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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