ORIGINAL ARTICLE

A Genotype-Guided Strategy for Oral $P2Y_{12}$ Inhibitors in Primary PCI

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ABSTRACT

BACKGROUND

It is unknown whether patients undergoing primary percutaneous coronary intervention (PCI) benefit from genotype-guided selection of oral $P2Y_{12}$ inhibitors.

METHODS

We conducted a randomized, open-label, assessor-blinded trial in which patients undergoing primary PCI with stent implantation were assigned in a 1:1 ratio to receive either a $P2Y_{12}$ inhibitor on the basis of early *CYP2C19* genetic testing (genotype-guided group) or standard treatment with either ticagrelor or prasugrel (standard-treatment group) for 12 months. In the genotype-guided group, carriers of *CYP2C19**2 or *CYP2C19**3 loss-of-function alleles received ticagrelor or prasugrel, and noncarriers received clopidogrel. The two primary outcomes were net adverse clinical events — defined as death from any cause, myocardial infarction, definite stent thrombosis, stroke, or major bleeding defined according to Platelet Inhibition and Patient Outcomes (PLATO) criteria — at 12 months (primary combined outcome; tested for noninferiority, with a noninferiority margin of 2 percentage points for the absolute difference) and PLATO major or minor bleeding at 12 months (primary bleeding outcome).

RESULTS

For the primary analysis, 2488 patients were included: 1242 in the genotype-guided group and 1246 in the standard-treatment group. The primary combined outcome occurred in 63 patients (5.1%) in the genotype-guided group and in 73 patients (5.9%) in the standard-treatment group (absolute difference, −0.7 percentage points; 95% confidence interval [CI], −2.0 to 0.7; P<0.001 for noninferiority). The primary bleeding outcome occurred in 122 patients (9.8%) in the genotype-guided group and in 156 patients (12.5%) in the standard-treatment group (hazard ratio, 0.78; 95% CI, 0.61 to 0.98; P=0.04).

CONCLUSIONS

In patients undergoing primary PCI, a *CYP2C19* genotype–guided strategy for selection of oral $P2Y_{12}$ inhibitor therapy was noninferior to standard treatment with ticagrelor or prasugrel at 12 months with respect to thrombotic events and resulted in a lower incidence of bleeding. (Funded by the Netherlands Organization for Health Research and Development; POPular Genetics ClinicalTrials.gov number, NCT01761786; Netherlands Trial Register number, NL2872.)

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In patients with ST-segment elevation myocardial infarction (STEMI), the preferred method of reperfusion is primary percutaneous coronary intervention (PCI) with stent implantation. In these patients, dual antiplatelet therapy, consisting of aspirin and a $P2Y_{12}$ inhibitor, is essential to prevent recurrent thrombotic events such as stent thrombosis.[1] Current guidelines[1,2] favor the more potent platelet inhibitors ticagrelor and prasugrel over clopidogrel because these drugs are more effective for the prevention of thrombotic events.[3,4] However, this greater efficacy comes with a higher risk of bleeding.[3,4]

Clopidogrel is a prodrug, transformed into its active metabolite by hepatic cytochrome P450 enzymes. The active metabolite irreversibly inhibits the $P2Y_{12}$ receptor on platelets, which results in inhibition of platelet aggregation. However, approximately 30% of white patients have an inadequate response to clopidogrel as measured with platelet-function tests.[5] Part of this variation in response can be explained by genetic variations, such as the *CYP2C19**2 and *CYP2C19**3 loss-of-function alleles.[6-9] In patients without these loss-of-function alleles, clopidogrel has shown similar efficacy to that of ticagrelor and prasugrel.[10-12] We therefore conducted the CYP2C19 Genotype-Guided Antiplatelet Therapy in ST-Segment Elevation Myocardial Infarction Patients — Patient Outcome after Primary PCI (POPular Genetics) trial to determine whether a *CYP2C19* genotype–guided strategy for selection of oral $P2Y_{12}$ inhibitors can reduce bleeding risk without increasing thrombotic risk in patients with STEMI undergoing primary PCI with stent implantation.

Methods

Trial Design

The POPular Genetics trial was an investigator-initiated, randomized, open-label, assessor-blinded trial performed at 10 European sites (8 in the Netherlands, 1 in Belgium, and 1 in Italy). It was sponsored by the Netherlands Organization for Health Research and Development, and Spartan Bioscience provided the Spartan RX point-of-care system and the reagents for free. Neither entity had any role in the design or execution of the trial or in the analysis of the data. Details of the design have been published previously.[13]

The trial was approved by the appropriate ethics committees and national authorities in each country. The trial was registered after the enrollment of the first 18 patients, as described in the Supplementary Appendix (available with the full text of this article at NEJM.org). An independent data and safety monitoring board monitored the trial and had full access to all data. An independent clinical-event committee whose members were unaware of the trial-group assignments adjudicated all outcomes. Trial monitoring was executed by an external service provider (Research Drive, Norg, the Netherlands). The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available at NEJM.org.

Major Protocol Revision

The initial plan was for the trial to compare a genotype-guided strategy for selecting oral $P2Y_{12}$ inhibitors with a standard-treatment strategy for which clopidogrel was recommended. However, the 2011 European Society of Cardiology (ESC) guideline for patients with acute coronary syndrome without ST-segment elevation recommended use of ticagrelor or prasugrel over clopidogrel.[14] In anticipation that the same recommendation would be made for patients with ST-segment elevation, we changed the treatment in the standard-treatment group from clopidogrel to ticagrelor or prasugrel. Because we were now testing guided de-escalation of therapy instead of guided escalation of therapy, there were major changes in the primary outcomes and hypotheses of the trial. These changes are summarized in the Supplementary Appendix under "Major Protocol Revision May 2012."

Trial Population

Patients were eligible for enrollment if they had signs or symptoms of STEMI lasting 30 minutes to 12 hours, underwent primary PCI with stent implantation, and were 21 years of age or older. Exclusion criteria are provided in Table S1 in the Supplementary Appendix. Because patients were asked to participate in the trial during the acute phase of myocardial infarction, many provided only oral informed consent before randomization. Such patients were eligible for the final analysis only if written informed consent was subsequently obtained.

Pretrial Treatment

Pretrial antithrombotic treatment was administered according to local protocol. This usually consist-

ed of a loading dose of aspirin, a P2Y$_{12}$ inhibitor, and heparin. Other antithrombotic periprocedural therapies were chosen at the discretion of the treating physician, as was the P2Y$_{12}$ inhibitor administered before randomization.

RANDOMIZATION AND TRIAL PROCEDURES

Using an Internet-based randomization procedure with computer-generated block randomization for each site, we randomly assigned patients in a 1:1 ratio to a *CYP2C19* genotype–guided strategy or to standard treatment with ticagrelor or prasugrel (Fig. S1 in the Supplementary Appendix). Patients were enrolled during or up to 48 hours after primary PCI.

In patients assigned to the genotype-guided strategy, *CYP2C19* genotyping was performed with the use of the TaqMan StepOnePlus assay at a central laboratory (St. Antonius Hospital, Nieuwegein, the Netherlands) or with an on-site point-of-care Spartan RX device (Spartan Bioscience). Use of the Spartan device began during the course of the trial; not all hospitals started using it simultaneously. Genetic testing for the *CYP2C19**2 and *CYP2C19**3 loss-of-function alleles was performed as soon as possible after randomization. Details of the logistics of these tests in this trial have been published previously.[15] Carriers of a loss-of-function *CYP2C19* allele were treated with ticagrelor or prasugrel, whereas noncarriers (*CYP2C19**1/*1) received clopidogrel according to the label instructions. If patients switched between P2Y$_{12}$ inhibitors, the use of a loading dose was at the discretion of the treating physician. Either ticagrelor or prasugrel was prescribed to each patient in the standard-treatment group, according to local protocol.

All patients were treated with a P2Y$_{12}$ inhibitor for at least 1 year after primary PCI. Patients were asked to fill out a questionnaire at 1 month, 6 months, and 12 months after primary PCI. Follow-up data were collected with the use of the hospital electronic health record. Questionnaires were used as an additional source of information. If necessary, the general practitioner, the patient's pharmacist, or the patient was contacted.

OUTCOMES

There were two primary outcomes. The first was the combined outcome of net adverse clinical events, which included death from any cause, myocardial infarction (defined according to the Third Universal Definition of Myocardial Infarction),[16] definite stent thrombosis (defined according to the Academic Research Consortium),[17] stroke (defined as a new neurologic deficit ending in death or lasting >24 hours, not due to another readily identifiable cause such as trauma), or major bleeding defined according to Platelet Inhibition and Patient Outcomes (PLATO) criteria (including major bleeding related to coronary-artery bypass grafting [CABG] as well as non–CABG-related major bleeding[18]), at 12 months (primary combined outcome). The second was PLATO major bleeding (CABG-related and non–CABG-related) or minor bleeding at 12 months (primary bleeding outcome). A complete list of secondary thrombotic and bleeding outcomes is provided in Tables S2 and S3 in the Supplementary Appendix.

STATISTICAL ANALYSIS

The incidence of the primary combined outcome was assumed to be 18.8% in the standard-treatment group and 16.9% in the genotype-guided group. These estimates were based on unpublished data from the Central Holland Acute Myocardial Infarction (CHAIR) study, the Ongoing Tirofiban in Myocardial Infarction Evaluation (On-TIME) 2 trial, and subanalyses of the PLATO trial and the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38.[10,11,19] Using a power of 80% and an alpha level of 0.05 and setting the noninferiority threshold for the absolute difference between the two groups in the incidence of the primary combined outcome at 2 percentage points, we calculated that 2474 patients would be needed to show noninferiority. For the primary bleeding outcome, the incidence was assumed to be 14.5% in the genotype-guided group and 18.9% in the standard-treatment group. Fewer patients were needed to show superiority for this outcome. Accounting for withdrawals and for approximately 200 patients enrolled before the May 2012 protocol amendment, we planned to include 2700 patients.

The end of the primary PCI procedure was defined as time 0, irrespective of when randomization took place. Owing to the logistics of obtaining informed consent, obtaining genotyping results, and (if necessary) switching the P2Y$_{12}$ inhibitor, outcome events during the first 24 hours after primary PCI were excluded from the primary analysis. The primary analysis followed the intention-to-treat principle and included all

patients enrolled after the May 2012 protocol amendment. In addition, a per-protocol analysis was performed. The primary combined outcome was first assessed in an analysis of the noninferiority of the *CYP2C19* genotype–guided strategy to standard treatment. If noninferiority was confirmed, superiority was assessed. For the primary bleeding outcome, the *CYP2C19* genotype–guided strategy was assumed to be superior to standard treatment. No adjustment for alpha error was performed to account for the assessment of two primary outcomes, because both analyses were required to show significance at a P value of less than 0.05 in order to assert a beneficial effect of the genotype-guided strategy. Both primary outcomes were also assessed in 26 prespecified subgroups. Two sensitivity analyses were planned. The first included events during the 24 hours after primary PCI, and the second analysis involved stratification according to center.

Time-to-event curves were constructed with the use of the Kaplan–Meier method. Differences between the survival curves were compared with the use of the log-rank test, and Cox proportional-hazards models were used to calculate hazard ratios with 95% confidence intervals. Confidence intervals for secondary outcomes have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible. P values were two-sided, and values of less than 0.05 were considered to indicate statistical significance. Data were analyzed with R software, version 3.6.0 (R Foundation for Statistical Computing).

RESULTS

PARTICIPANTS AND FOLLOW-UP

From June 2011 through April 2018, a total of 2751 patients were randomly assigned to a treatment group (Fig. 1). A screening log was kept at only one center; the records of those patients screened are shown in Table S4 in the Supplementary Appendix. Patients who underwent duplicate randomization in error, those who withdrew consent, and those who were enrolled before the protocol amendment of May 2012 were excluded from all analyses. Therefore, 2488 patients entered the intention-to-treat analysis (1242 in the genotype-guided group and 1246 in the standard-treatment group), of whom 3 were lost to follow-up. The database was locked on May 28, 2019, after all trial participants had completed at least 12 months of follow-up.

The two groups were balanced with regard to all baseline characteristics and non–trial-related medications and procedures (Table 1, and Tables S5 and S6 in the Supplementary Appendix). Table S7 in the Supplementary Appendix provides an overview of the genotype results, and Table S8 provides an overview of the intervals from symptom onset to the time that a patient was receiving the recommended therapy. In the genotype-guided group, 60.6% of the patients received clopidogrel and 39.1% received ticagrelor or prasugrel after their genetic results were available (Table 1). In the standard-treatment group, 92.7% of the patients were treated with ticagrelor or prasugrel and 7.0% with clopidogrel.

The percentage of patients who adhered to the recommended trial drug during the entire duration of follow-up, as assessed by the investigators, was 84.5% in the genotype-guided group and 82.0% in the standard-treatment group. Tables S9A, B, and C in the Supplementary Appendix provide an overview of how many patients switched or discontinued a $P2Y_{12}$ inhibitor and for what reasons, and Table S10 provides an overview of $P2Y_{12}$ inhibitor use during follow-up.

PRIMARY OUTCOMES

At 12 months, death from any cause, myocardial infarction, definite stent thrombosis, stroke, or PLATO major bleeding (the primary combined outcome) occurred in 63 patients (5.1%) in the genotype-guided group and in 73 patients (5.9%) in the standard-treatment group. The genotype-guided strategy met the prespecified criterion for noninferiority with respect to net adverse clinical events (absolute difference in incidence, −0.7 percentage points; 95% confidence interval [CI], −2.0 to 0.7; P<0.001 for noninferiority) (Fig. 2A and Table 2). The analysis for superiority did not support superiority of the genotype-guided strategy (hazard ratio, 0.87; 95% CI, 0.62 to 1.21; P=0.40). The primary bleeding outcome (PLATO major or minor bleeding) was significantly less common in the genotype-guided group than in the standard-treatment group (122 events [9.8%] vs. 156 [12.5%]; hazard ratio, 0.78; 95% CI, 0.61 to 0.98; P=0.04) (Fig. 2B and Table 3). The results of the per-protocol analysis and the sensitivity analyses were consistent with those of the primary analyses (Tables S11 and S12 in the Supplementary Appendix).

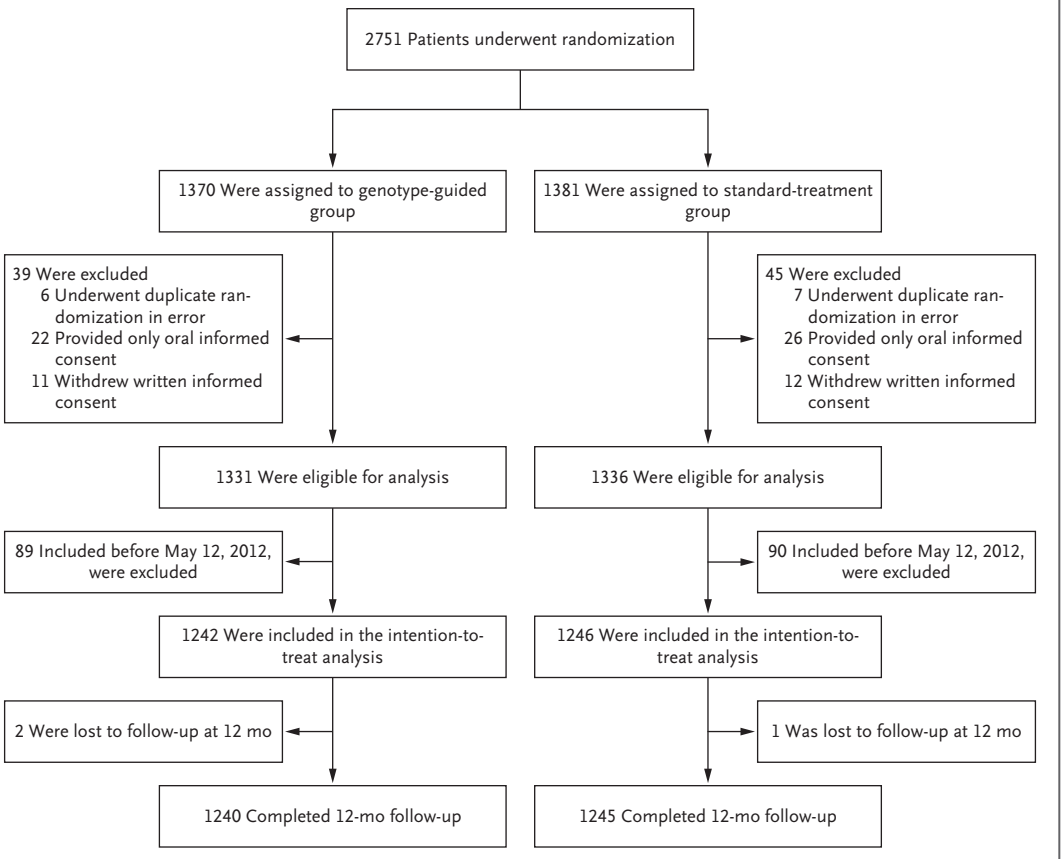

Figure 1. Randomization and Follow-up.

Patients who underwent randomization despite screening errors or who were not treated according to the protocol were also included in the intention-to-treat analysis. Vital status was known for nearly all patients (99.9%), and data for three patients (0.1%) were censored because their vital status was unknown.

SECONDARY OUTCOMES

There were no significant differences between the two groups for the combined thrombotic outcome consisting of death from vascular causes, myocardial infarction, definite stent thrombosis, or stroke (2.7% in the genotype-guided group and 3.3% in the standard-treatment group; hazard ratio, 0.83; 95% CI, 0.53 to 1.31) or for any of the other secondary thrombotic outcomes (Table 2, and Fig. S2 in the Supplementary Appendix). Furthermore, there was no difference in the incidence of PLATO major bleeding between the genotype-guided group and the standard-treatment group (2.3% in both groups; hazard ratio, 0.97; 95% CI, 0.58 to 1.63). The between-group difference in the primary bleeding outcome was driven by a lower incidence of PLATO minor bleeding in the genotype-guided group (7.6% vs. 10.5%; hazard ratio, 0.72; 95% CI, 0.55 to 0.94) (Fig. S3 in the Supplementary Appendix). Table 3 shows a full list of bleeding outcomes.

Analyses of the primary outcomes were performed in prespecified subgroups. The results were generally consistent with those in the whole cohort (Figs. S4 and S5 in the Supplementary Appendix).

DISCUSSION

In this trial, we investigated the possible clinical benefit of *CYP2C19* genotype–guided antiplatelet therapy in patients with STEMI undergoing primary PCI. There are two key findings from this trial. First, the use of a genotype-guided strategy, in which patients without a *CYP2C19* loss-of-function allele received clopidogrel, was not as-

Table 1. Baseline Characteristics of the Patients and Initial Antithrombotic Therapy.*

Characteristic	Genotype-Guided Group (N=1242)	Standard-Treatment Group (N=1246)
Baseline characteristics		
Age — yr	61.9±11.1	61.4±11.5
Age ≥75 yr — no. (%)	188 (15.1)	175 (14.0)
Female sex — no. (%)	317 (25.5)	309 (24.8)
Body-mass index†	27.5±6.67	27.0±4.27
Creatinine clearance <60 ml/min/1.73 m^2 at baseline — no./total no. (%)‡	121/1236 (9.8)	109/1239 (8.8)
Cardiovascular risk factors		
Current smoker — no./total no. (%)	562/1228 (45.8)	565/1233 (45.8)
Diabetes mellitus — no. (%)	150 (12.1)	138 (11.1)
Arterial hypertension — no. (%)	521 (41.9)	511 (41.0)
Hyperlipidemia — no./total no. (%)	260/1241 (21.0)	255/1243 (20.5)
Family history of coronary artery disease — no./total no. (%)	475/1170 (40.6)	467/1182 (39.5)
Other medical history — no. (%)		
Previous PCI with stenting	99 (8.0)	91 (7.3)
Previous coronary-artery bypass grafting	12 (1.0)	22 (1.8)
Previous myocardial infarction	97 (7.8)	87 (7.0)
History of coronary artery disease	133 (10.7)	118 (9.5)
Peripheral arterial disease	39 (3.1)	34 (2.7)
History of bleeding	30 (2.4)	23 (1.8)
Aspirin use before primary PCI — no./total no. (%)	1232/1240 (99.4)	1238/1245 (99.4)
$P2Y_{12}$ inhibitor use before primary PCI — no./total no. (%)	1198/1237 (96.8)	1190/1240 (96.0)
Initial antithrombotic therapy after randomization and genotyping — no./total no. (%)		
$P2Y_{12}$ inhibitor		
Any	1236/1239 (99.8)	1237/1240 (99.8)
Clopidogrel	751/1239 (60.6)	87/1240 (7.0)
Prasugrel	13/1239 (1.0)	28/1240 (2.3)
Ticagrelor	472/1239 (38.1)	1122/1240 (90.5)
None	3/1239 (0.2)	3/1240 (0.2)
Aspirin	1211/1239 (97.7)	1208/1240 (97.4)
Oral anticoagulation	51/1239 (4.1)	54/1240 (4.4)

* Plus–minus values are means ±SD. PCI denotes percutaneous coronary intervention.
† The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 66 patients in the genotype-guided group and 77 in the standard-treatment group.
‡ The creatinine clearance was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula.

sociated with a higher risk of combined death from any cause, myocardial infarction, definite stent thrombosis, stroke, or major bleeding 12 months after primary PCI than standard treatment with the more potent $P2Y_{12}$ inhibitors ticagrelor and prasugrel. Second, the use of clopidogrel in the genotype-guided group resulted in a lower risk of (mostly minor) bleeding than standard treatment.

Since the trial was designed, the incidence of thrombotic events after acute coronary syndromes has decreased considerably, particularly because

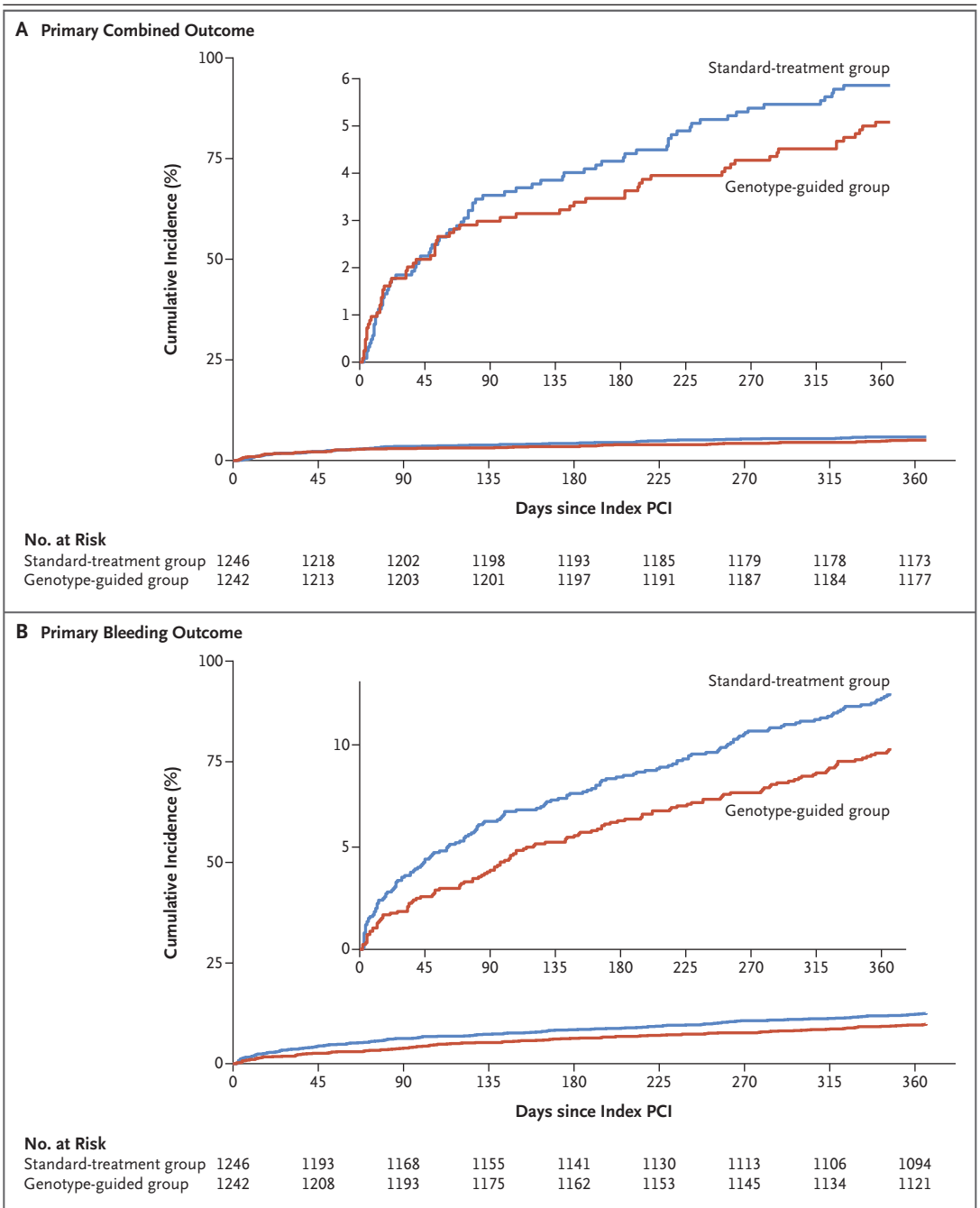

Figure 2. Incidence Curves for the Primary Outcomes.

Panel A shows the cumulative incidence of the primary combined thrombotic and bleeding outcome, consisting of death from any cause, myocardial infarction, definite stent thrombosis, stroke, or major bleeding defined according to Platelet Inhibition and Patient Outcomes (PLATO) criteria. Panel B shows the primary bleeding outcome of PLATO major or minor bleeding. The inset in each panel shows the same data on an enlarged y axis. PCI denotes percutaneous coronary intervention.

Table 2. Primary Combined Outcome and Secondary Thrombotic Outcomes.*

Outcome	Genotype-Guided Group (N=1242)	Standard-Treatment Group (N=1246)	Absolute Difference (95% CI)†	Hazard Ratio (95% CI)	P Value
	no. of patients (%)		*percentage points*		
Primary combined outcome‡					
Noninferiority analysis	63 (5.1)	73 (5.9)	–0.7 (–2.0 to 0.7)		<0.001§
Superiority analysis	63 (5.1)	73 (5.9)		0.87 (0.62 to 1.21)	0.40
Secondary thrombotic outcomes					
Combined ischemic outcome of death from vascular causes, myocardial infarction, definite stent thrombosis, or stroke					
Noninferiority analysis	34 (2.7)	41 (3.3)	–0.3 (–1.4 to 0.8)		
Superiority analysis	34 (2.7)	41 (3.3)		0.83 (0.53 to 1.31)	
Combined ischemic outcome of death from vascular causes, acute coronary syndrome, definite stent thrombosis, stroke, or urgent TVR	57 (4.6)	59 (4.7)		0.97 (0.67 to 1.40)	
Death from any cause	19 (1.5)	19 (1.5)		1.00 (0.53 to 1.89)	
Death from vascular causes	9 (0.7)	10 (0.8)		0.90 (0.37 to 2.22)	
Acute coronary syndrome	43 (3.5)	43 (3.5)		1.00 (0.66 to 1.53)	
Myocardial infarction	19 (1.5)	26 (2.1)		0.73 (0.41 to 1.32)	
Stroke	8 (0.6)	11 (0.9)		0.73 (0.29 to 1.82)	
Ischemic	7 (0.6)	10 (0.8)		0.70 (0.27 to 1.85)	
Hemorrhagic	1 (0.1)	1 (0.1)		1.00 (0.06 to 16.1)	
Definite stent thrombosis	2 (0.2)	3 (0.2)		0.67 (0.11 to 4.01)	
Definite, probable, or possible stent thrombosis	9 (0.7)	11 (0.9)		0.73 (0.29 to 1.81)	
Urgent TVR	15 (1.2)	15 (1.2)		1.00 (0.49 to 2.05)	

* All outcomes were confirmed by an independent adjudication committee. The 95% confidence intervals have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible. TVR denotes target-vessel revascularization.
† Integrated differences were used to calculate the absolute differences at 12 months for the two Kaplan–Meier curves. Therefore, these values differ from the absolute difference in the cumulative incidence at 12 months.
‡ The primary combined outcome was death from any cause, myocardial infarction, definite stent thrombosis, stroke, or major bleeding defined according to Platelet Inhibition and Patient Outcomes criteria.
§ The P value was not adjusted to account for the assessment of two primary outcomes.

of the use of newer-generation stents.[20] Other recent trials with similar populations, such as the Dual Antiplatelet Therapy after Drug-Eluting Stent Implantation in ST-Elevation Myocardial Infarction (DAPT-STEMI) trial and the Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes (TROPICAL-ACS) trial, have shown a similar incidence of thrombotic events.[21,22] With the lower-than-anticipated incidence of the primary combined outcome in our trial, the prespecified noninferiority margin was wider relative to the incidence than originally expected. The upper boundary of the 95% confidence interval for the primary combined outcome was 21% higher than the incidence in the standard-treatment group. However, the observed upper boundary of the 95% confidence interval in the per-protocol analysis (11% higher than the incidence in the standard-treatment group) (Table S11 in the Supplementary Appendix) gives stronger support to the conclusion that genotype-guided $P2Y_{12}$ treatment is noninferior to standard treatment for the occurrence of thrombotic events.

The results for both the thrombotic and bleeding outcomes of the trial are in line with data from observational studies and smaller trials investigating a genotype-guided strategy.[13,23-26]

Table 3. Primary and Secondary Bleeding Outcomes.*

Outcome	Genotype-Guided Group (N=1242)	Standard-Treatment Group (N=1246)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Primary bleeding outcome: PLATO major or minor bleeding	122 (9.8)	156 (12.5)	0.78 (0.61–0.98)	0.04†
Major or minor bleeding according to other criteria				
BARC type 2–5 bleeding	126 (10.1)	163 (13.1)	0.77 (0.61–0.97)	
TIMI major or minor bleeding	30 (2.4)	30 (2.4)	1.00 (0.61–1.67)	
Major bleeding, including CABG-related bleeding				
PLATO major bleeding	28 (2.3)	29 (2.3)	0.97 (0.58–1.63)	
BARC type 3–5 bleeding	31 (2.5)	29 (2.3)	1.08 (0.65–1.78)	
TIMI major bleeding	15 (1.2)	16 (1.3)	0.94 (0.47–1.90)	
Bleeding resulting in red-cell transfusion	19 (1.5)	18 (1.4)	1.06 (0.56–2.02)	
PLATO life-threatening or fatal bleeding	16 (1.3)	16 (1.3)	1.00 (0.50–2.01)	
Fatal bleeding	2 (0.2)	1 (0.1)	2.01 (0.18–22.1)	
Intracranial bleeding	6 (0.5)	4 (0.3)	1.51 (0.43–5.34)	
Intracranial fatal bleeding	0	0		
Non–CABG-related major bleeding				
Non–CABG-related PLATO major bleeding	25 (2.0)	23 (1.8)	1.09 (0.62–1.92)	
BARC type 3 or 5 bleeding	28 (2.3)	23 (1.8)	1.23 (0.71–2.13)	
Non–CABG-related TIMI major bleeding	15 (1.2)	13 (1.0)	1.16 (0.55–2.44)	
Non–CABG-related major or minor bleeding				
PLATO major or minor bleeding	119 (9.6)	152 (12.2)	0.78 (0.61–0.99)	
BARC type 2, 3, or 5 bleeding	123 (9.9)	159 (12.8)	0.77 (0.61–0.97)	
Non–CABG-related TIMI major or minor bleeding	27 (2.2)	25 (2.0)	1.09 (0.63–1.87)	
Minor bleeding				
PLATO minor bleeding	95 (7.6)	131 (10.5)	0.72 (0.55–0.94)	
BARC type 2 bleeding	96 (7.7)	138 (11.1)	0.69 (0.53–0.89)	
TIMI minor bleeding	18 (1.4)	20 (1.6)	0.90 (0.48–1.71)	

* All events were confirmed by an independent adjudication committee. The 95% confidence intervals have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible. On the Bleeding Academic Research Consortium (BARC) scale for bleeding, type 2 indicates any overt, actionable sign of bleeding; type 3 bleeding with a decrease in the hemoglobin level of 3 g or more per deciliter, any transfusion, cardiac tamponade, or intracranial or ocular involvement; type 4 coronary-artery bypass grafting (CABG)–related bleeding; and type 5 fatal bleeding. PLATO denotes Platelet Inhibition and Patient Outcomes, and TIMI Thrombolysis in Myocardial Infarction.

† The P value was not adjusted to account for the assessment of two primary outcomes.

Guided de-escalation was also investigated in the TROPICAL-ACS trial, which included 2610 patients with biomarker-positive acute coronary syndromes undergoing PCI. It showed that guided de-escalation of P2Y$_{12}$ inhibitor therapy (switching to clopidogrel) with the use of platelet-function testing was noninferior to prasugrel for the prevention of thrombotic events.[22] However, the incidence of bleeding was not significantly lower in the de-escalation group than in the prasugrel group. Furthermore, this method of guiding therapy requires patients to switch between P2Y$_{12}$ inhibitors multiple times if they have high platelet reactivity during treatment with clopidogrel, and it requires patients to revisit the clinic to perform platelet-function testing. On the basis of the TROPICAL-ACS trial, the latest ESC guidelines give a class IIb recommendation to use platelet-function testing

for guided de-escalation, especially in patients who are not deemed to be candidates for 12 months of potent antiplatelet therapy.[27]

Trials such as TROPICAL-ACS usually included Bleeding Academic Research Consortium (BARC) type 2 bleeding (any overt, actionable sign of bleeding) in their definition of net clinical benefit.[22,28] We chose to incorporate only major bleeding, which has an effect on morbidity and mortality similar to that of thrombotic outcomes.[29] Furthermore, although earlier trials consistently showed a lower incidence of minor bleeding with clopidogrel than with prasugrel or ticagrelor, this effect was not seen for major bleeding.[3,4,22,28] Our data confirm this finding. Therefore, guided de-escalation will mostly help to reduce minor bleeding. Nevertheless, minor bleeding is of clinical relevance, since it leads to medical intervention and influences treatment adherence and health care costs.[30-32]

Limitations of our trial include the open-label design, the lower-than-anticipated incidence of the primary combined outcome, and the fact that genetic variation is not the only factor contributing to high platelet reactivity. Moreover, there are more polymorphisms of the *CYP2C19* gene, although most are very rare,[13] that may be associated with increased thrombotic or bleeding risk. However, data on these other alleles are conflicting.[33] Therefore, our strategy based solely on the *CYP2C19* genotype may not be the most useful strategy for some patients.

In conclusion, in patients with STEMI undergoing primary PCI, a *CYP2C19* genotype–guided strategy for selection of oral $P2Y_{12}$ inhibitor therapy was noninferior to standard treatment with ticagrelor or prasugrel at 12 months with respect to thrombotic events and resulted in a lower incidence of bleeding.

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

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

APPENDIX

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