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ORIGINAL ARTICLE

Clopidogrel Versus Ticagrelor or Prasugrel After Primary Percutaneous Coronary Intervention According to CYP2C19 Genotype

A POPular Genetics Subanalysis

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BACKGROUND: Guidelines favor ticagrelor or prasugrel over clopidogrel in patients with myocardial infarction. However, the POPular Genetics trial (Patient Outcome After Primary Percutaneous Coronary Intervention [PCI]) showed that in patients with primary PCI, a *CYP2C19* genotype–guided strategy was associated with a lower bleeding risk without increasing thrombotic risk, compared with routine ticagrelor/prasugrel treatment. Nevertheless, optimal $P2Y_{12}$ inhibitor treatment in specific *CYP2C19* genetic subgroups is still a subject of debate.

METHODS: A prespecified subanalysis of the POPular Genetics trial was performed, using patients in whom *CYP2C19**2, *3, and *17 genotypes was determined. Two different analyses were planned. The first assessed the effect of the *CYP2C19**17 allele in clopidogrel-treated patients. The second compared the effect of clopidogrel in noncarriers of a loss-of-function allele with ticagrelor/prasugrel–treated patients, irrespective of *CYP2C19* genotype. Main outcomes were a thrombotic outcome (cardiovascular death, myocardial infarction, stent thrombosis, and stroke) and a bleeding outcome (PLATO [Platelet Inhibition and Patient Outcomes] major and minor bleeding) after 12 months.

RESULTS: A total of 2429 patients were used for analyses. In the first analysis, the *CYP2C19**17 polymorphism was not found to have a significant influence on thrombotic (adjusted hazard ratio, 0.95 [95% CI, 0.45–2.02]) or bleeding outcomes (adjusted hazard ratio, 0.74 [95% CI, 0.48–1.18]). In the second analysis, clopidogrel was associated with a lower number of bleeding events compared with ticagrelor/prasugrel (9.9% versus 11.7%, adjusted hazard ratio, 0.74 [95% CI, 0.56–0.96]), without a significant increase in thrombotic events (3.4% versus 2.5%, adjusted hazard ratio, 1.14 [95% CI, 0.68–1.90]).

CONCLUSIONS: In patients with primary PCI not carrying a *CYP2C19* loss-of-function allele, the use of clopidogrel compared with ticagrelor or prasugrel was associated with lower bleeding rates, without an increase in thrombotic events. No effect on clinical outcomes was found for the *CYP2C19**17 polymorphism.

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GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: acute coronary syndrome ■ clopidogrel ■ genetic testing ■ myocardial infarction ■ percutaneous coronary intervention ■ pharmacogenetics ■ ticagrelor

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WHAT IS KNOWN

- Guidelines favor ticagrelor and prasugrel over clopidogrel in myocardial infarction patients due to a lower thrombotic risk, albeit a higher bleeding risk.
- There is a wide variability in platelet reactivity in clopidogrel-treated patients, which can partially be explained by variations in the *CYP2C19* gene.

WHAT THE STUDY ADDS

- Carrying ≥1 *CYP2C19**17 allele has no effect on clinical outcomes in patients with ST-segment–elevation myocardial infarction.
- In patients with ST-segment–elevation myocardial infarction not carrying a *CYP2C19* loss-of-function allele, clopidogrel was associated with a reduction in bleeding–without increasing thrombotic events compared with ticagrelor and prasugrel.

Nonstandard Abbreviations and Acronyms

LoF	loss-of-function
PCI	percutaneous coronary intervention
PLATO	Platelet Inhibition and Patient Outcomes
POPular Genetics	Patient Outcomes After Primary PCI
Tailor PCI	Tailored Antiplatelet Therapy Following PCI
TRITON TIMI	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction

Dual antiplatelet therapy, consisting of aspirin and a $P2Y_{12}$ inhibitor, remains the cornerstone of antithrombotic treatment in patients with myocardial infarction. Guidelines favor ticagrelor and prasugrel because these showed a reduction in thrombotic events as compared with clopidogrel.[1,2] This higher efficacy, however, is hampered by a higher bleeding risk.[3,4]

Clopidogrel is a prodrug, transformed into its active metabolite by hepatic cytochrome P450 enzymes in the liver. There is a large variability in antiplatelet effect in patients treated with clopidogrel, which in part can be explained by genetic variations in the *CYP2C19* gene.[5] Patients carrying a *CYP2C19**2 or *3 loss-of-function (LoF) allele are at higher risk for having high on-treatment platelet reactivity when treated with clopidogrel, which is associated with a higher risk of stent thrombosis and recurrent atherothrombotic events.[6] In patients carrying a *CYP2C19**17 gain-of-function allele, clopidogrel efficacy might be better, with possibly higher bleeding rates.[7,8] However, data on the influence of *CYP2C19**17 on clinical outcome are conflicting and mostly derived from observational studies.[9] Its clinical relevance is, therefore, not clear.

In the recently published POPular Genetics trial (Patient Outcome After Primary Percutaneous Coronary Intervention [PCI]), a *CYP2C19* genotype–guided antiplatelet strategy, using clopidogrel in patients without LoF allele and ticagrelor or prasugrel in patients carrying ≥1 LoF alleles, showed a reduction in bleeding risk (defined as PLATO [Platelet Inhibition and Patient Outcomes] major or minor bleeding) compared with standard treatment with ticagrelor or prasugrel, without an increase in thrombotic risk.[10] Moreover, in a subanalysis of the PLATO trial, ticagrelor was not superior to clopidogrel regarding the thrombotic outcome.[11] Since then, thrombotic event rates have declined considerably.[12] At the same time, the incidence of bleeding events, which are associated with a substantial morbidity and mortality risk, remained high.[13] Therefore, the question of which antiplatelet strategy is best to balance thrombotic and bleeding risk in patients with ST-segment–elevation myocardial infarction after primary PCI is still open, in particular for different subgroups of noncarriers of *CYP2C19* LoF alleles.

In this prespecified subanalysis of the POPular Genetics trial, we study the effect of the *CYP2C19**17 allele in clopidogrel-treated patients and the safety and efficacy of clopidogrel in patients without an LoF allele, compared with ticagrelor and prasugrel.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

The detailed design and results of the POPular Genetics trial have been reported previously.[10,14] In brief, POPular Genetics was an open-label, randomized, multicenter trial with 2488 patients with ST-segment–elevation myocardial infarction undergoing primary PCI. It compared a standard treatment with ticagrelor or prasugrel with a *CYP2C19* genotype–guided strategy, where patients received clopidogrel if they did not carry a *CYP2C19**2 or *3 LoF allele and ticagrelor or prasugrel if they were carrier of such an LoF allele. Treatment and follow-up duration were 12 months. An institutional review board approved the trial, and all participants provided informed consent.

Blood samples were collected from patients in both treatment groups. During the trial, *CYP2C19* genotyping was performed in the genotype-guided group, where the presence of the *CYP2C19**2 and *3 polymorphism was determined using the Spartan RX point-of-care system or the TaqMan StepOnePlus assay. After the trial was completed, genotyping was performed in all patients in the standard treatment arm,

and both groups were tested for *CYP2C19**17. This was done by LGC Biosearch Technologies (Hoddesdon, United Kingdom) using a kompetitive allele–specific genotyping assay. For the analyses, an intention to treat analysis was performed in which patients were divided into a clopidogrel-treated or ticagrelor/prasugrel–treated group, based on the drug prescribed at discharge. Two different analyses were performed. The first analysis compared clopidogrel in *CYP2C19**1/*1 patients with clopidogrel in patients with a *1/*17 or *17/*17 genotype. No separate analysis for homozygous *CYP2C19**17 carriers was performed because of the low number of patients in this group (n=35). The second analysis compared clopidogrel-treated patients not carrying a *CYP2C19**2 or *3 LoF allele with ticagrelor- or prasugrel-treated patients irrespective of their CYP2C19 metabolizer status. In addition, we performed 2 sensitivity analyses, one including only patients without LoF alleles in both the clopidogrel and ticagrelor- or prasugrel-treated group and one on-treatment analysis.

Statistical Analysis

This prespecified subanalysis was not prospectively powered and is based on the number of patients in the original trial of whom the *CYP2C19* genetic profile was available. The outcomes were a thrombotic outcome consisting of cardiovascular death, myocardial infarction, stent thrombosis and stroke, a bleeding outcome consisting of PLATO major and minor bleeding, and the individual components of the thrombotic and bleeding outcome. The definitions were identical to those used in the POPular Genetics trial.[10] All outcomes were adjudicated by a blinded event committee.

Variables are presented as numbers (percentages) and means±SD. Missing baseline variables were not imputed. *P* values were calculated using Student *t* test for continuous variables, χ^2 tests for categorical variables, and 1-way ANOVAs for variables with multiple categories. A *P* value below 0.05 was considered statistically significant. Kaplan-Meier curves were estimated and the log-rank test was used to calculate *P* values. If a patient was lost to follow-up, it was censored after the last known contact. Cox proportional hazard models were used to calculate hazard ratios (HR) and the 95% CI. The Efron approximation was used to handle ties. To adjust for possible confounders, all baseline characteristics with a $P<0.10$ were selected for univariate regression analysis. If there was a significant interaction ($P<0.05$) in the univariate analysis, they were selected for multivariable regression analysis. The final model included only those characteristics with a significant interaction in the multivariable analysis. Main effects were included in the model. All analyses were performed using R version 3.6.0.

RESULTS

Figure 1 shows a flow chart of how the subgroups were selected. In the POPular Genetics cohort, *CYP2C19**2, *3, and *17 carrier status was available in 2100 patients, of which 1550 did not carry an LoF allele. In the remaining 388 patients, *CYP2C19* carrier status was unknown. Of these 388 patients, 329 were treated with ticagrelor or prasugrel and could therefore be included in the ticagrelor/prasugrel group of the second analysis. Of the 1550 patients not carrying an LoF allele, 821 were treated with clopidogrel and 729 with ticagrelor or prasugrel. Of the 821 clopidogrel-treated patients, 277 had a *1/*17 genotype, and 35 patients had a *17/*17 genotype. The baseline characteristics for the 2 analyses can be found in Tables 1 and 2. All groups were well balanced in baseline characteristics, except for the more common use of proton pump inhibitors and oral anticoagulation in the clopidogrel-treated patients as compared to the ticagrelor- or prasugrel-treated patients. Tables I and II in the Data Supplement show what variables were used in univariate and multivariate regression analysis and what variables were used in the final model.

Effect of the *CYP2C19**17 Allele in Clopidogrel-Treated Patients

For this analysis, 420 patients with a *CYP2C19**1/*1 genotype and 312 patients with a *CYP2C19**1/*17 or *17/*17 genotype were available. An overview of the outcomes is presented in Table 3. There were no significant differences between the patients with *CYP2C19**1/*1 genotype versus carriers of a *17 allele for the combined thrombotic outcome (3.8% versus 3.8%, adjusted hazard ratio, 0.95 [95% CI, 0.45–2.02], $P=0.90$; Figure 2A) and the combined bleeding outcome (11.2% versus 9.3%, adjusted hazard ratio, 0.74 [95% CI, 0.48–1.18], $P=0.21$; Figure 2B).

Clopidogrel in Patients Not Carrying a *CYP2C19**2 or *3 Allele Versus Ticagrelor or Prasugrel Irrespective of *CYP2C19* Genotype

For this analysis, 821 clopidogrel and 1608 ticagrelor- or prasugrel-treated patients were available. Table 4 shows an overview of the outcomes. There were no significant differences in the combined thrombotic outcome (3.4% versus 2.5%, adjusted hazard ratio, 1.14 [95% CI, 0.68–1.90], $P=0.62$; Figure 3A), whereas the combined bleeding outcome occurred significantly less frequently in clopidogrel-treated patients (9.9% versus 11.7%, HR, 0.74 [95% CI, 0.56–0.96], $P=0.03$; Figure 3B).

Sensitivity Analyses

Results for the 2 sensitivity analyses are presented in Table 5. The first analysis included 1550 patients without LoF allele, of which 821 patients were treated with clopidogrel and 729 with ticagrelor or prasugrel. The adjusted HR for the combined thrombotic outcome was 1.11 (95% CI, 0.61–2.03, $P=0.72$), whereas the adjusted HR for the combined bleeding outcome was 0.59 (95% CI, 0.44–0.80, $P<0.001$). The on-treatment analysis included the 821 clopidogrel-treated patients and 1613 ticagrelor- or prasugrel-treated patients. The adjusted HR for the combined thrombotic outcome was 0.98

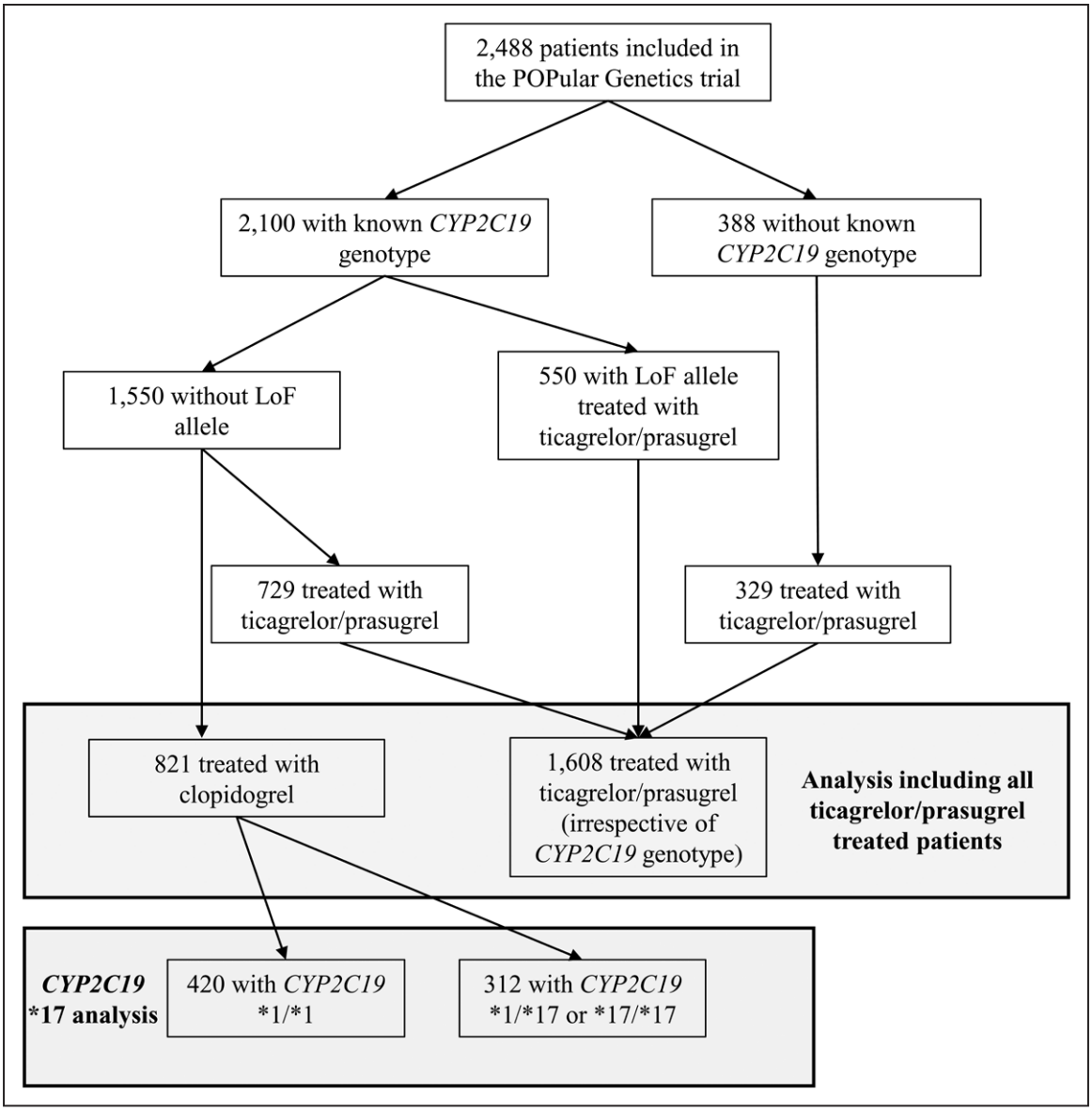

Figure 1. Flowchart of patients included in the different subgroup analyses.
LoF indicates loss-of-function.

(95% CI, 0.56–1.70, *P*=0.94), whereas the adjusted HR for the combined bleeding outcome was 0.68 (95% CI 0.52–0.90, *P*=0.008).

DISCUSSION

In this prespecified subanalysis of the POPular Genetics trial, which included patients with ST-segment–elevation myocardial infarction who underwent primary PCI and compared clopidogrel-treated noncarriers of *CYP2C19* LoF alleles with all ticagrelor- and prasugrel-treated patients, treatment with clopidogrel was associated with a significantly lower bleeding rate compared with treatment with ticagrelor or prasugrel. This finding held true in both the sensitivity analyses. The effect was primarily driven by a reduction of PLATO minor bleeding. There was no association found between clopidogrel use and a higher risk for the combined thrombotic outcome, although the number of patients with a recurrent myocardial infarction was numerically higher in clopidogrel-treated patients. These findings match the outcomes of the overall POPular Genetics trial.[10] Also in the PLATO genetic subanalysis, in which 3554 ticagrelor-treated patients without *CYP2C19* LoF allele were compared with 3516 clopidogrel-treated patients without *CYP2C19* LoF allele, similar to our second sensitivity analysis, the event rate for a combined thrombotic outcome consisting of cardiovascular death, myocardial infarction, and stroke was only numerically lower with the use of ticagrelor, not reaching statistical significance (8.8% versus 10.0%, HR, 0.86 [95% CI, 0.74–1.01], *P*=0.06).[11] This in contrast to the overall PLATO trial, which showed clear benefit in

Table 1. Baseline Characteristics of Clopidogrel-Treated Patients According to *CYP2C1917 Carrier Status**

	*CYP2C19**1/*1; N=420	*CYP2C19**17 carriers; N=312	*P* value
Age, y, mean±SD	61.2±10.8	62.8±11.2	0.06
Female sex, n (%)	105 (25.0)	89 (28.5)	0.33
BMI, kg/m^2, mean±SD	27.7±9.85	27.1±4.14	0.28
Creatinine clearance <60 mL/(min·1.73 m^2) at baseline,* n (%)	39 (9.4)	29 (9.4)	1.0
History, n (%)			
Current smoker	199 (48.2)	126 (40.6)	0.05
Hypertension	174 (41.4)	127 (40.7)	0.90
Dyslipidemia	83 (19.8)	63 (20.2)	0.96
Diabetes	43 (10.2)	32 (10.3)	1.0
Coronary artery disease	47 (11.2)	32 (10.3)	0.78
Peripheral arterial disease	17 (4.1)	11 (3.5)	0.87
Stroke	7 (1.7)	3 (1.0)	0.53
Bleeding	9 (2.1)	8 (2.6)	0.90
Discharge medication, n (%)			
Aspirin	404 (96.4)	302 (96.8)	0.94
$P2Y_{12}$ inhibitor after discharge			
Clopidogrel	420 (100)	312 (100)	
Vitamin K antagonist	26 (6.2)	13 (4.2)	0.30
Novel anticoagulant	6 (1.4)	8 (2.6)	0.41
ACE inhibitor	320 (76.4)	227 (72.8)	0.30
ATII antagonist	42 (10.0)	33 (10.6)	0.90
Beta blocker	370 (88.3)	276 (88.5)	1.0
Statin	408 (97.4)	300 (96.2)	0.47
Proton pump inhibitor	332 (79.2)	247 (79.2)	1.0
Procedural characteristics			
Access site			0.54
Femoral	133 (31.7)	106 (34.2)	
Radial	286 (68.3)	204 (65.8)	
Multivessel disease	205 (48.8)	168 (53.8)	0.20
Stent			
None	10 (2.4)	4 (1.3)	0.42
Bare metal stent	21 (5.0)	20 (6.4)	0.51
Biovascular scaffold	4 (0.1)	3 (1.0)	1.0
Drug eluting stent	393 (93.6)	292 (93.6)	1.0
Ostial lesion	28 (6.7)	20 (6.5)	1.0
Bifurcation lesion	82 (19.6)	64 (20.6)	0.79
Total stent length, mm, mean±SD	27.6±14.0	26.6±13.3	0.33

ACE indicates angiotensin-converting enzyme; ATII, angiotensin II; BMI, body mass index; and CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.
*Creatinine clearance was calculated with the use of the CKD-EPI formula.

reducing thrombotic risk with ticagrelor compared with clopidogrel, at the cost of increased non-coronary artery bypass grafting surgery related major bleeding rates.[3]

Table 2. Baseline Characteristics of Clopidogrel in Patients Without *CYP2C192 or *3 LoF Allele Versus Ticagrelor or Prasugrel in All Patients (Irrespective of *CYP2C19* Genotype)**

	Clopidogrel (no LoF allele); N=821	Ticagrelor and prasugrel; N=1608	*P* value
Age, y, mean±SD	62.0±10.9	61.3±11.3	0.14
Female sex, n (%)	224 (27.3)	388 (24.1)	0.10
BMI, kg/m^2, mean±SD	27.5±7.66	27.2±4.22	0.32
Creatinine clearance <60 mL/(min·1.73 m^2) at baseline,* n (%)	75 (9.2)	148 (9.2)	1.0
History, n (%)			
Current smoker	372 (45.9)	738 (46.3)	0.90
Hypertension	348 (42.4)	655 (40.7)	0.46
Dyslipidemia	172 (21.0)	332 (20.7)	0.91
Diabetes	89 (10.8)	186 (11.6)	0.64
Coronary artery disease	82 (10.0)	157 (9.8)	0.92
Peripheral arterial disease	31 (3.8)	41 (2.6)	0.12
Stroke	10 (1.2)	20 (1.2)	1.0
Bleeding	19 (2.3)	33 (2.1)	0.78
Discharge medication, n (%)			
Aspirin	794 (96.8)	1578 (98.3)	0.03
$P2Y_{12}$ inhibitor after discharge			
Clopidogrel	821 (100)	0 (0.0)	
Prasugrel 10 mg	0 (0.0)	38 (2.4)	
Prasugrel 5 mg	0 (0.0)	5 (0.3)	
Ticagrelor	0 (0.0)	1565 (97.3)	
Vitamin K antagonist	42 (5.1)	22 (1.4)	<0.001
Novel anticoagulant	14 (1.7)	3 (0.2)	<0.001
ACE inhibitor	618 (75.4)	1252 (78.0)	0.16
ATII antagonist	77 (9.4)	147 (9.2)	0.91
Beta blocker	726 (88.5)	1435 (89.4)	0.56
Statin	795 (97.0)	1560 (97.2)	0.83
Proton pump inhibitor	656 (80.0)	1217 (75.8)	0.02
Procedural characteristics			
Access site			0.23
Femoral	249 (31.1)	444 (28.2)	
Radial	552 (68.9)	1127 (71.7)	
Multivessel disease	402 (49.1)	739 (46.0)	0.17
Stent			
None	14 (1.7)	25 (1.6)	0.91
Bare metal stent	44 (5.4)	62 (3.9)	0.11
Biovascular scaffold	8 (1.0)	17 (1.1)	1.0
Drug eluting stent	766 (93.3)	1520 (94.5)	0.26
Ostial lesion	53 (6.8)	85 (5.6)	0.27
Bifurcation lesion	154 (19.8)	287 (18.7)	0.59
Total stent length, mm, mean±SD	27.3±13.7	28.8±17.8	0.07

ACE indicates angiotensin-converting enzyme; ATII, angiotensin II; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; and LoF, loss-of-function.
*Creatinine clearance was calculated with the use of the CKD-EPI formula.

Table 3. Outcomes in Clopidogrel-Treated Patients According to *CYP2C1917 Carrier Status**

Outcome, no. of patients (%)	*CYP2C19* *1/*1 (N=420)	*CYP2C19**17 carriers (N=312)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*	Adjusted *P* value
Thrombotic outcomes					
Cardiovascular death, MI, ST, and stroke	16 (3.8)	12 (3.8)	1.01 (0.48–2.13)	0.95 (0.45–2.02)	0.90
Cardiovascular death	1 (0.2)	3 (1.0)	4.04 (0.42–38.8)	…	0.23
Myocardial infarction	12 (2.9)	6 (1.9)	0.67 (0.25–1.79)	…	0.43
Stroke	3 (0.7)	3 (1.0)	1.34 (0.27–6.66)	…	0.72
ST	1 (0.2)	1 (0.3)	1.35 (0.08–21.6)	…	0.83
Bleeding outcomes					
PLATO major and minor bleeding	47 (11.2)	29 (9.3)	0.82 (0.52–1.31)	0.74 (0.48–1.18)	0.21
PLATO major	10 (2.4)	8 (2.6)	1.08 (0.43–2.74)	0.96 (0.38–2.43)	0.93
PLATO minor	37 (8.8)	22 (7.1)	0.79 (0.47–1.34)	0.73 (0.43–1.24)	0.24

Only clopidogrel-treated patients with normal CYP2C19 metabolism were included for this analysis (ie, *1/*1, *1/*17, and *17/*17). MI indicates myocardial infarction, PLATO, Platelet Inhibition and Patient Outcomes; and ST, stent thrombosis.

*Significant variables are shown in Table II in the Data Supplement.

Nevertheless, the treatment effect in the PLATO subanalysis was almost similar to that of the main trial, so the lack of statistical significance could also have been due to a lack of power. With respect to the use of prasugrel, a genetic subanalysis of the TRITON-TIMI (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction) 38 trial did not provide a direct comparison between prasugrel and clopidogrel in different *CYP2C19* genetic subgroups but did conclude that clopidogrel-treated patients have significantly worse outcomes when carrying an LoF allele compared with noncarriers, which was not found in prasugrel-treated patients.[15]

The primary analysis of the TAILOR-PCI trial (Tailored Antiplatelet Therapy Following PCI) included only patients who were carriers of *2 or *3 LoF alleles.[16] It compared 903 patients in a *CYP2C19* genotype–guided group, thus treated with ticagrelor, to 946 patients in a conventional therapy group, treated with clopidogrel, who were genotyped at the end of the follow-up period. The primary composite end point of cardiovascular death, myocardial infarction, stroke, stent thrombosis, and recurrent ischemia at 12 months, occurred less frequently in patients treated with ticagrelor but without reaching statistical significance (4% versus 5.9%, HR, 0.66 [95% CI, 0.43–1.02], *P*=0.056). Based on the results of these trials, one might conclude that in the absence of a *CYP2C19* LoF allele, the balance in net clinical benefit ends up equal for clopidogrel versus ticagrelor, albeit with a somewhat lower bleeding risk with clopidogrel and somewhat lower thrombotic risk with ticagrelor. In clinical practice, bleeding

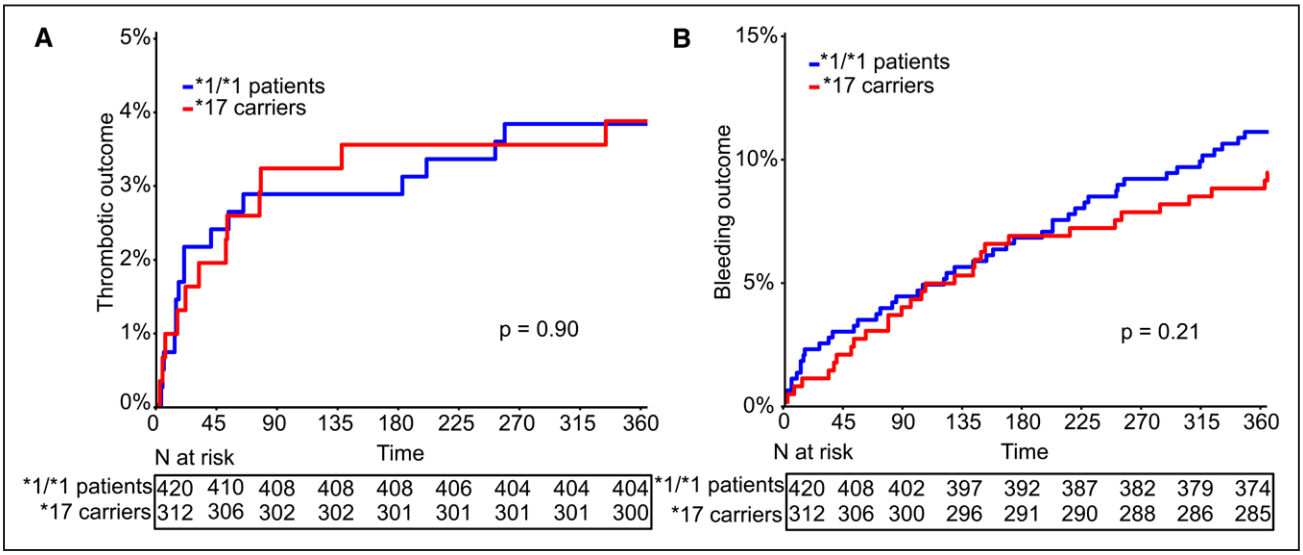

Figure 2. Outcomes of clopidogrel in *1/*1 patients vs *17 carriers.
Kaplan-Meier curves for (**A**) the thrombotic outcome, defined as cardiovascular death, myocardial infarction, stent thrombosis and stroke, and (**B**) the bleeding outcome, defined as PLATO (Platelet Inhibition and Patient Outcomes) major and minor bleeding in clopidogrel-treated *1/*1 patients vs *17 carriers. *P* values are adjusted for baseline differences.

Table 4. Outcomes of Clopidogrel in Patients Without *CYP2C192 or *3 Loss-of-Function Allele Versus Ticagrelor or Prasugrel Irrespective of *CYP2C19* Genotype**

Outcome, no. of patients (%)	Clopidogrel (N=821)	Ticagrelor or prasugrel (N=1608)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*	Adjusted *P* value
Thrombotic outcomes					
Cardiovascular death, MI, ST, and stroke	28 (3.4)	41 (2.5)	1.35 (0.83–2.18)	1.14 (0.68–1.90)	0.62
Cardiovascular death	4 (0.5)	8 (0.5)	0.98 (0.29–3.25)	0.44 (0.11–1.84)	0.26
Myocardial infarction	18 (2.2)	25 (1.6)	1.42 (0.77–2.59)	1.47 (0.79–2.77)	0.23
Stroke	6 (0.7)	13 (0.8)	0.90 (0.34–2.38)	0.82 (0.29–2.34)	0.71
ST	2 (0.2)	3 (0.2)	1.30 (0.22–7.81)	…	0.77
Bleeding outcomes					
PLATO major and minor bleeding	81 (9.9)	188 (11.7)	0.84 (0.64–1.09)	0.74 (0.56–0.96)	0.03
PLATO major	19 (2.3)	33 (2.1)	1.13 (0.64–1.98)	1.00 (0.55–1.81)	1.0
PLATO minor	63 (7.7)	159 (9.9)	0.77 (0.57–1.03)	0.69 (0.51–0.93)	0.02

Analysis of clopidogrel-treated patients without loss-of-function allele vs ticagrelor- and prasugrel-treated patients, irrespective of CYP2C19 metabolizer status. MI indicates myocardial infarction, PLATO, Platelet Inhibition and Patient Outcomes; and ST, stent thrombosis.

*Significant variables are shown in Table II in the Data Supplement.

and thrombotic risk should be weighted to choose the optimal treatment strategy for the individual patient.

Furthermore, we studied the effect of the *CYP2C19**17 gain-of-function polymorphism in clopidogrel-treated patients. This allele has been associated with higher enzyme activity, increased platelet inhibition, and an increased risk for bleeding, which was also found in the genetics subanalysis of the PLATO trial.[11,17] The evidence, however, is conflicting. A meta-analysis performed by Li et al,[8] containing data from 11 studies, found the *CYP2C19**17 allele to be associated with less atherothrombotic events in patients treated with clopidogrel (based on 6 studies), whereas an increased risk for bleeding events was found (based on 4 studies). Comparable results were found in a meta-analysis performed by Zabalza et al.[18] A meta-analysis performed by Bauer et al,[19] however, did not find any significant interaction for stent thrombosis or a composite of major adverse cardiac events related to the *CYP2C19**17 allele, although bleeding risk was not assessed. In a study performed by Lewis et al,[20] *CYP2C19**17 was in significant linkage disequilibrium with *CYP2C19**2 and was not found to be an independent predictor for pharmacokinetic and pharmacodynamic outcome in patients treated with clopidogrel. The effect found for the *17 allele was considered to be mostly, if not entirely, derived from nonindependence with the *CYP2C19**2 variant. Our data support this hypothesis, although no significant differences in thrombotic or bleeding outcomes were found according to *CYP2C19**17 genotype. Therefore, our data do not support routine testing of *CYP2C19**17 to guide antiplatelet therapy in clinical practice.

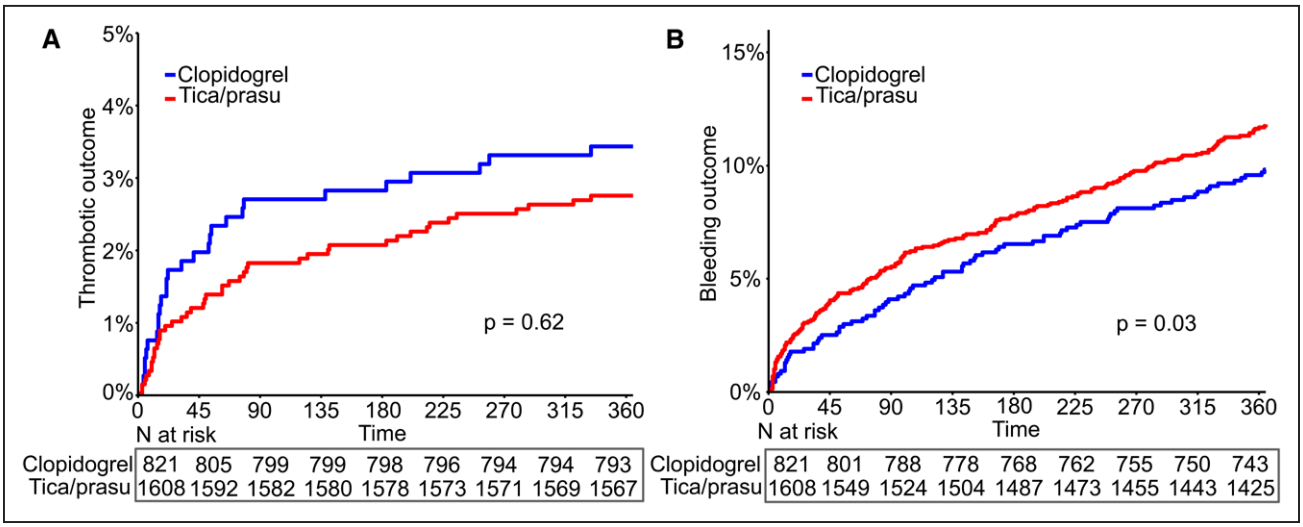

Figure 3. Outcomes of clopidogrel in patients without loss-of-function vs ticagrelor- or prasugrel-treated patients.
Kaplan-Meier curves for (**A**) the thrombotic outcome, defined as cardiovascular death, myocardial infarction, stent thrombosis, and stroke, and (**B**) the bleeding outcome, defined as PLATO (Platelet Inhibition and Patient Outcomes) major and minor bleeding in clopidogrel-treated patients without a loss-of-function allele vs ticagrelor- or prasugrel-treated patients. *P* values are adjusted for baseline differences.

Table 5. Outcomes of the Sensitivity Analyses

Outcome, no. of patients (%)	Clopidogrel	Ticagrelor or prasugrel	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*	Adjusted *P* value
Clopidogrel (n=821) vs ticagrelor or prasugrel (n=729) in patients without LoF alleles					
Cardiovascular death, MI, ST, and stroke	28 (3.4)	21 (2.9)	1.19 (0.68–2.09)	1.11 (0.61–2.03)	0.72
PLATO major and minor bleeding	81 (9.9)	103 (14.1)	0.68 (0.51–0.91)	0.59 (0.44–0.80)	<0.001
Clopidogrel (n=821) vs ticagrelor or prasugrel (n=1613) on-treatment analysis					
Cardiovascular death, MI, ST, and stroke	23 (2.8)	39 (2.4)	1.13 (0.68–1.89)	0.98 (0.56–1.70)	0.94
PLATO major and minor bleeding	72 (8.8)	177 (11.0)	0.76 (0.57–0.99)	0.68 (0.52–0.91)	0.008

Sensitivity analyses of clopidogrel-treated patients without loss-of-function alleles vs ticagrelor- and prasugrel-treated patients. LoF indicates loss-of-function; MI, myocardial infarction, PLATO, Platelet Inhibition and Patient Outcomes; and ST, stent thrombosis.

*Significant variables are shown in Table II in the Data Supplement.

Our findings are clinically relevant for different reasons. Although $P2Y_{12}$ inhibitors are primarily initiated to reduce thrombotic risk, the inevitable bleeding risk associated with the use of those agents is clearly associated with morbidity and mortality.[13] Therefore, the use of a tailored antiplatelet strategy capable of balancing the bleeding and thrombotic risks is expected to improve overall clinical outcome. Although trials studying the use of platelet function testing in tailoring antiplatelet therapy failed to show superiority compared with standard treatment and is, therefore, not routinely recommended, our results add to the growing body of evidence that *CYP2C19* genotype can be used to tailor antiplatelet therapy.[10,21,22] Recently published results from a large prospective multicenter study in France by Hulot et al[23] also demonstrate that the availability of genetic results within days after ST-segment–elevation myocardial infarction can have a major impact on the prescription patterns of cardiologists. Additionally, because the use of ticagrelor and prasugrel is far more expensive compared with generic clopidogrel, a strategy in which two-thirds of patients can be treated with generic clopidogrel without losing the efficacy of the antiplatelet treatment is likely to be cost-effective.[24] A cost-effectiveness analysis was also one of the primary objectives of the POPular Genetics trial and is expected to be published in the near future. Finally, ticagrelor is associated with side effects like dyspnea, which is a frequent reason to switch or even discontinue antiplatelet therapy,[25] whereas prasugrel needs a dose adjustment for the elderly and low body weight patients and is contraindicated in patients with previous stroke or transient ischemic attack.[4]

Some limitations to our analysis need to be mentioned. First, it is a subanalysis of a larger trial and therefore not powered for its primary outcome. In particular, in the analysis of *CYP2C19**17, the relatively low number of patients led us to the use of a dominant model (combining patients with *1/*17 and *17/*17 genotype) instead of a recessive model (comparing *17 homozygous patients to *1/*1 and *1/*17 patients). A possible effect limited to patients homozygous for the *CYP2C19**17 allele might have been underestimated or missed. Second, we only tested for the *2 and *3 LoF alleles, since the prevalence of other LoF alleles is very small (<1% for all LoF alleles combined). Therefore, a handful of clopidogrel-treated patients might now be identified as not carrying an LoF allele, although, in fact, they do. Third, due to the low number of patients treated with prasugrel, we cannot draw any conclusions for this drug specifically. Although the recently published ISAR-REACT 5 trial (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5) showed superiority of prasugrel over ticagrelor in patients with acute coronary syndrome, further research is needed to evaluate if our findings also apply to patients treated with prasugrel.[26]

CONCLUSIONS

In patients after primary PCI not carrying a *CYP2C19* LoF allele, the use of clopidogrel compared with ticagrelor or prasugrel was associated with lower bleeding rates, without significant increase in thrombotic events. No effect on clinical outcome was found for the *CYP2C19**17 gain-of-function polymorphism.

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Supplemental Materials

Tables I–II

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