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Platelet Responsiveness to Clopidogrel Treatment After Peripheral Endovascular Procedures

The PRECLOP Study: Clinical Impact and Optimal Cutoff Value of On-Treatment High Platelet Reactivity

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Objectives This study aimed to assess the clinical implications and optimal cutoff value of high platelet reactivity (HPR) in patients receiving clopidogrel for peripheral endovascular procedures.

Background As noted in coronary studies, HPR could be related to increased adverse events.

Methods This prospective trial included patients receiving clopidogrel 75 mg daily, before and after infrainguinal angioplasty or stenting. Platelet inhibition was assessed with the VerifyNow $P2Y_{12}$ point-of-care test. Primary endpoints were 1-year clinical events rate (composite endpoint of death, major stroke, major amputation, target vessel revascularization, and bypass) according to the $P2Y_{12}$ reaction units (PRU)-based quartile distribution, the estimation of the optimal PRU cutoff value for predicting clinical outcome, and the identification of independent predictors influencing event-free survival.

Results In total, 100 consecutive patients were enrolled. The 1-year cumulative events rate was 4% in the first quartile, 12% in the second, 52% in the third, and 84% in the fourth. Pairwise comparisons demonstrated a significant difference in the composite endpoint between successive quartiles (all $p < 0.05$ except for the first vs. second quartile). According to receiver-operating characteristic curve analysis, the optimal cutoff value for the composite endpoint was PRU $\geq$234 (area under the curve: 0.883; 95% confidence interval [CI]: 0.811 to 0.954; $p < 0.0001$; sensitivity: 92.1%; specificity: 84.2%). Cox multivariate regression analysis identified HPR (PRU $\geq$234) as the only independent predictor of an increased number of adverse events (hazard ratio: 16.9; 95% CI: 5 to 55; $p < 0.0001$).

Conclusions On-treatment HPR is associated with markedly increased adverse clinical events in patients undergoing peripheral endovascular procedures. Point-of-care clopidogrel assessment might be useful in individualizing antiplatelet therapy to attain superior clinical results. (High On-Treatment Platelet Reactivity Following Peripheral Endovascular Procedures [PRECLOP]; NCT01744613) (J Am Coll Cardiol 2013;61:2428–34) © 2013 by the American College of Cardiology Foundation

Platelets play a key role in the development of thrombotic complications in patients with documented atherosclerotic vascular disease, including those with coronary artery disease, cerebrovascular disease, and peripheral arterial disease (PAD) (1,2). Therefore, oral antiplatelet drug therapy with aspirin and clopidogrel is the cornerstone therapy in a variety of conditions characterized by the risk for arterial thrombosis (3,4).

Despite the high initial success rate of percutaneous coronary intervention (PCI), some patients will develop recurrent ischemic events due to stent restenosis/thrombosis, regardless of dual antiplatelet treatment (5,6). Moreover, the wide interindividual variability in the inhibitory effect of clopidogrel on platelet aggregation has been also widely established (7,8). Numerous studies have correlated on-treatment high platelet reactivity (HPR) resulting from low response to clopidogrel with an increased risk for cardiovascular events (9,10). This inadequate response to clopidogrel could be attributed to poor compliance to treatment, variable absorption of the drug and/or variable generation of the active metabolite, and various drug–drug interactions (11,12).

Platelet reactivity has been historically measured with light-transmittance aggregometry (LTA), but this method is technically complex and time-consuming (13). Therefore,

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several more practical, point-of care tests have been developed and are commonly used to assess a patient's response to clopidogrel. Among these tests, VerifyNow (Accumetrics Inc., San Diego, California), a genuine point-of-care assay that measures platelet-induced aggregation and expresses the results as platelet $P2Y_{12}$ reaction units (PRU), has been described as having advantages such as simplicity, speed, and user-friendliness (14,15). Published studies using this instrument (16,17) have investigated the relationship between HPR and long-term cardiovascular events after PCI and have derived an optimal PRU cutoff value to identify patients at risk for future ischemic events (18). However, there is a lack of knowledge on the possible correlation between HPR in patients receiving clopidogrel and adverse outcomes after peripheral endovascular procedures (PEPs) (19). Recently, Tepe et al. (20), in a study demonstrating the short-term superiority of dual antiplatelet therapy following infrainguinal angioplasty, also reported a trend of low responsiveness in patients receiving clopidogrel after endovascular treatment of PAD. We designed the PRECLOP (Platelet Responsiveness to Clopidogrel Treatment After PEPs) study, using the VerifyNow test, to prospectively evaluate levels of platelet reactivity that may correlate with adverse clinical events and to create a clinically meaningful cutoff value of platelet inhibition in patients with PAD treated with infrainguinal angioplasty or stenting.

Methods

This prospective, single-center study was approved by the Scientific and Ethics Committee at Patras University (Rio, Greece) and was registered in a dedicated electronic database (NCT01744613). The study included patients scheduled to undergo a percutaneous angioplasty or stenting procedure for the treatment of femoropopliteal PAD. All patients received dual antiplatelet therapy with clopidogrel 75 mg daily for at least 1 month prior to the procedure. Dual antiplatelet therapy with clopidogrel 75 mg and aspirin 100 mg daily was then prescribed for 6 months after the procedure, while single antiplatelet therapy with clopidogrel 75 mg daily was continued throughout the follow-up period. The study included patients from 18 to 84 years of age, with either severe life-style–limiting intermittent claudication classified as Rutherford stage of PAD 3, or critical limb ischemia (CLI) classified as Rutherford stages of PAD 4 to 6, due to an angiographically proven femoropopliteal lesion that was successfully treated with balloon angioplasty or stenting. Only patients with successful recanalization were included in the study. Infrapopliteal disease was treated if deemed necessary. Both de novo and in-stent restenotic lesions were included. All patients were enrolled after they signed an appropriate informed-consent form. Exclusion criteria were *procedural technical failure,* defined as the inability to successfully treat the index lesion and/or to obtain at least one patent straight arterial line to the distal foot; acute limb ischemia; coagulation disorders; and failure to comply with the pre- and post-procedural antiplatelet regimen (Fig. 1). Clopidogrel responsiveness was evaluated using the VerifyNow $P2Y_{12}$ assay point-of-care testing following peripheral blood sampling during admission, always before the procedure, as described elsewhere (21,22).

Endpoints. The study's primary endpoints were the 1-year cumulative clinical events rate (composite endpoint of death, bleeding, major amputation, or clinically driven target vessel re-intervention [TVR]) in relation to the quartile distribution of on-treatment platelet responsiveness to clopidogrel, expressed as platelet reactivity $P2Y_{12}$ reactive unites (PRU); the identification of any independent predictors influencing the event-free survival rate; as well as the estimation of the optimal cutoff PRU value for the

Abbreviations and Acronyms

CLI = critical limb ischemia
HPR = high platelet reactivity
PAD = peripheral arterial disease
PCI = percutaneous coronary intervention
PEP = peripheral endovascular procedure
PRU = platelet ($P2Y_{12}$) reaction units
ROC = receiver-operating characteristic

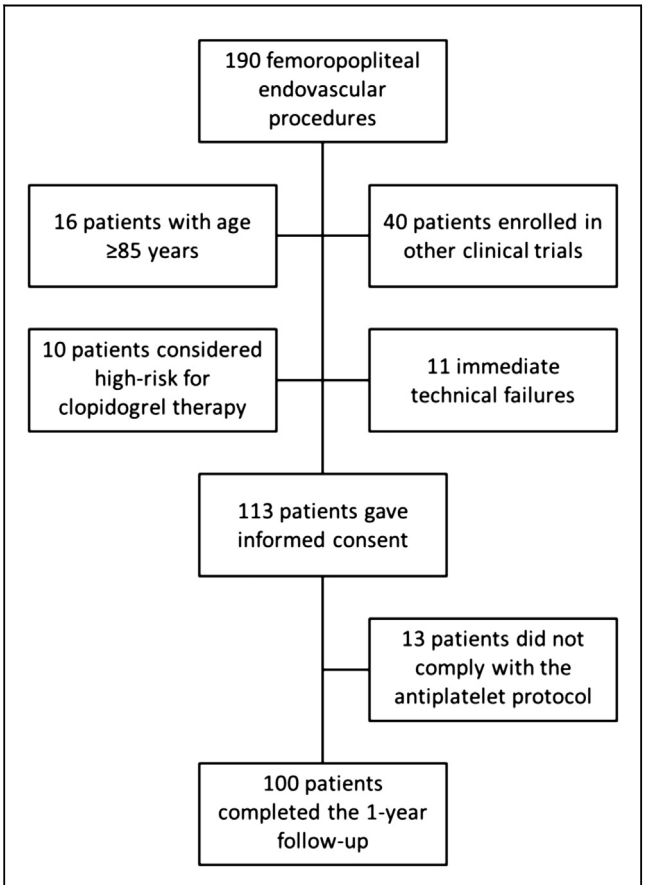

Figure 1 Study Flowchart

Patient recruitment and reasons of exclusion, with a final target sample of 100 cases at 1 year.