

Prasugrel Overcomes High On-Clopidogrel Platelet Reactivity Post-Stenting More Effectively Than High-Dose (150-mg) Clopidogrel

The Importance of *CYP2C19*2* Genotyping

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Objectives The primary aim of the study was to determine the antiplatelet effects of prasugrel versus high-dose clopidogrel in patients with high on-treatment platelet reactivity (HTPR) after percutaneous coronary intervention (PCI) and, secondarily, their relation to cytochrome (CYP) 2C19*2 carriage.

Background High on-treatment platelet reactivity after clopidogrel administration after PCI is linked to the loss-of-function *CYP2C19*2* allele and accompanied by an increased risk of adverse events.

Methods We performed a prospective, randomized, single-blind, crossover study of platelet inhibition by prasugrel 10 mg/day versus high-dose 150 mg/day clopidogrel in 71 (of 210 screened; 33.8%) post-PCI patients with HTPR. Platelet function was assessed by the VerifyNow assay (Accumetrics, San Diego, California), and real-time polymerase chain reaction genotyping was performed for *CYP2C19*2* carriage.

Results The primary endpoint of platelet reactivity (measured in platelet reactivity units) at the end of the 2 treatment periods was lower after prasugrel compared with clopidogrel (least-squares estimates 129.4, 95% confidence interval [CI]: 111.1 to 147.7 versus 201.7, 95% CI: 183.2 to 220.2; $p < 0.001$). The least-squares mean difference between the 2 treatments was -122.9 (95% CI: -166.7 to -79.2 , $p < 0.001$), and -47.5 (95% CI: -79.5 to -15.4 , $p = 0.004$), in carriers and non-carriers of at least 1 mutant allele, respectively. The HTPR rates were lower for prasugrel than for clopidogrel, in all patients (7.5% vs. 35.8%, $p < 0.001$), in carriers (5.3% vs. 47.4%, $p = 0.007$), and in noncarriers (8.8% vs. 29.4%, $p = 0.005$), respectively.

Conclusions In patients with HTPR after PCI, prasugrel is more effective compared with high clopidogrel in reducing platelet reactivity, particularly in *CYP2C19*2* carriers. Genotyping guidance might be helpful only in case an increased clopidogrel maintenance dose is considered. (Prasugrel Versus High Dose Clopidogrel in Clopidogrel Resistant Patients Post Percutaneous Coronary Intervention (PCI); [NCT01109784](#)) (J Am Coll Cardiol Intv 2011;4:403–10) © 2011 by the American College of Cardiology Foundation

Dual antiplatelet therapy with aspirin and clopidogrel has become the cornerstone of the medical regimen for prevention of ischemic events in patients undergoing percutaneous coronary intervention (PCI) with stent placement. Interindividual variability in platelet response to clopidogrel has been reported (1), with several mechanisms (intrinsic high platelet reactivity [PR], variability of the drug metabolism, and various drug interactions) being implicated for high

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post-clopidogrel treatment PR. The highly polymorphic cytochrome (CYP) P450 system of the liver plays a key role in clopidogrel metabolism, with the loss-of-function allele *CYP2C19*2* being associated with a blunted antiplatelet response to clopidogrel (2). High on-treatment platelet reactivity (HTPR) is associated with an increased risk of adverse events after PCI (3–5), with this risk specifically linked with the presence of the loss-of-function allele *CYP2C19*2* (6–8).

Abbreviations and Acronyms

CABG = coronary artery bypass grafting

CI = confidence intervals

CYP = cytochrome

HTPR = high on-treatment platelet reactivity

LS = least squares

PCI = percutaneous coronary intervention

PR = platelet reactivity

PRU = platelet reactivity unit(s)

The boxed warning to the clopidogrel label recently added by the U.S. Food and Drug Administration emphasized the increased risk of adverse cardiovascular outcomes in persons harboring the poor metabolizer genotypes and advocated implementing strategies aimed at adjusting clopidogrel dosing or the use of alternative antiplatelet agents (9). However, the issue of whether to perform *CYP2C19* testing was left up to the individual physician, as pointed out

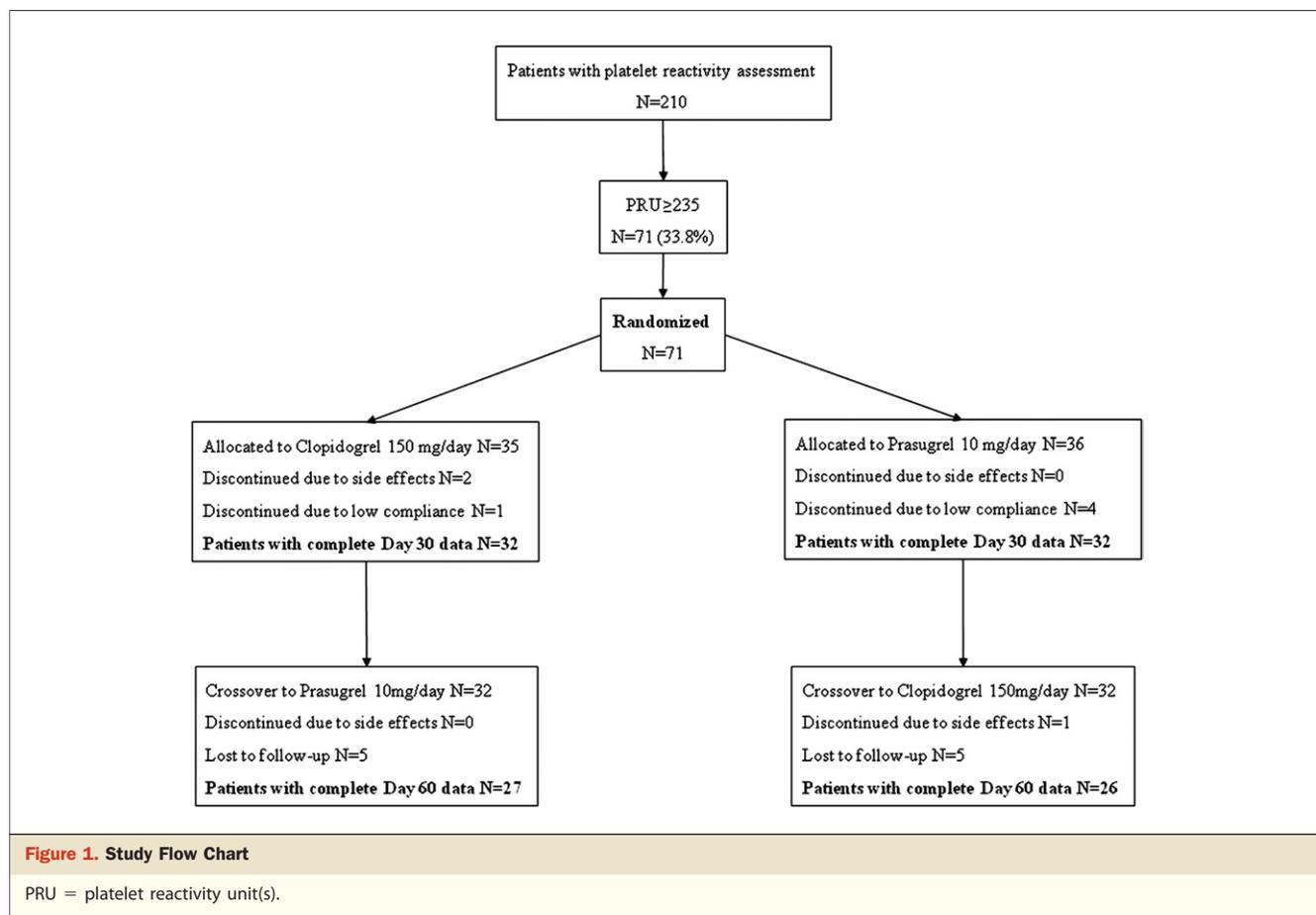
in the American College of Cardiology Foundation/American Heart Association clopidogrel clinical alert (10). Increasing the usual 75 mg/day clopidogrel to 150 mg/day seems to be a reasonable approach to overcome low responsiveness (11–14). More potent antiplatelet therapies could be an alternative for patients with HTPR. Prasugrel, like clopidogrel, binds to and inhibits the P2Y₁₂ receptor, but because of metabolic differences in the generation of the active metabolite, this inhibition occurs more rapidly, consistently, and to a greater extent than with standard or even high-dose clopidogrel (15–17). In vitro and in vivo studies of prasugrel indicate minor contribution of *CYP2C9* and *CYP2C19* to its metabolic activation (18). Prasugrel compared with clopidogrel resulted in better clinical outcomes in patients with acute coronary syndromes with planned PCI, at a cost of higher rates of TIMI (Thrombolysis In Myocardial Infarction) major bleeding (19).

Optimization of post-PCI platelet inhibition in patients with HTPR is a controversial issue, with little information available about the use of strategies of more benefit for such patients. The primary aim of the present study was to investigate the relative antiplatelet effects of prasugrel versus high-dose clopidogrel in patients with HTPR after PCI, as measured by a point-of-care assay. A secondary, hypothesis generating endpoint was to explore any possible association of this antiplatelet response to *CYP2C19*2* genotyping.

Methods

Study protocol. We performed a prospective, single-center, single-blinded, investigator-initiated, randomized, crossover study to compare platelet inhibition by prasugrel 10 mg/day versus high-dose clopidogrel 150 mg/day in patients with HTPR after PCI. All consecutive patients undergoing PCI with stent implantation in our institution were considered for PR assessment at 24 h after the procedure (or at 48 h in case of IIb/IIIa inhibitors administration). Patients were excluded if they had a history of bleeding diathesis, chronic oral anticoagulation treatment, contraindications to antiplatelet therapy, PCI or coronary artery bypass grafting (CABG) <3 months, hemodynamic instability, platelet count <100,000/ μ l, hematocrit <30%, and creatinine clearance <25 ml/min. Patients with a history of stroke were excluded from the study as they were considered to have contraindication for prasugrel administration. However, HTPR patients weighing <60 kg, or >75 years of age were not excluded, as they were considered to be at high risk for ischemic events. At the time of PCI, clopidogrel naïve patients and patients receiving clopidogrel 75 mg for <7 days without an initial loading dose received 600 mg clopidogrel. Patients receiving clopidogrel <7 days but with a 300-mg loading dose or patients receiving clopidogrel for >7 days did not receive any additional loading. All patients received an intra-arterial dose of 100 to 140 U/kg heparin. Use of periprocedural glycoprotein IIb/IIIa inhibitors was allowed, at the operator's discretion. After PCI, all patients received aspirin 325 mg/day for 1 month and 100 mg/day thereafter.

Patients with HTPR (as defined in the following text) were randomized (day 0) in a 1:1 ratio, using computerized random-number generation by an independent investigator, to clopidogrel 150 mg a day or prasugrel 10 mg a day until day 30 after randomization. A day 30 \pm 2 visit was performed for PR measurement and safety evaluation, with the blood sample being obtained 4 to 6 h after the last study drug dose. Patient compliance with antiplatelet therapy was assessed by interview and tablet counting, followed by crossover directly to the alternate therapy for an additional 30 days without an intervening washout period. At day 60 \pm 2, patients returned for the clinical and laboratory assessment as they did on the day 30 visit.



Physicians and operators who performed platelet function testing were blinded as to the actual drug used, and an independent physician monitored bleeding and adverse event data. A flow chart diagram of the study is shown in Figure 1.

Platelet function and genotyping assays. Peripheral venous blood samples were drawn in a fasting state with a loose tourniquet through a short venous catheter inserted into a forearm vein. The first 2 to 4 ml of blood was discarded to avoid spontaneous platelet activation, and blood was collected in 3.2% citrate (1.8 ml–draw plastic Vacuette tubes, Greiner, Monroe, North Carolina). Platelet-function testing was performed with the VerifyNow (Accumetrics, San Diego, California) point-of-care P2Y12 assay. An intra-assay variability of $2.1 \pm 1.3\%$ with a 6% coefficient of variation has been described (4). Results are reported as P2Y12 reactivity units (PRU), with a value ≥ 235 considered an indication of HTPR (3).

Genotyping was performed for variation in CYP2C19. Genomic deoxyribonucleic acid was isolated from 2 ml of ethylenediaminetetraacetic acid–anticoagulated whole blood from patients, using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Single nucleotide polymorphism CYP2C19*2 (G681A) was detected using

primers as previously described (20). Genotyping was performed in the LightCycler2.0 apparatus (Roche, Mannheim, Germany). Polymerase chain reaction amplification was carried out using LightCycler capillaries (Roche), with 50 ng of genomic deoxyribonucleic acid, 0.4 μM of each primer, and 0.2 μM of each fluorescent probe and reaction mixture (QuantiFast Probe PCR, Qiagen) in a total reaction volume of 20 μl .

Endpoints. Endpoints were pre-specified in the study protocol and statistical analysis plan. The primary endpoint was PR assessed at the end of the 2 study periods (pre-crossover and post-crossover). The HTPR rate during the same periods was a secondary endpoint. Bleeding (major, minor, or minimal according to the TIMI study criteria) and major adverse cardiac events (cardiovascular death, myocardial infarction, and stroke) were evaluated during the pre-crossover and post-crossover periods.

Statistical analysis. For sample size calculation, we hypothesized that prasugrel 10 mg would result in a PR absolute difference of 50 PRU compared with clopidogrel 150 mg (with the assumption that the within-patient standard deviation of the response variable is 70 PRU), based on previously published data (17). Choosing a power of 95% and a 2-sided alpha-level of 0.05, at least 53 patients in total

were required to reach statistical significance on the basis of the preceding assumptions.

Categorical data are presented as frequencies and group percentages, and continuous data as means ± SD. Two-sample *t* test and the Fisher exact test were used for comparison of continuous and categorical data, respectively. All tests were 2-tailed, and statistical significance was considered for *p* values <0.05. Analyses were performed using SPSS for Windows (version 16.0, SPSS, Chicago, Illinois). Only patients who successfully completed at least 1 period of the study were considered for analysis. The primary study endpoint was analyzed by a hierarchical analysis of covariance (or mixed-effects) model, with patient indicator as random effect, period and treatment as fixed factors, and PR at baseline as a covariate. Least squares (LS) estimates of the mean difference are presented, with 95% confidence intervals (CI) and a 2-sided *p* value for the treatment effect. Separate analyses of covariance were conducted for the before and after crossover period, with treatment as fixed effect and PR at baseline as a covariate. To test for period effect, we compared the absolute PR mean difference between pre-crossover period and post-crossover period within the 2 treatment sequences, with a 2-sample *t* test. To test for carry-over effect, we compared the PR average in pre-crossover period and post-crossover period between the 2 sequences with a 2-sample *t* test. The secondary study endpoint was analyzed with a chi-square Prescott test for subjects with both day 30 and day 60 data available. Bleeding events and major adverse cardiac events are reported in a descriptive manner.

The study was approved by the ethics committee of the University Hospital of Patras, Greece. All patients gave written informed consent.

Results

Of 210 patients with PR assessment, 71 (33.8%) were identified to have HTPR and were randomized. Until day 30, side effects leading to study drug discontinuation occurred in 2 patients, and low compliance was observed in 5 patients, leaving 64 patients available to test the study hypothesis. Baseline characteristics of patients analyzed are shown in Table 1. Among patients receiving clopidogrel followed by prasugrel, age was higher and body mass index was lower compared with the prasugrel followed by clopidogrel patients. The primary endpoint of PR was significantly lower in patients receiving prasugrel (129.4, 95% CI: 111.1 to 147.7) compared with high-dose clopidogrel (201.7, 95% CI: 183.2 to 220.2), with a LS mean difference of -72.3 (95% CI: -98.3 to -46.4, *p* < 0.001). Data for the pre-crossover and post-crossover periods are shown in Figure 2. Analysis of PR with body mass index (cut point 30

Table 1. Baseline Characteristics of Analyzed Patients

	Clopidogrel (n = 32)	Prasugrel (n = 32)	<i>p</i> Value
Age, yrs	67.9 ± 10.5	62.2 ± 10.8	0.03
Men	28 (87.5)	29 (90.6)	1.0
BMI, kg/m ²	27.9 ± 4.3	30.1 ± 3.9	0.03
Hyperlipidemia	22 (68.8)	19 (59.4)	0.6
Hypertension	22 (68.8)	21 (65.6)	1.0
Diabetes mellitus	13 (40.6)	10 (31.2)	0.6
Smoking	14 (43.8)	16 (50.0)	0.8
Prior myocardial infarction	3 (9.4)	5 (15.6)	0.7
Prior CABG	1 (3.1)	3 (9.4)	0.6
Prior PCI	2 (6.2)	3 (9.4)	1.0
Peripheral arterial disease	1 (3.1)	2 (6.2)	1.0
Statin use	32 (100)	31 (96.9)	1.0
Proton pump inhibitors use	32 (100)	30 (93.8)	0.5
Beta-blocker use	31 (96.9)	28 (87.5)	0.4
Nitrates use	12 (37.5)	8 (25)	0.4
Reason for PCI			
Myocardial infarction	16 (50)	14 (43.8)	0.8
Unstable angina	6 (18.8)	9 (28.1)	0.6
Stable angina	0 (0)	2 (6.2)	0.5
Ischemia in provocative test	10 (31.2)	7 (21.9)	0.6
GFR <60 ml/min	6 (18.8)	4 (12.5)	0.7
GP IIb/IIIa inhibitor administration	6 (18.8)	7 (21.9)	1.0
Chronic clopidogrel use, ≥7 days	6 (18.8)	8 (25.0)	0.8
PRU, day 0	292.0 ± 50.4	289.9 ± 42.9	0.9
One CYP2C19*2 allele	[n = 29] 9 (31.0)	[n = 30] 12 (40.0)	0.6

Data are presented as mean ± SD or n (%).
BMI = body mass index; CABG = coronary artery bypass grafting; GFR = glomerular filtration rate; GP = glycoprotein; PCI = percutaneous coronary intervention; PRU = platelet reactivity unit(s).

kg/m²) and age (cut point 65 years) as additional fixed factors showed similar results (LS mean difference, -72.2, 95% CI: -97.9 to -46.5, *p* < 0.001). No period or carry-over effect was found. The secondary endpoint of HTPR rate was lower for prasugrel (4 of 53, 7.5%) compared with clopidogrel (19 of 53, 35.8%, *p* < 0.001). Individual PR values according to treatment, with the HTPR threshold, are depicted in Figure 3.

Genotyping revealed carriage of 1 CYP2C19*2 loss-of-function allele in 35.6% of patients without any homozygote identified. The PR was significantly lower for prasugrel in both noncarriers and carriers, with a mean difference between the 2 treatments of -47.5 PRU (95% CI: -79.5 to -15.4, *p* = 0.004) and -122.9 PRU (95% CI: -166.7 to -79.2, *p* < 0.001) in noncarriers and carriers, respectively. Data for the pre-crossover and post-crossover periods are shown in Figure 4. Among carriers, 9 of 19 (47.4%) continued to demonstrate HTPR despite high clopidogrel maintenance dose, whereas only 1 of 19 (5.3%) remained poor responders to prasugrel (*p* = 0.007). Among noncarriers, 10 of 34 (29.4%) and 3 of 34 (8.8%) remained poor

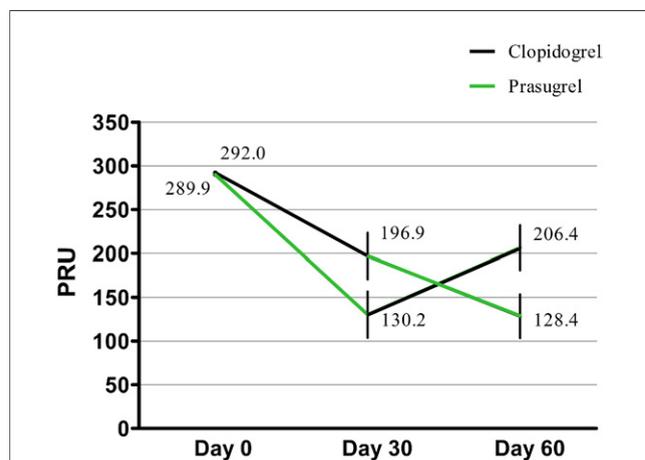


Figure 2. PR by Treatment Sequence

Data for the pre-crossover and post-crossover periods are depicted. Least-squares estimates and 95% confidence intervals are presented. **Black line** indicates clopidogrel; **green line** indicates prasugrel. PR = platelet reactivity; PRU = platelet reactivity unit(s).

responders to clopidogrel 150 mg and prasugrel ($p = 0.005$), respectively. A not pre-specified analysis of PR in relation to *CYP2C19*2* carriage separately for each treatment arm

showed that clopidogrel 150 mg resulted in less PR reduction in carriers, with a mean difference of -38.6 PRU between noncarriers and carriers ($p = 0.04$). The difference in PR reduction achieved by prasugrel between noncarriers and carriers was not statistically significant (30.8 PRU, $p = 0.1$). Although our study was not designed and adequately powered for this analysis, HTPR rates in noncarriers and carriers, separately for each treatment arm, did not differ significantly (28.6% vs. 50% , $p = 0.1$, for clopidogrel and 8.1% vs. 5% , $p = 1.0$, for prasugrel, respectively).

During the pre-crossover period, 1 patient had TIMI criteria major bleeding and 1 had acute myocardial infarction with documented in-stent thrombosis, both allocated to clopidogrel and both excluded from analysis. Three patients (allocated to prasugrel) experienced minor bleeding events. During the post-crossover period, 1 patient had TIMI major bleeding and another experienced a minor bleeding event (both allocated to clopidogrel). No deaths or strokes occurred in either treatment group. There were no differences between patients finally analyzed and patients randomized but discontinued before day 30.

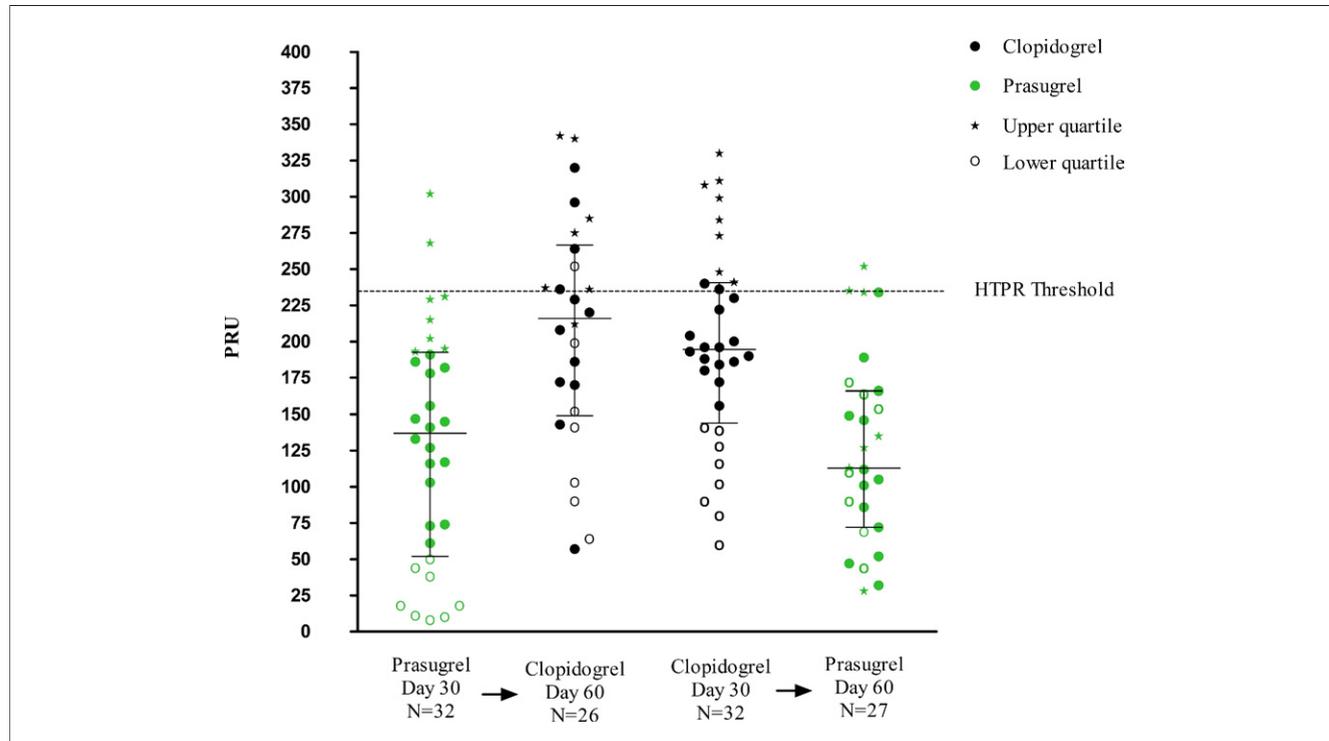


Figure 3. Individual PR Responses According to Treatment

Data for the pre-crossover and post-crossover periods are depicted. **Lines** represent medians, and **error bars** represent interquartile range. Patients' platelet reactivity (PR) in the upper quartile (**asterisks**) and lower quartiles (**open circles**) on day 30 are shown. The majority of patients in the upper and lower quartiles under prasugrel (**solid green circles**) on day 30 remained in the same quartiles under clopidogrel (**solid black circles**) on day 60. Patients in the upper and lower quartiles under clopidogrel on day 30 dispersed across all 4 quartiles under prasugrel on day 60. HTPR = high on-treatment platelet reactivity; PRU = platelet reactivity unit(s).

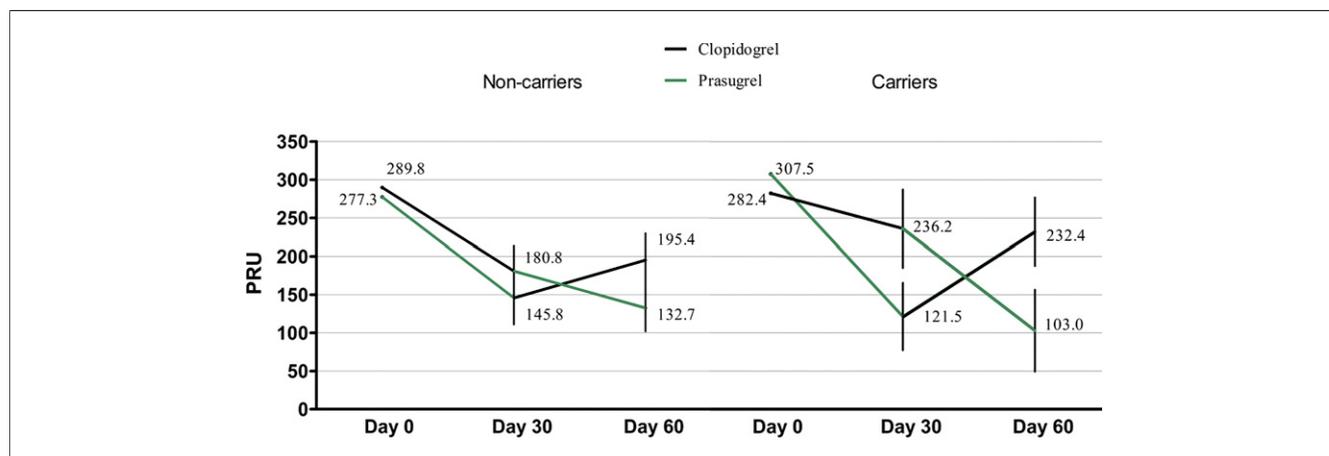


Figure 4. PR by Treatment Sequence in Noncarriers and Carriers of *CYP2C19*2* Allele

Data for the pre- and post-crossover periods are depicted. Least-squares estimates and 95% confidence intervals are presented. **Black lines** indicate clopidogrel; **green lines** indicate prasugrel. Abbreviations as in Figure 2.

Discussion

This study demonstrates that, among post-PCI patients with HTPR under usual clopidogrel treatment, prasugrel compared with high-dose clopidogrel results in higher platelet inhibition, with fewer patients remaining nonresponsive after prasugrel than after high-dose clopidogrel. This effect is closely linked to the presence of the allelic variant of *CYP2C19*2*. High clopidogrel dose, in contrast to prasugrel, is frequently ineffective in the presence of the *CYP2C19*2* allele.

Overcoming HTPR. Switching from the usual 75 mg/day clopidogrel to 150 mg/day overcomes low responsiveness in a variable proportion of patients (11–14). However, a suboptimal clopidogrel response was still present in 60% of diabetic patients in the OPTIMUS (Optimizing Antiplatelet Therapy in Diabetes Mellitus) study on the 150-mg regimen (14). In our study, in a population with HTPR, more than one-third of patients remained hypo-responsive after 1 month on high clopidogrel dose. The clinical impact of high clopidogrel maintenance dose in patients with HTPR 12 to 24 h after PCI was studied in the recently presented GRAVITAS (Gauging Responsiveness With a VerifyNow Assay—Impact on Thrombosis and Safety) trial (21). The primary outcome of cardiovascular death, myocardial infarction, or stent thrombosis occurred in 2.3% of the high-clopidogrel dose group versus 2.3% of the standard-dose group ($p = 0.98$). A significantly higher antiplatelet effect with prasugrel compared with high-dose clopidogrel has been reported in aspirin-treated patients with coronary artery disease (15), in stable patients undergoing planned PCI (16), and in acute coronary syndrome patients (17,22). Although there are no clinical data to support a “goal” of therapy to convert nonresponders into responders, the use of prasugrel seems to be an attractive

choice to overcome HTPR. Changing from clopidogrel to prasugrel maintenance therapy results in further reductions in maximal adenosine diphosphate–induced platelet aggregation, early after switching therapies in aspirin-treated healthy subjects or acute coronary syndrome patients (23,24). Our results are in the same line of evidence. It should be emphasized, however, that even with prasugrel, suboptimal platelet inhibition may occur, as we documented in 7.5% of our cases.

HTPR and *CYP2C19*2* carriage. In the ACCEL-DOUBLE (Accelerated Platelet Inhibition by a Double Dose of Clopidogrel According to Gene Polymorphism) study involving patients receiving clopidogrel 150 mg/day for at least 1 month, carriage of *CYP2C19* variant was related to increased PR and predicted the risk of HTPR (25). A better platelet inhibition was reported in 9 *CYP2C19*2* allele carriers by increasing the clopidogrel maintenance dose from 75 to 150 mg/day, although some of them had little or no response to the higher dose (26). In a recently published nonrandomized study by Barker et al. (27) of 41 genotyped patients with HTPR, increasing clopidogrel to 150 mg resulted in no significant difference between carriers and noncarriers. They concluded that carriage does not seem to have a major influence on dose effect. That study involved relatively few patients and had a limited statistical power. In our study, for 59 genotyped patients, we described a significantly smaller PRU reduction by high (150 mg) maintenance clopidogrel dose in carriers than in noncarriers. However, almost half of the carriers remained hypo-responsive, suggesting that a “tailored treatment” (with clopidogrel) may not be the ideal solution for HTPR, at least for carriers.

In contrast to clopidogrel, common functional *CYP* genetic variants or *ABCB1* polymorphisms (affecting clopi-

dogrel absorption) do not affect active drug metabolite levels, inhibition of platelet aggregation, or clinical cardiovascular event rates in patients treated with prasugrel (28–30). In a series of 7 patients with clinical resistance to clopidogrel manifesting as stent thrombosis, increasing the dose of clopidogrel did not override the effect of the *CYP2C19*2*, whereas a 10-mg dose increase of prasugrel did, suggesting that a strategy of an incremental increase in the clopidogrel in such patients is both time consuming and minimally effective (31). Although known genetic and nongenetic factors explain only a portion of the majority of variation in platelet inhibition (32,33), our data suggest a role for genotyping HTPR patients if high-dose clopidogrel is to be used.

Study limitations. As agreement between assays to identify patients with insufficient inhibition of platelet aggregation by clopidogrel is low, and the assessment of platelet function inhibition by clopidogrel is highly test specific, our results apply only for the method we used. The active metabolite concentrations of prasugrel and clopidogrel were not determined. Variations of pharmacokinetic and pharmacodynamic profiles in the early phase after initiation of clopidogrel with different loading protocols might have influenced the HTPR definition. As PR was assessed relatively early after glycoprotein IIb/IIIa administration (with abciximab used in only 1 case), some patients with HTPR in the initial cohort may have been misclassified as responders. Changing the aspirin dose from 325 mg to 100 mg during the study may have influenced the platelet function determination. However, because of the crossover design of the study, we believe this effect on our results is minimal. There was no washout period between treatments, as this could not be performed because of the use of coronary stents in PCI patients. The duration of treatment should have been adequate to remove any influence of the prior therapy, whereas no carryover effect was observed. The gain-of-function *CYP2C19*17* allele was not tested, as well as other *CYP2C19* loss-of-function alleles. The later, however, are of limited significance (8). The present study was not powered to detect clinical safety differences between the 2 treatment groups nor to draw any meaningful conclusions in this regard.

Clinical implications. High-dose clopidogrel affects *CYP2C19*2* carriers and noncarriers with HTPR differentially and is particularly ineffective in carriers. Testing for *CYP2C19* may have a role in these patients, although its value is diminished in that a significant proportion of *CYP2C19*2* carriers do not have HTPR on clopidogrel therapy, whereas HTPR is present in many patients with wild-type alleles. Ours is the first study to examine the relationship between prasugrel effectiveness and genotyping in patients with HTPR after PCI. As only a very small percentage of *CYP2C19*2* carriers remain nonresponsive to prasugrel, treatment with this agent is an attractive solution. In

essence, our results implicate that prasugrel treatment of patients with HTPR could bypass the need for genotyping. Further prospective large-scale studies must determine: 1) whether the benefits of prasugrel therapy in clopidogrel nonresponders outweigh any potential risk of increased bleeding; and 2) whether clopidogrel therapy—even in high doses—provides ischemic outcomes similar to those with prasugrel therapy for patients with the *CYP2C19* polymorphism. However, the low positive predictive accuracies for both platelet function assays (13.3% at best) and genetic testing for ischemic outcomes, and little or no predictive accuracies for bleeding events (7,29,34–36), remain a significant obstacle.

Conclusions

For patients with HTPR after standard clopidogrel treatment after PCI, prasugrel 10 mg/day is more effective than clopidogrel 150 mg/day in reducing PR. This effect is more prominent in patients carrying 1 loss-of-function *CYP2C19*2* allele. Hence, in HTPR patients, genotyping guidance might be helpful only in case an increased clopidogrel maintenance dose is considered. Measurement of platelet function in a post-PCI patient and subsequent treatment with prasugrel—if found with HTPR—seems to be the most effective strategy to overcome low responsiveness.

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