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The effect of CYP2C19 gene polymorphisms on the pharmacokinetics and pharmacodynamics of prasugrel 5-mg, prasugrel 10-mg and clopidogrel-75 mg in patients with coronary artery disease

Gurbel CYP2C19 genetics in GENERATIONS and FEATHER

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ABSTRACT

Background: *CYP2C19* genotype has been shown to impact response to clopidogrel 75-mg but not prasugrel 10-mg. Here, we assessed effects of *CYP2C19* metabolizer status on pharmacokinetics (PK) and pharmacodynamic (PD) responses to prasugrel 5-mg and 10-mg and clopidogrel 75-mg using data from two PK/PD studies in stable CAD patients (GENERATIONS and FEATHER).

Methods and Results: Active metabolite concentrations (area-under-the-curve, $AUC_{[0-t_{last}]}$), maximum platelet aggregation (MPA) measured by light transmission aggregometry, vasodilator-stimulated phosphoprotein platelet reactivity index, and VerifyNow P2Y12-platelet reactivity units (VN-PRU) were analyzed according to *CYP2C19*-predicted phenotype (extensive metabolizer [EM; N=154], *2-*8 non-carriers, versus reduced metabolizer [RM; N=41], *2-*8 carriers/*17 non-carriers). $AUC_{(0-t_{last})}$ was unaffected by metabolizer status for prasugrel 5-mg and 10-mg (geometric mean EM/RM ratios 1.00, 95% CI:[0.86,1.17], $p>0.99$; and 0.97, 95% CI:[0.85,1.12], $p=0.71$, respectively), but was lowered among reduced metabolizers receiving clopidogrel 75-mg (1.37, 95% CI: [1.14,1.65], $p<0.001$). Platelet reactivity was not significantly affected by *CYP2C19* metabolizer status for prasugrel 5-mg, or for prasugrel 10-mg by MPA and VN-PRU, but for clopidogrel 75-mg was significantly higher in reduced metabolizers (all measures $p<0.01$). Prasugrel 10-mg showed greater antiplatelet effects versus clopidogrel 75-mg (all comparisons $p<0.001$). Prasugrel 5-mg showed greater antiplatelet effects versus clopidogrel 75-mg in reduced metabolizers (all $p<0.001$), and comparable effects in extensive metabolizers (all $p\geq 0.37$).

Conclusions: In contrast to clopidogrel, prasugrel active metabolite PK was not influenced by *CYP2C19* genotype. Antiplatelet effect for prasugrel 10-mg was greater irrespective of

metabolizer status and for prasugrel 5-mg was greater for reduced metabolizers and comparable for extensive metabolizers versus clopidogrel 75-mg.

Clinical Trial Registration: NCT01107925 and NCT01107912

Keywords: prasugrel, clopidogrel, CYP2C19, platelet reactivity, coronary artery disease

Introduction

Clopidogrel and prasugrel are thienopyridine prodrugs that require cytochrome P450 (CYP)-mediated conversion to active metabolites that inhibit the P2Y₁₂ receptor. *CYP2C19* gene polymorphisms, most importantly the *2 loss-of-function allele, have been associated with alterations in the pharmacodynamics (PD) and clinical efficacy of clopidogrel, but not prasugrel, in patients undergoing percutaneous coronary interventions (PCI).^{1, 2} In the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON)-TIMI 38 study, a significantly reduced rate of the composite efficacy endpoint of cardiovascular death, myocardial infarction, or stroke was demonstrated in prasugrel-treated patients compared to clopidogrel-treated patients with acute coronary syndromes undergoing PCI.³ However, there was an increased risk for major bleeding in very elderly (VE, ≥ 75 years) and low body weight (LBW, < 60 kg) patients receiving the prasugrel 10-mg maintenance dose (MD). A lower prasugrel dose was suggested in these patients to reduce the bleeding risk based on population pharmacokinetic (PK) modeling in a TRITON-TIMI 38 substudy.⁴

The GENERATIONS and FEATHER studies compared pharmacokinetic (PK) and PD measures for prasugrel 5-mg and 10-mg and clopidogrel 75-mg in stable coronary artery disease (CAD) patients receiving aspirin. In the GENERATIONS study, maximum platelet aggregation (MPA) in response to 20 μ M adenosine diphosphate (ADP) for prasugrel 5-mg in VE patients met the primary non-inferiority criterion versus prasugrel 10-mg in non-elderly patients (NE, ≥ 45 - < 65 years); platelet inhibition was also significantly greater for prasugrel 5-mg versus clopidogrel 75-mg in VE patients⁵. In the FEATHER study, comparing LBW patients (< 60 kg) to higher body weight patients (HBW, ≥ 60 kg), prasugrel 5-mg in LBW patients reduced platelet reactivity to a

similar extent as prasugrel 10-mg in HBW patients, and to a greater extent than clopidogrel 75-mg.⁶

However, the influence of *CYP2C19* genotype on PK and PD response during prasugrel 5-mg treatment, particularly in LBW or VE CAD patients, is unknown. The objective of the current analysis was therefore to investigate the association of *CYP2C19* genotype-predicted metabolizer status (primarily extensive metabolizers [EM] versus reduced metabolizers [RM]) with the PK and PD profiles of prasugrel 5-mg and 10-mg and clopidogrel 75-mg in aspirin-treated stable CAD patients from the GENERATIONS and FEATHER studies.

Methods

The primary results, along with detailed descriptions of the methods for both studies, have been presented previously^{5, 6}; the study design, which was similar for both studies, is shown in Figure 1. In brief, both were international, multicenter, randomized, blinded, active-comparator, crossover studies in patients with stable CAD receiving background aspirin therapy.

GENERATIONS (N=155) and FEATHER (N=72) were Phase Ib trials. The present analysis included all subjects from GENERATIONS and FEATHER who received at least one dose of study drug, with at least one evaluable PK profile and/or PD measurement post-baseline, and a usable genetic sample.

The impact of *CYP2C19* genotype-predicted metabolizer status on PK was tested by assessing predicted metabolizer status relative to the active metabolite area under the concentration-time curve from the time of dosing to the last quantifiable measurement through 4 hours post-dose ($AUC_{[0-t_{last}]}$)^{5, 6}. Pharmacodynamic (antiplatelet) response was assessed as MPA to 20 μ m ADP by light transmission aggregometry; vasodilator- stimulated phosphoprotein platelet reactivity index (VASP-PRI); and VerifyNow[®] P2Y12 reaction units (VN-PRU) at day 12 ± 2 of the MD period within each treatment regimen^{5, 6}. Samples for PD analyses were drawn prior to MD on the last day of each study period, approximately 24 hours after the last MD. The current analysis involved separate comparisons of PK and PD responses primarily between two *CYP2C19*-predicted phenotypes – extensive metabolizers (EM) and reduced metabolizers (RM). Comparisons were performed both within and between treatment groups. PD and PK were assessed as described previously^{5, 6}.

Genotyping methodology

Patients participating in the genotyping substudy were consented for the collection and storage of DNA samples for research. Blood samples for testing were obtained at baseline prior to receiving study drug. DNA was extracted from peripheral blood using standard methods. Genotype data was generated using the Drug Metabolizing Enzyme and Transporter Gene (DME/T™) Plus assay system (Affymetrix Inc., Santa Clara, California) at Covance Genomic Laboratories, a CLIA-certified laboratory.

To assess the association of *CYP2C19* genetic variants with prasugrel and clopidogrel active metabolite exposure and PD response, alleles of *CYP2C19* previously shown to be involved in the metabolism of the two drugs were classified a-priori according to their predicted metabolizer phenotypes. This classification was defined according to literature-based predictions using the established common consensus or ‘star allele’ nomenclature ([http:// www.cypalleles.ki.se](http://www.cypalleles.ki.se))⁷. For 2-level *CYP2C19*-predicted phenotypes, EM was defined as *1/*1, *1/*17 or *17/*17; RM was defined as *1/*2-*8 or *2-*8/*2-*8. For patients with a *2-*8/*17 genotype, predicted metabolizer phenotype was defined as unknown and patients were not analyzed (see supplemental materials)². A 4-level phenotype was defined by taking into account the *17 allele (gain-of-function) and the number of loss-of-function alleles present, and thus further subdividing the RM group into intermediate metabolizer (IM: heterozygous for loss-of-function allele) and poor metabolizers (PM: homozygous for loss-of-function allele) and subdividing the extensive metabolizer group into ultrarapid metabolizers (UM: *CYP2C19**17 carriers) and extensive metabolizers (labeled as EM_{4L} to distinguish from extensive metabolizers by 2-level analysis: *1/ *1) (Supplemental Table 1). Safety was assessed based on overall rates of drug-related bleeding events summarized by treatment and extensive- versus reduced- metabolizer status.

Statistical Analysis

Demographic and baseline characteristics were summarized by *CYP2C19*-predicted phenotype and by treatment regimen. Categorical variables were compared using the Pearson Chi-square test. Continuous variables were summarized using summary statistics and means were compared using a two sample t-test.

The associations between *CYP2C19*-predicted phenotypes and PK and PD parameters were tested using linear mixed-effect models, with the outcomes being exposure to each drug's active metabolite log (AUC_[0-tlast]) and platelet function (MPA to 20 μ M ADP, VASP-PRI, and VN-PRU), respectively. The models contained *CYP2C19*-predicted phenotype as the predictor of main interest and other fixed effects including age (<75 years, $\geq$ 75 years) and body weight (<60 kg, $\geq$ 60 kg) cohorts. For PD response, baseline measurement was also included as a covariate. Two-sided p values were calculated, and a significance threshold of $p < 0.05$ was used for extensive versus reduced metabolizer comparisons within each treatment group. Similar models were used to analyze the *CYP2C19* effect by 4-level phenotype (UM/EM_{4L}/IM/PM).

For the between treatment analyses by *CYP2C19*-predicted phenotype (EM/RM), linear models for PK and PD responses included the following terms: sequence, period, treatment, age cohort, and body weight cohort as fixed effects and subject as a random effect. For the PD models, baseline measurement was used as an additional covariate. Measurements repeated within a subject were assumed to have compound symmetry correlation structure.

A Fisher's exact test was used to compare the event rates for bleeding between EM and RM groups within each treatment regimen.

Results

Patients

Among 227 total patients who entered the first treatment phase, and 215 who completed all 3 treatment periods, 212 patients from the GENERATIONS (n=146) and FEATHER (n=66) studies had DNA samples available and were included in this pooled pharmacogenetic analysis. *CYP2C19*-predicted phenotypes could not be assigned for 17 patients (16 with *2/*17 and 1 with a *9/*17 genotype), who were thus excluded from further analysis. Among the remaining 195 patients, 154 were classified as extensive metabolizers and 41 as reduced metabolizers (Supplemental Table 1). There were no statistically significant differences in baseline demographic characteristics between the predicted phenotype groups, although for the RM population mean age was lower, a numerically greater proportion were smokers, and a numerically lower proportion were Caucasian (Table 1).

Pharmacokinetic comparisons

As shown in Figure 2, there was no significant effect of *CYP2C19*-predicted phenotype on active metabolite exposure as measured by $AUC_{(0-t_{last})}$ for prasugrel 5-mg (geometric mean [GM] EM/RM ratio: 1.00, 95% CI:[0.86,1.17], $p>0.99$) or prasugrel 10-mg (GM ratio: 0.97, 95% CI:[0.85,1.12], $p=0.71$). In contrast, with clopidogrel 75-mg, reduced metabolizers had significantly lower exposure than extensive metabolizers as evidenced by the elevated EM/RM ratio (GM ratio: 1.37, 95% CI: [1.14, 1.65], $p<0.001$).

In reduced metabolizers, active metabolite exposure was significantly greater for both prasugrel 5-mg and 10-mg compared to clopidogrel 75-mg (GM ratios 1.83, [1.56, 2.14], $p<0.001$; and 4.11, [3.48, 4.86], $p<0.0001$, respectively). In reduced metabolizers receiving prasugrel versus

extensive metabolizers receiving clopidogrel 75-mg, active metabolite exposures remained significantly greater with either prasugrel 5-mg or 10-mg versus clopidogrel 75-mg (GM ratios 1.34, [1.12, 1.59], $p=0.002$; and 2.97, [2.48, 3.55], $p<0.001$, respectively). Active metabolite exposures were also significantly greater with prasugrel 5-mg or 10-mg for the combined RM and EM group versus clopidogrel extensive metabolizers (GM ratios 1.33, [1.23, 1.43], $p<0.001$; and 2.92, [2.71, 3.16], $p<0.001$, respectively) (Table 2).

Assessment of active metabolite exposure by 4-level phenotype (UM/ EM_{4L}/IM/PM) indicated no statistically significant differences between predicted phenotype groups for prasugrel 5-mg or prasugrel 10-mg; however, for clopidogrel 75-mg, exposure in the IM group was significantly reduced compared to either the UM or EM_{4L} group (see supplemental materials).

Pharmacodynamic comparisons

For within-treatment comparisons, platelet reactivity was not significantly different between extensive and reduced metabolizers for prasugrel 5-mg when measured by MPA, VASP-PRI, or VN-PRU (Table 3, Figure 3A-C). For prasugrel 10-mg, there were no significant differences between extensive and reduced metabolizers for VN-PRU and MPA; however, platelet reactivity was significantly higher in reduced metabolizers as assessed by VASP-PRI ($p=0.018$). For clopidogrel 75-mg, platelet reactivity was significantly higher for reduced metabolizers compared to extensive metabolizers for all measures: MPA ($p=0.006$), VASP-PRI ($p<0.001$) and VN-PRU ($p=0.001$).

For comparisons between treatments, platelet reactivity was significantly lower in patients receiving prasugrel 10-mg compared to clopidogrel 75-mg, irrespective of metabolizer phenotype (Table 2, $p<0.001$ for all comparisons). In reduced metabolizers, prasugrel 5-mg resulted in lower platelet reactivity compared to clopidogrel 75-mg ($p<0.001$), while in extensive

metabolizers responses were comparable for both treatments. Reduced metabolizers receiving prasugrel 5-mg had higher platelet reactivity compared to extensive metabolizers receiving clopidogrel 75-mg when determined by MPA ($p=0.025$), but this difference was not significant with VASP-PRI or VN-PRU. Platelet reactivity in the combined RM and EM group while receiving prasugrel 5-mg was not significantly different compared to the EM group while receiving clopidogrel 75-mg (Table 2).

When PD results were assessed by 4-level analysis (see supplemental materials), there were no significant effects observed across assays between the UM, EM_{4L}, and IM groups with prasugrel 5-mg. For prasugrel 10-mg, there were no significant differences by metabolizer group for MPA or VN-PRU; however, VASP-PRI was significantly lower in the IM versus the UM group. For clopidogrel 75-mg, platelet reactivity was significantly greater for the IM group versus either UM or EM_{4L} groups across all 3 platelet function tests (all $p<0.05$). The PM group was not analyzed due to the low number of patients ($n=3$).

Safety and Tolerability

Rates of treatment-related bleeding events (mainly mild bruising) were similar between extensive and reduced metabolizers within each treatment group, occurring for prasugrel 5-mg in 26/155 extensive metabolizers (16.8%) and 7/41 reduced metabolizers (17.1%), for prasugrel 10-mg in 49/156 extensive metabolizers (31.4%) and 13/42 reduced metabolizers (31.0%), and for clopidogrel 75-mg in 25/154 extensive metabolizers (16.2%) and 6/40 reduced metabolizers (15.0%) (extensive versus reduced metabolizers, all comparisons $p>0.05$).

Discussion

We found that the antiplatelet effect of prasugrel 10-mg was greater than that of clopidogrel 75-mg irrespective of *CYP2C19*-predicted metabolizer status, and that for prasugrel 5-mg, the antiplatelet effect was greater versus clopidogrel 75-mg in reduced metabolizers. This finding is relevant for daily practice, because previous studies have demonstrated that the efficacy of clopidogrel is strongly influenced by *CYP2C19* polymorphisms.⁸ While *CYP2C19* also contributes to prasugrel metabolism, there is no indication of a clinically relevant reduction in antiplatelet effect based on *CYP2C19*-predicted metabolizer status. To our knowledge, this is the first report to describe the effect of *CYP2C19*-predicted metabolizer status during therapy with prasugrel 5-mg.

One strength of our analysis was assessing effects of *CYP2C19*-predicted metabolizer status in parallel on both active metabolite exposure and platelet function, as measured by 3 different platelet reactivity tests. Our findings that both prasugrel 5-mg and 10-mg resulted in higher active metabolite exposure compared to clopidogrel 75-mg, irrespective of *CYP2C19*-predicted phenotype, is consistent with previous studies investigating the effect of prasugrel 10-mg^{1,9}. Also consistent with previous findings, clopidogrel active metabolite exposure was significantly lower in reduced metabolizers compared to extensive metabolizers.^{2,9} Notably, the overall prevalence of specific genotypes in this study population was similar to previous reports describing primarily Caucasian populations, and there were no significant differences in patient demographic characteristics between the EM and RM predicted phenotype groups.

In the present analysis we also examined results by 4-level predicted phenotype. The 2-level phenotype effectively compares loss-of-function allele carriers versus non-carriers, which adds to the underlying power for the analysis, but provides less information on the impact of certain

specific mutations. In particular, 2-level classification does not take into account the *17 gain-of-function allele, nor does it account for the effects of carrying 1 versus 2 copies of the *2 allele. Notably, in the 4-way analysis, despite reasonable sample sizes, there were no significant differences noted between patients with *17/*2-*8 non-carrier and *1/*1 genotypes for PK or PD response for prasugrel or clopidogrel, suggesting that *17 has a more limited impact than the loss-of-function alleles. In the present study, for both the 2-level and 4-level analyses patients with genotypes with unknown impact on antiplatelet drug response were excluded; those were primarily patients with both a loss-of-function and a gain-of-function allele (ie, *2/*17; n=17). Finally, the 2-way analysis also combined patients carrying 1 and 2 copies of the loss-of-function allele; however, as only 3 patients were *2-*8/*2-*8, this group was too small in number for meaningful assessment even in 4-way analysis in this study. Nonetheless, in previous publications the *2/*2 genotype – although present in only 2-3% of the Caucasian population – showed a strong correlation with worse clinical outcome, like stent thrombosis, in patients using clopidogrel after PCI⁹.

In 2 recent studies, increased rates of high on-treatment platelet reactivity measured by VASP-PRI were found in *2 carriers receiving prasugrel 10-mg^{10, 11}. In those studies, a 3-way classification scheme was used defining poor metabolizers (*2 carrier/*17 non-carrier), intermediate metabolizers (*2 carrier/*17 carrier and *2 non-carrier/*17 non-carrier), and ultrametabolizers (*2 non-carrier/*17 carrier). Despite the differences in classification, which hamper a direct comparison of study results, in our analysis platelet reactivity as measured by VASP-PRI was significantly higher in the IM group (*2-*8 carrier/*1 carrier, largely similar to the poor metabolizer classification in the reports of Grosdidier et al.¹¹ and Cuisset et al.¹⁰) compared to the UM group (*2-*8 non-carrier/*17 carrier) in patients treated with prasugrel 10-

mg. However, this finding was not supported by differences in prasugrel active metabolite levels between extensive and reduced metabolizers. Also, no significant differences were found between extensive and reduced metabolizers in MPA or VN-PRU for prasugrel 10-mg, nor in any PD measure following treatment with prasugrel 5-mg. Therefore, the mechanism and relevance of this isolated finding of higher platelet reactivity based on VASP-PRI results in prasugrel 10-mg IM patients remains uncertain.

One limitation of our analysis was the relatively small number of patients assessed. However, it should be noted that the crossover study design is advantageous in assessing the impact of metabolizer status, as patient-specific differences in metabolism that are not accounted for by *CYP2C19* prediction are controlled for, since the same patients receive each treatment. Although this analysis was not powered to assess clinical outcomes, adverse event rates for minor bleeding were similar between extensive and reduced metabolizers during each treatment period.

Conclusions

In our study, prasugrel active metabolite exposure was not influenced by *CYP2C19*-predicted metabolizer status in patients with stable CAD. In contrast, clopidogrel active metabolite exposure was significantly reduced in patients carrying the loss-of-function allele. Prasugrel 10-mg was associated with a lower platelet reactivity compared to clopidogrel 75-mg, irrespective of *CYP2C19*-predicted metabolizer status. Prasugrel 5-mg was associated with lower platelet reactivity compared to clopidogrel 75-mg in reduced metabolizers, whereas no significant difference in platelet reactivity was observed compared to clopidogrel in extensive metabolizers.

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Legends

Figure 1. Study design

Figure 2. Active metabolite exposure by treatment and *CYP2C19* metabolizer status.

$AUC_{(0-tlast)}$ = area under the concentration-time curve from time of dosing to last quantifiable concentration through 4 hours postdose; Clop = clopidogrel; EM = extensive metabolizers; GM = geometric mean; Pras = prasugrel; RM = reduced metabolizers

Figure 3. Pharmacodynamic response to prasugrel 5-mg and 10-mg and clopidogrel 75-mg according to *CYP2C19* metabolizer status as measured by (A) VASP-PRI (%) (B) VN-PRU and (C) MPA by light transmission aggregometry. ADP = adenosine diphosphate; Clop = clopidogrel; EM = extensive metabolizers; LSM Diff: = least squares mean difference; MPA = maximum platelet aggregation measured by light transmission aggregometry; RM = reduced metabolizers; Pras = prasugrel; VASP-PRI = vasodilator- stimulated phosphoprotein platelet reactivity index; VN-PRU = VerifyNow P2Y12 reaction units

Table 1. Patient demographic characteristics according to metabolizer status

Measure	EM (N=154)	RM (N=41)	p-value
Age	66.2 ±10.7	62.7 ±11.8	NS
Weight	83.8 ±19.0	85.6 ±18.3	NS
BMI	28.5 ±5.6	28.7 ±5.1	NS
Male	103 (66.9%)	28 (68.3%)	NS
Smoking status	32 (20.8%)	13 (31.7%)	NS
Race (Caucasian)	147 (95.5%)	36 (87.8%)	NS
Baseline MPA to 20µM ADP	77.3 ±9.3	78.8 ±9.0	NS

BMI = body mass index; MPA = median platelet aggregation; ADP = adenosine diphosphate;

EM = extensive metabolizer; RM = reduced metabolizer; NS = non-significant. Values reported for prasugrel 10 mg dosing period. For prasugrel 5 mg and clopidogrel 75 mg, RM (both N=40), values varied slightly; however all p-values were non-significant.

Table 2. Pharmacokinetic and pharmacodynamic differences between treatment groups

	AM-AUC		VASP-PRI (%)		VN-PRU		MPA (%)	
Comparison	LSM Ratio (95% CI)	P-value	LSM Difference (95% CI)	P-value	LSM Difference (95% CI)	P-value	LSM Difference (95% CI)	P-value
Pras 5-mg RM vs Clop 75 RM	1.83 (1.56, 2.14)	<0.001	-16.34 (-22.71, -9.96)	<0.001	-65.15 (-85.86, -44.43)	<0.001	-12.67 (-17.69, -7.65)	<0.001
Pras 10-mg RM vs Clop 75 RM	4.11 (3.48, 4.86)	<0.001	-36.30 (-43.28, -29.31)	<0.001	-136.42 (-159.55, 113.29)	<0.001	-22.00 (-27.39, -16.61)	<0.001
Pras 5-mg EM vs Clop EM	1.33 (1.22, 1.44)	<0.001	0.95 (-2.37, 4.26)	0.58	-1.72 (-11.47, 8.03)	0.73	-0.92 (-2.92, 1.08)	0.37
Pras 10-mg EM vs Clop EM	2.91 (2.67, 3.16)	<0.001	-23.12 (-26.40, -19.84)	<0.001	-95.21 (-105.01, -85.41)	<0.001	-12.4 (-14.43, -10.42)	<0.001
Pras 5-mg RM vs Clop 75 EM	1.34 (1.12, 1.59)	0.002	-0.82 (-8.21, 6.57)	0.82	-24.41 (-48.91, 0.08)	0.051	-5.84 (-10.91, -0.78)	0.025

Pras 10-mg RM vs	2.97	<0.001	-21.48	<0.001	-97.61	<0.001	-15.21	<0.001
Clop 75 EM	(2.48, 3.55)		(-29.28, -13.68)		(-124.13, -71.08)		(-20.60, -9.82)	
Pras 5-mg EM	1.33	<0.001	-0.17	0.91	-6.58	0.17	-1.60	0.11
+RM vs Clop EM	(1.23, 1.43)		(-3.26, 2.92)		(-15.90, 2.74)		(-3.55, 0.35)	
Pras 10-mg EM	2.93	<0.001	-23.20	<0.001	-95.22 (-104.75, -	<0.001	-12.61	<0.001
+RM vs Clop EM	(2.71, 3.16)		(-26.31, -20.08)		85.69)		(-14.58, -10.63)	

AM-AUC= active metabolite area under the curve; CI=confidence interval; Clop = clopidogrel; EM = extensive metabolizers; LSM = least-squares mean; MPA = maximum platelet aggregation to 20 μ M adenosine diphosphate; Pras = prasugrel; RM = reduced metabolizers; VASP-PRI = vasodilator-associated stimulated phosphoprotein platelet reactivity index; VN-PRU = VerifyNow P2Y12 reaction units.

Table 3. Pharmacodynamic response as measured by light transmission aggregometry, VASP and VerifyNow Assays

		LS Mean (SE)	LS Mean (SE)	LS Mean (95% CI)	P-value
		EM	RM	EM-RM	
VASP-PRI (%)	Pras 5-mg	38.97 (2.22)	40.03 (3.53)	-1.06 (-7.86, 5.74)	0.76
	Pras 10-mg	18.42 (1.84)	25.18 (2.97)	-6.76 (-12.34, -1.18)	0.018
	Clop 75-mg	45.23 (2.33)	60.21 (3.75)	-14.97 (-22.04, -7.90)	<0.001
VN-PRU	Pras 5-mg	151.67 (7.08)	134.91 (11.23)	16.76 (-4.63, 38.15)	0.124
	Pras 10-mg	65.50 (6.51)	74.88 (10.45)	-9.38 (-28.99, 10.24)	0.35
	Clop 75-mg	169.90 (7.37)	214.27 (11.74)	-44.37 (-66.8, -21.95)	0.001
MPA (%)	Pras 5-mg	53.45 (1.52)	49.21 (2.38)	4.25 (-0.35, 8.84)	0.070
	Pras 10-mg	42.35 (1.39)	40.86 (2.22)	1.49 (-2.70, 5.68)	0.48
	Clop 75-mg	56.28 (1.57)	63.04 (2.52)	-6.76 (-11.52, -2.01)	0.006

LS Mean = Least-squares mean; SE = standard error of the mean; CI = confidence interval; EM = extensive metabolizers; RM = reduced metabolizers; Pras = prasugrel; Clop = clopidogrel; VASP-PRI = vasodilator-associated stimulated phosphoprotein platelet reactivity index; VN-PRU = VerifyNow P2Y12 platelet reaction units; MPA = maximum platelet aggregation to 20 μ M ADP; ADP = adenosine diphosphate

Figure 1. Study design.

^a Randomization to a treatment sequence occurred at Visit 2. During Period 1, very elderly patients (GENERATIONS) or low body weight patients (FEATHER) received prasugrel 5-mg, while non-elderly or high body weight patients received prasugrel 10-mg.

^b Minimum of 10 days and maximum of 14 days between visits.

Figure 2. Active metabolite exposure by treatment and *CYP2C19* metabolizer status

Figure 3. Pharmacodynamic response to prasugrel 5-mg and 10-mg and clopidogrel 75-mg according to *CYP2C19* metabolizer status as measured by (A) VASP-PRI (%) (B) VN-PRU and (C) MPA by light transmission aggregometry.

Supplementary Materials

Supplemental Table 1. Definition and frequency of *CYP2C19* genotypes by predicted phenotype and treatment (PD population)

		<i>CYP2C19</i>	Pras 5-mg	Pras 10-mg	Clop 75-mg	Total
Predicted		Genotype	(n=211)	(n=211)	(n=211)	(n=212)*
phenotype			n (%)	n (%)	n (%)	n (%)
2-Level	4-Level					
EM	UM	*17/*17	16 (7.6)	16 (7.6)	16 (7.6)	16 (7.6)
		*1/*17	42 (19.9)	42 (19.9)	42 (19.9)	42 (19.8)
	EM _{4L}	*1/*1	96 (45.5)	96 (45.5)	96 (45.5)	96 (45.3)
RM		*1/*2	34 (16.1)	35 (16.6)	34 (16.1)	35 (16.5)
	IM	*1/*8	3 (1.4)	3 (1.4)	3 (1.4)	3 (1.4)
	PM	*2/*2	2 (1.0)	2 (1.0)	2 (1.0)	2 (0.9)
		*2/*3	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)
Unknown		*2/*17	16 (7.6)	15 (7.1)	16 (7.6)	16 (7.6)
		*9/*17	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)

*Note that all patients may not be identical between treatment groups. Abbreviations: PD = pharmacodynamic; Pras=prasugrel; Clop=clopidogrel; n=number of patients; EM = extensive metabolizers (2-level); RM = reduced metabolizers (2-level); UM =

ultrametabolizers (4-level); EM_{4L} = extensive metabolizers by 4-level analysis;; IM = intermediate metabolizers (4-level); PM = poor metabolizers (4-level)

Figure S1. Pharmacokinetic response according four level *CYP2C19*-predicted metabolizer status. Between predicted metabolizer group comparisons statistical significance $p \geq 0.05$ unless shown on figure. $AUC_{(0-t_{last})}$ = area under the curve from time 0 to last measure; Pras = prasugrel; Clop = clopidogrel; UM = ultrametabolizers; EM = extensive metabolizers; IM = intermediate metabolizers; PM = poor metabolizers

Figure S2. Pharmacodynamic response to clopidogrel 75-mg and prasugrel 5-mg and 10-mg according to four level *CYP2C19*-predicted metabolizer status as measured by (A) VASP-PRI; (B) VerifyNow-PRU; or (C) MPA to 20 μ M ADP by light transmission aggregometry. Between predicted metabolizer group comparisons, statistical significance $p \geq 0.05$ unless shown on figure; statistical significance for comparisons versus PM, data not shown due to low sample size.

UM = ultrametabolizers; EM = extensive metabolizers; IM = intermediate metabolizers; PM = poor metabolizers; Pras = prasugrel; Clop = clopidogrel; VASP-PRI = vasodilator- stimulated phosphoprotein platelet reactivity index; VN-PRU = VerifyNow P2Y12 reaction units; MPA = maximum platelet aggregation measured by light transmission aggregometry; ADP = adenosine diphosphate