses in the safety analysis set.

For time-to-event analyses, Cox proportional-hazards models were used, with the trial group as the explanatory variable; confidence intervals and P values were calculated with the use of Wald statistics. Confidence intervals for secondary and exploratory efficacy end points have not been adjusted for multiple comparisons, so inferences drawn from these intervals may not be reproducible. Follow-up data for patients without events were censored either on the censoring date for the primary analysis or on the date of the last clinical assessment, whichever came first. The results of Kaplan–Meier analyses are presented at 36 months, except for sensitivity analyses of dose, in which the results of Kaplan–Meier analyses are presented at 24 months, given the shorter mean duration of treatment with the reduced dose of ticagrelor.

To assess possible effects of missing data in the ticagrelor group, the event rate in the placebo group was used to estimate the intensity of a Poisson process. On the basis of the missing follow-up time, we used the Poisson process to estimate the number of events in the ticagrelor group that would have been observed if the patients had completed the trial. The comparison between ticagrelor and placebo was recalculated with these additional events.

To estimate the interaction between the trial group and prespecified subgroups, we added to the model the trial group, subgroup, and interaction term between trial group and subgroup. Specific analyses were also prespecified to test the consistency of effect for the two doses of ticagrelor. Primary efficacy and safety analyses were repeated in the subgroup of patients who had undergone randomization after the reduction in the dose of ticagrelor. In addition, the analyses of the primary efficacy and safety outcomes were performed with the use of a Cox model with a factor for the trial group and a time-dependent variable for the administration of the 60-mg dose of ticagrelor to estimate the treatment effect of the 60-mg dose as compared with placebo; we also performed on-treatment analy-

ses for each dose. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

From February 10, 2014, to May 24, 2016, a total of 20,108 patients were enrolled. Of these patients, 19,271 underwent randomization at 1315 sites in 42 countries in North America, South America, Asia, Africa, Australia, and Europe. One site that had enrolled 51 patients was closed by the sponsor before unblinding owing to inadequate adherence to good clinical practice in a different trial.[11] Therefore, 19,220 patients (9619 in the ticagrelor group and 9601 in the placebo group) were included in the modified intention-to-treat population (Fig. S1 in the Supplementary Appendix).

The last visit with a trial patient was conducted on January 25, 2019. The censoring date for the efficacy analyses was October 29, 2018. The median follow-up of the trial was 39.9 months, with a maximum of 57 months up to the censoring date for the primary analysis. Data regarding vital status were available for 99.9% of the patients at the end of the trial and were missing for 21 patients (13 in the ticagrelor group and 8 in the placebo group); of these patients, 10 were lost to follow-up, and 11 withdrew consent and had unknown vital status. Permanent discontinuation of ticagrelor or placebo was more frequent in the ticagrelor group than in the placebo group (34.5% vs. 25.4%), a difference driven by more frequent dyspnea and bleeding with ticagrelor (Fig. S2 in the Supplementary Appendix).

Among the patients who had undergone randomization, 73.9% were enrolled before the reduction in the ticagrelor dose, whereas 26.1% of the patients were enrolled after the dose reduction and were randomly assigned to receive the 60-mg dose of ticagrelor or placebo. Among the patients in the ticagrelor group, the median exposure was 7.7 months to the 90-mg dose and 32.1 months to the 60-mg dose; 76.5% of the total exposure to ticagrelor was to the 60-mg dose (Fig. S3 in the Supplementary Appendix).

BASELINE CHARACTERISTICS

The characteristics of the patients were well balanced between the two groups (Table 1). The median age was 66 years, and 31.4% of the patients were women. A total of 58.0% of the patients had undergone PCI (with or without stent placement), 21.8% had undergone CABG but not PCI, and 7.0% had undergone both PCI and CABG; 20.2% had no history of coronary revascularization and had received only medical treatment. Patients had received a diagnosis of diabetes a median of 10.0 years before randomization. Approximately one quarter of the patients (25.5%) reported having had diabetes-related complications. Most of the patients were receiving two or more antihyperglycemic medications (Table S2 in the Supplementary Appendix). More than half the patients were taking metformin, and more than 20% were receiving insulin.

EFFICACY OUTCOMES

Efficacy outcomes are summarized in Table 2. The primary composite efficacy outcome occurred in 736 of 9619 patients (7.7%) in the ticagrelor group and in 818 of 9601 patients (8.5%) in the placebo group, which corresponded to Kaplan–Meier rates of 6.9% and 7.6%, respectively, at 36 months (hazard ratio, 0.90; 95% confidence interval [CI], 0.81 to 0.99; $P=0.04$) (Fig. 1). The number of patients who would need to be treated to prevent one primary event at 36 months was 138. The proportional-hazards assumption of the Cox model that the treatment effect was consistent over time was verified. The lower frequency of the primary composite outcome in the ticagrelor group was driven by lower incidences of myocardial infarction and stroke than in the placebo group.

Secondary efficacy outcomes were analyzed according to a prespecified hierarchy that started with cardiovascular death. Since there was no significant between-group difference in the incidence of cardiovascular death, the formal analysis stopped. Additional secondary efficacy outcomes are presented in Table 2; there were fewer myocardial infarctions and fewer ischemic strokes in the ticagrelor group than in the placebo group.

Adjudicated causes of death are provided in Table S3 in the Supplementary Appendix. Although cardiovascular causes of death were more frequent than noncardiovascular causes, the most frequently adjudicated cause of death was "presumed cardiovascular cause" with an unknown detailed cause. Fatal myocardial infarction and fatal strokes accounted for 51 and 52 deaths,

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Ticagrelor (N=9619)	Placebo (N=9601)
Median age (IQR) — yr	66.0 (61.0–72.0)	66.0 (61.0–72.0)
Female sex — no. (%)	3043 (31.6)	2988 (31.1)
Median body-mass index (IQR)†	29.0 (26.1–32.6)	29.1 (26.0–32.8)
Current smoker — no. (%)	1056 (11.0)	1038 (10.8)
Race — no. (%)‡		
Asian	2211 (23.0)	2195 (22.9)
Black	205 (2.1)	198 (2.1)
White	6838 (71.1)	6858 (71.4)
Other	365 (3.8)	350 (3.6)
Geographic region — no. (%)		
Asia and Australia	2145 (22.3)	2143 (22.3)
Central and South America	1100 (11.4)	1078 (11.2)
Europe and South Africa	4884 (50.8)	4875 (50.8)
North America	1490 (15.5)	1505 (15.7)
Disease history — no. (%)		
Hypertension	8909 (92.6)	8867 (92.4)
Dyslipidemia	8386 (87.2)	8367 (87.1)
Angina pectoris	5444 (56.6)	5357 (55.8)
Multivessel coronary artery disease	5951 (61.9)	5984 (62.3)
History of coronary arterial revascularization — no. (%)		
Any	7678 (79.8)	7667 (79.9)
PCI§	5558 (57.8)	5596 (58.3)
CABG only	2120 (22.0)	2071 (21.6)
Both PCI and CABG	676 (7.0)	670 (7.0)
Neither PCI nor CABG¶	1941 (20.2)	1934 (20.1)
Median time since most recent CABG (IQR) — yr	4.4 (1.6–9.2)	4.1 (1.5–9.3)
Median time since most recent PCI (IQR) — yr	3.3 (1.5–6.7)	3.3 (1.5–6.6)
History of additional vascular disease — no. (%)		
Peripheral artery disease	827 (8.6)	860 (9.0)
Polyvascular disease‖	1268 (13.2)	1311 (13.7)
History of diabetes		
Median duration (IQR) — yr	10 (5–16)	10 (5–16)
Diabetes complications — no. (%)**	2480 (25.8)	2430 (25.3)
Median glycated hemoglobin level (IQR) — %	7.1 (6.4–8.1)	7.1 (6.4–8.1)
Median estimated GFR (IQR) — ml/min/1.73 m^2††	75.1 (60.5–89.8)	75.0 (60.6–89.5)

* There were no significant differences between the two groups. IQR denotes interquartile range.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race was reported by the patients.
§ This category includes patients who had undergone percutaneous coronary intervention (PCI) with or without stent placement irrespective of whether they also had undergone CABG.
¶ Patients in this category had substantial stenosis (≥50% lumen stenosis) on coronary angiography but had not undergone revascularization.
‖ Polyvascular disease was defined as arterial obstructive disease involving at least two vascular beds, in which vascular-bed involvement was characterized by the presence of coronary artery disease, peripheral artery disease, or carotid artery stenosis or cerebral revascularization.
** Diabetic complications were defined as retinopathy, autonomic neuropathy, peripheral neuropathy, or nephropathy.
†† The estimated glomerular filtration rate (GFR) was calculated with the use of the Modification of Diet in Renal Disease equation.

Table 2. Primary, Secondary, and Other Ischemic Efficacy Outcomes (Modified Intention-to-Treat Population).

Outcome	Ticagrelor (N=9619)		Placebo (N=9601)		Hazard Ratio (95% CI)*	P Value
	Patients with Event	K–M Estimate at 36 Mo†	Patients with Event	K–M Estimate at 36 Mo†		
	no. (%)	%	*no. (%)*	%		
Primary efficacy outcome						
Cardiovascular death, myocardial infarction, or stroke	736 (7.7)	6.9	818 (8.5)	7.6	0.90 (0.81–0.99)	0.04
Secondary efficacy outcomes						
Cardiovascular death	364 (3.8)	3.3	357 (3.7)	3.0	1.02 (0.88–1.18)	0.79
Myocardial infarction	274 (2.8)	2.6	328 (3.4)	3.3	0.84 (0.71–0.98)	
Ischemic stroke	152 (1.6)	1.5	191 (2.0)	1.8	0.80 (0.64–0.99)	
Death from any cause‡	579 (6.0)	5.1	592 (6.2)	4.9	0.98 (0.87–1.10)	
Exploratory outcomes						
Death from any cause, myocardial infarction, or stroke	919 (9.6)	8.5	1018 (10.6)	9.2	0.90 (0.83–0.99)	
Any stroke	180 (1.9)	1.7	221 (2.3)	2.1	0.82 (0.67–0.99)	
Acute limb ischemia or major amputation for vascular cause	13 (0.1)	0.1	29 (0.3)	0.3	0.45 (0.23–0.86)	
Death from any cause, myocardial infarction, stroke, acute limb ischemia, or major amputation for vascular cause	927 (9.6)	8.5	1039 (10.8)	9.4	0.89 (0.82–0.97)	
Coronary arterial revascularization	828 (8.6)	8.2	879 (9.2)	8.9	0.94 (0.86–1.04)	

* Confidence intervals (CIs) for secondary and exploratory efficacy end points have not been adjusted for multiple comparisons, so inferences drawn from these intervals may not be reproducible.
† K–M denotes Kaplan–Meier.
‡ This category includes data related to vital status in patients who withdrew consent, as stipulated in the statistical analysis plan.

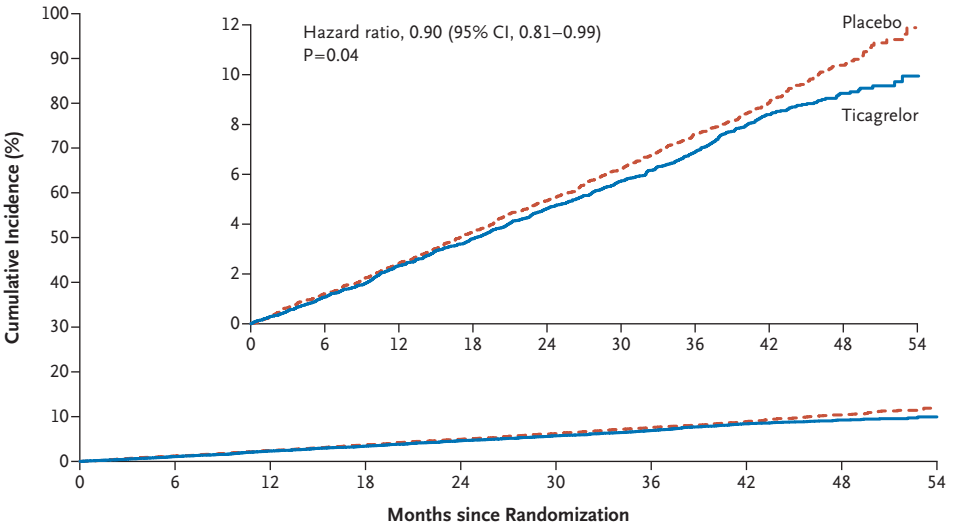
respectively, out of a total 1166 deaths. In a prespecified exploratory analysis, the number of events of the composite of acute limb ischemia or major amputation was lower with ticagrelor than with placebo (hazard ratio, 0.45; 95% CI, 0.23 to 0.86).

We conducted a prespecified sensitivity analysis of the primary outcome to account for the reduction in the ticagrelor dose during the trial; the results were consistent with those of the primary analysis (Table S4 in the Supplementary Appendix). In a sensitivity analysis performed to assess the possible effects of missing data, it was estimated that 757 primary outcome events (7.9%) would have occurred in the ticagrelor group, resulting in a hazard ratio of 0.93 (95% CI, 0.84 to 1.02). Selected prespecified subgroup analyses for the primary efficacy outcome are provided in Figure S4 in the Supplementary Appendix.

Given the proportion of patients who permanently discontinued either ticagrelor or placebo, we performed an on-treatment analysis in the safety analysis set; the findings were consistent with those in the modified intention-to-treat analysis (Table 2, and Table S5 in the Supplementary Appendix). There was a modest variation in treatment benefit according to the date of censoring of events relative to last dose of ticagrelor or placebo (Table S6 in the Supplementary Appendix).

SAFETY OUTCOMES

The results for the primary safety outcome, in an on-treatment analysis in the safety analysis set of 19,093 patients, are presented in Table 3



No. at Risk										
Ticagrelor	9619	9416	9237	9074	8909	8692	5974	3664	1684	170
Placebo	9601	9414	9246	9076	8909	8692	5934	3682	1685	174

Figure 1. Kaplan–Meier Analysis of the Primary Composite Efficacy Outcome.
The primary efficacy outcome was a composite of cardiovascular death, myocardial infarction, or stroke. The inset shows the same data on an expanded y axis.

and Figure 2. There was a higher frequency of TIMI major bleeding in the ticagrelor group than in the placebo group (2.2% vs. 1.0%; hazard ratio, 2.32; 95% CI, 1.82 to 2.94; P<0.001). The number of patients who would need to be treated for 36 months to cause one major bleeding event (i.e., the number needed to harm) was 93, as calculated in the modified intention-to-treat population of 19,220 patients. Serious adverse events were slightly less frequent with ticagrelor than with placebo (31.9% vs. 33.7%). Adverse events of interest occurred more frequently with ticagrelor than with placebo, a difference that was driven by a greater frequency of dyspnea in the ticagrelor group (Table 3).

Results that were consistent with the primary safety analysis were observed for other bleeding definitions. There was no significant between-group difference in the incidence of fatal bleeding episodes, although the number of events was higher in the ticagrelor group. Intracranial hemorrhage was more frequent with ticagrelor than with placebo, with 70 events and 46 events, respectively (0.7% vs. 0.5%; hazard ratio, 1.71; 95% CI, 1.18 to 2.48; P=0.005). This difference was driven by traumatic intracranial hemorrhages (41 vs. 16 events), whereas there was no significant between-group difference in the number of spontaneous events (28 vs. 27) or procedural events (1 vs. 3). A sensitivity analysis that evaluated the effect of the ticagrelor dose showed consistent results for TIMI major bleeding events in patients who received only the 60-mg dose of ticagrelor or corresponding placebo (Table S7 in the Supplementary Appendix). Selected prespecified subgroup analyses for the primary safety outcome are presented in Figure S5 in the Supplementary Appendix. There was no significant between-group difference in the predefined exploratory outcome of irreversible harm (death from any cause, myocardial infarction, stroke, fatal bleeding, or intracranial hemorrhage), as calculated in the modified intention-to-treat population (Fig. S6 in the Supplementary Appendix).

DISCUSSION

In this trial involving patients with stable coronary artery disease and diabetes, the addition of ticagrelor to low-dose aspirin was associated

Table 3. Safety Outcomes (Safety Population, On-Treatment Analysis).*

Outcome	Ticagrelor (N=9562)		Placebo (N=9531)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no. (%)	*no./100 patient-yr*	*no. %*	*no./100 patient-yr*		
Adjudicated adverse events†						
TIMI major bleeding	206 (2.2)	0.89	100 (1.0)	0.38	2.32 (1.82–2.94)	<0.001
TIMI major or minor bleeding	285 (3.0)	1.23	129 (1.4)	0.49	2.49 (2.02–3.07)	<0.001
TIMI major or minor bleeding or medical attention for bleeding	1072 (11.2)	4.61	485 (5.1)	1.85	2.51 (2.26–2.80)	<0.001
PLATO major bleeding	310 (3.2)	1.33	145 (1.5)	0.55	2.41 (1.98–2.93)	<0.001
BARC bleeding score‡						
3, 4, or 5	341 (3.6)	1.47	163 (1.7)	0.62	2.36 (1.96–2.84)	<0.001
4 or 5	17 (0.2)	0.07	11 (0.1)	0.04	1.73 (0.81–3.69)	0.16
5	17 (0.2)	0.07	10 (0.1)	0.04	1.90 (0.87–4.15)	0.11
Intracranial hemorrhage	70 (0.7)	0.30	46 (0.5)	0.18	1.71 (1.18–2.48)	0.005
Reported adverse events						
Serious adverse event	3049 (31.9)	13.12	3210 (33.7)	12.22	1.08 (1.03–1.13)	0.003
Adverse event leading to death	256 (2.7)	1.10	309 (3.2)	1.18	0.94 (0.79- 1.11)	0.45
Bleeding						
Any	1446 (15.1)	6.22	595 (6.2)	2.26	2.77 (2.52–3.05)	<0.001
Leading to discontinuation of ticagrelor or placebo	466 (4.9)	2.01	125 (1.3)	0.48	4.04 (3.32–4.92)	<0.001
Adverse events of interest§						
Any event	2562 (26.8)	11.02	1302 (13.7)	4.96	2.30 (2.15–2.46)	<0.001
Dyspnea						
Any	2049 (21.4)	8.82	700 (7.3)	2.66	3.33 (3.06–3.63)	<0.001
Leading to discontinuation of ticagrelor or placebo	661 (6.9)	2.84	75 (0.8)	0.29	9.27 (7.30–11.77)	<0.001
Gout	190 (2.0)	0.82	159 (1.7)	0.61	1.33 (1.08–1.64)	0.01
Renal impairment	225 (2.4)	0.97	220 (2.3)	0.84	1.15 (0.96–1.39)	0.14
Pneumonia	252 (2.6)	1.08	263 (2.8)	1.00	1.08 (0.91–1.28)	0.40
Bradyarrhythmia	137 (1.4)	0.59	120 (1.3)	0.46	1.28 (1.01–1.64)	0.05

* The on-treatment analysis was performed in the safety population (which included all the patients who had received at least one dose of ticagrelor or placebo); the treatment period was defined as the time from randomization until 7 days after the last dose was administered. PLATO denotes Platelet Inhibition and Patient Outcomes, and TIMI Thrombolysis in Myocardial Infarction.

† Adverse events in this category were adjudicated by an academic clinical events committee in a blinded approach.

‡ Bleeding in this category was defined according to a score of 3 to 5 on the Bleeding Academic Research Consortium (BARC) scale as follows: type 3, bleeding with a decrease in the hemoglobin of more than 3 g per deciliter, any transfusion, cardiac tamponade, or intracranial or ocular involvement; type 4, CABG-related bleeding; and type 5, fatal bleeding.

§ The adverse events of interest included dyspnea, gout, renal impairment, pneumonia, and bradyarrhythmia. Patients could have more than one category of event.

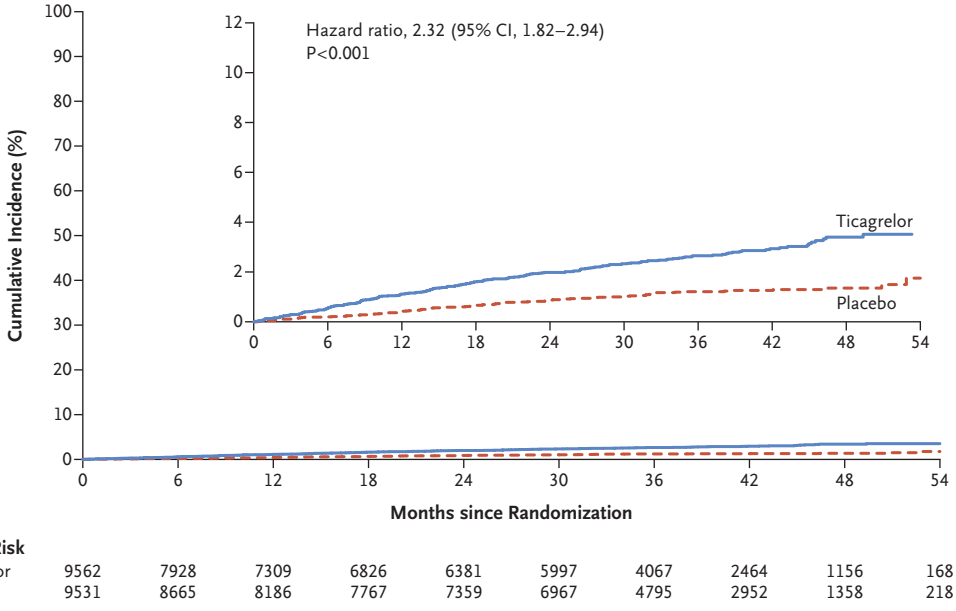


Figure 2. Kaplan–Meier Analysis of the Primary Safety Outcome.

The primary safety outcome was major bleeding, which was defined according to the Thrombolysis in Myocardial Infarction (TIMI) classification. Safety analyses were performed in the safety analysis set, which included all the patients who had received at least one dose of ticagrelor or placebo. Shown here are the results of the on-treatment analysis, which was performed in the safety population with the treatment period defined as the time from randomization until 7 days after the last dose was administered. The inset shows the same data on an expanded y axis.

with a lower risk of the primary efficacy outcome (a composite of cardiovascular death, myocardial infarction, or stroke) and a higher risk of major bleeding. In an exploratory analysis that weighed both efficacy and safety events, the risk of a composite outcome of net irreversible harm was not significantly lower in the ticagrelor group than in the placebo group, which suggests that ticagrelor therapy does not have a favorable risk–benefit ratio in this trial population.[14]

Rates of discontinuation were high in the two groups but were higher in the ticagrelor group, primarily due to an increased risk of bleeding and dyspnea. These findings are likely to reflect the side-effect profile that would be observed in clinical practice. When the results of the PEGASUS–TIMI 54 trial showed a better side-effect profile for the 60-mg twice-daily dose of ticagrelor than the 90-mg dose,[8,10] we lowered the dose of ticagrelor in our trial. Prespecified analyses that were performed according to dose provided results consistent with those in the primary analysis.

Previous studies have shown a benefit for long-term dual antiplatelet therapy with thienopyridine drugs after PCI and stenting,[15,16] including in patients with diabetes,[17] and evidence of benefit in patients with stable coronary artery disease who had a history of myocardial infarction,[18,19] including those with diabetes. Ticagrelor has shown superior efficacy to that of clopidogrel when added to low-dose aspirin in patients with an acute coronary syndrome and has been shown to be superior to placebo when added to aspirin in high-risk patients after myocardial infarction.[7,8] Prasugrel added to aspirin has also been shown to be superior to clopidogrel in patients with acute coronary syndromes treated with PCI, with a greater benefit in patients with diabetes, but did not show a benefit overall in

patients with acute coronary syndromes who were treated conservatively.[20-23] Our trial shows that adding ticagrelor to low-dose aspirin is effective in preventing ischemic cardiovascular events, including myocardial infarction, ischemic stroke, and acute limb ischemia or amputation. However, the prevention of ischemic events did not translate into a lower risk of cardiovascular death, presumably because fatal myocardial infarction and fatal stroke accounted for only a small fraction of all deaths (4.4% and 4.5%, respectively). The observed 10% lower incidence of ischemic events in the ticagrelor group, although significant, was less than the 16% lower incidence assumed at the time of the trial design.

In THEMIS, dual antiplatelet therapy with ticagrelor was associated with a higher frequency of intracranial hemorrhage than placebo. In the past, increases in the incidence of intracranial hemorrhage with dual antiplatelet therapy have been reported with ticagrelor,[7] clopidogrel,[24] and prasugrel.[22,25] Given these observations, it is of interest that investigators are evaluating an antibody-based agent to provide immediate and sustained reversal of the antiplatelet effects of ticagrelor.[26] It has been suggested that aspirin may not be needed when consistently effective $P2Y_{12}$ inhibition is present and may only increase bleeding risk without increasing efficacy.[27-29] Whether ticagrelor alone would have provided a superior risk–benefit ratio is speculative. Such a benefit was not borne out in the GLOBAL LEADERS trial in a general post-PCI population.[30,31] The ongoing TWILIGHT trial is testing a similar strategy.[32]

In conclusion, in patients with stable coronary artery disease and type 2 diabetes who did not have a history of myocardial infarction or stroke, ticagrelor plus aspirin was associated with a lower incidence of ischemic events than placebo plus aspirin at the expense of a higher incidence of major bleeding, including intracranial hemorrhage. As a result, there was no significantly lower incidence of the exploratory composite outcome of efficacy and safety with ticagrelor than with placebo.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

Supported by AstraZeneca.

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

We thank the patients for their participation and the site staff members who were involved in the conduct of the trial; C. Michael Gibson, M.D., of the Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center and Baim Institute for Clinical Research, Boston, and Gheorghe Doros, Ph.D. of Baim Clinical Research Institute and the Department of Biostatistics, Boston University, Boston, for supervising the statistical analyses; and Jayne Prats, Ph.D., for editorial assistance with an earlier version of the manuscript. Drs. Steg and Simon are participants in the French National Research Agency (ANR) Investissements d'Avenir program.

APPENDIX

The authors' full names and academic degrees are as follows: P. Gabriel Steg, M.D., Deepak L. Bhatt, M.D., M.P.H., Tabassome Simon, M.D., Kim Fox, M.D., Shamir R. Mehta, M.D., Robert A. Harrington, M.D., Claes Held, M.D., Marielle Andersson, M.Sc., Anders Himmelmann, M.D., Wilhelm Ridderstråle, M.D., Maria Leonsson-Zachrisson, M.D., Yuyin Liu, M.S., Grzegorz Opolski, M.D., Dmitry Zateyshchikov, M.D., Junbo Ge, M.D., José C. Nicolau, M.D., Ramón Corbalán, M.D., Jan H. Cornel, M.D., Petr Widimský, M.D., and Lawrence A. Leiter, M.D.

The authors' affiliations are as follows: the French Alliance for Cardiovascular Trials, Département Hospitalo-Universitaire FIRE, Hôpital Bichat, Université de Paris, INSERM Unité 1148 (P.G.S.), Assistance Publique–Hôpitaux de Paris (P.G.S., T.S.), Hôpital Saint Antoine, Department of Clinical Pharmacology, Unité de Recherche Clinique (T.S.), and Sorbonne Université (T.S.) — all in Paris; the National Heart and Lung Institute, Imperial College and Royal Brompton Hospital, London (P.G.S., K.F.); Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School (D.L.B.) and Baim Institute for Clinical Research (Y.L.) — both in Boston; the Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, ON (S.R.M.), and Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto (L.A.L.) — both in Canada; Stanford University, Stanford, CA (R.A.H.); the Department of Medical Sciences, Cardiology, Uppsala Clinical Research Center, Uppsala University, Uppsala (C.H.), and AstraZeneca BioPharmaceuticals Research and Development, Mölndal (M.A., A.H., W.R., M.L.-Z.) — both in Sweden; the Department of Cardiology, Medical University of Warsaw, Warsaw, Poland (G.O.); City Clinical Hospital No. 51, State Health Care Agency, Moscow (D.Z.); Zhongshan Hospital, Fudan University, Shanghai Institute of Cardiovascular Diseases, Shanghai, China (J.G.); Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (J.C.N.); Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile (R.C.); Northwest Clinics, Department of Cardiology, Alkmaar, Dutch Network for Cardiovascular Research, Utrecht, and Department of Cardiology, Radboud University Medical Center, Nijmegen — all in the Netherlands (J.H.C.); and Cardiocenter Charles University, Third Faculty of Medicine, University Hospital Kralovske Vinohrady, Prague, Czech Republic (P.W.).

REFERENCES

1. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229-34.
2. Krempf M, Parhofer KG, Steg PG, et al. Cardiovascular event rates in diabetic and nondiabetic individuals with and without established atherothrombosis (from the REduction of Atherothrombosis for Continued Health [REACH] Registry). Am J Cardiol 2010;105:667-71.
3. Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215-22.
4. Cavender MA, Steg PG, Smith SC Jr, et al. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. Circulation 2015;132:923-31.
5. Ferreiro JL, Angiolillo DJ. Diabetes and antiplatelet therapy in acute coronary syndrome. Circulation 2011;123:798-813.
6. Bhatt DL. Antiplatelet therapy: ticagrelor in ACS — what does PLATO teach us? Nat Rev Cardiol 2009;6:737-8.
7. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57.
8. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015;372:1791-800.
9. James S, Angiolillo DJ, Cornel JH, et al. Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J 2010;31:3006-16.
10. Bhatt DL, Bonaca MP, Bansilal S, et al. Reduction in ischemic events with ticagrelor in diabetic patients with prior myocardial infarction in PEGASUS-TIMI 54. J Am Coll Cardiol 2016;67:2732-40.
11. Bhatt DL, Fox K, Harrington RA, et al. Rationale, design and baseline characteristics of the effect of ticagrelor on health outcomes in diabetes mellitus patients intervention study. Clin Cardiol 2019;42:498-505.
12. Storey RF, Angiolillo DJ, Bonaca MP, et al. Platelet inhibition with ticagrelor 60 mg versus 90 mg twice daily in the PEGASUS-TIMI 54 trial. J Am Coll Cardiol 2016;67:1145-54.
13. Thomas MR, Angiolillo DJ, Bonaca MP, et al. Consistent platelet inhibition with ticagrelor 60 mg twice-daily following myocardial infarction regardless of diabetes status. Thromb Haemost 2017;117:940-7.
14. Steg PG, Bhatt DL. Is there really a benefit to net clinical benefit in testing antithrombotics? Circulation 2018;137:1429-31.
15. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371:2155-66.
16. Udell JA, Bonaca MP, Collet JP, et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. Eur Heart J 2016;37:390-9.
17. Meredith IT, Tanguay JF, Kereiakes DJ, et al. Diabetes mellitus and prevention of late myocardial infarction after coronary stenting in the randomized Dual Antiplatelet Therapy Study. Circulation 2016;133:1772-82.
18. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354:1706-17.
19. Bhatt DL, Flather MD, Hacke W, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. J Am Coll Cardiol 2007;49:1982-8.
20. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.
21. Wiviott SD, Braunwald E, Angiolillo DJ, et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel — Thrombolysis in Myocardial Infarction 38. Circulation 2008;118:1626-36.
22. Roe MT, Armstrong PW, Fox KAA, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med 2012;367:1297-309.
23. Wiviott SD, White HD, Ohman EM, et al. Prasugrel versus clopidogrel for patients with unstable angina or non-ST-segment elevation myocardial infarction with or without angiography: a secondary, prespecified analysis of the TRILOGY ACS trial. Lancet 2013;382:605-13.
24. Elmariah S, Doros G, Benavente OR, et al. Impact of clopidogrel therapy on mortality and cancer in patients with cardiovascular and cerebrovascular disease: a patient-level meta-analysis. Circ Cardiovasc Interv 2018;11(1):e005795.
25. Bhatt DL. Intensifying platelet inhibition — navigating between Scylla and Charybdis. N Engl J Med 2007;357:2078-81.
26. Bhatt DL, Pollack CV, Weitz JI, et al. Antibody-based ticagrelor reversal agent in healthy volunteers. N Engl J Med 2019;380:1825-33.
27. Bhatt DL, Grosser T, Dong JF, et al. Enteric coating and aspirin nonresponsiveness in patients with type 2 diabetes mellitus. J Am Coll Cardiol 2017;69:603-12.
28. Welsh RC, Roe MT, Steg PG, et al. A critical reappraisal of aspirin for secondary prevention in patients with ischemic heart disease. Am Heart J 2016;181:92-100.
29. Capodanno D, Mehran R, Valgimigli M, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. Nat Rev Cardiol 2018;15:480-96.
30. Vranckx P, Valgimigli M, Jüni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392:940-9.
31. Bhatt DL. Aspirin-still the global leader in antiplatelet therapy. Lancet 2018;392:896-7.
32. Baber U, Dangas G, Cohen DJ, et al. Ticagrelor with aspirin or alone in high-risk patients after coronary intervention: rationale and design of the TWILIGHT study. Am Heart J 2016;182:125-34.