ORIGINAL ARTICLE

Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes

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ABSTRACT

BACKGROUND

The relative merits of ticagrelor as compared with prasugrel in patients with acute coronary syndromes for whom invasive evaluation is planned are uncertain.

METHODS

In this multicenter, randomized, open-label trial, we randomly assigned patients who presented with acute coronary syndromes and for whom invasive evaluation was planned to receive either ticagrelor or prasugrel. The primary end point was the composite of death, myocardial infarction, or stroke at 1 year. A major secondary end point (the safety end point) was bleeding.

RESULTS

A total of 4018 patients underwent randomization. A primary-end point event occurred in 184 of 2012 patients (9.3%) in the ticagrelor group and in 137 of 2006 patients (6.9%) in the prasugrel group (hazard ratio, 1.36; 95% confidence interval [CI], 1.09 to 1.70; P=0.006). The respective incidences of the individual components of the primary end point in the ticagrelor group and the prasugrel group were as follows: death, 4.5% and 3.7%; myocardial infarction, 4.8% and 3.0%; and stroke, 1.1% and 1.0%. Definite or probable stent thrombosis occurred in 1.3% of patients assigned to ticagrelor and 1.0% of patients assigned to prasugrel, and definite stent thrombosis occurred in 1.1% and 0.6%, respectively. Major bleeding (as defined by the Bleeding Academic Research Consortium scale) was observed in 5.4% of patients in the ticagrelor group and in 4.8% of patients in the prasugrel group (hazard ratio, 1.12; 95% CI, 0.83 to 1.51; P=0.46).

CONCLUSIONS

Among patients who presented with acute coronary syndromes with or without ST-segment elevation, the incidence of death, myocardial infarction, or stroke was significantly lower among those who received prasugrel than among those who received ticagrelor, and the incidence of major bleeding was not significantly different between the two groups. (Funded by the German Center for Cardiovascular Research and Deutsches Herzzentrum München; ISAR-REACT 5 ClinicalTrials.gov number, NCT01944800.)

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*A list of the centers and investigators participating in the ISAR-REACT 5 trial is provided in the Supplementary Appendix, available at NEJM.org.

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According to the American Heart Association, approximately 720,000 persons in the United States will have a first episode of an acute coronary syndrome and approximately 335,000 will have a recurrent coronary event in 2019.[1] Dual antiplatelet therapy (an adenosine diphosphate receptor antagonist and aspirin) is the standard treatment for patients with acute coronary syndromes. The third-generation thienopyridine prasugrel and the cyclopentyltriazolopyrimidine ticagrelor provide greater, more rapid, and more consistent platelet inhibition than their predecessor clopidogrel.[2,3]

Randomized trials have shown the superiority of prasugrel and ticagrelor over clopidogrel in patients with acute coronary syndromes,[4,5] and both drugs received a class I recommendation for use in patients who have acute coronary syndromes with or without ST-segment elevation.[6-8] However, data are lacking on the relative merits of treatment for 1 year with ticagrelor as compared with prasugrel in patients with acute coronary syndromes for whom invasive evaluation is planned. Notably, the loading strategies of ticagrelor and prasugrel are different in patients who have acute coronary syndromes without ST-segment elevation. In these patients, ticagrelor is usually administered as pretreatment before diagnostic angiography,[4] but prasugrel is administered only after the coronary anatomy has been assessed by means of diagnostic angiography,[5] since no advantage has been observed when prasugrel is used as pretreatment.[9]

Against this background, we undertook this investigator-initiated, multicenter, randomized clinical trial to compare the efficacy and safety of two treatment strategies in patients with acute coronary syndromes. One strategy is based on ticagrelor, and the other is based on prasugrel.

Methods

Trial Design and Oversight

The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial was an investigator-initiated, phase 4, multicenter, randomized, open-label trial. The design and rationale of the trial have been published previously.[10] The first and last authors, with input from the steering committee, designed the trial. The Intracoronary Stenting and Antithrombosis Research Center, which is affiliated with Deutsches Herzzentrum München in Munich, Germany, was the data coordinating center. Data analysis was performed by the trial statistician. The first and last authors and the trial statistician vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, which is available with the full text of this article at NEJM.org. The first author wrote the first draft of the manuscript. All the authors agreed to submit the manuscript for publication. The funding institutions were not involved in writing the manuscript or interpreting the results. Commercially available ticagrelor or prasugrel tablets were prescribed by the treating physician and purchased by the patients. A detailed list of participating centers and investigators is provided in the Supplementary Appendix, available at NEJM.org.

Trial Population

Patients were eligible for enrollment in the trial if they were hospitalized for an acute coronary syndrome (ST-segment elevation myocardial infarction [STEMI], non–ST-elevation myocardial infarction [NSTEMI], or unstable angina) for which invasive evaluation was planned (i.e., the patient was scheduled to undergo coronary angiography). Exclusion criteria were determined predominantly from the summary of medical product characteristics of the trial drugs. The detailed exclusion criteria are listed in the Supplementary Appendix.

Randomization

In each participating center, treatment assignments were made with the use of sealed, opaque envelopes containing a computer-generated sequence that had been created at the coordinating center. Patients who met all the inclusion criteria and none of the exclusion criteria were randomly assigned in consecutive order to either ticagrelor or prasugrel, with a randomization ratio of 1:1. Time zero was defined as the time of randomization. Patients were stratified according to clinical trial site and clinical presentation (i.e., acute coronary syndromes with or without ST-segment elevation). Randomly permuted block sizes (of four, six, or eight) were used in each stratum.

Trial Protocol

Therapy with ticagrelor was started at a loading dose of 180 mg and continued at a maintenance dose of 90 mg twice daily. Patients who were assigned to ticagrelor received the loading dose as soon as possible after randomization.

Therapy with prasugrel was started at a loading dose of 60 mg and continued at a maintenance dose of 10 mg once per day. A reduced maintenance dose of 5 mg daily was recommended in patients who were 75 years of age or older and in those who had a body weight of less than 60 kg.

In the prasugrel group, timing of the initiation of the trial drug depended on the clinical presentation. In patients with ST-segment elevation, prasugrel was to be administered as soon as possible after randomization. In patients who had acute coronary syndromes without ST-segment elevation, administration of the loading dose of prasugrel was postponed until the coronary anatomy was known (with no pretreatment before diagnostic angiography) and before proceeding to percutaneous coronary intervention (PCI) (i.e., before the guidewire crossed the lesion). In patients with a coronary angiography–confirmed acute coronary syndrome who were not considered to be candidates for PCI but who were considered to be candidates for conservative therapy, dual antiplatelet therapy (aspirin and the randomly assigned trial medication) was recommended.

TRIAL END POINTS AND DEFINITIONS

The primary end point was the composite of death, myocardial infarction, or stroke at 1 year after randomization. Secondary end points included the safety end point, which was the incidence of bleeding at 1 year (type 3, 4, or 5 on the Bleeding Academic Research Consortium [BARC] scale, which ranges from 0 to 5, with higher values indicating more severe bleeding),[11] the incidence of the individual components of the primary end point at 1 year, and the incidence of definite or probable stent thrombosis at 1 year.[12] A detailed description of the end points is included in the Supplementary Appendix. All primary and secondary end points were adjudicated and classified according to source data (e.g. discharge letters, laboratory values, catheterization reports, electrocardiograms, and angiograms) by two members of the event adjudication committee who were unaware of the trial-group assignments.

FOLLOW-UP AND MONITORING

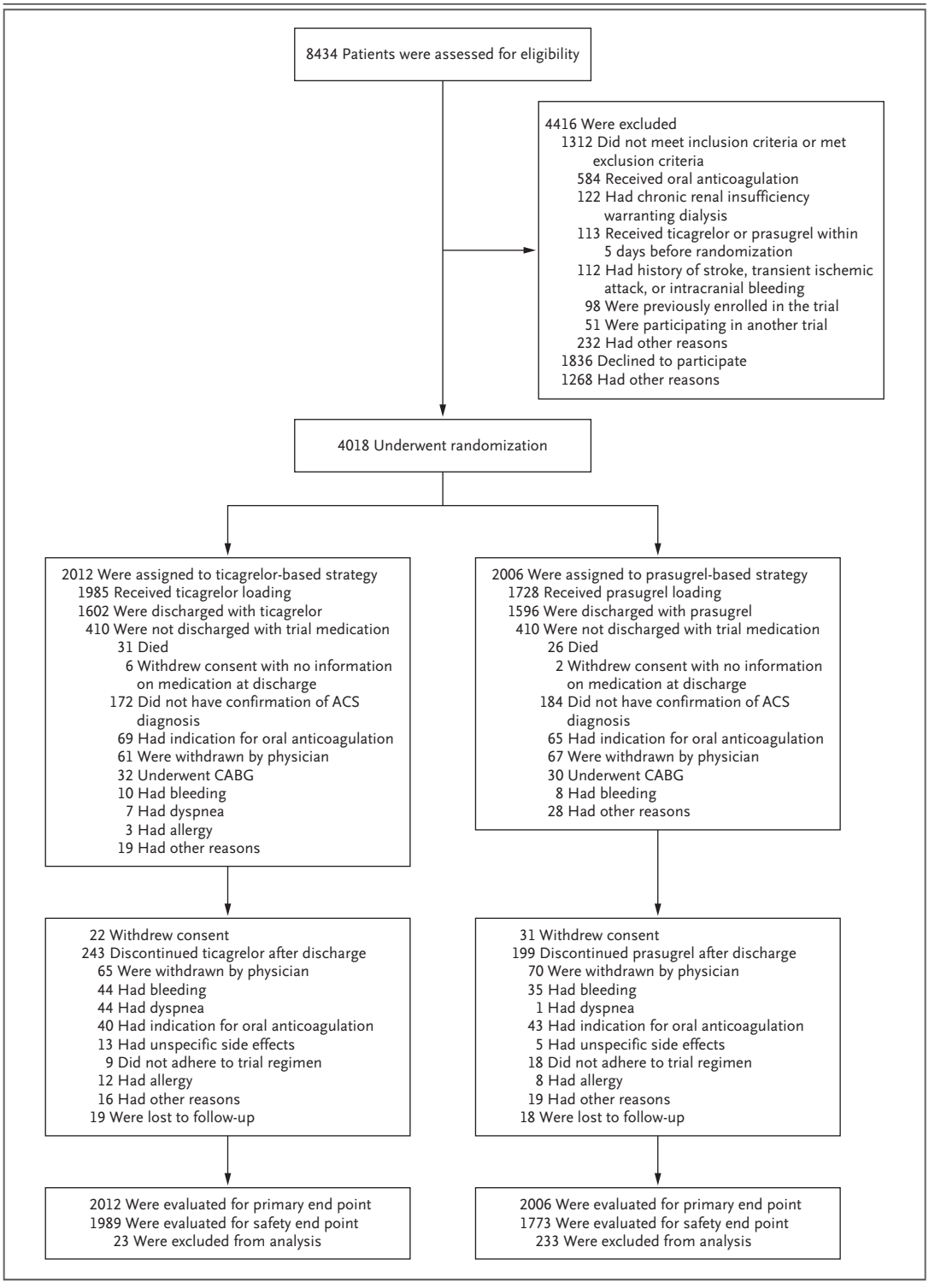
Clinical follow-up was scheduled at 30 days (with a window of ±10 days), 6 months (with a window of ±1 month), and 12 months (with a window of ±1 month). In case of potential end-point–related adverse events, source data were solicited. All serious adverse events and primary and secondary end points in this trial were monitored on-site. In addition, 100% of source data were checked for at least 10% of patients in all centers.

STATISTICAL ANALYSIS

The sample-size calculation was based on the assumption that the incidence of the primary end point would be 10.0% in the ticagrelor group[4] and 12.9% in the prasugrel group. With this assumption, we calculated that 1895 patients in each group would be needed for the trial to have 80% power to detect a relative risk that was lower by 22.5% in the rate of the primary end point in the ticagrelor group as compared with the prasugrel group with the use of a two-sided alpha level of 0.05, according to a chi-square test. Compensation for censoring of data for patients who were lost to follow-up required enrollment of 4000 patients.

Categorical variables such as demographic characteristics and medical history data were summarized with the use of frequencies and proportions and were compared with the use of the chi-square test. Continuous data were summarized with the use of means with standard deviations or medians with interquartile ranges and were compared with the use of Student's t-test or the nonparametric Wilcoxon rank-sum test.

The null hypothesis of the trial states that there is no difference between ticagrelor and prasugrel with respect to the treatment effect in patients with acute coronary syndromes for whom invasive evaluation is planned (hazard ratio, 1). The primary hypothesis test was performed by means of a Cox proportional-hazards model including the factor variables of trial group, participating center, and stratification according to clinical presentation (acute coronary syndromes with or without ST-segment elevation) as covariates. The confirmatory two-sided significance level was set at 5%. Similar Cox proportional-hazards models were used for the analysis of prespecified subgroups defined according to age (<75 years or ≥75 years), sex (male or female), smoking status (active smoker or not an active smoker), weight (<60 kg or ≥60 kg), the presence of diabetes mellitus (yes or no), renal function (dichotomized at the median creatinine value), cardiogenic shock (yes or no), clinical presentation (unstable angina, NSTEMI, or STEMI), and management strategy (PCI, coronary-artery bypass grafting [CABG], or conservative treatment).



The cumulative incidence of the primary end point was computed according to the complement of the Kaplan–Meier estimates of event-free survival. Cumulative incidence functions were computed for end points other than death to account for competing risks. Effect estimates of the secondary end points are presented along with corresponding 95% confidence intervals. The widths

Figure 1 (facing page). Screening, Randomization, Treatment, and Follow-up.

The specific design of the trial mandated routine pretreatment with ticagrelor in all patients in the ticagrelor group and no pretreatment with prasugrel in patients who had an acute coronary syndrome (ACS) without ST-segment elevation, so the loading dose was given to fewer patients in the prasugrel group than in the ticagrelor group. The primary end point was assessed in all patients according to the randomly assigned trial group, irrespective of the actual treatment received (the intention-to-treat population). Patients were evaluated from randomization (time zero) until death, withdrawal of consent, or the last contact date. The safety end point of type 3, 4, or 5 bleeding according to the Bleeding Academic Research Consortium (BARC) scale (which ranges from 0 to 5, with higher values indicating more severe bleeding) was analyzed in a modified intention-to-treat population, which included all patients who received at least one dose of the randomly assigned trial drug and were assessed for bleeding events up to 7 days after discontinuation of the trial drug. CABG denotes coronary-artery bypass grafting.

of the intervals are not adjusted for multiple comparisons because of the exploratory character of these analyses. An exception is the safety end point, which was the subject of hypothesis testing at an exploratory two-sided significance level of 5%.

All analyses, including the analysis of the primary end point, were performed according to the intention-to-treat principle (i.e., with inclusion of all patients according to the randomly assigned trial group, irrespective of the actual treatment received). Only the safety end point was analyzed in a modified intention-to-treat population, which included all patients who received at least one dose of the randomly assigned trial drug and were assessed for bleeding events up to 7 days after discontinuation of the trial drug. Patients were evaluated from randomization until death, withdrawal of consent, or the last contact date. Event-free survival with incomplete 1-year follow-up was counted as censored data for all time-to-event analyses.

RESULTS

PATIENTS

From September 2013 through February 2018, a total of 4018 patients were recruited in 23 centers (21 centers in Germany and 2 centers in Italy); 2012 patients were assigned to ticagrelor and 2006 patients were assigned to prasugrel (Fig. 1). The baseline characteristics of the patients are listed in Table 1. The suspected diagnosis at admission was STEMI in 41.1%, NSTEMI in 46.2%, and unstable angina in 12.7% of the patients. Before admission, 34.7% of patients in the ticagrelor group and 35.6% of patients in the prasugrel group were receiving aspirin, and 5.0% of patients in the ticagrelor group and 4.7% of patients in the prasugrel group were receiving clopidogrel. In patients presenting with STEMI, the interval from symptom onset to randomization was 3.2 hours (interquartile range, 1.8 to 7.7) in the ticagrelor group and 3.0 hours (interquartile range, 1.9 to 8.4) in the prasugrel group.

INTERVENTION AND FOLLOW-UP

A total of 84.1% of the patients underwent PCI, and 2.1% underwent CABG. Glycoprotein IIb/IIIa inhibitors were used in 12.3% of the patients who underwent PCI. In more than 99% of the patients who were receiving aspirin at discharge, the daily dose was 100 mg or less. (Angiographic and procedural characteristics are listed in Tables S1 and S2, respectively, in the Supplementary Appendix.)

In patients undergoing PCI for acute coronary syndromes without ST-segment elevation, the interval from randomization to receipt of the loading dose was 6 minutes (interquartile range, 1 to 25) in the ticagrelor group and 61 minutes (interquartile range, 30 to 142) in the prasugrel group. Since the specific design of the trial mandated routine pretreatment with ticagrelor in all patients but no pretreatment with prasugrel in patients who had acute coronary syndromes without ST-segment elevation, the loading dose of the trial medication was given to more patients in the ticagrelor group (1985 of 2012 patients [98.7%]) than in the prasugrel group (1728 of 2006 patients [86.1%]).

At discharge, 81.1% of patients in the ticagrelor group and 80.7% of patients in the prasugrel group received the randomly assigned trial drug (Table S3 in the Supplementary Appendix). At the 1-year follow-up, 243 of 1602 patients (15.2%) who were receiving ticagrelor at discharge and 199 of 1596 patients (12.5%) who were receiving prasugrel at discharge had discontinued the trial therapy ($P=0.03$). The median interval from randomization to discontinuation of the trial drug after discharge was 84 days (interquartile range, 23 to 181) in the ticagrelor group and 109 days (interquartile range, 35 to 220) in the prasugrel group

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Ticagrelor Group (N=2012)	Prasugrel Group (N=2006)
Age — yr	64.5±12.0	64.6±12.1
Female sex — no. (%)	478 (23.8)	478 (23.8)
Cardiovascular risk factors — no./total no. (%)		
Diabetes	463/2011 (23.0)	429/2005 (21.4)
Use of insulin for diabetes	143/2011 (7.1)	137/2005 (6.8)
Current smoker	682/2002 (34.1)	667/1999 (33.4)
Arterial hypertension	1432/2008 (71.3)	1384/2003 (69.1)
Hypercholesterolemia	1178/2007 (58.7)	1163/2003 (58.1)
Medical history — no./total no. (%)		
Myocardial infarction	311/2010 (15.5)	320/2005 (16.0)
PCI	453/2011 (22.5)	463/2004 (23.1)
Aortocoronary bypass surgery	115/2011 (5.7)	130/2005 (6.5)
Cardiogenic shock — no. (%)	31 (1.5)	34 (1.7)
Blood pressure — mm Hg		
Systolic†	144±25	143±24
Diastolic‡	82±15	82±14
Heart rate — beats/min§	77±16	76±16
BMI¶	27.8±4.6	27.8±4.4
Weight <60 kg — no./total no. (%)	108/2003 (5.4)	94/1988 (4.7)
Creatinine level — μmol/liter‖	88±27	88±31
Diagnosis at admission — no. (%)		
Unstable angina	249 (12.4)	261 (13.0)
NSTEMI	930 (46.2)	925 (46.1)
STEMI	833 (41.4)	820 (40.9)
Coronary angiography — no. (%)	2003 (99.6)	2001 (99.8)
Treatment strategy — no./total no. (%)**		
PCI	1676/2009 (83.4)	1701/2005 (84.8)
CABG	47/2009 (2.3)	36/2005 (1.8)
Conservative therapy	285/2009 (14.2)	268/2005 (13.4)
Other††	1/2009 (<0.1)	0

* Plus–minus values are means ±SD. There were no significant between-group differences in demographic and clinical characteristics at baseline. CABG denotes coronary-artery bypass grafting, NSTEMI non–ST-elevation myocardial infarction, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.
† Systolic blood pressure was not available in 3 patients (1 in the ticagrelor group and 2 in the prasugrel group).
‡ Diastolic blood pressure was not available in 16 patients (7 in the ticagrelor group and 9 in the prasugrel group).
§ The heart rate was not available in 2 patients (1 in each group).
¶ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. The BMI was not available in 31 patients (12 in the ticagrelor group and 19 in the prasugrel group).
‖ To convert the values for creatinine to milligrams per deciliter, divide by 88.4. The creatinine level was not available in 6 patients (5 in the ticagrelor group and 1 in the prasugrel group).
** The treatment strategy was not available in 4 patients who withdrew consent.
†† One patient in the ticagrelor group underwent surgery for aortic dissection.

(P=0.01). The types of antithrombotic therapy received by patients who discontinued the trial medication after discharge are listed in Table S4 in the Supplementary Appendix.

Patients were contacted by telephone (83% of contacts), at a hospital or outpatient visit (10%), or with a structured follow-up letter (7%). One-year follow-up was complete in all but 90 patients (41 patients in the ticagrelor group and 49 patients in the prasugrel group). Follow-up was incomplete because of withdrawal of written informed consent for trial participation in 53 patients (22 patients in the ticagrelor group and 31 patients in the prasugrel group). Among patients with incomplete 1-year follow-up data, the median length of follow-up was 31 days (interquartile range, 3 to 109) in the ticagrelor group and 32 days (interquartile range, 5 to 55) in the prasugrel group (P=0.57). There were no significant differences in baseline characteristics between patients with complete 1-year follow-up and those with incomplete 1-year follow-up, except with respect to coronary angiography, which was performed less frequently among patients with incomplete follow-up (Table S5 in the Supplementary Appendix).

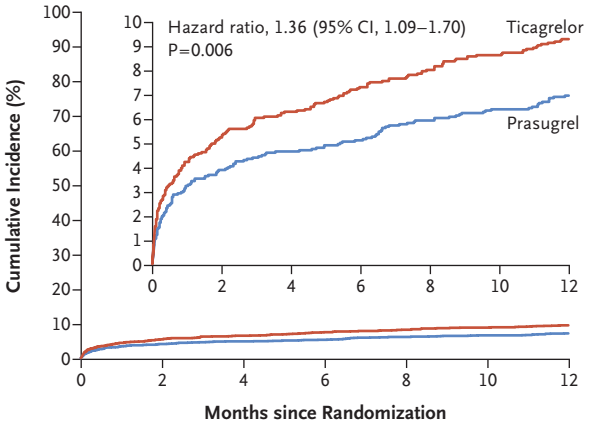


Figure 2. Cumulative Incidence of the Primary End Point at 1 Year.
The Kaplan–Meier curves show the cumulative incidence of the primary end point, which was a composite of death, myocardial infarction, or stroke at 1 year. The inset shows the same data on an enlarged y axis.

END POINTS

A primary end-point event — death from any cause, myocardial infarction, or stroke at 1 year after randomization — occurred in 184 of 2012 patients (9.1%) (Kaplan–Meier estimate at 1 year, 9.3%) in the ticagrelor group and 137 of 2006 patients (6.8%) (Kaplan–Meier estimate at 1 year, 6.9%) in the prasugrel group (hazard ratio, 1.36; 95% confidence interval [CI], 1.09 to 1.70; P=0.006) (Fig. 2 and Table 2). The composite of death from cardiovascular causes, myocardial infarction, or stroke occurred in 161 of 2012 patients (8.1%) in the ticagrelor group and 124 of 2006 patients (6.3%) in the prasugrel group (hazard ratio, 1.32; 95% CI, 1.04 to 1.66).

The incidences of the individual components of the primary end point are shown in Table 2. The rate of death from any cause at 1 year was 4.5% in the ticagrelor group and 3.7% in the prasugrel group (hazard ratio, 1.23; 95% CI, 0.91 to 1.68). The incidence of myocardial infarction was 4.8% in the ticagrelor group and 3.0% in the prasugrel group (hazard ratio, 1.63; 95% CI, 1.18 to 2.25). The incidence of stroke was 1.1% in the ticagrelor group and 1.0% in the prasugrel group (hazard ratio, 1.17; 95% CI, 0.63 to 2.15). The incidence of definite or probable stent thrombosis was 1.3% in the ticagrelor group and 1.0% in the prasugrel group (hazard ratio, 1.30; 95% CI, 0.72 to 2.33). Data from the analysis of the primary end point in the prespecified subgroups are shown in Figure S1 in the Supplementary Appendix.

In the modified intention-to-treat analysis (including all patients who received at least one dose of the randomly assigned trial drug and were assessed for bleeding events up to 7 days after discontinuation of the trial drug), major bleeding (BARC type 3 through 5) was observed in 5.4% of patients in the ticagrelor group and in 4.8% of patients in the prasugrel group (hazard ratio, 1.12; 95% CI, 0.83 to 1.51; P=0.46) (Fig. 3). In the intention-to-treat population, major bleeding (BARC type 3 through 5) was observed in 5.8% of patients in the ticagrelor group and 5.6% of patients in the prasugrel group (hazard ratio, 1.04; 95% CI, 0.80 to 1.34). In the intention-to-treat population, BARC type 1 or 2 bleeding was reported by the investigators in 13.8% of patients in the ticagrelor group and 15.1% of patients in the prasugrel group (hazard ratio, 0.90; 95% CI, 0.76 to 1.06).

Table 2. Clinical End Points.*

End Point	Ticagrelor Group (N=2012)	Prasugrel Group (N=2006)	Hazard Ratio (95% CI)	P Value
Primary end point: death, myocardial infarction, or stroke — no. (%)	184 (9.3)	137 (6.9)	1.36 (1.09–1.70)	0.006
Death — no. (%)				
From any cause	90 (4.5)	73 (3.7)	1.23 (0.91–1.68)	
From cardiovascular cause	63 (3.2)	59 (3.0)		
From noncardiovascular cause	27 (1.4)	14 (0.7)		
Myocardial infarction — no. (%)†	96 (4.8)	60 (3.0)	1.63 (1.18–2.25)	
Type 1 — no.	52	35		
Type 2 — no.	4	3		
Type 4a — no.	19	11		
Type 4b — no.	20	11		
Type 5 — no.	1	0		
STEMI — no.	31	14		
Stroke				
Any — no. (%)	22 (1.1)	19 (1.0)	1.17 (0.63–2.15)	
Ischemic — no.	16	17		
Hemorrhagic — no.	6	2		
Definite or probable stent thrombosis — no. (%)	26 (1.3)	20 (1.0)	1.30 (0.72–2.33)	
Definite stent thrombosis — no. (%)	22 (1.1)	12 (0.6)		
Secondary safety end point: BARC type 3, 4, or 5 bleeding — no./total no. (%)‡	95/1989 (5.4)	80/1773 (4.8)	1.12 (0.83–1.51)	0.46
BARC 3a	47	41		
BARC 3b	32	31		
BARC 3c	4	2		
BARC 4	8	2		
BARC 5a	1	0		
BARC 5b	3	4		

* The percentages shown are Kaplan–Meier estimates. Cumulative incidence functions were computed for end points other than death to account for competing risks.
† Myocardial infarction was classified as spontaneous infarction (type 1), infarction caused by ischemic imbalance (type 2), infarction related to PCI (type 4a), infarction related to thrombosis of a coronary stent (type 4b), and infarction related to CABG (type 5).
‡ On the Bleeding Academic Research Consortium (BARC) scale, type 3a indicates overt bleeding with a decrease in the hemoglobin level of 3 to less than 5 g per deciliter or any transfusion; type 3b, overt bleeding with a decrease in the hemoglobin level of 5 g or more per deciliter or leading to cardiac tamponade, surgical intervention, or the use of intravenous vasoactive agents; type 3c, intracranial hemorrhage or intraocular bleeding compromising vision; type 4, CABG-related bleeding; type 5a, probable fatal bleeding; and type 5b, definite fatal bleeding. Data on bleeding were analyzed in all patients who received at least one dose of the randomly assigned trial drug and were assessed for bleeding events up to 7 days after discontinuation of the trial drug.

DISCUSSION

In this investigator-initiated, randomized, multicenter trial, prasugrel was superior to ticagrelor with respect to the composite end point of death, myocardial infarction, or stroke at 1 year after randomization in patients with acute coronary syndromes who were scheduled to undergo invasive evaluation. The lower incidence of the composite end point was primarily driven by fewer myocardial infarctions in the prasugrel group than in the ticagrelor group. The benefit of fewer ischemic events with prasugrel did not occur at the expense of an increased risk of bleeding. The results were consistent across the whole spectrum of presentation of acute coronary syndromes.

A particular feature of this trial is that it did not simply compare two antiplatelet drugs. Rather, it compared two antiplatelet treatment strategies involving two different drugs. We had hypothesized that the ticagrelor-based strategy would be superior to the prasugrel-based strategy. The superiority assumption was based on several considerations. Although direct head-to-head comparisons of pretreatment with no pretreatment with ticagrelor in patients who have acute coronary syndromes without ST-segment elevation are lacking, pretreatment with ticagrelor was associated with an early benefit over clopidogrel in the Study of Platelet Inhibition and Patient Outcomes (PLATO).[4] In contrast, in another trial, pretreatment with prasugrel was not beneficial in patients who had acute coronary syndromes without ST-segment elevation, and it was associated with an increased incidence of major bleeding complications.[9] On the basis of the rationale that a stronger platelet inhibition at the time of PCI reduces periprocedural thrombotic risk, the pretreatment strategy with ticagrelor was considered to be advantageous. However, the present trial shows that a prasugrel-based strategy with deferred loading after knowledge of coronary anatomy in patients with acute coronary syndromes without ST-segment elevation was superior to a ticagrelor-based strategy with routine pretreatment.

Also, previous findings suggest a consistent benefit of ticagrelor but not a consistent benefit of prasugrel in patients with acute coronary syndromes who receive conservative therapy. In PLATO, ticagrelor was superior to clopidogrel not only in patients who underwent PCI but also in those who received conservative treatment.[13] Conversely, in the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial, prasugrel was not superior to clopidogrel in patients who had acute coronary syndromes without ST-segment elevation and who did not undergo revascularization.[14] Whereas in PLATO only 61% of the patients underwent PCI during the index hospitalization,[4] PCI was performed much more frequently in the present trial (84%). Therefore, the contribution of patients who did not undergo PCI to the overall results was relatively small. Finally, pharmacodynamic studies showing a stronger antiplatelet effect of ticagrelor[15] and the potential beneficial pleiotropic effects of ticagrelor, particularly those related to increased release of adenosine,[16] favored the expectation of superiority of ticagrelor over prasugrel in the current trial.

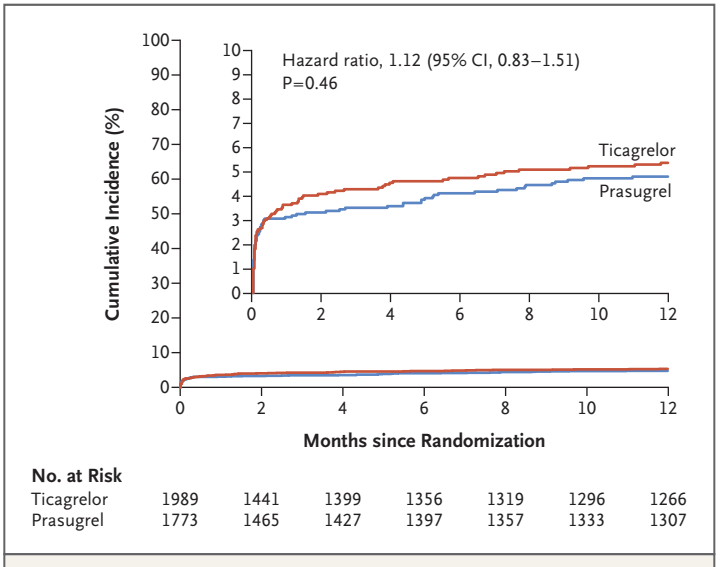


Figure 3. Cumulative Incidence of the Safety End Point at 1 Year.

The Kaplan–Meier curves show the cumulative incidence of the safety end point, which was the incidence of BARC type 3, 4, or 5 bleeding at 1 year. The analysis was performed in a modified intention-to-treat population, which included all patients who received at least one dose of the randomly assigned trial drug and were assessed for bleeding events up to 7 days after discontinuation of the trial drug. The inset shows the same data on an enlarged y axis.

An unexpected finding was that the risk of ischemic events (the composite of death, myocardial infarction, or stroke) at 1 year after randomization in the ISAR-REACT 5 trial was significantly lower in the prasugrel group than in the ticagrelor group. A randomized head-to-head comparison trial that aimed to assess clinical outcomes with ticagrelor versus prasugrel in patients with acute coronary syndromes was discontinued prematurely after recruitment of 1230 patients.[17] In that trial, 95% of recruited patients presented with STEMI, so the number of patients with acute coronary syndromes without ST-segment elevation was negligible. The incidence of the primary composite net clinical end point assessed after 7 days did not differ between the ticagrelor and prasugrel groups. However, reimbursement constraints led to a high incidence of switching to clopidogrel after discharge; this precluded a reliable comparison of clinical outcomes with the two trial drugs during the 1-year follow-up period.[17,18]

An interaction between treatment effect and aspirin dosage has been reported for ticagrelor[19]

but not for prasugrel.[20] However, the actual dose of aspirin in the present trial was 100 mg per day or less, as compared with a dose of 300 mg per day or more in 54% of the U.S. patients in PLATO.[19] Moreover, compliance issues (the once-daily administration of prasugrel vs. a twice-a-day regimen for ticagrelor), differences in half-life, the reversibility of action, interactions with other drugs, and the different side-effect profile of the two drugs may also warrant consideration.

The incidence of the primary end point in the ticagrelor group was close to the predicted event rate for that group (9.3% and 10.0%, respectively). The finding of a lower incidence of the primary end point in the prasugrel group than in the ticagrelor group was not anticipated during the sample-size calculation. The incidence of myocardial infarction was lower in the present trial than in previous pivotal trials.[4,5] This may be explained in part by differences in the definition of myocardial infarction. Although the adjudication of end points was performed in a blinded manner, the open-label nature of the trial remains a limitation. Moreover, most of the follow-up was conducted by telephone and not with face-to-face contact.

In conclusion, among patients who presented with acute coronary syndromes with or without ST-segment elevation, the incidence of the composite end point of death, myocardial infarction, or stroke was significantly lower among patients who received prasugrel than among those who received ticagrelor. The incidence of major bleeding was not higher in the prasugrel group than in the ticagrelor group.

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

APPENDIX

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REFERENCES

1. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics — 2019 update: a report from the American Heart Association. Circulation 2019; 139(10):e56-e528.

2. Brandt JT, Payne CD, Wiviott SD, et al. A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. Am Heart J 2007;153(1):66.e9-66.e16.

3. Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation 2009;120:2577-85.

4. 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.

5. 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.
6. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64(24):e139-e228.
7. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2019;40:87-165.
8. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127(4):e362-e425.
9. Montalescot G, Bolognese L, Dudek D, et al. Pretreatment with prasugrel in non–ST-segment elevation acute coronary syndromes. N Engl J Med 2013;369:999-1010.
10. Schulz S, Angiolillo DJ, Antoniucci D, et al. Randomized comparison of ticagrelor versus prasugrel in patients with acute coronary syndrome and planned invasive strategy — design and rationale of the iNtracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial. J Cardiovasc Transl Res 2014;7:91-100.
11. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736-47.
12. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.
13. James SK, Roe MT, Cannon CP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised PLATelet inhibition and patient Outcomes (PLATO) trial. BMJ 2011;342:d3527.
14. 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.
15. Lemesle G, Schurtz G, Bauters C, Hamon M. High on-treatment platelet reactivity with ticagrelor versus prasugrel: a systematic review and meta-analysis. J Thromb Haemost 2015;13:931-42.
16. Wittfeldt A, Emanuelsson H, Brandrup-Wognsen G, et al. Ticagrelor enhances adenosine-induced coronary vasodilatory responses in humans. J Am Coll Cardiol 2013;61:723-7.
17. Motovska Z, Hlinomaz O, Miklik R, et al. Prasugrel versus ticagrelor in patients with acute myocardial infarction treated with primary percutaneous coronary intervention: multicenter randomized PRAGUE-18 Study. Circulation 2016;134:1603-12.
18. Motovska Z, Hlinomaz O, Kala P, et al. 1-Year outcomes of patients undergoing primary angioplasty for myocardial infarction treated with prasugrel versus ticagrelor. J Am Coll Cardiol 2018;71:371-81.
19. Mahaffey KW, Wojdyla DM, Carroll K, et al. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. Circulation 2011;124:544-54.
20. Kohli P, Udell JA, Murphy SA, et al. Discharge aspirin dose and clinical outcomes in patients with acute coronary syndromes treated with prasugrel versus clopidogrel: an analysis from the TRITON-TIMI 38 study (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38). J Am Coll Cardiol 2014;63:225-32.