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The challenge for predicting bleeding events by assessing platelet reactivity following coronary stenting

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ABSTRACT

Background: Predicting future bleeding events represents an unmet medical need that will ultimately improve outcomes during dual antiplatelet therapy (DAPT). Although low platelet reactivity (LPR) may be linked to bleeding, standardized and clinically validated threshold for reliable DAPT bleeding risk stratification is lacking. We sought to define the predictive value of LPR for future bleeding events in a large cohort of post-stenting single-center Korean patients.

Methods: Consecutive patients (n = 800) who underwent coronary interventions with drug-eluting stents were enrolled from March 2010 to October 2014. Among them, 699 (80%) were treated with 75 mg/daily clopidogrel, 93 (19%) with 10 mg/daily prasugrel, and 8 (1%) with 180 mg/daily ticagrelor, all on top of 100 mg/daily aspirin. Bleeding was assessed by BARC 2–5 scale, and events were collected for 1-year post stenting. Platelet reactivity on DAPT was measured by the VerifyNow P_2Y_{12} assay at 1 month following coronary intervention.

Results: There were a total of 18 (2.1%) bleeding events. The LPR value defined as ≤139 PRU (AUC: 0.867, $p < 0.0001$) was an independent predictor for bleeding (HR = 21.26, 95% CI: 6.19–73.0, $p < 0.0001$) by univariate analysis, and remains significant (HR = 11.49; 95% CI: 2.89–45.67, $p < 0.0004$) following multivariate analysis adjustment. However, the specificity (81.7%) and sensitivity (83.3%) of the test was low challenging the assay utility to predict bleeding.

Conclusion: Despite being an independent predictor for bleeding, LPR failed to reliably triage such patients due to low specificity and sensitivity of the test. There is an urgent need for a randomized trial with uniformed DAPT regimen, bleeding definition, and careful follow-up.

1. Introduction

Dual antiplatelet therapy (DAPT) consisting of aspirin and a P_2Y12-inhibitor combination is a mainstream pharmacologic strategy to prevent ischemic thrombotic events in patients following percutaneous coronary interventions (PCIs) [1]. However, applying conventional [2,3], and especially more aggressive [4,5] DAPT strategies has been associated with an increased risk for bleeding. Moreover, bleeding has been recently recognized as a critical adverse event severely impacting patient survival [6,7]. Therefore, any attempts to predict further bleeding risks events in PCI-treated patients, and potentially adjust DAPT regimen are of critical importance. Some evidence suggests that heightened residual platelet reactivity during DAPT may predict future thrombotic events [8,9], while alternative data link low platelet reactivity (LPR) with greater bleeding risks [10]. However, the randomized evidence is inconclusive, if not negative, with regard to improved vascular outcomes [11,12], and virtually lacking for predicting bleeding by tailoring DAPT regimens. Moreover, the proposed cut-off values for dichotomizing platelet reactivity are unacceptably variable, heavily dependent on test applied, DAPT duration, and woefully small sample sizes challenging the predictive relevance of individual DAPT monitoring. We sought to determine the optimal prognostic LPR cut-off value (if any) for bleeding in patients treated with DAPT in a large cohort of post-stenting patients of Korean descent.

2. Methods

2.1. Patients

Between March 2010 and October 2014, the total of 800 post-PCI patients (Dong-A University Medical Center, Busan, Korea) receiving maintenance DAPT (75 mg/day clopidogrel, or 10 mg/day prasugrel, or 180 mg/day ticagrelor, all on top of 100 mg aspirin) were included in the prospective observational cross-sectional study. Written informed consent was obtained from all patients, and the study protocol was approved by the Ethical Review Board of Dong-A University Hospital. Exclusion criteria were DAP maintenance <1 month, hemodynamic instability, malignancies, active bleeding or major surgery within 4 weeks, severe chronic renal failure and other types of antiplatelet agents (e.g. cilostazol, glycoprotein IIb/IIIa receptor blocker).

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2.2. Platelet testing

Blood sampling for the platelet assay was obtained after 1 month after PCI during DAPT maintenance. Samples were drawn from an antecubital vein into Vacutainer tube containing 3.2% sodium citrate using a 21-gauge needle. The platelet function tests were performed by experienced laboratory personnel blinded to clinical data in accordance to the manufacturer's instructions. The conventional VerifyNow™ assay (Accumetrics, San Diego, CA, USA) is a whole blood, cartridge-based, optical detection system designed to measure platelet aggregation. The technology is described in details elsewhere [13]. Briefly, within the analyzer cartridge there is a channel in which inhibition of the ADP P_2Y12 receptor is measured. This channel contains ADP as a platelet agonist and prostaglandin E1 (PGE1) for suppression of intracellular-free calcium levels to eliminate the non-specific contribution of ADP binding to P_2Y1 receptors. The numerical results are digitally expressed as P_2Y12 reaction units (PRU). Every measurement was done in duplicate with the mean calculation, but in case of measurements with more than a 20% difference of the mean curve from at least one curve or the correlation coefficient less than 0.98 resulted in the measurement being discharged and testing being performed again.

2.3. Bleeding definition

Clinically relevant bleeding complications were recorded by BARC type ≥2 scale [14] within 1 year of follow-up. There were no secondary endpoints in the study.

2.4. Statistical analysis

Continuous variables are expressed as means ± standard deviations and were analyzed using Student's t-test. Categorical variables were summarized in terms of numbers and percentages, and were compared by using chi-square test or Fisher exact test. Univariable and multivariable Cox proportional hazard regression were used to determine independent factors associated with incidences of variables. All data with a p value < 0.2 in the univariable analysis were then entered into a multivariable model. The ability of the assay to discriminate between patients with and without bleeding at 1 year was evaluated by ROC curve analysis (using MedCalc Version 12.2.1, MedCalc software, Mariakerke, Belgium). The optimal cut-off value was calculated by determining criteria for LPR. The matched cut-off value was defined as the point providing the greatest sum of sensitivity and specificity. A p value < 0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

3. Results

The baseline demographics and clinical characteristics of the entire patient population, and dependent on experiencing bleeding event are presented in Table 1 Background clinical variables and admission biomarkers were distributed fairly even, and none of them predict future bleeding risks. The majority of patients (80%) were treated with clopidogrel, 11% with prasugrel, and only 1% received ticagrelor. Bleeding events occurred in 18 patients (2.3%). There were less bleeding after clopidogrel (n = 12, or 1.7%), then on prasugrel (n = 5, or 5.4%), or ticagrelor (n = 1, or 12.5%).The details of individual bleeding cases are summarized in Table 2. Residual platelet reactivity was about 3-fold lower in patients who experience future bleeding event when compared with no bleeding cohort. The details are presented in Table 3. The ROC curve analysis revealed high AUC (95%CI) = 0.867, but low sensitivity (83.3%), and specificity (81.7%) for the VerifyNow assay to predict bleeding (Fig. 1). By applying standard cut-off values, 20% of patients exhibited LPR by VerifyNow test. The individual data points of residual platelet reactivity dependent on bleeding are presented in Fig. 2. Patients with LPR demonstrated a significantly higher risk for bleeding events compared with non-bleeding patients (HR = 21.26, 95% CI: 6.194–72.99, p < 0.0001) by univariated analysis. Moreover, multivariate analysis revealed that VerifyNow assay was capable to independently predict 1-year bleeding risk (HR = 11.49, 95% CI: 2.9–45.7, p = 0.0004).

Table 1
Baseline demographics and clinical characteristics.

Variables	Overall (n = 800)	Bleeding (n = 18)	No-bleeding (n = 782)	P-value[a]
Age, years	64.3 ± 10.3	62.8 ± 11.4	64.3 ± 10.4	0.560
Male sex, n (%)	585 (67)	15 (83)	570 (73)	0.243
BMI, kg/m^2	24.5 ± 3.1	23.8 ± 3.2	24.6 ± 3.1	0.279
Risk factors				
Diabetes mellitus, n (%)	292 (33)	7 (39)	285 (36)	0.505
Hypertension, n (%)	460 (52)	9 (50)	451 (58)	0.338
Dyslipidemia, n (%)	351 (40)	5 (28)	346 (44)	0.124
Smoking, n (%)	123 (15)	2 (11)	121 (16)	0.460
Medical history				
Stroke, n (%)	65 (7)	3 (17)	62 (8)	0.174
CABG, n (%)	12 (1)	0 (0)	12 (2)	0.759
CKD, n (%)	45 (5)	2 (11)	43 (6)	0.269
Platelets count, 103^{ul}	240 ± 101	272 ± 80	240 ± 101	0.176
Hb, g/dl	13.2 ± 1.7	13.1 ± 1.6	13.2 ± 1.7	0.852
HbA1c, %	6.6 ± 3.0	6.3 ± 1.0	6.6 ± 3.1	0.723
Creatinine, mg/dL	1.2 ± 1.2	1.2 ± 0.6	1.2 ± 1.2	0.931
eGFR	73.1 ± 43.9	68.8 ± 29.3	73.2 ± 44.2	0.670
Ejection fraction, %	54.8 ± 10.8	56.4 ± 5.9	54.8 ± 10.9	0.557
Prior medical therapy				
Statins, n (%)	541 (62)	13 (72)	528 (66)	0.445
CCB, n (%)	500 (57)	9 (50)	491 (63)	0.193
ARB, n (%)	142 (16)	3 (17)	139 (18)	0.600
ACE inhibitors, n (%)	109 (12)	1 (6)	108 (14)	0.272
Beta blockers, n (%)	355 (40)	9 (50)	346 (44)	0.400

[a] Between bleeding and non-bleeding groups; BMI — body mass index; CABG — coronary artery bypass grafting; CKD — chronic kidney disease; Hb — hemoglobin; eGFR — estimated glomerular filtration rate; CCB — calcium-channel blockers; ARB — angiotensin receptor blockers.

Table 2
Summary of individual bleeding events.

Patients	Sex	Age	DAPT duration (day)	BARC type	Bleeding site	Agent
No 1	M	64	418	3c	ICH	Clopidogrel
No 2	F	64	225	3a	GI	Clopidogrel
No 3	M	71	545	3a	GI	Clopidogrel
No 4	M	70	320	3a	Hb drop	Clopidogrel
No 5	M	52	309	3b	GI	Clopidogrel
No 6	M	43	270	3b	Minor surgery	Clopidogrel
No 7	M	63	212	3b	GI	Clopidogrel
No 8	M	74	310	3b	GI	Clopidogrel
No 9	M	80	186	3a	Heavy bruising	Clopidogrel
No 10	F	60	301	2	Mouth	Clopidogrel
No 11	M	52	12	3a	Right arm hematoma	Clopidogrel
No 12	M	51	363	3a	GI	Clopidogrel
No 13	M	47	100	3a	Hb drop	Prasugrel
No 14	F	72	355	3b	Minor surgery	Prasugrel
No 15	M	83	10	3a	Hb drop	Prasugrel
No 16	M	52	160	3a	GI	Prasugrel
No 17	M	65	214	2	Skin (Petechiae)	Prasugrel
No 18	M	68	56	2	Skin wound	Ticagrelor

ICH = intracranial hemorrhage; GI = gastrointestinal; Hb = hemoglobin.

4. Discussion

The most important finding of the index study is the fact that patients with LPR while on DAPT maintenance for 1 month exhibit significantly higher risk for future bleeding events over the next 11 months. The major obstacle, however, is that among 160 (20%) patients with LPR in our study, only 13 of them experienced later bleeding event. Five of 18 patients, moreover, had residual platelet reactivity above the cut-off value for LPR (>139PRU) but still experienced bleeding event. Such complex dichotomization clearly suggests that there are no easy solutions to predict future bleeding risk, and indirectly supports the motion that causes of future bleeding while on DAPT are heterogeneous, and not necessarily exclusively dependent on LNR. Recently, there was an explosion of publications regarding the monitoring of platelet activity

Table 3
Residual platelet reactivity at 1 month DAPT dependent on future bleeding events.

Test	Overall (n = 800)	Bleeding (n = 18)	No-bleeding (n = 782)	P*
VerifyNow, PRU	211 ± 70	85 ± 71	214 ± 88	<0.0001

Between bleeding and no-bleeding groups.
* difference between bleeding and non-bleeding cohorts.