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# Clopidogrel 150 mg/day to Overcome Low Responsiveness in Patients Undergoing Elective Percutaneous Coronary Intervention

## Results From the VASP-02 (Vasodilator-Stimulated Phosphoprotein-02) Randomized Study

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**Objectives** We investigated whether maintenance therapy with clopidogrel 150 mg/day produces greater platelet inhibition than the standard 75-mg/day dose and whether the higher maintenance dose increases platelet inhibition in low responders to clopidogrel 75 mg/day.

**Background** Patients show interindividual variability in their platelet response to clopidogrel. Low responders could potentially obtain greater clinical benefit from greater doses of clopidogrel.

**Methods** One hundred fifty-three elective percutaneous coronary intervention patients were randomized to clopidogrel 150 mg/day (n = 58) or 75 mg/day (n = 95) for 4 weeks, with vasodilator-stimulated phosphoprotein assay-guided switching to clopidogrel 150 mg/day after 2 weeks in low responders (platelet reactivity index ≥69%). All patients received aspirin 75 mg/day.

**Results** After 2 weeks, clopidogrel 150 mg/day produced a significantly lower platelet reactivity index than clopidogrel 75 mg/day (43.9 ± 17.3% vs. 58.6 ± 17.7%; $p < 0.0001$). The proportion of low responders was significantly lower in patients randomized to clopidogrel 150 mg/day than in those randomized to clopidogrel 75 mg/day (8.6% vs. 33.7%; $p = 0.0004$). In the clopidogrel 75 mg/day group, 64.5% (20 of 31) of low responders became responders after switching to clopidogrel 150 mg/day for 2 weeks. No major bleeds occurred during the study; the incidence of minor bleeds was similar in each treatment group.

**Conclusions** In elective percutaneous coronary intervention patients, a 150-mg/day clopidogrel maintenance dose produces greater inhibition of platelet function than clopidogrel 75 mg/day. In low responders to clopidogrel 75 mg/day, switching to clopidogrel 150 mg/day overcomes low responsiveness in a majority of patients. These findings warrant further clinical evaluation. (VASP-02; EudraCT number: 2004-005230-40). (J Am Coll Cardiol Intv 2008;1:631–8) © 2008 by the American College of Cardiology Foundation

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Clopidogrel in association with aspirin is currently the reference antiplatelet strategy to prevent the thrombotic complications of percutaneous coronary intervention (PCI) with stenting (1). Clopidogrel is a thienopyridine compound that, after hepatic metabolization, inhibits adenosine diphosphate (ADP)-induced platelet aggregation by specific and irreversible blockade of the platelet $P2Y_{12}$ receptor (2,3). It exerts a dose-dependent inhibition of platelet aggregation and prolongation of the bleeding time (4,5). During the 1990s, the maintenance dose of 75 mg daily was initially chosen because its biological effects were similar to those of ticlopidine 250 mg twice daily. A greater maintenance dose of clopidogrel was not selected for safety reasons, mostly the fear of an increased bleeding risk (4,5). However, a wide interindividual variability of clopidogrel responsiveness has been observed (6–8), and patients exhibiting low response to clopidogrel are at risk for worsened cardiovascular outcomes (9,10).

**Abbreviations and Acronyms**

**ADP** = adenosine diphosphate
**CI** = confidence interval
**MFI** = mean fluorescence intensity
**OR** = odds ratio
**PCI** = percutaneous coronary intervention
**$PGE_1$** = prostaglandin $E_1$
**PPI** = proton-pump inhibitor
**PRI** = platelet reactivity index
**VASP** = vasodilator-stimulated phosphoprotein

The mechanisms of this interindividual variability to clopidogrel responsiveness are not yet completely resolved but are the result of poor compliance (11), variable metabolization of the pro-drug in the liver (12,13), intrinsic high platelet reactivity (6), variable intestinal absorption (14), or possible drug–drug interactions (15–18). Therefore, to improve clinical outcome, faster onset of action and better inhibition of platelet function are required, which can be achieved by the use of increased loading doses of clopidogrel (19–21). In parallel, prasugrel, a more potent thienopyridine compound, demonstrates greater inhibition of platelet aggregation and a lower proportion of biological nonresponders compared with the standard doses of clopidogrel (22). In addition, TRITON–TIMI-38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction-38) clearly demonstrated the clinical benefit of inhibiting platelet function more strongly in the setting of PCI; however, increased bleeding, including fatal bleeding, was observed (23).

Although the authors of several studies have demonstrated the advantage of greater loading doses in PCI (19–21), the question of the chronic maintenance dose of clopidogrel after PCI is less well addressed. Thus, 4 studies have shown a greater platelet inhibition with 150 mg/day of clopidogrel compared with 75 mg/day. These data were obtained in studies with a small sample size or in diabetic patients (24–27). The primary objectives of our study were: 1) to compare the biological effects of 150 mg/day versus 75 mg/day clopidogrel in patients undergoing elective PCI; and 2) to assess, in patients defined as nonresponders to the approved 75 mg/day maintenance dose of clopidogrel, whether doubling the dose would result in improved biological parameters. To define the biological responsiveness to clopidogrel, we used the vasodilator-stimulated phosphoprotein (VASP) phosphorylation assay because it is a selective biochemical marker of the $P2Y_{12}$ receptor activation (28) instead of a global platelet function test, such as light transmission aggregometry, which might be influenced by many factors.

## Methods

**Patients.** Patients were enrolled between April 2005 and December 2007 in this open, randomized, multicenter clinical trial. They were patients age ≥18 years scheduled for elective coronary stenting. Exclusion criteria were as follows: acute coronary syndrome, thienopyridine use before the enrollment, contraindication to clopidogrel or aspirin treatment, or the presence of a disease requiring chronic anticoagulant therapy. The study protocol was approved by the institutional ethics committee, and all patients gave written informed consent for participation.

**Blood sampling.** Samples were obtained before clopidogrel administration, between 10 and 12 h after the clopidogrel loading dose and at 2 and 4 weeks after the start of the maintenance dose of clopidogrel (Fig. 1). Whole blood was collected into 0.129 mol/l sodium citrated 4.5-ml tubes (BD Vacutainer, Becton Dickinson, Plymouth, United Kingdom) for VASP assay and into 1 K3E BD Vacutainer 3-ml tube (Becton Dickinson) for blood cell counts. Citrated blood samples were shipped by road transport to the central laboratory (EFS-Alsace, Strasbourg, France), where analyses of platelet VASP phosphorylation were performed within 36 h after blood sampling. This organization was feasible because of the high temporal stability (48 h) during transport and storage at room temperature of citrated blood samples for quantitative flow cytometric analysis of VASP phosphorylation (29).

**Flow cytometry.** Platelet VASP phosphorylation state was determined by quantitative flow cytometry with the Platelet VASP assay and following the instructions of the manufacturer (Diagnostica Stago/Biocytex, Asnières, France). This method has been previously described and used to monitor the platelet inhibition by thienopyridines (7,28,30–33). In brief, citrated whole blood was incubated with prostaglandin $E_1$($PGE_1$) or $PGE_1$ and ADP for 10 min and fixed with paraformaldehyde, after which the platelets were permeabilized with nonionic detergent. The cells were labeled with a primary monoclonal antibody against serine 239-phosphorylated VASP (16C2), followed by a secondary fluorescein isothiocyanate-conjugated polyclonal goat anti-mouse antibody. The platelet population was identified with

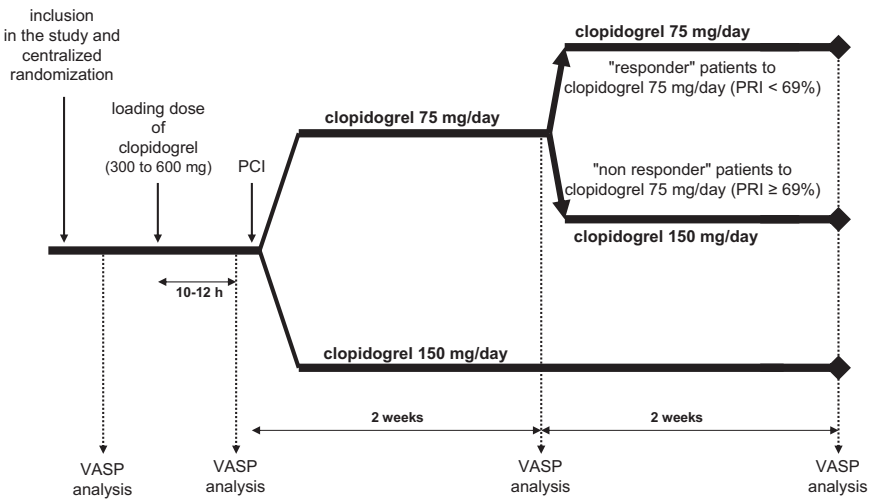


**Figure 1. Design of the VASP-02 Study**

Flow Chart of the Study. PCI = percutaneous coronary intervention; PRI = platelet reactivity index; VASP = vasodilator-stimulated phosphoprotein.

an anti-CD61 phycoerythrin-labeled antibody. Analyses were performed on a Becton Dickinson FACS Calibur spectrometer at a medium rate, and 10,000 platelets were gated. A platelet reactivity index (PRI) was calculated from the mean fluorescence intensity (MFI) of samples incubated with $PGE_1$ or $PGE_1$ and ADP according to the formula:

$$PRI = [(MFI_{(PGE1)} - MFI_{(PGE1+ADP)})/MFI_{(PGE1)}] \times 100$$

**Study protocol.** The study protocol is shown in Figure 1. After enrollment, the day before the coronary stenting procedure, patients received a loading dose of clopidogrel (300 to 600 mg at the physician's discretion) and were then randomly assigned to receive 75 (1 tablet) or 150 mg (2 tablets) once-daily clopidogrel for 2 weeks. The randomization sequence was provided by the central laboratory. We randomized patients in a ratio of 3:2 for clopidogrel 75 mg versus clopidogrel 150 mg using a 30% projected rate of nonresponders with the clopidogrel 75-mg dose, on the basis of our previous study (30). In addition to the randomized study medication, each patient received 75 mg/day of aspirin.

As we reported previously, patients with a PRI ≥69% were considered as low responders to clopidogrel (30). The threshold of 69% was chosen on the basis of the results of our previous study, in which we found that approximately 30% of the patients receiving clopidogrel treatment were undistinguishable from untreated patients, the value of 69% corresponding to the mean minus 2 SDs (30). After the first 2 weeks of treatment, the VASP assay was performed, and the daily doses of clopidogrel (75 or 150 mg) were maintained for each patient for the 2 next weeks, except for patients who had a high PRI (≥69%) and were declared low responders to clopidogrel 75 mg/day. In these patients, the daily dose of clopidogrel was switched from 75 to 150 mg for the 2 next weeks, after which the VASP assay was performed again. Compliance with clopidogrel treatment was checked by counting the tablets of clopidogrel remaining in the blister packs at each visit.

**Follow-up.** A clinical follow-up was established at 2 and 4 weeks after the PCI. Ischemic events were defined as death secondary to any cardiovascular cause, stroke, myocardial infarction, documented ischemia requiring target-vessel revascularization, or improvement of medical treatment. Minor bleeding corresponded to the increase of skin bleeding (after shaving for example), appearance of epistaxis, or gum bleeding about which the patient complains. Major bleeding was defined as intracranial bleeding or any decrease in hemoglobin requiring a transfusion.

**Statistical analyses.** Results are expressed as the mean ± SD. For univariate analysis, qualitative data were analyzed with a bilateral Fisher exact test. Nonparametrical tests were used to compare continuous values between groups (Mann-Whitney or Kruskal-Wallis tests, depending on the number of groups; Wilcoxon rank sum test for paired tests). Continuous variables were further dichotomized (with the median as cutoff value) for subsequent logistic regression to predict a high or a low value of PRI, on the basis of age, gender, body weight, platelet count, cardiovascular risk factors, history of coronary artery disease, clopidogrel treatment, and concomitant medications. All significance levels were set at 0.05. Computations were performed with SPSS 14.0 (SPSS Inc., Chicago, Illinois).

## Results

The characteristics of the study population after randomization are shown in Table 1. No difference was observed between the study groups. The PRI values before clopidogrel were 86.2 ± 4.7% for the 75-mg/day group and 86.1 ± 4.0% for the 150-mg/day group (p = 0.72). After 2 weeks of clopidogrel treatment (mean 15.2 ± 2.5 days), the PRIs were decreased and significantly lower in patients receiving clopidogrel 150 mg/day compared with those receiving 75 mg/day (43.9 ± 17.3% vs. 58.6 ± 17.7%; p < 0.0001) (Fig. 2).

The mean relative reduction of PRI from the baseline value measured before the loading dose was −32% with clopidogrel 75 mg/day and −49% with clopidogrel 150 mg/day (p < 0.0001). Strikingly, the range of the interindividual variability of the response to clopidogrel remained wide at 150 mg/day (from 3% to 77%) as it is at 75 mg/day (from 7% to 88%). However, the proportion of low responders (according to the threshold of 69%) was substantially lower with clopidogrel 150 mg/day than with 75 mg/day (5 of 58 [8.6%] vs. 32 of 95 [33.7%], respectively; p = 0.0004). Multivariate analysis (Table 2) showed the significant effect of the greater maintenance dose of clopidogrel on the PRI at 2 weeks (odds ratio [OR]: 0.140, 95%

**Table 1. Baseline Characteristics of Patients According to the Clopidogrel Maintenance Dose**

| | Clopidogrel | | |
|---|---|---|---|
| | 75 mg/day (n = 95) | 150 mg/day (n = 58) | p Value |
| Age, yrs | 64.3 ± 9.7 | 65.9 ± 9.7 | 0.28 |
| Male gender | 77 (81) | 49 (84) | 0.59 |
| Weight, kg | 83.6 ± 13.5 | 83.7 ± 12.4 | 0.78 |
| Current smoking | 17 (18) | 7 (12) | 0.34 |
| Hypercholesterolemia | 58 (61) | 42 (72) | 0.15 |
| Arterial hypertension | 65 (68) | 32 (55) | 0.10 |
| Diabetes mellitus | 23 (24) | 14 (24) | 0.99 |
| Previous MI | 11 (12) | 6 (10) | 0.81 |
| Previous PTCA | 11 (12) | 12 (21) | 0.11 |
| Previous CABG | 5 (5) | 6 (10) | 0.24 |
| Concomitant medications | | | |
| Beta-blocker | 66 (69) | 41 (71) | 0.87 |
| ACE inhibitor | 31 (33) | 16 (28) | 0.51 |
| AII-R blocker | 23 (24) | 15 (26) | 0.82 |
| Statin | 73 (77) | 47 (81) | 0.54 |
| Proton-pump inhibitor | 24 (26) | 17 (29) | 0.61 |
| Procedural variables | | | |
| LAD | 50 (53) | 24 (41) | 0.18 |
| Cx | 24 (25) | 16 (28) | 0.75 |
| RCA | 29 (31) | 27 (47) | 0.05 |
| ≥1 BMS implantation | 40 (42) | 23 (40) | 0.77 |
| ≥1 DES implantation | 56 (59) | 37 (64) | 0.55 |
| GP IIb/IIIa inhibitor | 5 (5) | 1 (2) | 0.19 |
| Platelet count ($\times 10^3/\mu l$) | 256 ± 74 | 52 ± 69 | 0.58 |
| Leukocyte count ($\times 10^3/\mu l$) | 7.2 ± 2.0 | 7.3 ± 2.2 | 0.89 |
| Red cell count ($\times 10^3/\mu l$) | 4.5 ± 0.4 | 4.6 ± 0.4 | 0.06 |

Values are mean ± SD or n (%).

AII-R = angiotensin II receptor; ACE = angiotensin-converting enzyme; BMS = bare-metal stent; CABG = coronary artery bypass grafting; Cx = circumflex artery; DES = drug-eluting stent; GP = glycoprotein; LAD = left anterior descending artery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery.

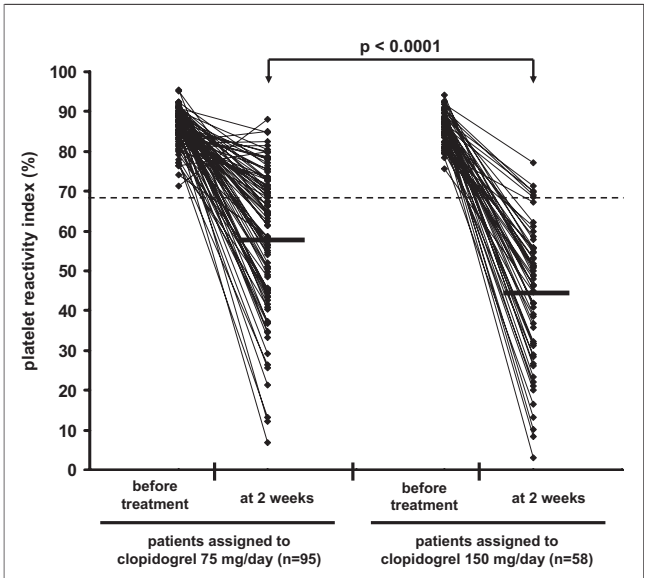


**Figure 2. Platelet Reactivity Index at 2 Weeks According to the Maintenance Dose of Clopidogrel**

The **horizontal broken line** represents the threshold of 69% used to define the low-responder patients (see text for details).

**Table 2. Determinants of Platelet Reactivity Index (VASP Method) 2 Weeks After the Initiation of the Clopidogrel Treatment (Logistic Regression)**

| Variable | OR | 95% CI | p Value |
|---|---|---|---|
| Age (>65 yrs) | 0.511 | 0.190–1.377 | 0.184 |
| Gender (male) | 0.503 | 0.146–1.736 | 0.277 |
| Weight (>83 kg) | 2.710 | 1.140–6.443 | 0.024 |
| Current smoking | 0.567 | 0.164–1.957 | 0.369 |
| Hypercholesterolemia | 1.282 | 0.512–3.213 | 0.596 |
| Arterial hypertension | 1.856 | 0.657–5.242 | 0.243 |
| Diabetes mellitus | 0.646 | 0.428–3.925 | 0.646 |
| History of CAD | 0.637 | 0.210–1.931 | 0.425 |
| Clopidogrel loading dose | 0.944 | 0.575–1.549 | 0.819 |
| Clopidogrel maintenance dose (150 mg/day) | 0.140 | 0.055–0.358 | < 0.0001 |
| ACE inhibitor | 1.711 | 0.605–4.841 | 0.311 |
| AII-R blocker | 1.311 | 0.432–3.977 | 0.632 |
| Statin | 0.923 | 0.340–2.504 | 0.875 |
| Proton-pump inhibitor | 2.546 | 0.960–6.753 | 0.060 |
| Platelet count (>243,000 platelets/$\mu l$) | 0.829 | 0.338–2.034 | 0.683 |

CAD = coronary artery disease; CI = confidence interval; OR = odds ratio; VASP = vasodilator-stimulated phosphoprotein; other abbreviations as in Table 1.

confidence interval [CI]: 0.055 to 0.358; $p < 0.0001$). Greater body weight was also significantly associated with greater PRI (OR: 2.710, 95% CI: 1.140 to 6.443; $p = 0.024$), whereas a similar but nonsignificant trend was observed with concomitant medication with proton-pump inhibitors (PPIs) (OR: 2.546, 95% CI: 0.960 to 6.753; $p = 0.060$).

Thirty-two patients receiving clopidogrel 75 mg/day were declared low responders. At 2 weeks, most of them had a modest decrease of the PRI (from 85.4 ± 4.6% to 76.2 ± 5.0%; $p < 0.0001$) (Fig. 3) without reaching the threshold of 69%. In 31 of these patients, the increase in the daily dose to 150 mg/day resulted in a further decrease of the PRI, from 76.2 ± 5.0% to 61.5 ± 12.3% ($p < 0.0001$) (Fig. 3). One patient did not comply with the protocol, which led to an increase in PRI after being asked to switch from 75 to 150 mg. The PRI values in this patient were high at 2 (73.5%) and at 4 weeks (73.0%). Thus, 20 of the 31 low responders (64.5%) became responders to clopidogrel, whereas 11 (35.5%) remained low responders. The PRI values before clopidogrel administration were no different between responders and low responders (86.7 ± 4.7% vs. 85.4 ± 4.6%, respectively; $p = 0.17$).

Interestingly, in the 118 patients receiving clopidogrel 75 or 150 mg/day and in whom the clopidogrel maintenance dose was not modified during the month of the study, the PRI was found to be remarkably stable between the visits at 2 weeks and at 4 weeks (intraclass correlation coefficient = 0.893, 95% CI: 0.846 to 0.926; $p < 0.0001$) (Fig. 4).

The clinical events during 1-month follow-up are shown in Table 3. Only 1 patient presented a documented ischemic event requiring the improvement of medical treatment without new PCI. This patient was assigned to receive 75 mg/day and was a nonresponder to this dose (PRI: 73.5%). No fatal cardiovascular events or major bleedings were recorded during the 1-month follow-up. There was no significant difference in the rate of minor bleedings between the 75- and 150-mg groups.

The PRI measured 10 to 12 h after the clopidogrel loading dose correlated well with PRI at 2 weeks, when the loading dose was 600 mg but not 300 mg. It suggests that the PRI at 10 to 12 h after a 600-mg load could predict the overall responsiveness of the patient, including during chronic therapy (Table 4).

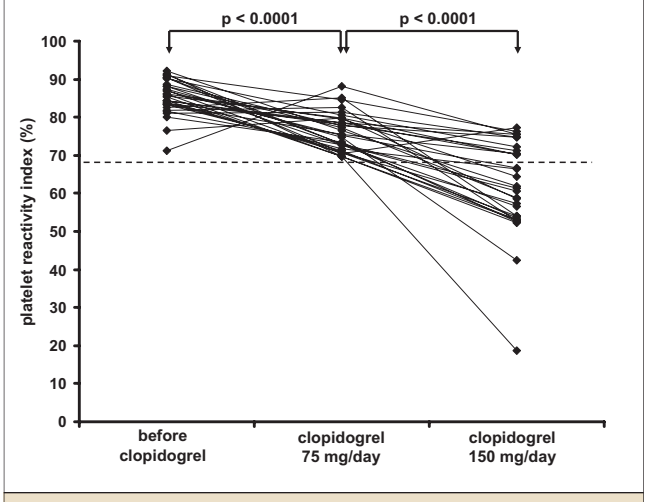


**Figure 3. Effect of Increasing the Maintenance Dose of Clopidogrel From 75 to 150 mg/day in Low Responders to 75 mg/day (n = 31)**

The **horizontal broken line** represents the threshold of 69% used to define the low-responder patients (see text for details).

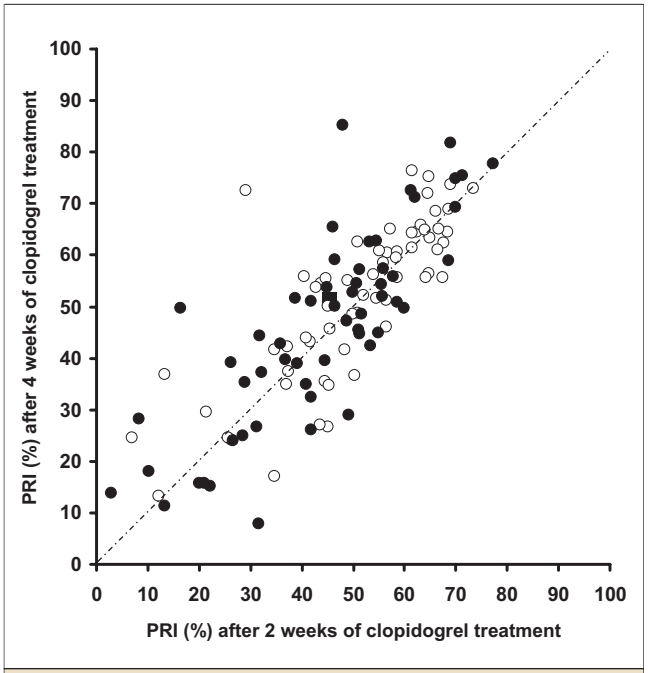


**Figure 4. Stability of the Clopidogrel Effect at Constant Maintenance Dose**

Stability of the clopidogrel effect on the platelet reactivity index (PRI) between the visits at 2 weeks and at 4 weeks in patients whose clopidogrel maintenance dose (75 mg/day **[open circles]**; n = 62 and 150 mg/day **[closed circles]**; n = 56) was not modified. The **broken line** represents theoretical equality between PRI values at 2 weeks and 4 weeks.

**Table 3. One-Month Clinical Follow-Up**

| | Clopidogrel | | | |
|---|---|---|---|---|
| | 75 mg/day (n = 62) | 150 mg/day (n = 58) | 75–150 mg/day (n = 31) | p Value |
| Ischemic event | 1 (1.6) | 0 (0) | 0 (0) | 0.486 |
| Cardiovascular death | 0 (0) | 0 (0) | 0 (0) | — |
| Minor bleed | 14 (22.6) | 11 (19.0) | 3 (9.7) | 0.318 |
| Major bleed | 0 (0) | 0 (0) | 0 (0) | — |

Values are n (%).

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 1, NO. 6, 2008
DECEMBER 2008:631–8

**Table 4. Correlation Between PRI 10 to 12 h After a 600-mg Clopidogrel Loading Dose and the 75-mg/day Maintenance Dose at 2 Weeks**

| | 10–12 h PRI Range, % | PRI at 2 Weeks, % | Nonresponders to Clopidogrel 75 mg/day, % |
|---|---|---|---|
| Quartile 1 | 79.9–89.3 | 73.4 ± 7.3 | 73 |
| Quartile 2 | 74.1–79.4 | 68.6 ± 11.9 | 67 |
| Quartile 3 | 66.2–73.7 | 62.0 ± 10.1 | 27 |
| Quartile 4 | 18.6–65.9 | 41.7 ± 18.1 | 18 |

Correlation between platelet reactivity index (PRI) measured 10 to 12 h after a 600-mg clopidogrel loading dose and the patient response to the clopidogrel 75-mg/day maintenance dose at 2 weeks (n = 45).

## Discussion

The 2 major results of this study are: 1) the confirmation that a stronger inhibition of platelet activation is measured when clopidogrel is administered at 150 mg/day compared with the recommended maintenance dose of 75 mg/day; and 2) that increasing the dose of clopidogrel to 150 mg/day in individuals detected as low responders improved the biological outcome, as evaluated with the $P2Y_{12}$-selective VASP phosphorylation test (30,34). The greater inhibition of platelet activation obtained by clopidogrel 150 mg/day compared with the standard dose of 75 mg/day is in line with the results described by von Beckerath et al. (24) and Angiolillo et al. (35) in post-PCI and Angiolillo et al. (25) in diabetic patients using conventional aggregometry or the VerifyNow P2Y12 assay (Accumetrix, San Diego, California).

Overall, these results are not surprising, considering the dose-dependent nature of the inhibition exerted by the thienopyridine compounds on platelet functions either as a loading dose or under chronic treatment (4,5,19–22,36–38). Thus, several studies are concordant now that demonstrate better biological efficacy of clopidogrel by doubling the maintenance dose. Greater inhibition of platelet function with clopidogrel might also be associated with reduced ischemic events (10). However, the definite clinical benefit of 150 mg/day clopidogrel has still to be demonstrated in a large-scale clinical trial, and the ongoing CURRENT–OASIS 7 (Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNTs–Optimal Antiplatelet Strategy for InterventionS) trial is addressing this issue. Although our study was not designed to measure clinical outcomes, the lack of increased bleeding events, including minor bleeding, in patients receiving 150 mg/day clopidogrel for 1 month is reassuring data.

The second result of this study is the individual responsiveness to clopidogrel observed at 150 mg/day in patients categorized as low responders at 75 mg/day. Indeed, each patient showed a decrease in the PRI with the double dose of clopidogrel, and 65% of this population reached values below the threshold of 69%. These results, which agree with those of other studies, definitely demonstrate that "resistance" to clopidogrel can be overcome by dose titration. It should thus be possible to individually adapt the dosage on the basis of a biological test (39). This of course raises the question of the appropriate test to perform and the appropriate threshold of responsiveness that should be reached (31,40).

At present, 3 tests to monitor thienopyridine therapy are widely used in published reports: light transmission aggregometry, the VerifyNow P2Y12 assay, and the VASP assay. The clinical usefulness of light transmission aggregometry in monitoring antiplatelet therapy is limited by the need for a large sample volume, complexity of sample preparation, high level of expertise required, time-consuming protocols, high cost, and variability of results from different laboratories. The VerifyNow assay is based on platelet aggregation, with the great advantage of being semiautomated, calibrated, and standardized. The VASP assay is $P2Y_{12}$-selective and very reproducible, and the use of the commercially available kit reduces interlaboratory variability of results. These 3 methods are well correlated, but the VASP assay is yet recognized as the gold standard to monitor thienopyridine therapy (34). The appropriate threshold is also a matter of debate, depending on the threshold of biological efficacy (30) or on the threshold of clinical efficacy (31). Recently used to adapt the loading dose before PCI (39), the VASP assay seems perhaps more suited to adapt the maintenance dose that is less "aggressive" than the loading dose and is not performed during the acute phase of the coronary syndrome.

Multivariate analysis confirmed the significant effect of the double maintenance dose of clopidogrel on the decrease in PRI. However, body weight was also found to have a significant effect on the PRI. Thus, patients with a high body weight presented with a high PRI regardless of the maintenance dose. This observation is in agreement with the observations of Feher et al. (41), who described more effective platelet inhibition with clopidogrel in patients presenting with a lower body mass index, and the observation in the TRITON study, in which the authors suggested a greater bleeding risk with prasugrel in low body weight patients (23).

Similarly, concomitant medication with a PPI tends to increase the PRI, which fits in with the findings of Gilard et al. (17), who reported that concomitant administration of omeprazole decreases the biological efficacy of clopidogrel as measured by the VASP method. The clinical impact of body weight or the concomitant use of a PPI on the individual responsiveness to clopidogrel must be confirmed by large-scale trials before generating recommendations such as the systematic doubling the maintenance dose of clopidogrel in these cases. However, other predictors might have not been identified in our analysis because of insufficient statistical power, but this was not the aim of our study.

**Study limitations.** Three limitations must be mentioned concerning this study. First, the sample size lacked statisti-

cal power to measure a clinical benefit of the increased maintenance dose of clopidogrel. This study was designed only to demonstrate a biological benefit of a higher dose of clopidogrel. Although it is known that patients with sufficient response to clopidogrel are at weak risk of cardiovascular events (10), studies demonstrating improvement of clinical outcomes with clopidogrel at 150 mg/day are still required.

Second, the study did not include a control group of "nonresponders" who were maintained on clopidogrel 75 mg/day (for comparison with nonresponders whose maintenance dose was increased from 75 to 150 mg/day). However, the study was originally designed to see whether changing the dose could overcome poor responsiveness, which we show here. However, there is remarkable stability of the PRI at 2 weeks in the individuals in whom the dose of clopidogrel was maintained.

Finally, this was an open study, and a double-blind design was not used. However, the main criterion was a biological parameter using a standardized assay, and the technicians performing the platelet function assays were unaware of the maintenance clopidogrel dose that each patient had received.

## Conclusions

Our study demonstrates that the 150-mg/day maintenance dose clopidogrel, compared with 75 mg/day, results in a stronger inhibition of the platelet reactivity index measured by the VASP phosphorylation assay. In addition, increasing the maintenance dose to 150 mg/day could overcome low responsiveness to the standard maintenance dose of clopidogrel. The clinical efficacy and the safety of the 150-mg/day maintenance dose remain to be demonstrated in large-scale clinical trials.

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**Key Words:** clopidogrel ■ coronary stenting ■ platelet function.