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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

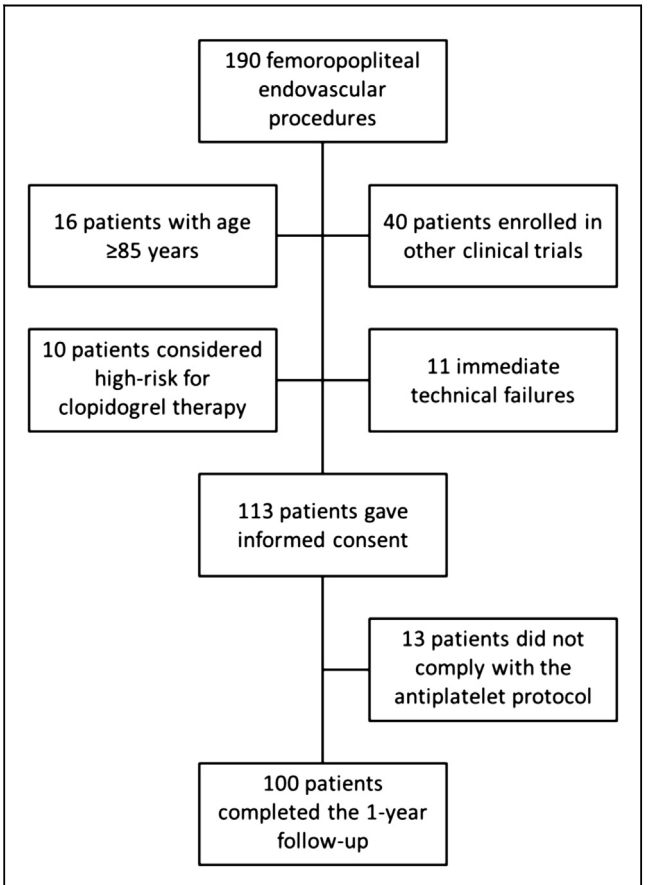

Figure 1 Study Flowchart

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

prediction of clinical outcomes following PEPs. Secondary endpoints included procedure- and drug-related complication rates.

Statistical analysis. This was an open-label study; no blinding or masking was involved in data collection or analysis. The population was stratified into quartiles according to the recorded PRU values, and a cumulative-events analysis was performed at 1 year. We tested the null hypothesis that the 1-year composite endpoint of cumulative adverse clinical events after femoropopliteal angioplasty or stenting was not influenced by the quartile distribution of PRU values. As this study's population included patients with either intermittent claudication or CLI, the 1-year clinical events rate was expected to be around 40% (23). Preliminary statistical power analysis estimated that a minimum enrollment of 88 patients would be required to detect a 20% difference in the 1-year clinical events rate between the first and fourth quartiles (alpha error: 5%; beta error: 10%). We set a target of 100 patients to account for any patient dropouts or cases lost to follow-up. The composite endpoint in the study's quartiles was analyzed using the multiple-comparisons chi-square test. We then assessed the ability of PRU point-of-care examination to distinguish between patients with and without clinical events at 1-year follow-up using receiver-operating characteristic (ROC) curve analysis, and the optimal cutoff PRU value was determined by estimating the value resulting in the maximum sum of sensitivity and specificity (area under the curve).

Following identification of the PRU optimal cutoff value, a univariate and multivariate stepwise regression analysis with a Cox proportional hazards regression statistical model was performed in search of independent predictors of the study's primary endpoint (Fig. 2). Patients' demographics and procedural details are presented in detail in Table 1. Only covariates with a p value <0.15 according to an exploratory univariate analysis were included in the multivariate regression model (22). Dependent variables finally evaluated by the Cox multivariate stepwise regression analysis were diabetes mellitus, renal disease, hypertension, smoking habit, baseline clinical symptoms (intermittent claudication or CLI), and PRU values below or above the cutoff value as determined by ROC analysis. Cox regression was also employed to illustrate time-to-event event-free survival in various patient groups following adjustment for the covariates mentioned.

Variables are reported as mean ± SD. Continuous variables were compared by standard t test if originating from a normal distribution; alternatively, a nonparametric test (Mann-Whitney) was used. Group proportions were compared with the chi-square test or with the Fisher exact test in cases of small counts of events ($n < 5$). The threshold for statistical significance was established at alpha <0.05, and 95% confidence intervals (CIs) are reported in cases of significant results. All statistical analyses were performed with SPSS version 20.0 (Systat, Inc., Chicago, Illinois).

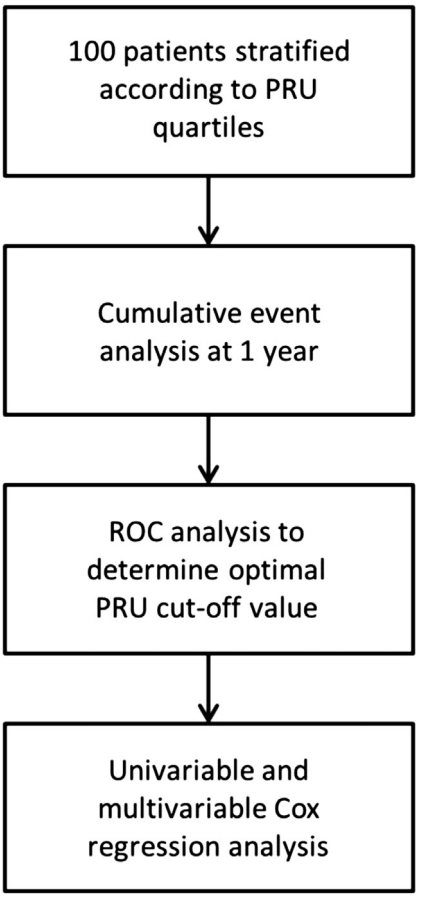

Figure 2 **Statistical Methods**

Steps and methods of the statistical analysis employed in the present study.

Results

In total, 100 consecutive patients (71 men; mean age: 68.5 ± 9.2 years) treated with femoropopliteal percutaneous angioplasty or stenting and fulfilling the study's inclusion criteria were enrolled in the study and distributed in four quartiles (25 patients each) according to their PRU values (progressively increased PRU values from the first to fourth quartiles). Significantly more diabetic patients were included in the third compared to the first quartile, and more smokers were included in the fourth compared to the first quartile. Most of the treated lesions were classified as Treatment Assessment Services for the Courts (TASC) Class II A, whereas TASC II classifications of the lesions were similar among the four quartiles. Patients' demographic characteristics, lesion characteristics, and procedural details, as well as their quartile-based comparisons, are analytically demonstrated in Table 1.

Table 1 Quartile Distribution and Univariate Analysis of Patients Demographics and Procedural Details

Variable	Quartile				p Value	Total Cohort (n = 100)
	First (n = 25)	Second (n = 25)	Third (n = 25)	Fourth (n = 25)		
Age, yrs	64.0 ± 10.6	69.1 ± 7.8	70.2 ± 9.3	70.6 ± 8.0	0.40	68.5 ± 9.2
Male	21 (84)	21 (84)	20 (80)	19 (76)	0.82	71 (71)
Comorbidity/risk factor						
Hypercholesterolemia	22 (88)	18 (72)	20 (80)	16 (64)	0.37	76 (76)
Hypertension	19 (76)	23 (92)	20 (80)	24 (96)	0.13	86 (86)
De novo lesions	19 (76)	20 (80)	18 (72)	19 (76)	0.93	76 (76)
Smoking	14 (56)	22 (88)	15 (60)	23 (92)	0.03	74 (74)
CLI	13 (52)	11 (44)	18 (72)	21 (84)	0.03	70 (70)
Diabetes	9 (36)	13 (52)	19 (76)	16 (64)	0.03	57 (57)
Ischemic heart disease	8 (32)	8 (32)	6 (24)	10 (40)	0.69	32 (32)
Treatment history						
Femoropopliteal treatment	25 (100)	25 (100)	25 (100)	25 (100)	n/a	100 (100)
Stent placement	19 (76)	19 (76)	20 (80)	21 (84)	0.88	79 (79)
Adjunctive BTK treatment	8 (32)	9 (36)	11 (44)	9 (36)	0.84	37 (37)
Proton-pump inhibitors	8 (32)	7 (28)	8 (32)	4 (16)	0.53	27 (27)
Renal disease	3 (12)	1 (4)	6 (24)	5 (20)	0.20	15 (15)
Lesion length, mm	75.3 ± 52.2	71.5 ± 45.7	76.1 ± 52.4	85.0 ± 47.0	0.34	76.8 ± 49.3
Occlusions	19 (76)	17 (68)	19 (76)	21 (84)	0.62	76 (76)
TASC A	13	12	8	10	0.49	43
TASC B	4	5	7	5	0.76	21
TASC C	5	5	6	5	0.98	21
TASC D	3	3	4	5	0.83	15

Values are mean ± SD or n (%).
BTK = below the knee; CLI = critical limb ischemia; TASC = Treatment Assessment Services for the Courts.

There were 38 adverse clinical events in the total patient cohort. The majority were TVR events (36 of 38; 94.7%), as the remaining events included 1 major amputation and 1 death due to major ischemic stroke in patients with PRU values of 339 and 414, respectively. None of the patients were lost to follow-up. The 1-year composite endpoints were 4% (n = 1 of 25 events) in the first quartile, 12% (n = 3/25 events) in the second quartile, 52% (n = 13 of 25 events) in the third quartile, and 84% (n = 21 of 25 events) in the fourth quartile. The multiple-comparisons chi-square test detected a significant difference in the distribution of events among the separate quartiles ($p < 0.0001$), whereas pairwise comparisons identified significantly fewer events in the first versus the third quartile ($p < 0.0001$), first versus fourth ($p < 0.0001$), second versus third ($p = 0.0012$), second versus fourth ($p < 0.0001$), and third versus fourth ($p = 0.007$). There was no significant difference in the composite endpoint between the first and second quartiles ($p = 0.14$) (Fig. 3).

ROC curve analysis demonstrated that PRU values were significant discriminators of major events at 1 year, with an area under the curve of 0.883 (95% CI: 0.811 to 0.954; $p < 0.0001$), and indicated that PRU ≥234 was the optimal cutoff value for the prediction of the primary composite outcome, demonstrating a 92.1% sensitivity and a 84.2% specificity (Fig. 4). The test's positive and negative predictive values were 67.3% and 93.9%, respectively.

According to subgroup univariate analysis, CLI (78.4% vs. 46.9%; $p < 0.0001$), chronic renal disease (70.6% vs. 42.9%; $p = 0.002$), and diabetes mellitus (21.6% vs. 4.1%; $p = 0.004$) were related to an increased rate of HPR (PRU value above the cutoff of 234). The majority of the patients enrolled were receiving statin therapy (76%) for the treatment of hyperlipidemia. Statistical analysis did not detect any association between statin use and HPR or outcomes.

Cox multivariate stepwise backward logistic regression analysis indicated that a PRU value above the cutoff value of

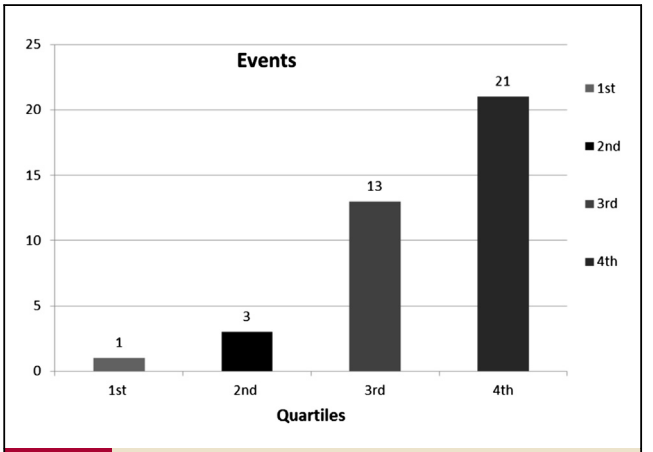

Figure 3 Cumulative Adverse Events

Schematic representation of clinical adverse events according to quartile distribution of platelet ($P2Y_{12}$) reaction units (PRU).

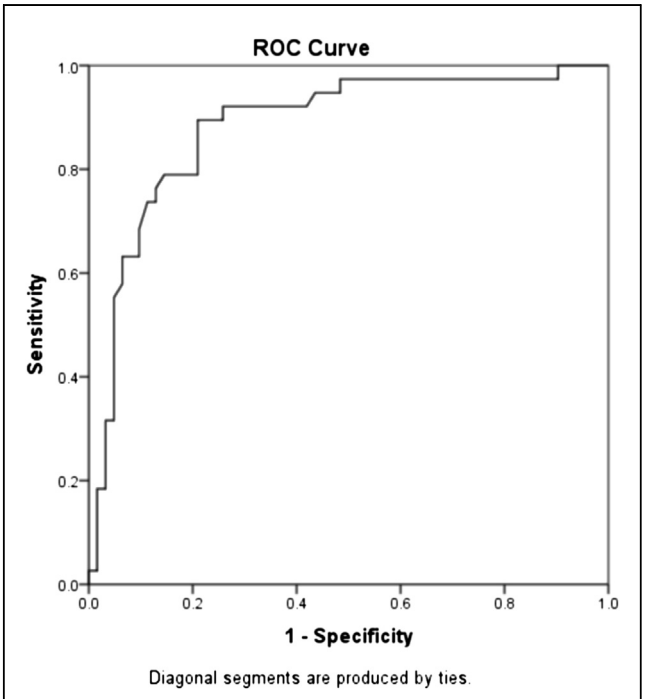

Figure 4 ROC Analysis

Receiver-operating characteristic (ROC) curve indicating the optimal cutoff value of platelet ($P2Y_{12}$) reaction units (PRU) that predicts adverse clinical outcomes.

234 was the only independent predictor of increased adverse clinical events, with an adjusted hazard ratio of 16.94 (95% CI: 5 to 55; $p < 0.0001$) (Fig. 5). The Cox regression model–adjusted plots, as stratified according to the quartile distribution of PRU, are demonstrated in Fig. 6. None of the remaining analyzed variables were shown to affect the primary outcome measure. In this study, the first event was noted nearly 3 months after the procedure, and no acute or subacute thromboischemic events were noted up to 30 days post-procedure. However, the majority of TVR events occurred due to reocclusion of the target vessel (22 of 36 [61.1%]). In 11 of the 36 femoropopliteal TVR cases (30.5%), additional BTK interventions were performed to improve runoff (1 intervention in the first quartile, 1 in the second, 5 in the third, and 4 in the fourth). Overall, 4 bleeding events (4.0%) requiring further intervention were noted (3 of 49 patients in the first 2 quartiles with a PRU below the cutoff value, and 1 of 51 patients in the fourth quartile with PRU above the cutoff value [6.1% vs. 2.0%, respectively; $p = 0.14$]). Specifically, there was 1 case of major retroperitoneal bleeding (1%) in a patient in the second quartile with a PRU of 194 who required transfusion of 2 U of red blood cells due to a hemoglobin drop of nearly 4 g/dl. He was discharged from the hospital 48 hours after the procedure. There were 2 pseudoaneurysms (2%) (1 each in patients in the first and second quartiles, with PRU values of 90 and 185, respectively), both successfully managed with percutaneous ultrasound–guided thrombin injection. Finally, bleeding through the puncture site resulting in a large groin

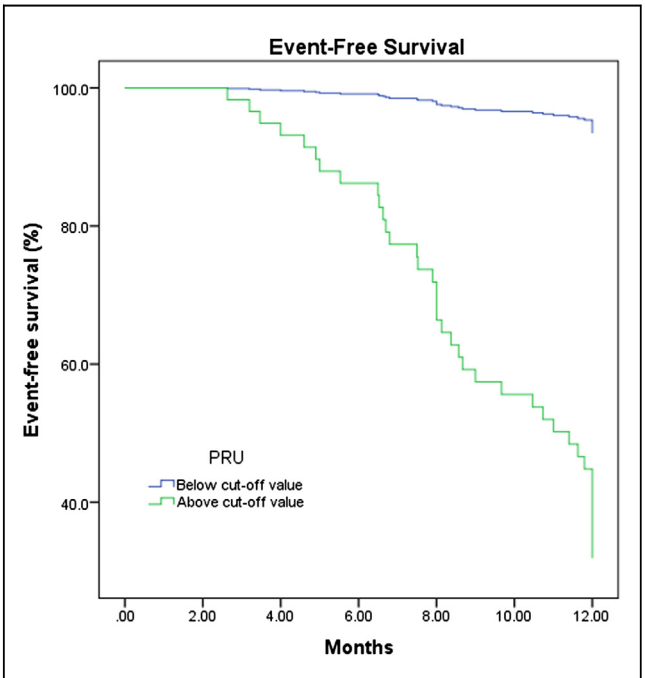

Figure 5 Event-Free Survival and Cutoff Value

Cox regression analysis adjusted plots of event-free survival stratified according to the platelet ($P2Y_{12}$) reaction units (PRU) cutoff value.

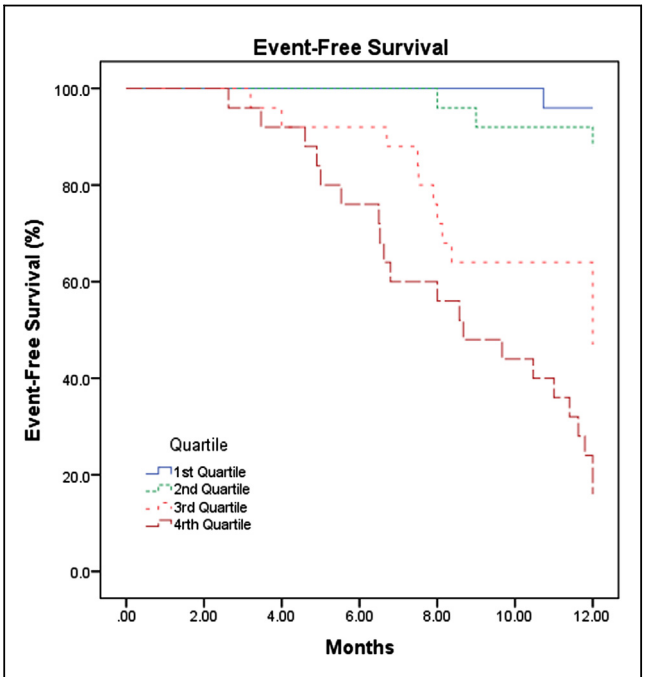

Figure 6 Quartile-Based Event-Free Survival

Cox regression analysis adjusted plots of event-free survival stratified according to the quartile distribution of platelet ($P2Y_{12}$) reaction units (PRU).

hematoma occurred in 1 patient (1%) with a PRU of 310 and was managed with prolonged manual compression. When excluding TVR events, there were no significant differences in the rest of the adverse clinical events in patients with PRU values below the cutoff value compared to those with PRU values above the cutoff value. One ischemic stroke resulting in death and 1 major amputation occurred, each in patients with PRU values ≥234 ($p = 0.16$ in each case). No other complications were observed.

Discussion

Inhibition of platelet aggregation using oral antiplatelet therapy with clopidogrel is widely used following endovascular or surgical peripheral revascularization procedures (3,19). Although numerous trials have reported the clinical significance of on-treatment HPR following PCI (18), data demonstrating the correlation of platelet responsiveness with clinical outcomes of PEPs are scarce. Moreover, the optimal PRU cutoff value of platelet inhibition influencing outcomes of peripheral angioplasty or stenting has not been recognized. This study demonstrated that an inadequate response to clopidogrel, identified using point-of-care testing just prior to the procedure, is a new strong independent predictor of reduced event-free survival, adversely influencing midterm clinical outcomes of peripheral angioplasty and stenting. The multivariate Cox regression analysis demonstrated that patients receiving clopidogrel with residual platelet reactivity above the optimal cutoff value had an unexpected almost 17-fold increased risk for clinical events (Figs. 5 and 6).

The authors performed a quartile-distribution analysis due to the progressively increasing event rate observed across PRU quartiles, as previously reported (22). According to our results, the 50 patients included in the first 2 quartiles (PRU between 55 and 242) demonstrated a significantly lower cumulative clinical events rate compared to the 50 patients included in the third and fourth quartiles (PRU between 244 and 426) at 1-year follow-up.

ROC analysis identified PRU ≥234 as the optimal cutoff value to predict clinical outcomes of infrainguinal angioplasty or stenting. This was in line with the majority of the coronary studies, as according to a recent meta-analysis, a PRU value ≥230 was associated with a significant twofold increased rate of the composite endpoint of death, myocardial infarction, and stent thrombosis (24). Compared to the results reported from several coronary studies, in the PRECLOP study, the specific point-of-care assay demonstrated analogous sensitivity and specificity (92.1% and 84.2%, respectively) and positive and negative predictive values, validating its accuracy in predicting clinical outcomes of PAD treatment (16,22,24). The 93.9% negative predictive value of the test indicates that patients with a PRU below the cutoff value are unlikely to experience a clinical adverse event up to 1 year after the revascularization procedure, regardless of the technique or endovascular device used, the characteristics and location of the lesion, and the clinical stage of the disease, whereas the 67.3% positive predictive value points out that nearly three fourths of the patients with a PRU above the cutoff value could develop recurrent clinical symptomatology within 1 year following the procedure. Notably, although the cumulative 1-year event rate of the entire cohort was 38%, a subgroup analysis indicated that in patients with a PRU below the cutoff value, the cumulative clinical events rate dropped to 6.1% (3 of 49) compared to 68.6% (35 of 51) in patients with a PRU above the cutoff value.

The events noted during follow-up were mainly clinically driven endovascular re-intervention procedures, as 1 death and 1 major above-the-knee amputation were reported. Although the hypothesis was generated on the basis of current evidence, the obvious correlation between disease recurrence and on-treatment HPR suggests the need for long-term antiplatelet therapy not only to reduce thromboembolic cardiovascular events but also to limit the phenomenon of symptomatic vascular restenosis following PEPs. No procedure-related deaths were noted, and bleeding events were rare, with no significant difference in bleeding rates between the groups with PRU values below and above the cutoff value, demonstrating the safety profile of standard clopidogrel therapy before, during, and following peripheral angioplasty and stenting. Moreover, all bleeding events were puncture related and could have presumably occurred even if antiplatelet therapy was not prescribed, and no drug-related side effects were noted to discourage the continuation of clopidogrel.

Study limitations. Limitations of this study include the single-center design, and the small number of patients investigated might generate an inherent bias and did not enable the assessment of the correlation between PRU and bleeding events. Furthermore, the generally small numbers of events made it difficult to achieve fully adjusted models. Larger trials are required to further evaluate the results reported herein and to provide a therapeutic window for clopidogrel in the ambit of peripheral endovascular treatment (25). Additionally, on-treatment platelet reactivity was assessed only with point-of-care testing, and no standard laboratory method was available as a control. Nonetheless, the VerifyNow assay was previously used in several PCI studies and is currently widely accepted as an accurate test of on-treatment platelet reactivity, and absolute PRU values measured by the VerifyNow point-of-care assay have been correlated with the results of laboratory-assessed ADP-induced optical aggregometry (12,13,18,23–27). Finally, this study investigated platelet responsiveness in elective procedures in which all subjects were treated with a maintenance dose of clopidogrel 75 mg once daily for at least 1 month prior to the index procedure. Hence, the effect of a periprocedural loading dose of clopidogrel (300 to 600 mg) was not studied. However, on the basis of clopidogrel pharmacokinetics and on previously reported data from coronary trials, the authors can only speculate that the results should not differ significantly (9,16–18).

Following the results of the PRECLOP study, the authors advocate the use of the specific point-of-care testing to detect HPR during clopidogrel treatment to recognize patients at higher risk for clinical adverse events and to encourage individualized, alternative antiplatelet regimens, such as a doubled clopidogrel dose or newer antiplatelet drugs (e.g., prasugrel, ticagrelor), with the aim of improving clinical outcomes after PEPs.

Conclusions

The PRU cutoff value optimal for predicting clinical outcomes of peripheral angioplasty and stenting, assessed with VerifyNow point-of-care testing, was ≥234. Patients with on-treatment HPR experienced significantly more clinical events, and a PRU above the cutoff value was identified as a strong independent predictor of decreased event-free survival at 1-year follow-up.

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