

Pharmacodynamic Effect of Switching Therapy in Patients With High On-Treatment Platelet Reactivity and Genotype Variation With High Clopidogrel Dose Versus Prasugrel The RESET GENE Trial

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Background—High on-treatment platelet reactivity (HTPR) is associated with adverse outcomes. We aim to compare the novel thienopyridine prasugrel versus double-dose clopidogrel in patients with HTPR and explore the interaction between CYP2C19 genotype and both drugs.

Methods and Results—Consecutive stable patients undergoing percutaneous coronary intervention were screened with the Multiplate Analyzer P2Y12 assay, defining HTPR as area under the curve >450. Those with HTPR were randomized to prasugrel (10 mg/day) or high-dose clopidogrel (150 mg/day) for 2 weeks and then crossed-over to, respectively, clopidogrel and prasugrel, repeating the P2Y12 assay at the end of each cycle. Clinical follow-up (until 3 months) and CYP2C19 genotyping was performed in all patients. The primary end point was platelet reactivity after 14 days of prasugrel versus high-dose clopidogrel. Thirty-two patients were randomized to prasugrel and then high-dose clopidogrel or to high-dose clopidogrel followed by prasugrel. Prasugrel was associated with a significantly lower platelet reactivity than high-dose clopidogrel was (325.8 versus 478.5 area under the curve, $P=0.028$). No patient treated with prasugrel exhibited HTPR, whereas 9 (28.1%) receiving high-dose clopidogrel still had prevalence of HTPR ($P=0.001$). Similar findings were obtained changing cutoffs or considering platelet reactivity as a continuous variable. Genotyping showed the same efficacy between high-dose clopidogrel and prasugrel in the 18 (56.3%) CYP2C19*2 noncarriers (HTPR in 12.5% versus 0, $P=0.274$), whereas it was significantly worse in the 14 (43.7%) carriers (HTPR in 43.7% versus 0, $P=0.003$).

Conclusions—HTPR is successfully abolished by therapy with prasugrel irrespective of CYP2C19 genotype. Conversely, high-dose clopidogrel can address HTPR only in CYP2C19*2 noncarriers.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01465828. (*Circ Cardiovasc Interv.* 2012;5:698-704.)

Key Words: clopidogrel ■ coronary artery disease ■ platelet reactivity ■ prasugrel

Dual antiplatelet therapy with aspirin and clopidogrel has become the cornerstone preventive means of ischemic events in patients undergoing percutaneous coronary intervention (PCI).¹⁻³ However, substantial between-subject variability in platelet response (PR) to clopidogrel has been reported,⁴ with several mechanisms being implicated for high on-treatment platelet reactivity (HTPR). The mechanisms leading to a poor response to clopidogrel are not clearly understood; clinical, cellular, and genetic factors have been proposed.⁵

Previous investigations have shown that administration of a higher clopidogrel loading dose enhances platelet inhibition and leads to better response profiles than standard dosing does.^{6,7} Increasing the usual 75 mg/day clopidogrel to 150 mg/day seems to be a reasonable approach to overcome low responsiveness.⁸⁻¹¹

The P2Y12 inhibition achieved by prasugrel, because of metabolic differences in the generation of the active metabolite, occurs more rapidly, consistently, and to a greater extent than with standard clopidogrel.¹²⁻¹⁴ In vitro and in vivo studies

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of prasugrel indicate minor contribution of CYP2C9 and CYP2C19 to its metabolic activation,¹⁵ but optimization of post-PCI platelet inhibition in patients with HTPR remains 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 antiplatelet effects of prasugrel (10 mg/day) versus high-dose clopidogrel (150 mg/day) in stable patients with HTPR, also taking into account genotype variation.

WHAT IS KNOWN

- Substantial patient variability in platelet response to clopidogrel has been reported with high on-treatment platelet reactivity in a significant proportion of patients.
- Treatment with prasugrel is associated with greater platelet inhibition than treatment with high-dose clopidogrel.
- Loss-of-function alleles in CYP2C19 results in a reduced availability of clopidogrel with a consequently a lower antiplatelet effect.

WHAT THE STUDY ADDS

- This study confirmed that prasugrel is associated with greater platelet inhibition than high-dose clopidogrel, and this effect is seen more in CYP2C19*2 carriers.
- CYP2C19*2 carriers could be identified by an area under the curve cutoff value (600 area under the curve).

Methods

Design

The pharmacodynamic effects of switching the Rapy in patiEntS with high on-trEatment plateleT reactivity and GENotypE variation with high clopidogrel dose versus prasugrel (RESET GENE) trial was an investigator-initiated, single-center, open-label, crossover randomized study with blinded analyses and endpoint adjudication. The trial complied with current guidelines, was approved by the local ethics committee, and was registered on clinicaltrials.gov (NCT01465828).

Patients and Procedures

All consecutive stable patients undergoing PCI with drug-eluting stents in our institution were considered for PR assessment 24 hours after the procedure. Patients were excluded if they presented with acute coronary syndrome, were on chronic oral anticoagulants, had received PCI or coronary artery bypass grafting <3 months before screening, had history of prior bleeding, bleeding diathesis, contraindications to antiplatelet therapy, hemodynamic instability, platelet count <100000/ μ L, hematocrit <30%, or creatinine clearance <25 mL/min. Patients with a history of stroke, weighing <60 kg or >75 years of age were also excluded from the study as they were considered to have contraindications to prasugrel.

At the time of PCI, clopidogrel-naive patients and patients receiving clopidogrel 75 mg for <7 days without an initial loading dose were given a 600-mg clopidogrel loading dose. Patients receiving clopidogrel <7 days but with a recent (<7 days) 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. After PCI, all patients received aspirin 100 mg/day thereafter.

After signing the written informed consent, patients with HTPR (defined as area under the curve [AUC] >450 or >45 U according with the manufacturer's instructions) were offered enrollment in the randomized trial. Randomization sequence was based on a computer-generated random-number sequence, and allocation concealment was achieved by using numbered sealed envelopes. Included subjects were randomized (day 0) in a 1:1 ratio to high-dose clopidogrel (150 mg/day) or prasugrel (10 mg/day) until day 15 after randomization. At day 0 genotyping assays were also performed by analyzing a peripheral venous blood sample collected in K3 ethylenediaminetetraacetic acid (EDTA) tubes (5 mL). At day 15 \pm 2, a visit was performed for repeat PR measurement and safety evaluation, with blood samples being obtained 4 to 6 hours after the last drug dose, followed by crossover directly to the alternate therapy for an additional 15 \pm 2 days without an intervening washout period (as any washout would have been clinically and ethically unsound as all patients had recently received a drug-eluting stent). At day 30 \pm 2, all patients returned for the clinical and laboratory assessment, as they did on the day-15 visit. After day 30 the practitioner was informed and every patient assumed the drug with that obtained the best AUC reduction. Additional clinical follow-up by telephone interviews or direct visits was obtained at 3, 9, and 12 months.

Platelet Function Assays

Whole blood aggregation was determined using multiple electrode aggregometry on a new-generation impedance aggregometry (Multiplate Analyzer; Dynabyte Medical, Munich, Germany). The system detects the electrical impedance change because of the adhesion and aggregation of platelets on 2 independent electrode-set surfaces in the test cuvette.¹⁶⁻¹⁸ We used hirudin as anticoagulant, as recommended by the manufacturer. We used adenosine-diphosphate (ADP) and prostaglandin-E1 (PGE1) as agonists, on the basis of previous reports, which have indicated that ADP+PGE1-induced platelet aggregation is superior to the common ADP test in the identification of low responders.^{19,20} A 1:2 dilution of whole blood anticoagulated with hirudin and 0.9% NaCl was stirred at 37°C for 3 minutes in the test cuvettes, ADP (6.4 μ mol) and PGE1 (9.4 nmol) were added, and the increase in electrical impedance was recorded continuously for 6 minutes.²¹ The mean values of the 2 independent determinations are expressed as the AUC of the aggregation tracing AUC. All platelet function tests were performed by personnel unaware of patient therapy.

Genotyping Assay

DNA was isolated from EDTA anticoagulated whole blood using MagNA Pure LC instrument (Roche Diagnostics, Germany) and the MagNA Pure LC total DNA isolation kit I (Roche Diagnostics) according to the manufacturer's instructions. CYP2C19*2 (OMIM # 124020) allelic variant (rs1799990) was determined by a 200-bp polymerase chain reaction amplification on the basis of the PRNP Ensembl (Ensembl accession number ENST00000371321). Standard polymerase chain reaction was performed using the following primers: F5'- AAT TAC AAC CAG AGC TTG GC-3' and R5'- TAT CAC TTT CCA TAA AAG CAA G-3', in a GeneAmp PCR System 9700 (Applied Biosystems) using HotStarTaq Master Mix (HotStarTaq Master Mix Kit, QIAGEN Inc) as follows: 32 cycles of 95°C for 30 seconds, 57°C (for 30 seconds), and 72°C for 1 minute, with an initial denaturing step of 95°C for 15 minutes and a final extension step of 72°C for 10 minutes). All sequencing analyses were carried out, to exclude preanalytical and analytical errors, on both strands using Big Dye Terminator v3.1 Cycle Sequencing kit (Applied Biosystems), run on an ABI 3130 Genetic Analyzer (Applied Biosystems) and repeated on PCR products obtained from new nucleic acid extractions. All genotype tests were performed by personnel unaware of patient therapy.

End Points

The primary end point of the study was PR after 14 days of prasugrel versus high-dose clopidogrel. Secondary end points included the rate of HTPR (defined as >450 AUC and inhibition of platelet aggregation >20%); major adverse cerebro cardiovascular events, ie, the composite of death, myocardial infarction [defined

according to the Academic Research Consortium statement],²² target vessel revascularization or stroke), major bleedings (Bleeding Academic Consortium 3–5),²³ minor bleeding (Bleeding Academic Consortium 2), and (net adverse clinical events, ie, the composite of major adverse cerebro cardiovascular events and major bleedings) up to 12 months.

Statistical Analysis

The sample size was computed hypothesizing that prasugrel therapy would result in a platelet function absolute difference of 150 AUC (35% relative reduction) compared with high-dose clopidogrel (with the assumption that the within-patient SD of the response variable is 120 AUC) based on previously published data.²⁴ Choosing a 95% power and a 2-sided 5% α , at least 32 patients (16 for each group) were needed. Normal distribution was tested with the Kolmogorov–Smirnov test. Continuous variables are reported as mean±SD, and categorical ones as n (%). Pearson χ^2 test was used for comparison of categorical data, whereas a Student *t* test for independent groups was used to assess differences in continuous variables. In addition, period and sequence effects, which may occur in crossover studies, were evaluated to perform an unbiased estimation of the treatment effect. To test for sequence treatment effects, we evaluated the functional end points within the 2 treatment sequences in which patients received either prasugrel or clopidogrel. In particular, we compared the precrossover with the postcrossover functional values within the treatment sequence in which patients were randomized to clopidogrel first and then prasugrel, and within the other sequence in which patients were randomized to prasugrel first and then clopidogrel. Then, the absolute mean differences between the precrossover and the postcrossover values and comparisons of these between-treatment differences achieved in each sequence were computed. To test for period effects, for each sequence the average of the difference of the 2 periods and the sum of these 2 averages were calculated and then the 2 achieved averages of each sequence were compared. Only patients who successfully completed ≥ 1 period of the study were considered for analysis. Receiver-operating characteristic curves were used to identify the best cutoff value of baseline platelet function to detect subjects with the loss-of-function allele CYP2C19*2. Statistical significance was set at the 2-sided 0.05 level. Computations were performed with SPSS 17 (IBM, Armonk, NY).

Results

Of 180 patients with PR assessment, 42 patients (23%) with HTPR were identified, and 32 patients were finally enrolled and randomly assigned to either prasugrel followed by high-dose clopidogrel or high-dose clopidogrel followed by prasugrel (Figure 1), as 10 patients were excluded from randomization because of absolute contraindications to prasugrel assumption. All enrolled subjects completed both treatment periods, thus serving as their own control and were evaluated for genotype assessment. Patient baseline characteristics are described in Table 1.

At day 0, pharmacodynamic analyses showed (Table 2) no significant difference in PR in the 2 groups (576 ± 97.2 AUC in the prasugrel group and 573.3 ± 87.1 AUC in the high-dose clopidogrel group, $P=0.957$).

After treatment with prasugrel, patients had a significantly greater inhibition of platelet aggregation compared with treatment with high-dose clopidogrel ($49.7 \pm 42.9\%$ versus $9.3 \pm 5.2\%$, $P=0.036$). In the precrossover period, prasugrel decreased AUC more than high-dose clopidogrel did (180.5 ± 40.6 versus 380.5 ± 60.1 respectively, $P<0.001$). After crossover patients initially allocated to the clopidogrel group presented a remarkable lower AUC (Figure 2), in contrast with the other group, which showed an increased AUC after switching to clopidogrel (330 ± 100.8 versus 256 ± 157.2 , respectively, $P=0.07$).

Analysis of individual response according to treatment showed that in some patients values of AUC >450 persisted after treatment with clopidogrel (Figure 3), whereas no such case occurred after prasugrel treatment (9 [28.1 versus 0%], respectively; $P=0.001$). Genotyping revealed at least carriage of 1 CYP2C19*2 loss-of-function allele in 14 patients (43.7%) with 2 (12.5%) homozygotes identified. PR was significantly lower ($P=0.045$) for prasugrel in carriers (Figure 4), whereas no differences were observed in noncarriers ($P=0.575$). Although our study was not designed and adequately powered for this analysis, 6 (43.7%) of 14

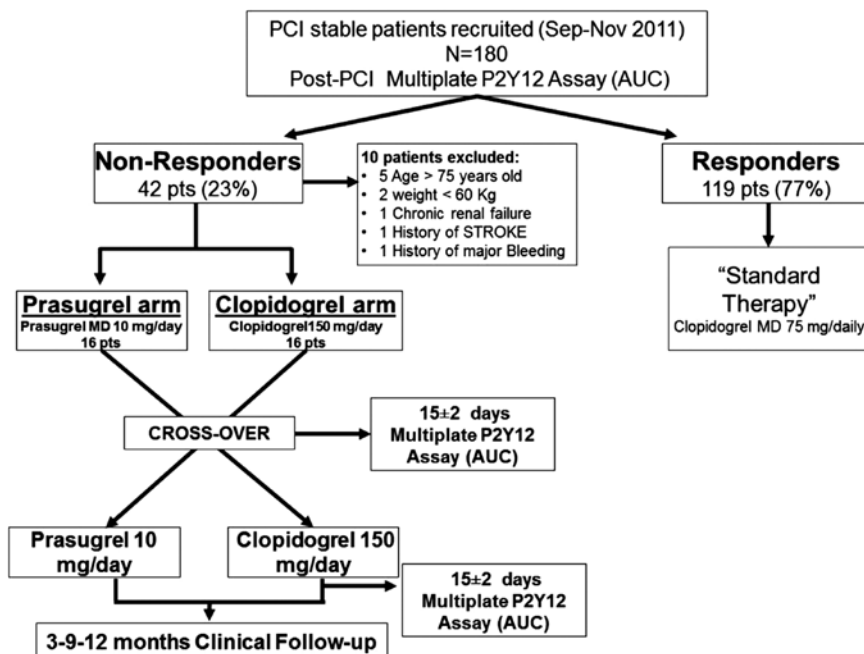


Figure 1. Study profile. AUC indicates area under the curve; PCI, percutaneous coronary intervention.

Table 1. Patient Baseline Characteristics

	Patients Randomized to Prasugrel Followed by High-Dose Clopidogrel (n=16)	Patients Randomized to High-Dose Clopidogrel Followed by Prasugrel (n=16)	P
Male sex	14 (87.5%)	13 (83.3%)	0.62
Age, y	61.8±10.4	62.2±8.6	0.90
Body mass index, kg/m ²	27.8±3.6	28.3±2.7	0.65
Serum creatinine, mg/dL	0.98±0.61	0.86±0.30	0.48
Hyperlipidemia	10 (62.5%)	8 (50.0%)	0.47
Hypertension	12 (75.0%)	11 (68.7%)	0.69
Diabetes mellitus	4 (25.0%)	5 (31.2%)	0.69
Smoking	8 (50.0%)	8 (50.0%)	1
Prior myocardial infarction	6 (37.5%)	3 (18.7%)	0.23
Prior percutaneous coronary intervention	6 (37.5%)	3 (18.7%)	0.23
Prior coronary artery bypass grafting	1 (6.3%)	0	0.30
Medical therapy			
Statins	12 (75.0%)	14 (87.5%)	0.36
Proton pump inhibitors	9 (56.2%)	10 (62.5%)	0.71
β-blockers	10 (62.5%)	10 (62.5%)	1
Nitrates	4 (25.0%)	6 (37.5%)	0.44
Angiotensin-converting enzyme-inhibitors	6 (37.5%)	4 (25.0%)	0.44
Aspirin 325 mg	16 (100%)	16 (100%)	1
CYP2C19*2 heterozygous	8 (50.0%)	4 (25.0%)	0.14
CYP2C19*2 homozygous	0	2 (12.5%)	
Chronic clopidogrel use, >7 days	8 (50.0%)	6 (37.5%)	0.47
Platelet reactivity on day 0 (area under the curve/min)	576.0±97.2	573.3±87.1	0.93

carriers continued to demonstrate HTPR despite high-dose clopidogrel, whereas no one remained a poor responder to prasugrel ($P=0.003$). Two (12.5%) of 18 noncarriers remained poor responders to clopidogrel, whereas all responded to prasugrel ($P=0.274$). The prevalence of HTPR (ie, AUC >450) in noncarriers and carriers, separately for each treatment arm, did not differ significantly (43.7 versus 12.5%, $P=0.248$, for clopidogrel and 0 in both groups, $P=1.0$, for prasugrel, respectively).

During the study period 7 patients, initially allocated to prasugrel, had ≥ 1 adverse event: 3 were minor bleedings, and 4 were uncomplicated chest pain events. In patients allocated to clopidogrel 3 had an event: 1, minor bleeding, and 2, uncomplicated chest pain event.

Analysis of the receiver-operating characteristic curve identified a 600 AUC cutoff for the identification of carriers of the

CYP2C19*2 allele, with 75% sensibility and 72% specificity (95% CI; $P=0.032$; Figure 5).

Discussion

The RESET GENE trial confirms the hypothesis that treatment with prasugrel is associated with greater platelet inhibition than treatment with high-dose clopidogrel in a prospective study enrolling stable patients after PCI. After therapy with prasugrel there were no nonresponders, whereas several patients remained nonresponders despite treatment with high-dose clopidogrel.

Similar findings to those presently reported have been found in other studies, where patients treated with prasugrel had significantly lower rates of HTPR compared with patients treated with clopidogrel.²⁵ Specifically, the clinical impact of

Table 2. Pharmacodynamic Results

	Patients Randomized to Prasugrel Followed by High-Dose Clopidogrel (n=16)	Patients Randomized to High-Dose Clopidogrel Followed by Prasugrel (n=16)	P
Baseline platelet reactivity (AUC/min)	576.0±97.2	573.3±87.1	0.957
Platelet reactivity after 15 days of therapy (AUC/min)	325.8±104.7	478.5±208.5	0.028
Inhibition of platelet aggregation	49.7±42.9%	9.3±5.2%	0.036
Difference in platelet reactivity from baseline to day 15 (AUC/min)	251.2±102.1	94.5±150.6	0.002

AUC indicates area under the curve.

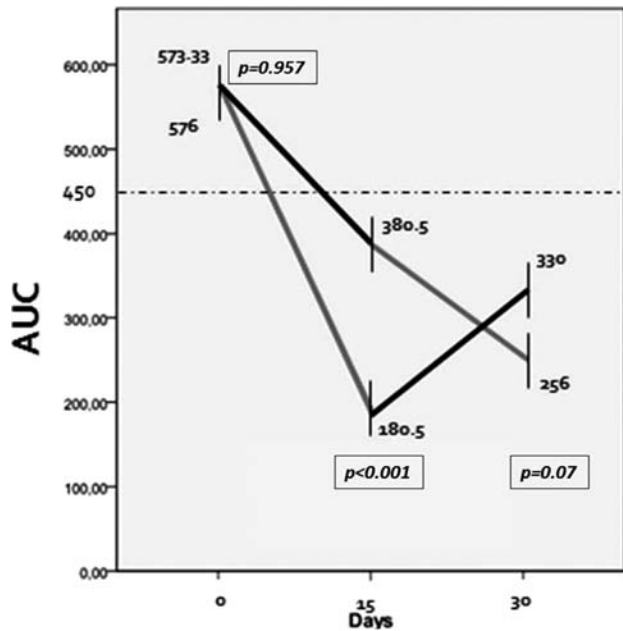


Figure 2. Overall platelet response according to treatment (gray=prasugrel; black=high-dose clopidogrel). AUC indicates area under the curve.

high-dose clopidogrel in patients with HTPR 12 to 24 hours after PCI was studied in the GRAVITAS (Gauging Responsiveness With a VerifyNow Assay–Impact on Thrombosis and Safety) trial.²⁶ The primary outcome of cardiovascular death, myocardial infarction, or stent thrombosis occurred in 2.3% of those treated with high-dose clopidogrel versus 2.3% of the standard-dose group. A significantly higher antiplatelet effect with prasugrel compared with high-dose clopidogrel

has been reported in aspirin-treated patients with coronary artery disease,¹² in stable patients undergoing planned PCI,¹³ and in acute coronary syndrome patients.^{14,27} Although there are no clinical data recommending a specific goal of therapy to convert nonresponders into responders, the use of prasugrel seems to be an attractive choice to overcome HTPR. Switching from clopidogrel to prasugrel maintenance therapy results in further reductions in maximal ADP-induced platelet aggregation.^{28,29}

Our results are indeed supportive of these prior findings, and confirm that more than one third of such stable PCI patients may exhibit HTPR with standard-dose clopidogrel. The most likely explanation of this phenomenon is genetic variation of CYP2C19, which is implicated in the metabolism of clopidogrel. It has been largely demonstrated that the loss of function of CYP2C19*2 allele is involved in HTPR. In our experience, up to half the patients with HTPR showed a genotype variation in terms of the presence of 1 or 2 copies of the CYP2C19*2 allelic variant. In fact, noncarriers, after testing with either drug, showed a similar response before and after crossover. Finally, we formally appraised the relationship between AUC after treatment with the study drugs and the genotype assessment for the CYP2C19*2 variation. The ensuing receiver-operating characteristic curve identified 600 as the AUC cutoff value, with a 75% sensibility and a 72% specificity.

Despite the abovementioned findings, it should be borne in mind that the correlation between genotype assessment, HTPR, and clinic events remains uncertain, and that 3 pertinent meta-analyses has provided disparate conclusions. In 2010, Mega et al³⁰ showed that carriage of even 1 reduced-function CYP2C19 allele seemed to be associated with a significantly increased risk of major adverse cerebro cardiovascular events, particularly stent thrombosis, whereas in 2011, Holmes et al³¹ concluded that overall there was no significant association between genotype with cardiovascular events. Zabalza et al³² found that the different results of the previous meta-analysis mainly derived from high heterogeneity between studies analyzing the relationship between CYP2C19 loss-of-function alleles and major cardiovascular outcomes, likely resulting from publication bias. Finally in the Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel (TRIGGER-PCI)³³ trial switching from clopidogrel to prasugrel in patients with HTPR afforded effective platelet inhibition. However, given the low rate of adverse ischemic events after PCI with contemporary drug-eluting stents in stable coronary artery disease, the clinical utility of this strategy could not be demonstrated. In fact, the study was stopped prematurely because of a lower-than-expected incidence of the primary end point, thus the clinical utility of this strategy could not be demonstrated.

Limitations

This work has several limitations, including the small sample, open-label design, and lack of washout periods. Notably, even a 150-mg clopidogrel dose might not be enough to overcome resistance in some patients. In addition, as the assessment of platelet function inhibition by clopidogrel is highly test specific, our results apply mainly to the method we used. Moreover, the gain-of-function CYP2C19*17 allele was not tested. Finally, the present study was not powered to detect

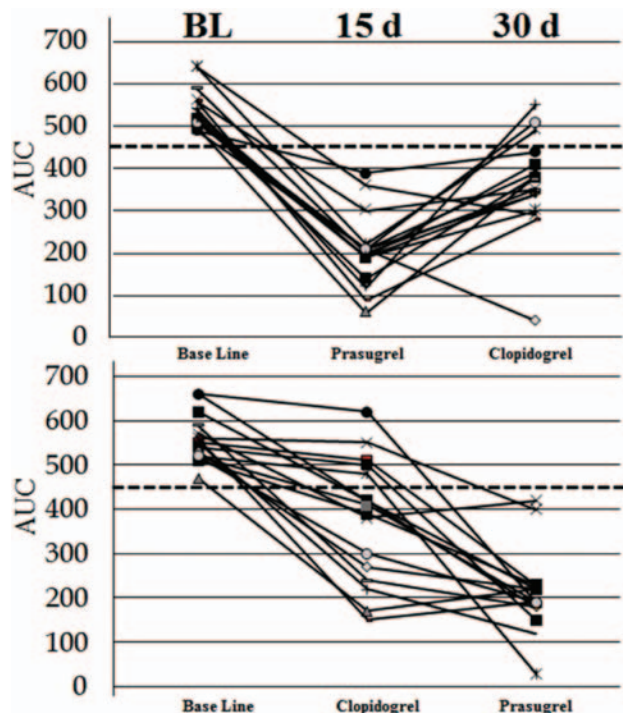


Figure 3. Individual platelet response according to treatment. AUC indicates area under the curve.

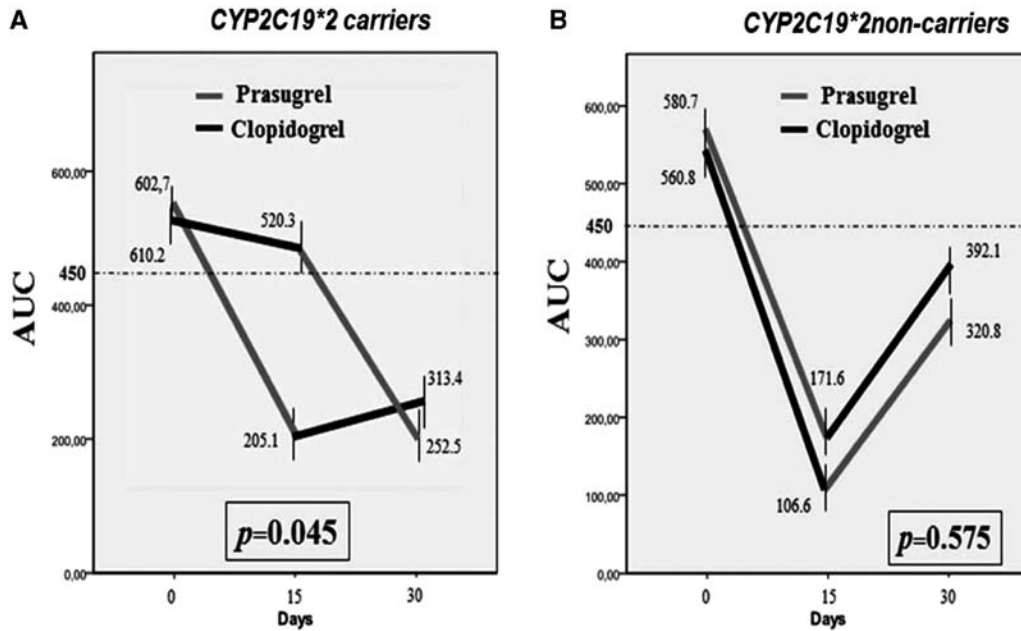


Figure 4. Platelet reactivity at different time points according to treatment and genotype. AUC indicates area under the curve.

differences in clinical efficacy or safety between prasugrel or high-dose clopidogrel and was not designed to be powered for an additive genetic model that would be expected to be the pharmacokinetic-appropriate model.

Conclusions

The RESET GENE trial demonstrated that, in HTPR patients, double dose (150 mg) of clopidogrel, although reducing the platelet function, is less effective than prasugrel standard dose.

Moreover, despite fact that the study was not powered for an additive genetic model, it showed that prasugrel is more effective in CYP2C19*2 carriers. Finally, receiver-operating characteristic curve analysis could identify the CYP2C19*2 carriers.

Our findings need to be confirmed by further clinical studies.

Disclosures

None.

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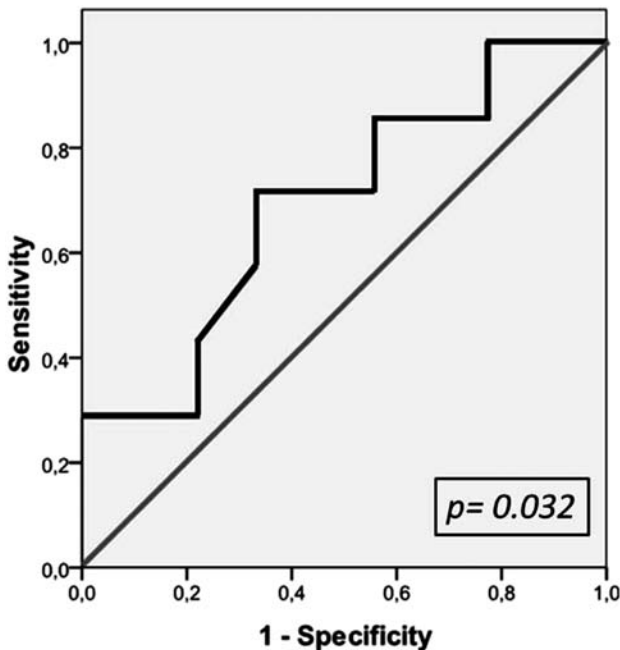


Figure 5. Receiver-operating characteristic curve to identify the best cutoff of area under the curve (AUC)/min (ie, maximizing sensitivity and specificity) to recognize CYP2C19*2 carriers. A 600 AUC/min value was found as the best cutoff, with 75% sensitivity and 72% specificity.

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