An Optimal Window of Platelet Reactivity by LTA Assay for Patients Undergoing Percutaneous Coronary Intervention

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Abstract

Objective This study was aimed to investigate an optimal therapeutic window for platelet reactivity (PR) to predict the lowest ischemic and bleeding events in patients underwent percutaneous coronary intervention (PCI) and treated with dual antiplatelet agents.

Design A total of 1709 patients who had received coronary stent implantation and had taken aspirin 100 mg in combination with clopidogrel 75 mg daily for >5 days were consecutively recruited and their platelet reactivity was determined by light transmittance aggregometry (LTA). All patients were followed up for 12 months. The primary end-point was the net adverse clinical events (NACE) of cardiovascular death, nonfatal myocardial infarction (MI), target vessel revascularization (TVR), stent thrombosis (ST) and any bleeding.

Result By using the receiver-operating curve (ROC) analysis, the optimal cutoff values were found to be 37.5% and 25.5% respectively in predicting ischemic and bleeding events. Patients were classified into 2 groups according to PR: inside the window group (IW) [adenosine diphosphate (ADP) induced platelet aggregation (PL\textsubscript{ADP} 25.5%-37.4%)] and outside the window group (OW) (PL\textsubscript{ADP} <25.5% or ≥37.5%). The incidence of NACE was 16.8% and 23.1% respectively in the IW and OW group. The hazard ratio of NACE in IW-group was significantly lower [0.69 (95% CI: 0.54–0.89; P = 0.004)] than that in the OW-group during 12 month follow-up.

Conclusion An optimal therapeutic window of 25.5%-37.4% for PL\textsubscript{ADP} predicts the lowest risk of NACE, which could be referred for tailored antiplatelet treatment while using LTA assay.

Trial and clinical registry Trial registration number: ClinicalTrials.gov NCT01968499. Registered 18 October 2013 - Retrospectively registered.

Introduction

Dual antiplatelet therapy with aspirin and an adenosine diphosphate (ADP)-receptor (P2Y\textsubscript{12}) inhibitor is a cornerstone of the pharmacological treatment for patients with coronary artery disease undergoing percutaneous coronary intervention (PCI)[1].

Clopidogrel is one of the most widely used P2Y\textsubscript{12} inhibitor, which undergoes a two-step metabolic transformation before binding to the platelet P2Y\textsubscript{12} receptor[2]. Studies have shown wide variability of platelet clopidogrel response[3], indicating that a substantial proportion of patients have inappropriate platelet inhibition at a regular dose of clopidogrel 75mg once daily. It has been reported that high on-treatment platelet reactivity (HOPR) leads to increased risk of thrombotic events [4–8], while low on-treatment platelet reactivity (LOPR) leads to increased risk of bleeding after PCI [9, 10]. Thus, it is important to identify an optimal platelet inhibition or on-treatment platelet reactivity (PR) by different platelet function tests [11, 12].

This study was to investigate an optimal therapeutic window for PR determined by light transmission aggregometry (LTA) to predict the lowest ischemic and bleeding events in patients underwent PCI and treated with dual antiplatelet agents.

Methods
This is a prospective, single-center, registration study conducted at the First Affiliated Hospital of Nanjing Medical University, Nanjing, China. The study was registered at URL: https://www.clinicaltrials.gov (Unique identifier: NCT01968499) and was approved by the ethics committee of the First Affiliated Hospital of Nanjing Medical University. Written informed consent was obtained from each patient.

**Study population**

Patients who had undergone coronary stent implantation and taken aspirin 100 mg in combination with clopidogrel 75 mg daily for > 5 days were consecutively recruited. Exclusion criteria were patients: 1) intolerant to aspirin or clopidogrel (e.g. history of allergic reactions or gastrointestinal bleeding); 2) taking any other antiplatelet agents in addition to aspirin and clopidogrel (e.g. cilostazol); 3) taking any anticoagulant agents (e.g. vitamin K antagonists, new oral anticoagulants); 4) with myelodysplastic syndrome or abnormal baseline platelet counts of < 80×10^9/L or > 450×10^9/L; 5) with hemoglobin < 90 g/L; 6) with cancer or any other complications that may not suitable to be recruited at the discretion of the investigators.

**Platelet reactivity measurements**

Six milliliter venous blood was collected into 3.2% citrate vacutainer tubes in the morning 2 h after the patients’ taking clopidogrel (if glycoprotein (GP) IIb/IIIa inhibitors were used, testing would be performed 24 h after drug discontinuation). Blood samples were subjected to platelet function test by LTA within 2 h as previously described[13]. In brief, samples were centrifuged at 200g for 8 min to obtain platelet-rich plasma (PRP). Platelet poor plasma (PPP) was prepared by centrifuging the remaining blood at 2465g for 10 min. Platelet counts were adjusted by the addition of PPP to the PRP to achieve a count of 250×10^9/L. ADP (final concentration 5 µmol/L) induced platelet aggregation (PL_{ADP}) was detected using a Chronolog Model 700 aggregometer (Chrono-log Corporation, Havertown, PA, USA).

**Study end-points**

The primary end-point was set as the net adverse clinical events (NACE), a composite of ischemic events including cardiovascular death, nonfatal myocardial infarction (MI), target vessel revascularization (TVR), stent thrombosis (ST) and any bleeding defined by the Thrombolysis in Myocardial Infarction (TIMI) criteria[14]. MI was defined in accordance with the Third Universal Definition proposed in 2007[15]. ST was defined as definite or probable according to the Academic Research Consortium definitions[16]. All the clinical events were independently adjudicated by two investigators blinded to the results of PR tests. Disagreements were resolved by discussion or consultation with a third investigator (Li).

**Statistical analysis**

Statistical analysis was performed using SPSS 22.0 soft-ware (SPSS, Chicago, IL, USA). Continuous variables are expressed as means ± standard deviations (SD) or medians (range [or Inter Quartile Range]). Categorical variables are expressed as frequencies and percentages. Two-sided Mann–Whitney tests were used to compare PL_{ADP} between groups. The time to primary endpoint between groups was compared using the Kaplan–Miller method. Survival curves were compared using the log-rank test and hazard ratios were calculated using Cox’s regression models. Sensitivity and specificity of PL_{ADP} in predicting thrombotic events...
were calculated at different thresholds by receiver-operating curve (ROC) analysis. A two-sided $P < 0.05$ was statistically significant.

**Results**

A total of 1709 eligible patients from April 2011 to October 2016 in the First Affiliated Hospital of Nanjing Medical University underwent PCI were enrolled. There were 45 (2.6%) ischemic events and 328 (19.2%) bleeding events occurred during the 12-month follow up. Ischemic events included 20 deaths, 20 MI, 21 ST and 11 TVR. Bleeding events included 5 major bleeding, 27 minor bleeding and 296 minimal bleeding.

**Relationship between PR and 1-year outcome**

Patients with ischemic events during follow-up had a higher $PL_{ADP}$ level compared to those without (36% [IQR: 25–45] vs. 29% [IQR: 20–40]; $P = 0.054$). ROC analysis was performed to evaluate the value of $PL_{ADP}$ in predicting ischemic events. As a result, a $PL_{ADP}$ cut-off value of 37.5% provided a sensitivity of 48.9%, specificity of 70%, and the largest area under the curve value of 0.58 (Fig. 1a). By comparison, the recommended cutoff value of 46% by LTA provides a sensitivity of 20% and a specificity of 84.3%. While adopting 37.5% as a new cut-off value, 521 patients (30.5%) were defined with HOPR, who experienced a higher rate of ischemic events compared with those without (4.2% vs. 1.9%; $P = 0.007$, Fig. 2a).

On the other hand, patients who experienced bleeding events had significantly lower $PL_{ADP}$ compared with those without bleeding (25% [IQR 18–38] vs. 30% [IQR 21–41]; $P < 0.001$). By ROC analysis, a cut-off value of 25.5% provided a sensitivity of 50.3%, a specificity of 62.6%, and the largest area under the curve of 0.57 in predicting bleedings (Fig. 1b). Using this new cut-off value, 682 (39.9%) patients were defined with LOPR, who experienced a higher rate of bleeding events compared to those without (24.2% vs. 15.8%; $P < 0.001$, Fig. 2b).

The risk of ischemic events and NACE was non-significantly higher in patients with HOPR compared with those in normal responders (4.2% vs. 2.2%; HR 1.99; $P = 0.063$ and 19.8% vs. 16.8%; HR 1.19; $P = 0.247$, for ischemic events and NACE, respectively) (Table 1, Fig. 3), while the risk of total bleeding and NACE was significantly higher in patients with LOPR compared with those in normal responders (24.2% vs. 15.8%; HR 1.61; $P = 0.001$ and 25.7% vs. 16.8%; HR 1.64; $P < 0.001$, for bleeding and NACE, respectively) (Table 1, Fig. 3).
Table 1
Multivariate analysis based on PL$_{\text{ADP}}$ tri-classification

| One-year outcome | PL$_{\text{ADP}}$ | Normal responder* | HOPR† | LOPR‡ |
|------------------|------------------|------------------|-------|-------|
|                  | n (%)            | n (%)            | HR (95% CI) | P     | n (%)            | HR (95% CI) | P     |
| Net clinical outcome | 85 (16.8)        | 103 (19.8)       | 1.19 (0.89, 1.61) | 0.247 | 175 (25.7)       | 1.64 (1.25, 2.14) | 0.000 |
| MACE             | 11 (2.2)         | 22 (4.2)         | 1.99 (0.96, 4.10) | 0.063 | 12 (1.8)         | 0.83 (0.37, 1.89) | 0.660 |
| Death            | 5 (1.0)          | 12 (2.3)         | 2.34 (0.82, 6.66) | 0.111 | 3 (0.4)          | 0.45 (0.11, 1.88) | 0.273 |
| MI               | 5 (1.0)          | 9 (1.7)          | 1.78 (0.60, 5.31) | 0.303 | 6 (0.9)          | 0.93 (0.28, 3.05) | 0.903 |
| ST               | 5 (1.0)          | 11 (2.1)         | 2.23 (0.77, 6.43) | 0.138 | 5 (0.7)          | 0.78 (0.23, 2.70) | 0.693 |
| TVR              | 1 (0.2)          | 6 (1.2)          | 5.86 (0.70, 48.86) | 0.102 | 4 (0.6)          | 3.33 (0.37, 29.89) | 0.282 |
| Bleeding         | 80 (15.8)        | 83 (16.1)        | 0.99 (0.73, 1.36) | 0.967 | 165 (24.2)       | 1.61 (1.23, 2.12) | 0.001 |
| Major + Minor    | 10 (2.0)         | 5 (1.0)          | 0.47 (0.16, 1.39) | 0.172 | 17 (2.5)         | 1.17 (0.53, 2.60) | 0.701 |
| Minimal          | 70 (13.8)        | 78 (15.1)        | 1.09 (0.78, 1.52) | 0.603 | 148 (21.7)       | 1.59 (1.19, 2.13) | 0.002 |

Risk factors included in the analysis of net clinical outcome: Sex, age, BMI, Smoking, Hypertension, Diabetes, CABG history, PCI history, Hemoglobin, Platelet count, eGFR, APTT, INR.

Risk factors included in the analysis of MACE: Sex, Age, BMI, Smoking, Hypertension, Diabetes, CABG history, PCI history.

Risk factors included in the analysis of bleeding: Sex, Age, Hypertension, Diabetes, Hemoglobin, Platelet count, eGFR, INR, APTT.

*Normal responder: 25.5% $\leq$ PL$_{\text{ADP}}$ < 37.5% (control group).

† HOPR: PL$_{\text{ADP}}$ $\geq$ 37.5%.

‡ LOPR: PL$_{\text{ADP}}$ < 25.5%.

PL$_{\text{ADP}}$, ADP induced platelet aggregation; HOPR, high on-treatment platelet reactivity; LOPR, low on-treatment platelet reactivity; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; ST, stent thrombosis; TVR, target vessel revascularization; BMI, body mass index; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; eGFR, estimated glomerular filtration rate; APTT, activated partial thromboplastin time; INR, international normalized ratio.
Optimal PR or therapeutic window of PR to prevent ischemic and bleeding events

According to the ROC curve analysis, we defined an optimal window of PL$_{\text{ADP}}$ between 25.5% and 37.5% after dual antiplatelet treatment. As a result, 29.6% of the study population was comprised within this therapeutic window in this study.

We classified the patients into 2 groups according to PR: inside the window group (IW) [PL$_{\text{ADP}}$(25.5%-37.4%)] and outside the window group (OW) (PL$_{\text{ADP}}$ <25.5% or ≥ 37.5%). The baseline demographic characteristics, clinical, angiographic and biological characteristics and medication history were described in Table 2. There were no significant differences of all the baseline characteristics between the 2 groups.
|                | IW*  | OW†  | P     |
|----------------|------|------|-------|
|                | n = 506 | n = 1203 |       |
| Age            | 65(58,72) | 64(56,71) | 0.104 |
| Gender (%)     | 74.70 | 75.40 | 0.763 |
| BMI (%)        | 24.73(22.84,26.60) | 24.51(22.76,26.54) | 0.702 |
| History of CABG (%) | 1.20 | 0.70 | 0.376 |
| History of PCI (%) | 10.50 | 8.10 | 0.122 |
| Cardiovascular risk factor |       |       |       |
| Smoking (%)    | 46.20 | 46.30 | 0.983 |
| Hypertension (%) | 68.00 | 64.70 | 0.188 |
| Diabetes (%)   | 26.50 | 25.10 | 0.551 |
| Angiography and intervention |       |       |       |
| SYNTAX         | 15(9,21.50) | 15(9,21.50) | 0.44 |
| Length of stent | 39(24,66) | 39(24,62) | 0.856 |
| Number of stent | 2(1,3) | 2(1,3) | 0.737 |
| Biology        |       |       |       |
| HB(g/L)        | 136(125,146) | 136(125,146) | 0.988 |
| PLT (×109)     | 186(157,227) | 186(155,222) | 0.996 |
| LDL (mmol/L)   | 2.57(2.06,3.24) | 2.49(2.04,3.12) | 0.382 |
| eGFR (ml/min.1.732) | 89.51(77.34,103.95) | 89.59(76.43,104.85) | 0.93 |
| APTT (s)       | 25.90(23.50,28.40) | 25.70(23.60,28.20) | 0.787 |
| INR            | 1.02(0.98,1.07) | 1.02(0.98,1.06) | 0.609 |
| Medications    |       |       |       |
| ACEI/ARB (%)   | 57.70 | 56.20 | 0.564 |

* IW: 25.5% ≤ P_{\text{ADP}} < 37.5%.

† OW: P_{\text{ADP}} < 25.5% or ≥ 37.5%.

IW, inside the window; OW, outside the window; BMI, body mass index; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; MACE, major adverse clinical events; HB, Hemoglobin; PLT, platelet count; LDL, low density lipoprotein; eGFR, estimated glomerular filtration rate; APTT, activated partial thromboplastin time; INR, international normalized ratio; ACEI/ARB, angiotension converting enzyme inhibitors/ angiotension receptor blocker; IIb/IIIa, glycoprotein IIb/IIIa inhibitors.
|          | IW* | OW†   | P   |
|----------|-----|-------|-----|
| β blocker (%) | 66.80 | 65.10 | 0.497 |
| Statin (%)     | 96.40 | 96.20 | 0.815 |
| IIb/IIIa (%)   | 2.20  | 1.20  | 0.108 |

* IW: 25.5% ≤ $\text{PL}_{\text{ADP}}$ < 37.5%.
† OW: $\text{PL}_{\text{ADP}}$ < 25.5% or ≥ 37.5%.

IW, inside the window; OW, outside the window; BMI, body mass index; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; MACE, major adverse clinical events; HB, Hemoglobin; PLT, platelet count; LDL, low density lipoprotein; eGFR, estimated glomerular filtration rate; APTT, activated partial thromboplastin time; INR, international normalized ratio; ACEI/ARB, angiotension converting enzyme inhibitors/ angiotension receptor blocker; IIb/IIIa, glycoprotein IIb/IIIa inhibitors.

We further analyzed the prognosis according to new defined therapeutic window. The NACE rate of the IW-group patients was lower than that of the OW-group patients (16.8% vs. 23.1%; $P = 0.004$) (Fig. 2c). Kaplan-Meier analysis showed a significant difference in NACE and bleeding between patients within and outside the window, though no significant difference was found in ischemic events ($P = 0.004$, 0.438 and 0.024 for NACE, ischemic events and bleeding, respectively) (Fig. 4). The hazard ratio of NACE during 12 month follow-up for OW-group was significantly higher [1.44 (95% CI: 1.12–1.85; $P = 0.004$)] compared with IW-group after adjusting for age, gender, body mass index (BMI), history of smoking, hypertension, diabetes, coronary artery bypass grafting (CABG), PCI, hemoglobin, platelet count, estimated glomerular filtration rate (eGFR), activated partial thromboplastin time (APTT), and international normalized ratio (INR) (Table 3).
Table 3
Multivariate analysis based on the therapeutic window

| One-year outcome               | IW† | OW‡ | HR   | 95%CI | P  |
|-------------------------------|-----|-----|------|-------|----|
|                               | n (%) | n (%) |      |       |    |
| Net clinical outcome          | 506  | 1203 | 1.44 | 1.12–1.85 | 0.004 |
| MACE                          | 11(2.2) | 34(2.8) | 1.34 | 0.68–2.64 | 0.403 |
| Death                         | 5(1.0) | 15(1.2) | 1.27 | 0.46–3.51 | 0.640 |
| MI                            | 5(1.0) | 15(1.2) | 1.30 | 0.47–3.59 | 0.608 |
| ST                            | 5(1.0) | 16(1.3) | 1.41 | 0.52–3.87 | 0.500 |
| TVR                           | 1(0.2) | 10(0.8) | 4.49 | 0.57–35.17 | 0.150 |
| Bleeding                      | 80(15.8) | 248(20.6) | 1.33 | 1.03–1.72 | 0.028 |
| Major + Minor                 | 10(2.0) | 221(1.8) | 0.86 | 0.40–1.84 | 0.700 |
| Minimal                       | 70(13.8) | 226(18.8) | 1.38 | 1.05–1.81 | 0.022 |

Risk factors included in the analysis of net clinical outcome: Sex, age, BMI, Smoking, Hypertension, Diabetes, CABG history, PCI history, Hemoglobin, Platelet count, eGFR, APTT, INR.

Risk factors included in the analysis of MACE: Sex, Age, BMI, Smoking, Hypertension, Diabetes, CABG history, PCI history.

Risk factors included in the analysis of bleeding: Sex, Age, Hypertension, Diabetes, Hemoglobin, Platelet count, eGFR, INR, APTT.

* IW: 25.5% ≤ PL<sub>ADP</sub> < 37.5%.

† OW: PL<sub>ADP</sub> < 25.5% or ≥ 37.5%.

Discussion

In this study, we identified an optimal therapeutic window of 25.5% – 37.4% for PL<sub>ADP</sub> as determined by LTA for patients underwent PCI and on the treatment of regular-dose aspirin and clopidogrel, and approximately one third (29.6%) of the patients meet this therapeutic window. Patients inside the window presented significantly lower risk of NACE than those outside the window during 12-month follow-up.

Several studies have tried to identify a threshold of PR that could stratify patients at risk of ischemic events. Bliden et al. [17] found that HOPR (defined as PL<sub>ADP</sub> ≥ 50% measured by LTA with ADP concentration of 5 µmol/L) was the only variable being significantly related to ischemic events after adjusting parameters of hypertension, diabetes and use of calcium channel inhibitors. Gurbel et al. [6] demonstrated that HOPR (defined as PL<sub>ADP</sub> ≥ 46% measured by LTA with ADP concentration of 5 µmol/L) was an independent risk factor for ischemic events within 2 years of non-emergent PCI (OR = 3.9, p < 0.001).
The cutoff value of PL\textsubscript{ADP} in our study is 37.5%, which is lower than the previous study. However, as demonstrated by the GRAVITAS trial, when HOPR was defined as ≥ 230 PRU by VerifyNow P2Y\textsubscript{12} test, high-dose clopidogrel compared with standard-dose clopidogrel did not reduce the incidence of major adverse cardiovascular events[18], while the post-hoc analysis found that the achievement of a PRU < 208 was associated with significantly improved clinical outcomes. Consistent with the GRAVITAS trial, our result suggests that a lower cutoff value of PL\textsubscript{ADP} might bring more low responders to the intensified anti-platelet treatment and consequently reduce more ischemic events.

In addition to recurrent ischemic events, the prognostic importance of bleeding complications following PCI has also been established. ADAPT-DES trial showed that HOPR (defined by > 208 PRU, by VerifyNow P2Y\textsubscript{12} test) was inversely related to TIMI major bleeding (adjusted HR: 0.73, 95% CI: 0.61 to 0.89, p = 0.002)[3]. Studies suggested a possible link between LOPR and bleeding [7–9, 18–23]. With the LTA method, Tsukahara et al[24] found that high-responsiveness was the independent predictor of major bleeding in patients receiving drug-eluting stents and treated with thienopyridine. Parodi et al[25] reported that LOPR (PL\textsubscript{ADP}<40%, 10µmol/L ADP, LTA assay) were the independent predictor of bleeding events. Consistent with previous studies, we confirmed the predictive value of PR on the occurrence of bleeding events after PCI as measured with the LTA assay, and we suggested a cutoff value of PL\textsubscript{ADP}<25.5% to predict the bleeding events.

The optimal therapeutic window of PL\textsubscript{ADP} is uncertain, Campo[26] and Mangiacapra et al[1] have reported two therapeutic windows for PR measured with the VerifyNow P2Y\textsubscript{12} assay. However, in Campo’s study, they reported all clinical events (ischemic and bleeding) after 1 month and up to 1 year of follow-up. Patients with adverse events during the first month were excluded. In Mangiacapra’s study, only short-term outcome of 1-month clinical events were analyzed. By contrast, using the two thresholds for ischemic and bleeding events, we found an optimal therapeutic window for PL\textsubscript{ADP} by LTA assay, ranging from 25.5–37.4%, which was associated with the lowest 1-year incidence of NACE. To the best of our knowledge, our study was the first that use LTA method to demonstrate an optimal therapeutic window for PL\textsubscript{ADP} regarding the 1-year clinical outcome.

Our study has important clinical implications. According to the results, post-PCI evaluation of PR carries important prognostic information, and the antiplatelet treatment should be guided referring to optimal therapeutic window of PR instead of single cutoff value. In particular, for patients with HOPR and higher ischemic risk, more aggressive antiplatelet strategies might be useful. On the other hand, for patients with LOPR and higher bleeding risk, conservative antiplatelet therapies should also be indicated until PR falls within the desired range.

**Conclusion**

An optimal therapeutic window of 25.5%-37.4% for PL\textsubscript{ADP} predicts the lowest risk of net adverse cardiovascular events, which could be referred for tailored antiplatelet treatment while using platelet aggregation assay by light transmittance aggregometry.

**Declarations**
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Conflict of interest

The authors had no conflict of interest to declare.

Availability of data and material

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability

Not applicable.

Authors’ contributions

Jing Wang, Jianzhen Teng and Jiazheng Ma analyzed and interpreted data, and wrote the manuscript; Xiaofeng Zhang, Jing Wang, Qian Gu, Zekang Ye, Inam Ullah, Chuchu Tan, Samee Abdus, Lu Shi and Xiaoxuan Gong provided patients, collected data, and critically reviewed the manuscript; Chunjian Li designed the study and critically reviewed the manuscript. All authors approved the manuscript for submission.

Ethics approval

This study was approved by the ethics committee of the First Affiliated Hospital of Nanjing Medical University based on the Declaration of Helsinki.

Consent to participate

Written informed consent was obtained from each patient.

Consent for publication

Written informed consent for publication was obtained from all participants.

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Figures

**Figure 1**

ROC Curves for Ischemic and Bleeding Events (a) Receiver-operating characteristic (ROC) analysis for ischemic events. (b) ROC analysis for bleeding events. PLADP values are in the opposite direction for the 2 curves. AUC, area under the curve; CI, confidence interval; PLADP, ADP induced platelet aggregation.
Figure 2

Incidence of Ischemic and Bleeding Events Stratified by Platelet Reactivity (a) Ischemic events; (b) Bleeding events; (c) Net adverse clinical events. *p<0.05; **p<0.001. PLADP, ADP induced platelet aggregation; NACE, net adverse clinical events; IW, inside the window; OW, outside the window.
Figure 3

1-year Adverse Events in Groups of Different Level of PLADP Patients were stratified into groups of normal responders (25.5-37.4), HOPR (≥37.5%) and LOPR (<25.5%). **, P value for bleeding events <0.001. ††, P value for NACE <0.001. PLADP, ADP induced platelet aggregation; HOPR, high on-treatment platelet reactivity; LOPR, low on-treatment platelet reactivity; NACE, net adverse clinical events.

Figure 4
Kaplan-Miller Analysis of Clinical Events (a) Ischemic events; (b) Bleeding events; (c) Net adverse clinical events. NACE, net adverse clinical events; IW, inside the window; OW, outside the window.