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Pharmacogenomic Approach to Selecting Antiplatelet Therapy in Patients With Acute Coronary Syndromes

The PHARMCLO Trial

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ABSTRACT

BACKGROUND Although clopidogrel is still frequently used in patients with acute coronary syndromes (ACS), its efficacy is hampered by interpatient response variability caused by genetic polymorphisms associated with clopidogrel's metabolism.

OBJECTIVES The goal of this study was to evaluate whether selecting antiplatelet therapy (clopidogrel, prasugrel, or ticagrelor) on the basis of a patient's genetic and clinical characteristics leads to better clinical outcomes compared with the standard of care, which bases the selection on clinical characteristics alone.

METHODS Patients hospitalized for ACS were randomly assigned to standard of care or the pharmacogenomic arm, which included the genotyping of ABCB1, CYP2C19*2, and CYP2C19*17 using an ST Q3 system that provides data within 70 min at each patient's bedside. The patients were followed up for 12 $\pm$ 1 month for the primary composite endpoint of cardiovascular death and the first occurrence of nonfatal myocardial infarction, nonfatal stroke, and major bleeding defined according to Bleeding Academic Research Consortium type 3 to 5 criteria.

RESULTS After enrolling 888 patients, the study was prematurely stopped. Clopidogrel was used more frequently in the standard-of-care arm (50.7% vs. 43.3%), ticagrelor in the pharmacogenomic arm (42.6% vs. 32.7%; $p = 0.02$), and prasugrel was equally used in both arms. The primary endpoint occurred in 71 patients (15.9%) in the pharmacogenomic arm and in 114 (25.9%) in the standard-of-care arm (hazard ratio: 0.58; 95% confidence interval: 0.43 to 0.78; $p < 0.001$).

CONCLUSIONS A personalized approach to selecting antiplatelet therapy for patients with ACS may reduce ischemic and bleeding events. (Pharmacogenetics of Clopidogrel in Patients With Acute Coronary Syndromes [PHARMCLO]; NCT03347435) (J Am Coll Cardiol 2018;71:1869–77) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CI = confidence interval

HR = hazard ratio

Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor antagonist is the mainstay of treatment of acute coronary syndromes (ACS). Prasugrel and ticagrelor have proved to be superior to clopidogrel in preventing ischemic events but lead to an increased risk of bleeding complications. International guidelines (1-4) strongly suggest using front-line treatment with prasugrel or ticagrelor, and only using clopidogrel if these other drugs are unavailable or contraindicated. However, the use of more potent antiplatelet drugs involves a fundamental trade-off between decreasing the risk of ischemia and increasing the risk of bleeding. For this reason, clopidogrel is frequently chosen in the real world (5-8), but when balancing ischemic/bleeding risks, only the clinical characteristics of individual patients are taken into account.

SEE PAGE 1878

Clopidogrel leads to substantial variability in patient responses, and this limits its effectiveness (9). In addition to clinical factors, the reasons for this variability include genotypes: loss-of-function or gain-of-function polymorphisms in the cytochrome P450 2C19 gene are frequently observed and are not only responsible for increasing/reducing enzymatic activity, but also for inducing high/low on-treatment platelet reactivity after clopidogrel exposure, both of which affect its effectiveness in preventing ischemic and bleeding events (10-13). Genetic variants of the genes regulating clopidogrel absorption, such as ABCB1, have also been shown to affect clopidogrel bioavailability, on-treatment platelet reactivity, and clinical outcomes (14).

It can therefore be hypothesized that knowing a patient's genetic profile of clopidogrel metabolism may lead to more personalized, and therefore more efficient, antiplatelet therapy. The present study was designed to test the hypothesis that selecting antiplatelet therapy on the basis of a combination of genetic information and a patient's clinical characteristics would lead to better clinical outcomes compared with the standard of care based on clinical characteristics alone.

METHODS

PATIENT POPULATION. Unselected patients of European ancestry who were hospitalized because of ST-segment elevation or non-ST-segment elevation ACS were considered eligible for enrollment. The diagnosis of ACS was based on the presence of ≥2 of the following criteria: 1) ischemic symptoms at rest lasting >20 min; 2) electrocardiographic changes with ST-segment elevation or depression of at least 1 mm in 2 contiguous leads; and 3) the typical rise and fall of cardiac biomarker troponin I or T levels above the 99th percentile of the upper reference limit.

The major exclusion criteria were as follows: 1) an inability to provide informed consent or follow study procedures; 2) any contraindication to the use of $P2Y_{12}$ receptor antagonists; 3) a life expectancy of <1 year; 4) thrombolytic therapy within the previous 24 h; 5) enrollment in another randomized trial or observational registry; and 6) prior knowledge of the patients' ABCB1, CYP2C19*2, or CYP2C19*17 genotype.

The study protocol was approved by the ethics committee of the coordinating center and afterward by the ethics committee of each participating center. All patients provided written informed consent before participating in the trial.

RANDOMIZATION. Immediately after the diagnosis of ACS, the patients were randomly assigned to the strategy of selecting a $P2Y_{12}$ receptor antagonist on the basis of their clinical characteristics plus the genotyping results, or on the basis of their clinical characteristics alone. An automatic telephone randomization system was used to assign the patients to treatment in a 1:1 ratio based on a centralized list. The randomization list was stratified according to diagnosis (ST-segment elevation vs. all the rest) and center by using the SAS PLAN procedure (SAS Institute, Inc., Cary, North Carolina). The investigators had to digitize the patient's date of birth, diagnosis, and site number by means of an interactive voice system to obtain the assigned allocation. The data were confirmed by e-mail, and the printout was included in the patient's case report form.

GENOTYPING. The patients assigned to the strategy that included genotyping underwent genetic testing for ABCB1 3435 (7q21.1; rs1045642), CYP2C19*2 (10q24.1-q24.3; rs4244285), and CYP2C19*17 (10q24.1-q24.3; rs12248560). Blood samples were taken from all of the patients randomized to the pharmacogenomic arm for deoxyribonucleic acid extraction. The genotyping was conducted by using the ST Q3 system, a compact platform enabling the laboratory analysis of deoxyribonucleic acid by means of real-time polymerase chain reaction. The ST Q3 is designed as a low-entry-cost, portable system for foolproof use by unskilled personnel as a point-of-care instrument. The reaction takes place in a disposable lab-on-chip, which is pre-functionalized with all of the required reagents. The user only has to add the sample by means of a simple loading system, after which the disposable device self-seals and provides the results in approximately 70 min (15) (Online Appendix A).

STUDY PROCEDURE AND FOLLOW-UP. The patients randomized to the arm that included genotyping received 1 of the $P2Y_{12}$ receptor antagonists (clopidogrel, prasugrel, or ticagrelor) on the basis of an algorithm that considered the results of genetic testing in addition to clinical variables. Patients already taking $P2Y_{12}$ antagonists could be enrolled, but if switching was necessary to implement the protocol, it was not counted as switching. Switching was counted only if it occurred after the selection of the definite $P2Y_{12}$ receptor antagonist.

It is important to underline that the genetic algorithm was designed to consider the 3 genes simultaneously, but the ultimate decision concerning antiplatelet therapy also took into account the patient's clinical characteristics and was left to the discretion of the prescribers (Online Appendix A, Online Figure 1).

The clinical variables used to individualize the choice of $P2Y_{12}$ receptor antagonist were age, weight, ischemic risk, bleeding risk, diabetes, history of stroke/transient ischemic attack or intracranial bleeding, history of bleeding, active bleeding, anemia, and chronic kidney disease.

Given the TRITON-TIMI-38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction-38) trial findings and the exclusion criteria, prasugrel was not prescribed for: 1) patients whose coronary anatomy was unknown; 2) those at high bleeding risk (particularly those with a history of stroke or transient ischemic attack, those >75 years of age, and those with a body weight <60 kg); 3) those receiving fibrinolytic therapy within the previous 24 h; 4) those with active internal bleeding; 5) those with severe liver disease; 6) those taking oral anticoagulant therapy that could not be stopped; or 7) those with known clinically important thrombocytopenia (16).

Given the PLATO (Platelet Inhibition and Patient Outcomes) trial exclusion criteria, ticagrelor was contraindicated in: 1) patients with active pathological bleeding; 2) those with a history of intracranial bleeding; 3) those requiring dialysis; 4) those taking oral anticoagulant therapy that could not be stopped; 5) those with known clinically important thrombocytopenia; 6) those receiving fibrinolytic therapy within the previous 24 h; and 7) those taking concomitant therapy with strong cytochrome P450 3A inhibitors or inducers (17).

In the standard-of-care arm, the decision regarding which $P2Y_{12}$ receptor antagonist to use was based on clinical characteristics as described earlier and the clinicians' preference. The patients were followed-up for 12 months by means of outpatient visits or standardized telephone contacts scheduled 1, 6, and 12 ± 1 months after randomization.

STUDY OUTCOMES. The primary endpoint was the composite of cardiovascular death and the first occurrence of nonfatal myocardial infarction, nonfatal stroke, and major bleeding defined according to the Bleeding Academic Research Consortium type 3 to 5 within 12 months of randomization.

The secondary endpoint was the composite of the primary endpoint plus the occurrence of definite or probable stent thrombosis. Secondary non-prespecified endpoints were the composite of the first occurrence of the ischemic endpoints (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and the composite of the first occurrence of the Bleeding Academic Research Consortium type 3 to 5-defined major bleeding (Online Appendix B).

All of the events were adjudicated by an independent clinical events committee consisting of 3 cardiologists who were unaware of the study group assignments. Two cardiologists reviewed the medical records and, in the case of disagreement, the opinion of the third member was required. Only adjudicated endpoints were considered for the statistical analysis.

STATISTICAL ANALYSIS. The sample size was calculated on the assumption that the cumulative incidence of the primary endpoint in the standard-of-care arm after 12 months would be 25%. Given a relative risk reduction in the pharmacogenomic arm of 20%, 95% power, and a type alpha error of 5%, the calculated sample size was 1,806 patients in each arm.

Descriptive statistics were used to compare the baseline characteristics of the 2 groups to test the randomization process. The primary analysis was based on the intention-to-treat principle. Cox proportional hazards models were used to analyze the data relating to the primary and secondary endpoints. The proportional hazards assumption for the Cox regression model was confirmed by using the Schoenfeld residuals test. An Andersen-Gill intensity model analysis was not pre-specified but was conducted to account for repeated occurrences of all of the components of the primary endpoint during the study period, using a time-dependent model.

The cumulative incidence of the endpoints during the 12 months of follow-up was graphically represented by means of Aalen-Johansen curves, and the significance of the differences between the subdistribution of the hazards was tested by using the

TABLE 1 Demographic, Clinical, Angiographic, and Treatment Characteristics of the Study Population

	All Patients (N = 888)	Pharmacogenomic Arm (n = 448)	Standard-of-Care Arm (n = 440)
Demographics			
Age, yrs	70.9 ± 12.2	71.1 ± 12.3	70.7 ± 12.1
Age groups			
<70 yrs	361/888 (40.6)	186/448 (41.5)	175/440 (39.8)
70–80 yrs	275/888 (31.0)	130/448 (29.0)	145/440 (33.0)
>80 yrs	252/888 (28.4)	132/448 (29.5)	120/440 (27.2)
Female	283/888 (32.0)	153/448 (34.2)	130/440 (29.6)
Cardiovascular risk factors			
Family history	198/888 (22.3)	96/448 (21.4)	102/440 (23.2)
Hypertension	660/888 (74.3)	331/448 (73.9)	329/440 (74.8)
Dyslipidemia	483/888 (54.4)	251/448 (56.0)	232/440 (52.7)
Diabetes mellitus	235/888 (26.5)	113/448 (25.2)	122/440 (27.7)
Habitual smoking	200/888 (22.5)	92/448 (20.5)	108/440 (24.6)
BMI			
<25 kg/m^2	117/888 (13.2)	62/448 (13.8)	55/440 (12.5)
25–30 kg/m^2	619/888 (69.7)	311/448 (69.4)	308/440 (70.0)
>30 kg/m^2	152/888 (17.1)	75/448 (16.8)	77/440 (17.5)
History			
Previous MI	191/888 (21.5)	96/448 (21.4)	95/440 (21.6)
Previous stable angina	50/888 (5.6)	25/448 (5.6)	25/440 (5.7)
Previous PCI*	169/888 (19.0)	81/448 (18.1)	88/440 (20.0)
Previous CABG	80/888 (9.0)	43/448 (9.6)	37/440 (8.4)
Previous stroke	63/888 (7.1)	35/448 (7.8)	28/440 (6.4)
Peripheral arterial disease	85/888 (9.6)	40/448 (8.9)	45/440 (10.2)
Permanent atrial fibrillation	41/888 (4.7)	22/448 (4.9)	19/440 (4.3)
Chronic kidney disease	76/888 (8.6)	35/448 (7.8)	41/440 (9.3)
COPD	71/888 (8.0)	33/448 (7.4)	38/440 (8.6)
Acute coronary syndrome			
STEMI	244/888 (27.5)	114/448 (25.5)	130/440 (29.5)
NSTEMI	602/888 (67.8)	316/448 (70.5)	286/440 (65.0)
Unstable angina	17/888 (1.9)	7/448 (1.6)	10/440 (2.3)
No acute coronary syndrome†	25/888 (2.8)	11/448 (2.4)	14/440 (3.2)

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Fine-Gray model. All of the tests were 2-sided at a significance level of 0.05. No interim analysis was performed, and no multiplicity test correction was made. The statistical analyses were made by using the R-package Survival version 2.41-3 and R Statistical software version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 888 patients were recruited between June 12, 2013, and February 18, 2015. A total of 448 patients were randomized to the pharmacogenomic arm and 440 to the standard-of-care arm. This grouping represents 24.6% of the pre-specified sample size because, on February 18, 2015, the Ethics Committee of Modena (Italy) required that the trial be prematurely stopped and all of the patients followed-up as planned because of the lack of in vitro diagnosis certification for the ST Q3 instrument.

The mean age of the population was 70.9 ± 12.2 years (range 35 to 97 years), with 28.4% of the patients >80 years of age. Virtually all of the patients (98.1%) experienced the typical rise and fall of cardiac markers indicating an acute myocardial infarction, and 96.3% underwent coronary angiography. Seventy-three percent underwent revascularization: 62.2% by means of a percutaneous coronary intervention and 11% by means of coronary artery bypass grafting. All of these characteristics indicate a high-risk study population. The concomitant treatments were those currently used for patients with ACS. The 2 groups were well balanced in terms of the patients' baseline characteristics (Table 1).

GENOTYPES. Table 2 shows the genotype distributions of the patients in the pharmacogenomic arm. Briefly, genotyping revealed that 47.1% had at least 1 copy of the ABCB1 3435 allele, and 26.4% were homozygous; 29.2% had at least 1 copy of the loss-of-function CYP2C19*2 allele, and 4.3% were homozygous; and 31.3% had at least 1 copy of the gain-of-function CYP2C19*17 allele, and 7.8% were homozygous.

The distribution of the $P2Y_{12}$ receptor antagonists used during the acute phase and the 12 months of follow-up in the pharmacogenomic arm was clopidogrel in 43.3% of the patients, prasugrel in 7.6%, and ticagrelor in 42.6%. The corresponding figures in the standard-of-care arm were clopidogrel 50.7%, prasugrel 8.4%, and ticagrelor 32.7%. The difference in the distribution of the treatments with the various $P2Y_{12}$ receptor antagonists between the 2 arms was statistically significant ($p = 0.02$). After the selection of the $P2Y_{12}$ receptor antagonist, 6.8% of the patients in the pharmacogenomic arm and 5.6% in the standard-of-care arm changed their $P2Y_{12}$ receptor antagonist at least once. Upon discharge, 6.5% of the patients in the pharmacogenomic arm and 8.2% of those in the standard-of-care arm were not receiving any $P2Y_{12}$ receptor antagonist, mainly because of misdiagnosis, normal coronary angiograms, or the concomitant use of oral anticoagulant agents.

OUTCOMES. One patient in the pharmacogenomic arm was lost to follow-up. The primary endpoint occurred in 71 patients (15.9%) in the pharmacogenomic arm and 114 (25.9%) in the standard-of-care arm (hazard ratio [HR]: 0.58; 95% confidence interval [CI]: 0.43 to 0.78; $p < 0.001$) (Central Illustration, Table 3). In patients receiving clopidogrel, the primary endpoint occurred in 48 patients in the pharmacogenomic arm

(24.7%) and 79 (35.4%) in the standard-of-care arm (hazard ratio: 0.68; 95% confidence interval: 0.47 to 0.97; p = 0.03) (Figure 1).

Definite or probable stent thrombosis was observed in only 8 patients (3 in the pharmacogenomic arm and 5 in the standard-of-care arm), thus precluding an outcome analysis of this secondary endpoint.

Ischemic endpoints occurred in 58 patients (13%) in the pharmacogenomic arm and 94 (21.4%) in the standard-of-care arm (HR: 0.57; 95% CI: 0.41 to 0.8; p < 0.001) (Figure 2). Bleeding endpoints occurred in 19 patients (4.2%) in the pharmacogenomic arm and 30 (6.8%) in the standard-of-care arm (HR: 0.62; 95% CI: 0.35 to 1.1; p = 0.1) (Figure 3).

Repeated ischemic and bleeding endpoints were also less frequent in the patients randomized to the pharmacogenomic arm: 85 versus 136 endpoints (HR: 0.61; 95% CI: 0.4 to 0.8; p < 0.001).

DISCUSSION

Over the last 10 years, there have been substantial advances in our understanding of the genetic variability associated with patient responses to clopidogrel treatment (10-14). However, although these genetic associations have been widely replicated and the effect sizes are sufficiently large to be predictive in the clinical setting, there are limited examples of the use of pharmacogenetic data concerning clopidogrel metabolism to guide clinical practice (18-23).

This prospective, randomized multicenter study provides evidence that the use of genomic medicine to select $P2Y_{12}$ receptor antagonists can be successfully incorporated into the clinical care of patients with ACS. This scenario may be considered one of the most challenging clinical settings in which to use pharmacogenetic data to guide clinical practice because of the urgency of the situation and the need to start drug treatment promptly. In our case, this approach was made feasible by the development of a bedside instrument capable of providing genotype results within 70 min of blood sampling.

In patients with ACS, the selection of a $P2Y_{12}$ receptor antagonist (clopidogrel, ticagrelor, or prasugrel) is based on their individual clinical characteristics to obtain the best trade-off between ischemic events and bleeding complications. The main finding of the present study is that selecting treatment on the basis of genetic data related to clopidogrel metabolism in addition to considerations concerning the patients' clinical characteristics may

TABLE 1 Continued

	All Patients (N = 888)	Pharmacogenomic Arm (n = 448)	Standard-of-Care Arm (n = 440)
Coronary angiography			
Angiography performed	855/888 (96.3)	433/448 (96.6)	422/440 (95.9)
Single-vessel disease	265/855 (30.9)	124/433 (28.6)	141/422 (33.4)
2-vessel disease	234/855 (27.3)	125/433 (28.8)	109/422 (25.8)
3-vessel disease	231/855 (27.0)	119/433 (27.4)	112/422 (26.5)
Left main coronary artery	105/855 (12.2)	60/433 (13.8)	45/422 (10.6)
Left anterior descending coronary artery	460/855 (53.8)	236/433 (54.5)	224/422 (53.1)
Circumflex coronary artery	315/855 (36.8)	174/433 (40.1)	140/422 (33.1)
Right coronary artery	406/855 (47.4)	203/433 (46.8)	203/422 (48.1)
Other vessels	265/855 (30.9)	125/433 (28.8)	140/422 (33.1)
Revascularization			
PCI	532/855 (62.2)	268/433 (61.8)	264/422 (62.6)
CABG	92/855 (10.7)	49/433 (11.3)	43/422 (10.1)
Medical treatment‡			
Aspirin	860/888 (97.0)	437/448 (97.6)	423/440 (96.1)
Beta-blocker	751/888 (84.6)	382/448 (85.3)	369/440 (83.9)
ACE inhibitor and ARB	658/888 (74.1)	342/448 (76.3)	316/440 (71.8)
Lipid-lowering drug	761/888 (85.6)	386/448 (86.2)	375/440 (85.2)
Calcium-channel inhibitor	243/888 (27.4)	120/448 (26.8)	123/440 (28.0)
Warfarin	48/888 (5.4)	21/448 (4.7)	27/440 (6.1)

Values are mean ± SD or n/N (%). p > 0.05 for all comparisons. *A total of 93% of the PCIs involved stenting. †This category includes patients with a misdiagnosis of acute coronary syndrome. ‡All of the medical treatments were prescribed during hospitalization and at discharge.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

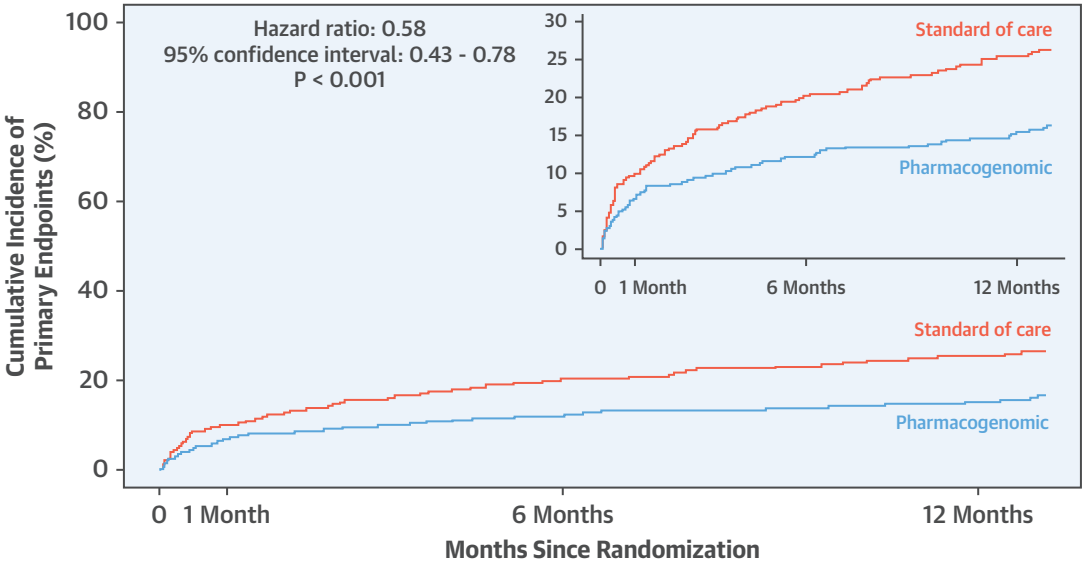
TABLE 2 Frequency Distribution of Genetic Variants and Selected $P2Y_{12}$ Receptor Antagonist

	Pharmacogenomic Arm (n = 448)	Standard-of-Care Arm (n = 440)
ABCB1 3435 genotype		
Wild type (C/C)	119/448 (26.5)	NA
Heterozygous (C/T)	211/448 (47.1)	NA
Homozygous (T/T)	118/448 (26.4)	NA
CYP2C19*2 genotype		
Wild type (*1/*1)	298/448 (66.5)	NA
Heterozygous (*1/*2)	131/448 (29.2)	NA
Homozygous (*2/*2)	19/448 (4.3)	NA
CYP2C19*17 genotype		
Wild type (*1/*1)	273/448 (60.9)	NA
Heterozygous (*1/*17)	140/448 (31.3)	NA
Homozygous (*17/*17)	35/448 (7.8)	NA
$P2Y_{12}$ receptor antagonist*		
Clopidogrel	194/448 (43.3)	223/440 (50.7)
Prasugrel	34/448 (7.6)	37/440 (8.4)
Ticagrelor	191/448 (42.6)	144/440 (32.7)
$P2Y_{12}$ receptor antagonist switch†	27/397 (6.8)	22/393 (5.6)
No $P2Y_{12}$ receptor antagonist‡	29/448 (6.5)	36/440 (8.2)

Values are n/N (%). *$P2Y_{12}$ receptor antagonist prescribed during hospitalization and at discharge. The p value for global comparison = 0.02. †Any switch from one $P2Y_{12}$ receptor antagonist to another during the 12-month follow-up. ‡Patients who did not receive any $P2Y_{12}$ receptor antagonists during hospitalization or at discharge (because of misdiagnosis, a high bleeding risk, or concomitant oral anticoagulant therapy).

NA = not applicable.

CENTRAL ILLUSTRATION Pharmacogenomic Approach to the Selection of Antiplatelet Therapy: Primary Composite Endpoint After 12 Months



No. at risk				
Pharmacogenomic arm	448	416	390	295
Standard-of-care arm	440	397	349	280

Notarangelo, F.M. et al. J Am Coll Cardiol. 2018;71(17):1869–77.

Cumulative incidence of the primary composite endpoint after 12 months according to study arm. Aalen-Johansen curves of the cumulative incidence of the primary endpoint (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and Bleeding Academic Research Consortium type 3 to 5–defined major bleeding). The differences between the subdistribution hazards in the 2 study arms shown in all of the panels were tested by using the Fine-Gray model. The **inset** shows the same data on an enlarged y-axis.

lead to a significantly lower rate of ischemic and bleeding events compared with usual practice.

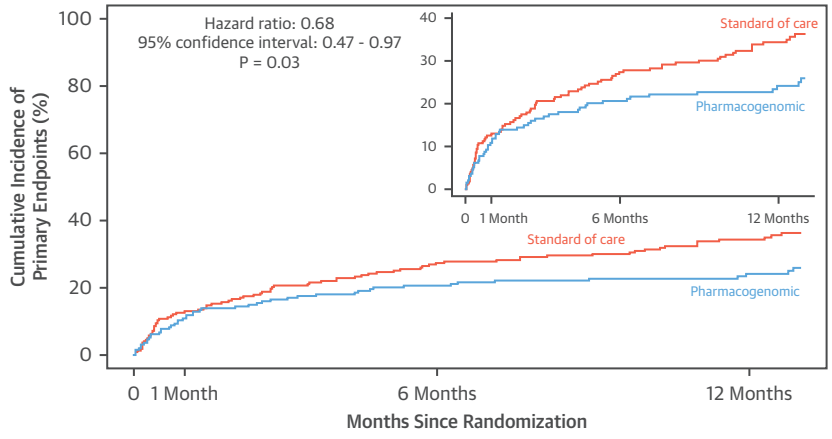
STUDY LIMITATIONS. Although it is relatively easy to explain why knowledge of a patient's genetic data may lead to a better clinical outcome, it is more difficult to explain the magnitude of this effect. Given the premature discontinuation of the study after the enrollment of only 25% of the planned number of patients, it is possible that the observed differences between the 2 arms may simply be attributable to chance. Alternatively, it is possible that the effect size in our sample size calculation may have simply been underestimated: a retrospective analysis of the TRITON-TIMI-38 trial by Mega et al. (14) showed that the absolute difference in cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was 7.3% between the most and least favorable ABCB1 and 2C19*2 genetic profile, with a relative difference of 50%. Another possible explanation may be related to the percentage of patients receiving clopidogrel or ticagrelor in the standard-of-care arm. Because ticagrelor proved to be more effective than clopidogrel in the PLATO trial (17), it is possible that some of the benefit observed in the present study may have been related to the more frequent use of clopidogrel in the

TABLE 3 First Occurrence of the Individual Components of the Primary Composite Endpoint

	Pharmacogenomic Arm (n = 448)	Standard-of-Care Arm (n = 440)	Hazard Ratio (95% CI)
Cardiovascular death	28	34	–
Nonfatal myocardial infarction	21	47	–
Post-PCI myocardial infarction	1	7	–
Post-CABG myocardial infarction	1	9	–
Nonfatal stroke	5	7	–
Combined major bleeding (BARC type 3 + 4 + 5)*	17	26	–
Primary composite endpoint	71	114	0.58 (0.43-0.78)

Values are n. *Major bleeding according to the Bleeding Academic Research Consortium (BARC) definition.
CI = confidence interval; other abbreviations as in Table 1.

FIGURE 1 **Cumulative Incidence of the Primary Endpoint in the Group of Patients Receiving Clopidogrel**



No.at risk

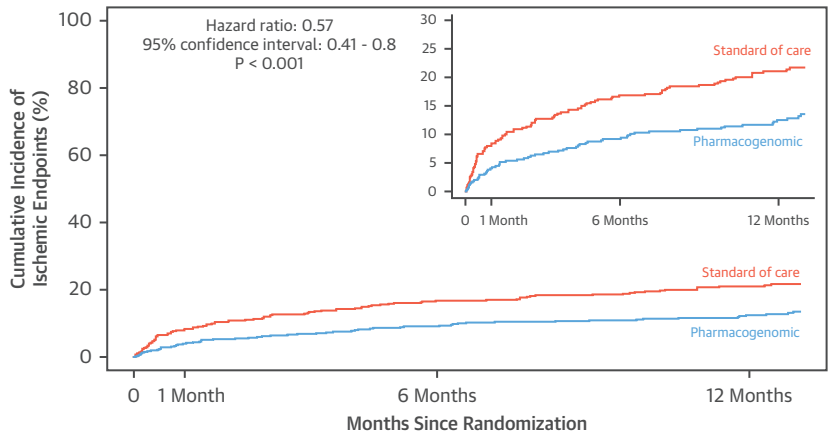
Pharmacogenomic arm	194	173	152	102
Standard-of-care arm	223	195	161	127

Aalen-Johansen curves of the cumulative incidence of the primary endpoint in the subgroup of patients who received clopidogrel during the study. The **inset** shows the same data on an enlarged y-axis.

standard-of-care arm. Finally, the ascertainment bias associated with the single-blind nature of the study may also partially account for the magnitude of the effect size.

Genotype-guided antiplatelet therapy may be seen as an alternative approach to personalized treatment in ACS. Other strategies based on platelet function tests have been evaluated but all have failed to show any significant clinical benefit (24-26), and it is only recently that the de-escalation of antiplatelet therapy has been shown to be not inferior to prasugrel when based on platelet function test results (27). The major

FIGURE 2 **Cumulative Incidence of the Ischemic Endpoints After 12 Months According to Study Arm**

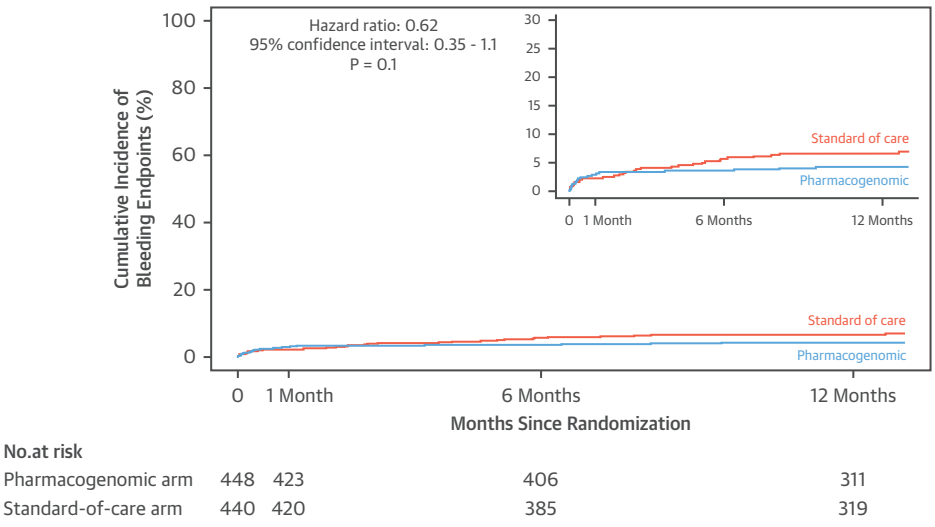


No. at risk

Pharmacogenomic arm	448	428	402	304
Standard-of-care arm	440	404	362	294

Aalen-Johansen curves of the cumulative incidence of the ischemic endpoints. The **inset** shows the same data on an enlarged y-axis.

FIGURE 3 Cumulative Incidence of the Bleeding Endpoints After 12 Months According to Study Arm



No.at risk				
Pharmacogenomic arm	448	423	406	311
Standard-of-care arm	440	420	385	319

Aalen-Johansen curves of the cumulative incidence of the bleeding endpoints. The **inset** shows the same data on an enlarged y-axis.

limitation of platelet function tests is the great variability of the results, but this limitation can be overcome by genetic testing (28). Two randomized trials of personalized antiplatelet therapy based on the genotyping of Chinese patients undergoing percutaneous coronary interventions have shown a significant reduction in major adverse cardiovascular events (29,30), and our own randomized findings are in line with this outcome, although given the premature discontinuation of the study, no definite conclusion can be drawn. A number of randomized clinical trials with structured and standardized study protocols based on cytochrome P450 2C19 genotyping are ongoing and will soon provide important results that will allow fine-tuning in this field (31).

CONCLUSIONS

The findings of this study show that the implementation of multiple genotyping to guide antiplatelet therapy in patients with ACS is feasible across different institutions. Our data also suggest that a more personalized approach to the selection of antiplatelet therapy may lead to a clinically meaningful reduction in ischemic and bleeding complications. Future studies of genotype-guided antiplatelet therapy are required to confirm these data and clarify the cost efficacy of genotyping in the challenging setting of ACS before implementing it in everyday clinical practice.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Selection of $P2Y_{12}$ receptor antagonists on the basis of genotype information pertaining to clopidogrel metabolism in addition to clinical variables may improve clinical outcomes in patients with ACS.

TRANSLATIONAL OUTLOOK: Larger prospective studies are needed to confirm the value of incorporating genetic data in the selection of antiplatelet therapy for patients with ACS and those undergoing percutaneous revascularization.

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KEY WORDS acute coronary syndromes, clopidogrel, pharmacogenomic

APPENDIX For supplemental Methods, follow-up, endpoint definitions, a figure, and a list of investigators, please see the online version of this paper.