Clinical implications of high residual platelet reactivity on clopidogrel treatment: the RECLOSE studies

Repercusiones clínicas de la reactividad plaquetaria residual alta en el tratamiento con clopidogrel: los estudios RECLOSE

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High residual platelet reactivity (HRPR) on clopidogrel treatement is associated with an increased risk of adverse events after percutaneous coronary intervention (PCI) and the three REsponsiveness to CLopidogrel and Stent Thrombosis (RECLOSE) studies showed this relationship, the futility of a tailored therapy with increasing dose of clopidogrel, and that nonresponsiveness to clopidogrel is a modifiable risk factor.

RECLOSE-1 [1,2]

This study is based on a cohort of of 804 patients who had successful sirolimus- or paclitaxel-eluting stent implantation. All patients received a loading dose of 600 mg of clopidogrel, and residual platelet reactivity was assessed by light transmittance aggregometry (LAT) using 10 μmol of adenosine diphosphate as agonist. Patients with platelet aggregation by 10 μmol ADP ≥70% were defined as nonresponders. All patients received chronic dual antiplatelet treatment (aspirin 325 mg and clopidogrel 75 mg daily) for 6 months. The primary end point was the incidence of definite/probable early, subacute, and late stent thrombosis at 6-month follow-up.

The incidence of 6-month definite/probable stent thrombosis was 3.1% in the entire polulation. All stent thromboses were subacute or late. Out of the 804 patients, 105 (13%) were not responsive to clopidogrel. The incidence of stent thrombosis was 8.6% in nonresponders and 2.3% in responders (p<0.001). By multivariable analysis, the predictors of stent thrombosis were: nonresponsiveness to clopidogrel (hazard ratio [HR]=3.08; 95% confidence interval [CI]: 1.32 to 7.16; p<0.009), left ventricular ejection fraction (HR=0.95; 95% CI: 0.92 to 0.98; p<0.001), total stent length (HR=1.01, 95% CI: 1.00 to 1.02; p<0.010), and ST-segment elevation acute myocardial infarction (HR=2.41; 95% CI: 1.04 to 5.63; p≤0.041). The cardiac mortality rate was 8.6% in the nonresponders and 1.4% in responders (p<0.001). The incidence of the composite of cardiac death and definite or probable stent thrombosis was 10.5% in the nonresponders and 2.7% in the responders (p<0.001).

We assessed also the association between nonrespinsiveness to clopidogrel and nonresponsiveness to aspirin. Responsiveness to aspirin was assessed by LAT using arachidonic acid as agonist (1-mM). The incidence of dual nonresponsiveness to aspirin and clopidogrel was 6%. Definite/probable DES thrombosis was 11.1% and of cardiac death 8.9%. Thus, dual nonresponsiveness to clopidogrel and aspirin further increased the risk of stent thrombosis.

We assessed also the impact of clopidogrel nonresponsiveness in the subset of patients treated for unprotected left main disease[3]. Two-hundred and fifteen consecutive patients were treated with DES for ULMD. The incidence of HRPR after clopidogrel loading was 18.6%. The median follow-up was 19.3 months. The overall estimated 1-, 2- and 3-year cardiac mortality rate was 3.9±1.3%, 7.5±2.2%, and 12.2±03.4%, respectively. The 3-year cardiac mortality rate was 8.0±3.1% in the low residual platelet reactivity (LRPR) group and 28.3±10.4% in the HRPR group (p<0.005). The 3-year

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stent thrombosis rate was 4.2±1.8% in the LRPR group and 16.0±7.3% in the HRPR group (p <0.021). By forward stepwise regression analysis, HRPR after clopidogrel loading was the only independent predictor of cardiac death (HR=3.82; 95% CI: 1.38 to 10.54; p<0.010) and stent thrombosis (HR=3.69; 95% CI: 1.12 to 12.09; p<0.031).

RECLOSE-2 [4]

The RECLOSE-2 tested the hypothesis that HRPR after clopidogrel loading is an independent prognostic marker of risk of long-term thrombotic events in 1789 consecutive patients with acute coronary syndromes (ACS) undergoing an invasive procedure and antithrombotic treatment adjusted according to the results of platelet function tests. Patients with HRPR as assessed by adenosine diphosphate test (≥70% platelet aggregation) received an increased dose of clopidogrel (150-300 mg/d) or switched to ticlopidine (500-1000 mg/d) under adenosine diphosphate test guidance. The primary end point was a composite of cardiac death, myocardial infarction, any urgent coronary revascularization, and stroke at 2-year follow-up. Secondary end points were stent thrombosis and each component of the primary end point. The primary end point event rate was 14.6% (36/247) in patients with HRPR and 8.7% (132/1525) in patients with LRPR (absolute risk increase = 5.9%; 95% CI: 1.6%-11.1%; p=0.003). Stent thrombosis was higher in the HRPR group compared with the low residual platelet reactivity group (6.1% [15/247] vs 2.9% [44/1525]; absolute risk increase=3.2%; 95% CI: 0.4%-6.7%; p=0.01). By multivariable analysis, HRPR was independently associated with the primary end point (HR=1.49; 95% CI: 1.08-2.05; p=0.02) and with cardiac mortality (HR=1.81; 95% CI: 1.18-2.76; p=0.006). Among patients with HRPR after clopidogrel loading, there were no differences either in the primary end point rate or in cardiac mortality among patients with an ADP test result of less than 70% after treatment adjustment vs patients with a persistent ADP test result of 70% or greater (primary end point event rates, 14.4% and 14.9%, respectively; p=0.91; cardiac mortality rates, 8.5% and 11.7%, respectively; p=0.41).

RECLOSE-3 [5]

The RECLOSE-2 adjusted antiplatelet therapy using an increased maintenance dosage of clopidogrel or ticlopidine. Despite some positive effect on in vitro tests, the tailored therapy failed to show clinical benefit in clopidogrel nonresponders after a loading dose of 600 mg. The RECLOSE-3 verified in ACS patients, if nonresponsiveness to clopidogrel should be considered as a nonmodifiable risk factor for thrombotic events or if tailored therapy with use of new antithrombotic agents such as prasugrel, which provide more potent and predictable in vitro platelet aggregation inhibition, have a positive effect on clinical outcome. The RECLOSE-3 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 mmol/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.
Out of 1,550 screened patients, 302 were clopidogrel nonresponders. The result of the ADP test was 77.6±6.2% after clopidogrel loading . 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 inversely related to the risk of 2-year cardiac death (HR=0.32; p=0.036). Thus, 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.

In conclusion, the RECLOSE studies have shown that nonresponsiveness to clopidogrel increases dramatically the risk of stent thrombosis and cardiac mortality in patients undergoing PCI. If prasugrel is not routinely used, assessment of in vitro residual platelet reactivity after clopidogrel loading should be considered to guide patient care decisions.

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