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Routine *CYP2C19* Genotyping to Adjust Thienopyridine Treatment After Primary PCI for STEMI



Results of the GIANT Study

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate prospectively the clinical impact of routine transmission of *CYP2C19* genotype in the management of acute ST-segment elevation myocardial infarction with primary percutaneous coronary intervention.

BACKGROUND Response to clopidogrel differs widely among patients, notably because of *CYP2C19* genetic polymorphisms.

METHODS *CYP2C19* genotype (6 alleles) was determined centrally and communicated within 4.1 ± 1.9 days of primary percutaneous coronary intervention in 1,445 patients with ST-segment elevation myocardial infarction recruited at 57 centers in France. *CYP2C19* metabolic status was predicted from genotype and served to adjust thienopyridine treatment. The primary endpoint was differences in 12-month outcomes (death, myocardial infarction, and stent thrombosis) between patients with the wild-type genotype or gain-of-function allele (class 1, $n = 1,118$) and those with loss-of-function (LOF) alleles (class 2, $n = 272$) who received optimized thienopyridine treatment.

RESULTS Detection of LOF alleles resulted in adjustment of P2Y₁₂ inhibition in 85% of patients, with significantly higher use of prasugrel or double-dose clopidogrel. The primary endpoint did not differ between class 1 and class 2 patients (3.31% vs. 3.04%, respectively; $p = 0.82$). In contrast, carriers of LOF alleles without treatment adjustment had significantly worse outcomes (15.6%; $p < 0.05$). Bleeding rates were not different between groups.

CONCLUSIONS In a real-world setting, a complete *CYP2C19* genotype can be mostly determined in <7 days using analysis of saliva deoxyribonucleic acid collected during the in-hospital phase among patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. Genotype information led to stronger platelet inhibition treatment in the vast majority of LOF allele carriers and to similar clinical outcomes as in patients carrying the wild-type genotype or gain-of-function allele. (Genotyping Infarct Patients to Adjust and Normalize Thienopyridine Treatment [GIANT]; [NCT01134380](https://doi.org/10.1016/j.jcin.2020.01.219)) (J Am Coll Cardiol Intv 2020;13:621-30)

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CYP2C19 = cytochrome P450 2C19

DNA = deoxyribonucleic acid

GOF = gain-of-function

LOF = loss-of-function

MACCE = major adverse cardiac and cerebrovascular event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

Inhibition of the P2Y₁₂ platelet receptor is a major objective in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) (1,2). Clopidogrel is a second-generation P2Y₁₂ irreversible inhibitor that requires enteric metabolism and 2-step hepatic transformation to produce its active metabolite (3). Several cytochromes are involved in this oxidative process, but the most important is cytochrome P450 2C19 (*CYP2C19*). *CYP2C19* activity depends on genetic polymorphisms, and loss-of-function (LOF) alleles (notably *CYP2C19**2 and *CYP2C19**3) are present in 15% to 30% of the population according to ethnicity (4). Evidence suggests that such patients are at higher risk for ischemic events after ACS or PCI (5-12). This higher risk is explained by a significant reduction in clopidogrel bioactivation, leading to subsequent high platelet reactivity (13). Prasugrel and ticagrelor are high-intensity P2Y₁₂ inhibitors and do not depend upon *CYP2C19* activity, but a systematic switch to these drugs is associated with a higher bleeding risk. Conversely, *CYP2C19* gain-of-function (GOF) alleles (such as *CYP2C19**17) are present in 5% to 20% of the population and can be linked to an increase in biological activity, with a controversial impact on increased response to clopidogrel and bleeding risk (14-16).

SEE PAGE 631

Recent observational (17) and randomized (18-20) studies have shown that *CYP2C19* genotype-guided strategy for the selection of oral P2Y₁₂ inhibitors can reduce the increased thrombotic risk observed in *CYP2C19* LOF allele carriers while limiting the incidence of bleeding associated with a systematic use of potent P2Y₁₂ inhibitors. In these studies, *CYP2C19**2 and *CYP2C19**3 genotype was determined using point-of-care genetic testing or on-site genetic analyzers, which allowed rapid (<24 h in most cases)

genotype assessment and drug adjustment (19-21). However, these techniques are not accessible to all cardiology centers, and it is currently unclear if the use of routine *CYP2C19* genotyping to tailor P2Y₁₂ inhibitors in a real-world situation will be associated with a similar benefit. In addition, more extensive genetic techniques are required to screen for a more comprehensive set of *CYP2C19* LOF (*2 to *6) and GOF (*17) alleles (22), thus providing better prediction of *CYP2C19* metabolic activity (23).

The objective of the GIANT (Genotyping Infarct Patients to Adjust and Normalize Thienopyridine treatment) (NCT01134380) study was to prospectively assess the clinical impact of routine transmission to the cardiology team, in charge of patients with ST-segment elevation myocardial infarction (STEMI) treated with primary PCI and coronary stenting, of *CYP2C19* metabolic status, predicted according to *CYP2C19* genotype on the basis of 6 screened alleles and using simple noninvasive saliva sampling, and of potential adjustment and optimization of thienopyridine treatment according to pre-specified recommendations. Our main hypothesis was that routine *CYP2C19* genotyping and genotype-guided adjustment for higher intensity thienopyridine treatment in *CYP2C19* LOF allele carriers would reduce the high rate of ischemic events observed in these patients when treated with clopidogrel compared with patients with the *CYP2C19* wild-type genotype or GOF allele.

METHODS

Additional information is available in the [Online Appendix](#).

TRIAL DESIGN AND PATIENTS. The GIANT study was a prospective, multicenter, observational study performed at 57 sites in France ([Online Appendix](#)). The protocol was approved by ethics committees and national authorities, and all enrolled patients provided informed and signed consent to participate in the study and to genetic analyses. The population

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TABLE 1 Patient Classification Method

Observed genotype	*17/*17 *1/*17	*1/*1 *2/17 *3/*17 *4/*17	*1/*2 *1/*3 *1/*4 *1/*6	*2/*2
Predicted phenotype	Rapid	Normal	Slow	Very slow

consisted of all patients presenting with STEMI of <24-h onset and admitted for primary PCI. Complete CYP2C19 genetic profiling was performed in the study patients. The genotyping results were communicated to the study investigators for potential adjustment and optimization of thienopyridine treatment according to recommendations at the time of the recruitment period.

GENOTYPING METHODS. Saliva deoxyribonucleic acid (DNA) collectors (Oragene DNA, DNA Genotek, Ottawa, Ontario, Canada) were shipped to a central laboratory (La Pitié Salpêtrière, Paris, France) for DNA extraction and genetic analysis. Screening for CYP2C19 LOF (*2, *3, *4, *5, or *6) and GOF (*17) alleles was performed using commercially available TaqMan allelic discrimination assays (Thermo Fisher Scientific, Waltham, Massachusetts) on a 7900HT sequence detection system (Applied Biosystems, Courtaboeuf, France) as previously described (24). These genotype results were then used to classify patients into 4 different groups predicting CYP2C19 metabolic activity, as shown in Table 1. The prediction was based on available scientific information at the time of the study (23). Notably, carriers of the GOF *17 allele were considered rapid metabolizers. In addition, because of the lack of definitive evidence at the time the study was performed, compound carriers of both GOF and LOF alleles (i.e., *2/*17, *3/*17, and *4/*17) were considered normal metabolizers.

TREATMENT ADJUSTMENT. The study site received the predicted CYP2C19 metabolic status for each patient, and patient treatment was adjusted according to the clinical pharmacogenetics implementation consortium guidelines for CYP2C19 genotype and clopidogrel therapy (23). It was recommended on the basis of the results that very slow metabolizers should be treated with prasugrel and slow metabolizers with either prasugrel or a double dose of clopidogrel. The remaining groups were treated according to the investigator’s preference. Patients with normal and rapid CYP2C19 metabolic status (corresponding to wild genotype or GOF allele) were defined as class 1, and those with reduced CYP2C19 metabolic activity (i.e., carriers of LOF alleles) who received high-intensity thienopyridine treatment were defined as class 2. Last, patients with reduced CYP2C19

metabolic activity (i.e., carriers of LOF alleles) who did not receive high-intensity thienopyridine treatment as recommended were defined as class 3.

OBJECTIVES. The primary objective was to demonstrate that the rate of ischemic events observed in CYP2C19 LOF allele carriers detected by routine genotyping and receiving adjusted higher intensity thienopyridine treatment is similar to that observed in patients with the CYP2C19 wild-type genotype or GOF allele receiving a standard thienopyridine treatment. The primary endpoint was the difference in 12-month outcomes (including death, myocardial infarction [MI], and stent thrombosis) between class 1 and class 2 patients. The secondary endpoint involved the difference in 12-month major adverse cardiac and cerebrovascular events (MACCE) between and the major bleeding complications (on the basis of the criteria used in the STEEPLE [Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation] clinical trial [25]) at 12 months between groups.

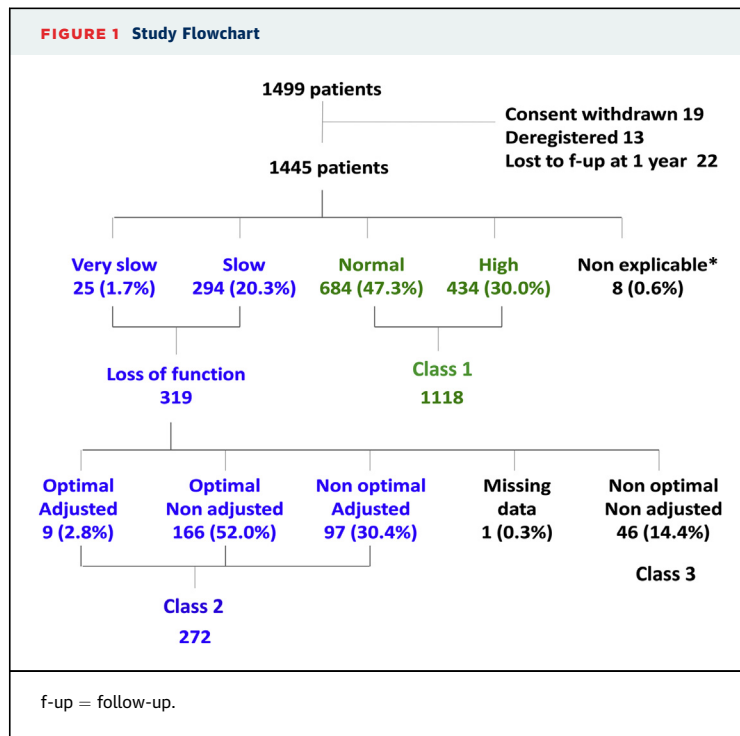
DATA MANAGEMENT AND SAMPLE SIZE. All data were entered into an electronic case report form (Clinigrid, Paris, France). Independent monitoring and data management were carried out by the Cardiovascular European Research Center (Massy, France). All outcomes were adjudicated by an independent committee (Online Appendix).

The primary endpoint was used to define the cohort size according to historical rates in previous French studies. The LOF cohort required 330 patients to detect a difference with non-slow responders with 80% power and alpha error of 5% (on the basis of a superiority design). As LOF represented 28% of screened patients in prior genotyping studies, the final size of the global cohort was 1,500 patients, after taking into account an estimation of follow-up loss.

Patients were first analyzed in a per-protocol analysis, taking into account class 1 patients and class 2 patients but excluding class 3 patients (patients with reduced CYP2C19 metabolic activity who did not receive high-intensity thienopyridine treatment as recommended by the protocol). Class 3 patients were then compared with class 1 and 2 patients in a secondary analysis.

RESULTS

A total of 1,499 patients were included at 57 centers in France from June 2010 through January 2012. After adjustment for major protocol deviations, the final analysis was carried out in 1,445 patients (Figure 1). CYP2C19 genotyping was successfully achieved for



1,437 patients (99.4%), and CYP2C19 metabolic status was communicated 4.1 ± 1.9 days after the PCI procedure, with a delay of shipment of the saliva samples to the central genetic laboratory of 3.8 ± 1.7 days. Only 18.4% received the genotyping results in the first 48 h after PCI, but 93.6% of patients received their results within 7 days.

TABLE 2 CYP2C19 Genotyping

Thienopyridine responder (group 1)	
Rapid	
*17/*17	65 (4.5)
*1/*17	369 (25.7)
Normal	
*1/*1	584 (40.6)
*2/*17	98 (6.8)
*3/*17	1 (0.1)
*4/*17	1 (0.1)
Thienopyridine resistant (group 2)	
Slow	
*2/*1	275 (19.1)
*2/*6	2 (0.1)
*3/*1	2 (0.1)
*4/*1	11 (0.8)
*6/*1	4 (0.3)
Very slow	
*2/*2	25 (1.7)

Values are n (%).

On the basis of the results of genotype profiling (Table 2, Figure 1), patients were divided into 3 different classes according to CYP2C19 genotype and predicted metabolism status and subsequent antiplatelet therapy adjustment. Class 1 was composed of 1,118 patients with wild-type genotype (47.3%) or GOF allele (30%) and with, respectively, predicted normal or rapid CYP2C19 metabolism status. Of the remaining 319 patients whose genotypes indicated slow and very slow metabolism status (20.3% and 1.7%, respectively) and resistance to clopidogrel, 272 patients (85%) in whom treatment was adjusted or already optimal according to the genotype were considered class 2 (Figure 1). Class 3 was composed of 46 patients with slow and very slow metabolism status who did not receive high-intensity thienopyridine treatment and were thus not appropriately adjusted (Online Table 1).

The baseline characteristics and procedural data of class 1 and 2 study patients are shown in Table 3 and were well balanced between groups. Pre- and post-genotyping antiplatelet treatments are described in Table 4. After the genotype results were provided, there was a significantly higher prescription of high-dose clopidogrel (150 mg/day) or prasugrel in class 2 patients.

PRIMARY ENDPOINT. As shown in Figure 2, class 2 patients (slow and very slow metabolizers in whom thienopyridine treatment was adjusted) had similar 12-month rates of death, MI, and stent thrombosis as observed in class 1 patients (3.04% in class 1 vs. 3.31% in class 2; hazard ratio: 1.10; 95% confidence interval: 0.49 to 2.44; $p = 0.82$, log-rank test). Reciprocally, the 46 slow and very slow responders with nonadjusted or inappropriate treatment (class 3) had significantly higher rates of death, MI, and stent thrombosis compared with class 2 patients (15.6%; $p < 0.05$ vs. class 1 or class 2). The 7 outcomes in class 3 patients included 4 deaths and 3 episodes of MI or stent thrombosis.

SECONDARY ENDPOINTS. Class 2 patients had a similar rate of MACCE at 12 months compared with patients in class 1, as shown in Table 5. The overall rate of major bleeding was low (1.9%), and no differences were observed between the classes of patients. Similar results were observed when considering both major and minor bleeding (3.58% in class 1 vs. 3.31% in class 2; $p = NS$).

ADDITIONAL ANALYSES. There was no significant difference in the occurrence of MACCE at 12 months according to CYP2C19 metabolism status (2.53% in rapid, 3.36% in normal, 2.80% in slow, and 9.09% in

very slow metabolizers; $p = 0.34$). Similar results were observed for major and minor bleeding (3.22% in rapid, 3.65% in normal, and 3.60% in slow metabolizers; $p = 0.92$). No bleeding was observed in very slow metabolizers.

We then performed additional analyses to further characterize the influence of the GOF allele (*CYP2C19**17). We first observed that none of the 65 patients with the *17/*17 genotype presented MACCE over the 12-month follow-up period, compared with 2.98% among *1/*17 carriers, 3.00% in compound carriers of both GOF and LOF alleles (*2/*17), and 3.42% in patients with the *1/*1 wild-type genotype. However, rates of major and minor bleeding were similar across these genotypes (3.07% in *17/*17 carriers, 3.25% in *1/*17 carriers, 3.00% in *2/*17 carriers, and 3.76% in *1/*1 carriers; $p = 0.96$).

We finally performed a sensitivity analysis by considering the 100 compound carriers of both GOF and LOF alleles (*2/*17, *3/*17, and *4/*17) as slow metabolizers instead of normal metabolizers, as initially planned (Table 2). This reclassification did not change our primary results, and the primary endpoint was not statistically different between groups (hazard ratio: 1.12; 95% confidence interval: 0.55 to 2.29; $p = 0.73$, log-rank test).

SUBGROUP ANALYSIS. Subgroup analysis did not show any significant differences associated with sex or acute MI localization regarding the occurrence of MACCE between the study groups.

The occurrence of outcomes was not different in the 44 class 2 patients who were adjusted to high-dose clopidogrel (150 mg/day) compared with the 225 class 2 patients adjusted to prasugrel: 4.54% versus 3.11% for the primary endpoint ($p = 0.63$), 11.36% versus 9.78% for MACCE ($p = 0.75$), and 2.27% versus 2.22% for major bleeding ($p = 0.98$).

DISCUSSION. In this study, we found that: 1) in a real-world setting, a complete *CYP2C19* genotype can be determined in ≤ 7 days in a vast majority of patients using analysis of saliva DNA collected during the in-hospital phase of STEMI management; 2) the detection of LOF alleles and prediction of reduced *CYP2C19* metabolism in 22% of patients allowed the adjustment of P2Y₁₂ inhibition, leading to the use of prasugrel or double-dose clopidogrel, in 85% of patients; 3) the 1-year clinical outcomes of patients with reduced *CYP2C19* metabolism and high-intensity thienopyridine therapy did not differ from those of patients with normal or rapid *CYP2C19* metabolism; and 4) reciprocally, the remaining 15% of patients with reduced *CYP2C19* metabolism without

TABLE 3 Demographic and Procedural Data

	N	Class 1 (n = 1,118)	Class 2 (n = 272)	p Value
Male	1,390	918 (82.1)	211 (77.6)	0.09
Age (yrs)	1,390	58.6 ± 12.9	57.8 ± 12.0	0.22
CV history				
Myocardial infarction	1,390	49 (4.4)	19 (7.0)	0.08
PCI	1,390	70 (6.3)	19 (7.0)	0.66
CABG	1,390	7 (0.6)	4 (1.5)	0.24
Stroke	1,390	21 (1.9)	10 (3.7)	0.07
Risk factors				
Family history	1,390	201 (18.0)	55 (20.2)	0.39
Smoking				
Former or current		747 (66.9)	195 (71.7)	0.13
Treated diabetes	1,390	152 (13.6)	42 (15.4)	0.43
Dyslipidemia	1,389	477 (42.7)	120 (44.1)	0.67
Hypertension	1,389	424 (38.0)	119 (43.8)	0.08
Lesions				
Single-vessel disease		624 (55.8)	144 (52.9)	0.44
2-vessel disease		347 (31.0)	84 (30.9)	
3-vessel disease		145 (13.0)	43 (15.8)	
Treated lesions	1,829	1,466	363	
LM		10 (0.7)	3 (0.8)	0.71
LAD		629 (42.9)	132 (36.4)	0.02
LCx		258 (17.6)	84 (23.1)	0.01
RCA		568 (38.7)	143 (39.4)	0.82
Bypass surgery		1 (0.1)	1 (0.3)	0.35
TIMI flow grade of the culprit lesions	1,829			
0		749 (51.1)	196 (54.0)	0.25
1		130 (8.9)	21 (5.8)	
2		157 (10.7)	42 (11.6)	
3		430 (29.3)	104 (28.6)	
Procedural data				
Ejection fraction >50% at presentation	990	403 (50.3)	87 (46.0)	0.29
Radial access	1,390	780 (69.8)	182 (66.9)	0.36
Thromboaspiration	1,390	609 (54.5)	140 (51.7)	0.89
Patients with implanted stents	1,390	1,111 (99.4)	270 (99.3)	0.84
Treated lesions/patient		1.31 ± 0.65	1.33 ± 0.64	0.36
Total number of stents	1,780	1,428	352	
Direct stenting		421 (29.5)	111 (31.5)	0.45
Number of stents/patient		1.43 ± 0.84	1.49 ± 0.85	0.27
Number of DES/patient		0.42 ± 0.77	0.48 ± 0.80	0.16
Number of BMS/patient		0.93 ± 0.86	0.96 ± 0.93	0.22
Procedural success*	1,390	1,110 (96.1)	246 (97.4)	0.46
TIMI flow grade 0		8 (0.7)	0 (0.0)	0.65
TIMI flow grade 1		5 (0.4)	1 (0.4)	
TIMI flow grade 2		29 (2.6)	6 (2.2)	
TIMI flow grade 3		1,076† (96.2)	264 (97.4)	

Values are n (%) or mean ± SD. * <30% residual stenosis and TIMI flow grade >2. †2 patients with TIMI flow grade 3 and procedural failure.

BMS = bare-metal stent; CABG = coronary artery bypass grafting; CV = cardiovascular; DES = drug-eluting stent; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LM = left main coronary artery; PCI = percutaneous coronary intervention; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

appropriate adjustment of P2Y₁₂ inhibitors had a significantly worse prognosis.

To the best of our knowledge, this is the first real-world, large-scale, observational and prospective study to evaluate the role of a pragmatic strategy to determine *CYP2C19* genotype and tailor antiplatelet

TABLE 4 Antithrombotic Treatment

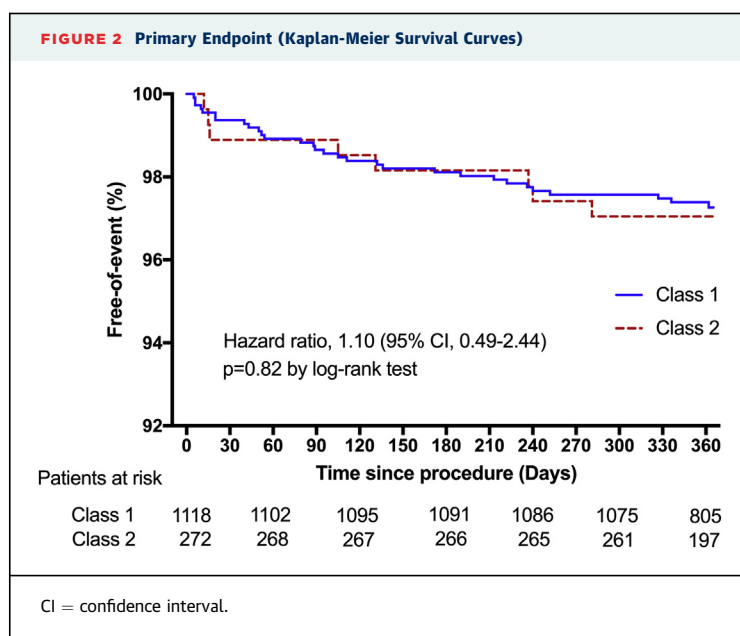
	N	Class 1	Class 2	p Value
Per or pre-procedure				
Low-molecular weight heparin	1,390	411 (36.8)	119 (43.7)	0.03
Unfractionated heparin	1,390	788 (70.5)	181 (66.5)	0.21
Glycoprotein IIb/IIIa inhibitors	1,389	588 (52.6)	153 (56.2)	0.66
Aspirin	1,390	1,061 (94.9)	259 (95.2)	0.83
Daily dose	1,390	160 (75-250)	160 (75-250)	
Loading dose during procedure	1,390	250 (250-250)	250 (250-250)	
Bivalirudin	1,390	34 (3.0)	12 (4.4)	0.27
Thienopyridine				
Before genotyping				
Before genotyping	1,383			
Clopidogrel 75 mg		400 (36.1)	95 (35.2)	0.75
Clopidogrel 150 mg		112 (10.1)	24 (8.9)	
Prasugrel		595 (53.7)	151 (55.9)	
After genotyping				
After genotyping	1,377			
Clopidogrel 75 mg		498 (44.8)	3 (1.1)	<0.0001
Clopidogrel 150 mg		99 (8.9)	44 (16.2)	
Prasugrel		514 (46.3)	225 (82.7)	

Values are n (%) or median (range).

therapy after primary PCI (**Central Illustration**). Our study provides important information by showing that adjustment of antiplatelet treatment on the basis of *CYP2C19* genotype can be performed in the week following MI and primary PCI, which appears to blunt the risk for ischemic events associated with the *CYP2C19* LOF alleles, which was similar to the risk among patients without *CYP2C19* LOF alleles. Our results thus extend the previous demonstration that a rapid (<24 h) *CYP2C19*-genotype-guided strategy for selection of P2Y₁₂ inhibitor can reduce high on-treatment platelet reactivity (RAPID GENE

[Reassessment of Anti-Platelet Therapy Using an Individualized Strategy Based on Genetic Evaluation] study [19]) and ischemic events (PHARMCLO [Pharmacogenetics of Clopidogrel in Acute Coronary Syndromes] [20] and POPular GENETICS [Cost-Effectiveness of Genotype Guided Treatment With Antiplatelet Drugs in STEMI Patients: Optimization of Treatment] [18] studies) in *CYP2C19**2 carriers. Indeed, in these 3 studies, *CYP2C19* genotype was principally achieved with point-of-care genetic testing, which provided results in 1 to 2 h (18-21) and consequently led to adjusted antiplatelet therapy in the first day after genotyping (18). An important proportion of recurrent ischemic events occur in the immediate days following MI and PCI, and more rapid genotyping could therefore indicate more rapid therapy adjustment during this high-risk period. However, the acute management of MI typically includes higher loading doses or the use of more potent and *CYP2C19*-independent P2Y₁₂ inhibitors (1). Reciprocally, numerous studies evaluating the impact of *CYP2C19**2 and other LOF alleles on clinical outcomes after MI, ACS, or PCI found an association with higher long-term major adverse cardiac event and stent thrombosis rates in patients chronically treated with clopidogrel 75 mg/day (6,8,12). This is in line with our results, which showed that the carriers of *CYP2C19* LOF alleles but without antiplatelet therapy adjustment had a 15.6% rate of death, MI, or stent thrombosis at 1 year compared with 3.3% for the adjusted population ($p < 0.05$) or 3.04% for the GOF or wild genotype population. The similar outcomes between class 1 (rapid and normal metabolizers) and class 2 (slow and very slow metabolizers with drug adjustment) patients suggest a potential benefit associated with the use of more potent P2Y₁₂ inhibitors in *CYP2C19* LOF allele carriers. This adjustment was based mainly on increased use of prasugrel, from 55.9% to 82.7%. Overall, our results suggest that *CYP2C19* genotyping can be performed in the days following MI to appropriately select long-term treatment with P2Y₁₂ inhibitors, and this strategy is associated with a reduction of ischemic events in *CYP2C19* LOF allele carriers.

In the GIANT study, we performed a more comprehensive assessment of 6 *CYP2C19* alleles. Although the *CYP2C19**2 allele is the most frequent LOF allele, other rare alleles are also associated with reduced *CYP2C19* activity (4). By screening 4 additional LOF alleles (*3, *4, *5, and *6), we found 17 carriers who would have been wrongly considered as normal metabolizers with a single screening of *CYP2C19**2. Because of the low frequency of these alleles, however, it is impossible to ascertain whether



the *CYP2C19* genotype-guided strategy is associated with a beneficial effect in these few patients as in *CYP2C19**2 carriers. This would deserve further investigations in larger cohorts of patients. In addition, the *CYP2C19**17 allele is associated with increased *CYP2C19* activity and controversial impact of the response to clopidogrel. Some studies have suggested increased bleeding risk in these patients as a result of a higher response to clopidogrel (16,23,26). In this study, these patients were identified as rapid metabolizers, but this did not trigger specific recommendations for drug adjustment. Additional analyses did not reveal a significant influence of the *17 allele on the results, although we found that none the 65 *17/*17 carriers had MACCE during the 12-month follow-up period. Last, compound carriers of both the *2 LOF and *17 GOF alleles were considered normal metabolizers in our study. This classification was based on available evidence at the time when this study was performed, but new evidence suggests that these patients could present with reduced *CYP2C19* activity (27). In our study, however, we did not see any particular differences in the rate of major adverse cardiac events or bleeding in these 98 patients (6.8%). Reciprocally, the primary endpoint was not affected by the reclassification of these compound carriers as slow metabolizers. Further studies are now needed to better specify the optimal adjustment strategy in these patients with less frequent *CYP2C19* genotypes.

The results of the recent POPular-GENETICS study (18) suggest that the *CYP2C19* genotype-guided strategy for the selection of P2Y₁₂ inhibitor resulted in a lower incidence of bleeding in the genotype-guided group compared with standard treatment. We did not observe such a result in our study, however, with a lower rate of major and minor bleeding events in our patients. This could be due to the differences in the criteria used to define bleeding events between studies or to difficulties identifying minor bleeding events that did not require hospitalization in our study. Nevertheless, the lower use of more potent P2Y₁₂ inhibitors as long-term antiplatelet therapy in patients who are predicted to be good responders to clopidogrel 75 mg/day (class 1 in our study) would likely be associated with a reduction in bleeding events. Recent registries have shown that a majority of patients still receive clopidogrel in the management of acute MI, such as in the recent TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia), SCAAR (Swedish Coronary Angiography and Angioplasty Registry) registry-based trial, in which 66% of

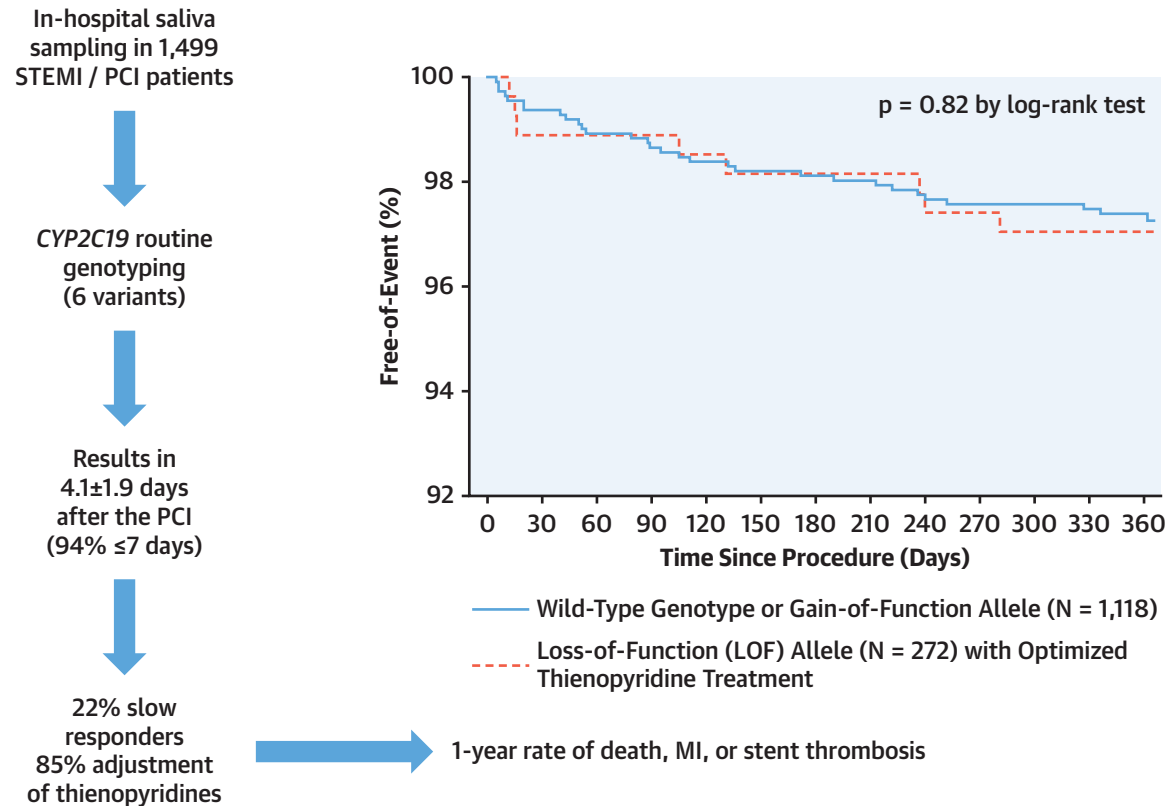
TABLE 5 Twelve-Month Events

	Class 1 (n = 1,118)	Class 2 (n = 272)	HR (95% CI)	p Value
12-month MACCE	96 (8.6)	27 (9.9)	1.19 (0.76-1.86)	0.45
Cardiac death	4 (0.4)	2 (0.7)		
Non-STEMI	18 (1.6)	4 (1.5)		
STEMI	4 (0.4)	0 (0.0)		
TVR	45 (4)	15 (5.5)		
Stroke	3 (0.3)	0 (0.0)		
Stent thrombosis	13 (1.2)	2 (0.7)	0.46 (0.11-2.59)	0.44
Definite	11 (1)	2 (0.7)		
Acute/subacute	6 (0.5)	1 (0.4)		
Late	5 (0.4)	1 (0.4)		
Probable	1 (0.1)	0 (0.0)		
Acute/subacute	1 (0.1)	0 (0.0)		
Major bleeding events	20 (1.8)	6 (2.2)	1.45 (0.52-4.05)	0.44
Digestive	1.0	0.7		
Intracranial	0.5	1.5		
Access site	0.2	0.0		

Values are n (%) or %.
 CI = confidence interval; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular events; STEMI = ST-segment elevation myocardial infarction; TVR = target vessel revascularization.

patients received clopidogrel, 28.5% received ticagrelor, and the remaining patients were treated with prasugrel (28).

The respective role of genotyping versus phenotyping assessment to guide P2Y₁₂ inhibition has been a subject of debate (29). GRAVITAS (Gauging Responsiveness With a VerifyNow Assay—Impact on Thrombosis and Safety) (30), ARCTIC (Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy) (31), ANTARTIC (Tailored Antiplatelet Therapy Versus Recommended Dose of Prasugrel) (32), and TRIGGER-PCI (Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) (33) are the most important of several randomized trials that have evaluated the benefits of a tailored approach on the basis of a systematic evaluation of platelet reactivity. None of these studies has succeeded in validating the role of phenotyping testing. Conversely, genotype evaluation could appear as a more complex and time-consuming approach, but our results indicate that the delay to obtain *CYP2C19* genotyping from a genetic laboratory does not affect the benefit of genotype-guided adjustment. Our results, combined with those of other observational and randomized trials, indicate that management of patients with MI could be improved by the systematic implementation of a *CYP2C19* genotype-guided strategy.

CENTRAL ILLUSTRATION A Pragmatic Strategy to Genotype *CYP2C19* in STEMI/PCI Patients and Adjust Thienopyridine Therapy in LOF CarriersHulot, J.-S. et al. *J Am Coll Cardiol Intv.* 2020;13(5):621-30.

LOF = loss-of-function; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

STUDY LIMITATIONS. The absence of randomization, either at the time of primary PCI to obtain a control group of patients without genotyping or after genotyping to set up a balanced control group of untailored treatment in LOF allele carriers, limits the impact of our findings but permitted the implementation of a genotyping strategy in an all-comers population undergoing primary PCI at more than 50 centers. As a complementary analysis, we reported a higher rate of clinical events in class 3 patients, but the reason for disrespecting the genotype adjustment was left to the physician's discretion and is potentially linked to the identification of different characteristics in these patients. In addition, an important proportion of patients were initially treated with clopidogrel, whereas current guidelines instead support the use of a more potent thienopyridine (prasugrel or ticagrelor) in the acute management of STEMI. The relevance of *CYP2C19* genotype in patients with

STEMI receiving prasugrel or ticagrelor as initial pharmacotherapy remains to be determined, especially in the context of early de-escalation of antiplatelet treatment after the acute phase, as established in TROPICAL-ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes Trial) (29,34). Finally, an adjustment strategy was recommended according to genotype but was ultimately decided by the prescribing physician. Therefore, our study was not designed to directly evaluate and compare optimal adjustment strategies. A small proportion of LOF allele carriers (16.2%) were adjusted to high-dose clopidogrel (150 mg/day), a strategy that has been shown not to be as effective as prasugrel or ticagrelor to reduce on-treatment high platelet reactivity. However, we did not observe increased rates of outcomes in patients adjusted to clopidogrel 150 mg/day compared with

those adjusted to prasugrel 10 mg/day. Similarly, 43.6% of normal and rapid *CYP2C19* metabolizers received prasugrel 10 mg/day, and our study was not designed to evaluate de-escalation to clopidogrel 75 mg/day in those patients.

CONCLUSIONS

In a real-world setting, a complete *CYP2C19* genotype can be determined in <7 days in a vast majority of patients using analysis of saliva DNA collected during the in-hospital phase of patients with an acute MI treated with primary PCI. Genotype information led to stronger platelet inhibition treatment in the vast majority of LOF allele carriers and ultimately to similar clinical outcomes as in patients carrying the wild genotype or GOF allele.

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PERSPECTIVES

WHAT IS KNOWN? Response to clopidogrel differs widely among patients, notably because of *CYP2C19* genetic polymorphisms. Patients with *CYP2C19* LOF alleles have a higher risk for major adverse cardiac events after ACS or percutaneous intervention, but *CYP2C19* genotyping is not performed in daily practice.

WHAT IS NEW? In a real-world setting, a complete *CYP2C19* genotype could be determined in <7 days in a vast majority of patients using analysis of saliva DNA collected during the in-hospital phase of patients with acute MI treated with primary PCI. Genotype information led to stronger platelet inhibition treatment in the vast majority of LOF allele carriers and ultimately to similar clinical outcomes as in patients carrying the wild genotype or GOF allele.

WHAT IS NEXT? The implementation of a pragmatic strategy to determine *CYP2C19* genotype and tailor antiplatelet therapy after primary PCI should be evaluated.

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KEY WORDS clopidogrel, CYP2C19, genetics, real-life setting, STEMI

APPENDIX For supplemental information including Methods, a table, and a list of steering committee members, clinical events adjudication committee members, and centers, please see the online version of this paper.