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Prasugrel in Clopidogrel Nonresponders Undergoing Percutaneous Coronary Intervention

The RECLOSE-3 Study (REsponsiveness to CLOpidogrel and StEnt Thrombosis)

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ABSTRACT

OBJECTIVES This study sought to investigate the efficacy of prasugrel compared with clopidogrel in clopidogrel nonresponders.

BACKGROUND Clopidogrel nonresponsiveness is a strong marker of the risk of cardiac death and stent thrombosis after a percutaneous coronary intervention (PCI). It is unknown whether clopidogrel nonresponsiveness is a nonmodifiable risk factor or whether prasugrel with more potent and predictable platelet inhibition as measured by ex vivo techniques is associated with a positive effect on clinical outcome.

METHODS The RECLOSE-3 (REsponsiveness to CLOpidogrel and StEnt thrombosis) study screened clopidogrel nonresponders after a 600-mg loading dose of clopidogrel. Clopidogrel nonresponders switched to prasugrel (10 mg/day) the day of the PCI, and an adenosine diphosphate (ADP) test (10 μmol/l of ADP) was performed 6 days after the PCI. The primary endpoint was 2-year cardiac mortality. Patient outcome was compared with the RECLOSE-2-ACS study.

RESULTS We screened 1,550 patients, of whom 302 were clopidogrel nonresponders. The result of the ADP test was 77.6 ± 6.2%. After switching to prasugrel, the ADP test result decreased to 47.1 ± 16.8%. The 2-year cardiac mortality rate was 4% in the RECLOSE-3 study and 9.7% in nonresponders of the RECLOSE-2-ACS study ($p = 0.007$). The definite and probable stent thrombosis rates were 0.7% and 4.4%, respectively ($p = 0.004$). On multivariable analysis, prasugrel treatment was related to the risk of 2-year cardiac death (hazard ratio: 0.32, $p = 0.036$).

CONCLUSIONS Clopidogrel nonresponsiveness can be overcome by prasugrel (10 mg/day), and optimal platelet aggregation inhibition on prasugrel treatment is associated with a low rate of long-term cardiac mortality and stent thrombosis. (J Am Coll Cardiol Intv 2015;8:1563–70) © 2015 by the American College of Cardiology Foundation.

Several studies have shown that high residual platelet reactivity while on clopidogrel treatment is a strong marker of the risk ischemic events in patients undergoing percutaneous coronary intervention (PCI) (1-16). Prasugrel in clopidogrel nonresponders is effective in providing platelet aggregation inhibition in most patients (17). No evidence exists showing that the achievement of optimal platelet aggregation inhibition in clopidogrel nonresponders by prasugrel modifies the risk profile of these patients. The TRIGGER-PCI (Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy with Prasugrel) trial is the only randomized trial that compared prasugrel with clopidogrel in clopidogrel nonresponders and was terminated prematurely for futility due to the low event rate (18).

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

ADP = adenosine diphosphate

CI = confidence interval

HR = hazard ratio

MI = myocardial infarction

PCI = percutaneous coronary intervention

The RECLOSE-3 (REsponsiveness to CLOpidogrel and StEnt thrombosis) study sought to determine the efficacy of prasugrel treatment in clopidogrel nonresponders undergoing a PCI.

METHODS

PATIENT SELECTION AND INTERVENTIONS. From April 2010 to December 2012, consecutive patients undergoing PCI were screened for nonresponsiveness to clopidogrel using a loading dose of 600 mg of clopidogrel and assessing platelet reactivity with light transmittance aggregometry.

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There were no exclusion criteria except current treatment with prasugrel. All patients with high residual platelet reactivity were switched to prasugrel (10 mg/day or 5 mg in patients older than 75 years of age or with a history of stroke if the adenosine diphosphate [ADP] test result was <70%) the same day of the PCI. All patients underwent drug-eluting stent implantation, and the PCI was performed using standard techniques. Dual antiplatelet treatment was prescribed for at least 6 months. Because of the nonrandomized study design, the clinical outcome of clopidogrel nonresponders who switched to prasugrel was compared with that of the historical cohort of clopidogrel nonresponders in the RECLOSE-2-ACS (n = 248) study. Details of this study were previously reported (15). Briefly, the RECLOSE-2-ACS study enrolled 1,789 patients with acute coronary syndromes (ACS) and treated with PCI, of whom 248 were clopidogrel nonresponders. Clopidogrel nonresponders had an increased long-term dose of clopidogrel (150 to 300 mg/day) or switched to ticlopidine (500 to 1,000 mg/day) under ADP test results guidance, with the goal of reaching an ADP test result of <70% platelet aggregation. The primary endpoint was a composite of cardiac death, myocardial infarction, any urgent coronary revascularization, and stroke at 2-year follow-up. Secondary endpoints were stent thrombosis and each component of the primary endpoint. The 2-year cardiac mortality rate was 9.7% in clopidogrel nonresponders and 4.3% in clopidogrel responders, and the clopidogrel nonresponsiveness was independently associated with the risk of 2-year cardiac death (hazard ratio [HR] compared with clopidogrel responders (HR: 1.81; 95% confidence interval [CI]: 1.18 to 2.76; p = 0.006) (15).

PLATELET REACTIVITY ASSESSMENT. Blood samples anticoagulated with 0.129 mol/l sodium citrate (9:1 ratio) for platelet reactivity assessment was obtained at least 12 h after clopidogrel loading and 6 days after the PCI while the patient was on prasugrel treatment. Platelet-rich plasma, obtained by centrifuging whole blood for 10 min at 200*g*, was stimulated with 10 μmol/l of ADP (Mascia Brunelli, Milan, Italy) and residual aggregation was assessed using an APACT 4 light transmittance aggregometer (Helena Laboratories, Milan, Italy). The 100% line was set using platelet-poor plasma and the 0 baseline established with platelet-rich plasma (adjusted from 18×10^9/l up to 30×10^9/l). Platelet aggregation (according to the Born method) was evaluated considering the maximal percentage of platelet aggregation in response to stimulus. High residual platelet reactivity was defined as platelet aggregation by ADP ≥70% (5,10–13).

FOLLOW-UP. All patients had scheduled examinations at 1, 6, 12, and 24 months. All other possible information derived from hospital readmission or by the referring physician, relatives, or municipality live registries was entered into the prospective database.

ENDPOINTS. The primary endpoint of the study was the 2-year cardiac mortality. Secondary endpoints were: 1) myocardial infarction (MI); 2) ischemic stroke; 3) composite of cardiac death and MI, 4) stent thrombosis; 5) major bleeding; and 6) degree of platelet aggregation inhibition as assessed by light transmittance aggregometry. All deaths were considered cardiac unless an unequivocal noncardiac cause could be documented. The diagnosis of non-Q-wave MI was on the basis of an increase in creatine kinase-myocardial band isoenzyme or troponin I >3 times the upper limit of normal or for patients with elevated values on admission, as a re-elevation of creatine kinase-myocardial band or troponin I values. A Q-wave MI was defined as the development of new Q waves in 2 or more electrocardiographic leads, and in addition to creatine kinase-myocardial band or troponin I elevation. Ischemic stroke was defined as an acute neurological defect lasting more than 24 h without computed tomography evidence of bleeding. Stent thrombosis was defined according to the Academic Research Consortium criteria (19). Major bleeding was defined according to the Thrombolysis In Myocardial Infarction-38 criteria (20).

The study was approved by the institutional review committee of Careggi Hospital, and all patients gave written informed consent to participate in the study and undergo PCI.

STATISTICAL ANALYSIS. In the RECLOSE-3 study, the statistical hypothesis assumed a decrease of 50% in 2-year cardiac mortality in patients switched to