Total Thrombus-formation Analysis System Predicts Periprocedural Bleeding Events in Patients With Coronary Artery Disease Undergoing Percutaneous Coronary Intervention

Yu Oimatsu, MD; Koichi Kaikita, MD, PhD; Masanobu Ishii, MD; Tatsuro Mitsuse, MD; Miwa Ito, MD; Yuichiro Arima, MD, PhD; Daisuke Sueta, MD, PhD; Aya Takahashi, MT; Satomi Iwashita, MT; Eiichiro Yamamoto, MD, PhD; Sunao Kojima, MD, PhD; Seiji Hokimoto, MD, PhD; Kenichi Tsujita, MD, PhD

**Background**—Periprocedural bleeding events are common after percutaneous coronary intervention. We evaluated the association of periprocedural bleeding events with thrombogenicity, which was measured quantitatively by the Total Thrombus-formation Analysis System equipped with microchips and thrombogenic surfaces (collagen, platelet chip [PL]; collagen plus tissue factor, atheroma chip [AR]).

**Methods and Results**—Between August 2013 and March 2016, 313 consecutive patients with coronary artery disease undergoing elective percutaneous coronary intervention were enrolled. They were divided into those with or without periprocedural bleeding events. We determined the bleeding events as composites of major bleeding events defined by the International Society on Thrombosis and Hemostasis and minor bleeding events (eg, minor hematoma, arteriovenous shunt and pseudoaneurysm). Blood samples obtained at percutaneous coronary intervention were analyzed for thrombus formation area under the curve (PL24-AUC10 for PL chip; AR10-AUC30 for AR chip) by the Total Thrombus-formation Analysis System and P2Y12 reaction unit by the VerifyNow system. Periprocedural bleeding events occurred in 37 patients. PL24-AUC10 levels were significantly lower in patients with such events than those without (P=0.002). Multiple logistic regression analyses showed association between low PL24-AUC10 levels and periprocedural bleeding events (odds ratio, 2.71 [1.22–5.99]; P=0.01) and association between PL24-AUC10 and periprocedural bleeding events in 176 patients of the femoral approach group (odds ratio, 2.88 [1.11–7.49]; P=0.03). However, PL24-AUC10 levels in 127 patients of the radial approach group were not significantly different in patients with or without periprocedural bleeding events.

**Conclusions**—PL24-AUC10 measured by the Total Thrombus-formation Analysis System is a potentially useful predictor of periprocedural bleeding events in coronary artery disease patients undergoing elective percutaneous coronary intervention. (J Am Heart Assoc. 2017;6:e005263. DOI:10.1161/JAHA.116.005263.)

**Key Words:** antiplatelet drug • bleeding • cardiovascular disease • cardiovascular intervention • complication • new device • thrombogenicity
how total antithrombotic effect in which different types of drugs affected might be associated with periprocedural bleeding events in CAD patients undergoing PCI.

The Total Thrombus-formation Analysis System (T-TAS®; Fujimori, Co, Tokyo, Japan), a microchip-based flow chamber system for evaluation of whole-blood thrombogenicity, was recently developed as an easy-to-use system for quantitative analysis of thrombus formation.11,12 Using this system, we reported previously the usefulness of the area under the flow pressure curve under constant flow speed of 10 μL/min until 30 minutes for the atheroma (AR) chip (AR10-AUC30) levels determined by T-TAS®, in the assessment of the pharmacological effects of edoxaban, a direct oral anticoagulant, in patients who undergo total knee arthroplasty,13 and that the AR10-AUC30 level was a significant predictor of the efficacy of vitamin K antagonist and other direct oral anticoagulants.14 We also reported that low AR10-AUC30 level was a significant predictor of periprocedural bleeding events in patients with atrial fibrillation who undergo catheter ablation,14 and that the area under the flow pressure curve under constant flow speed of 10 μL/min until 30 minutes for the platelet (PL) chip (PL24-AUC10) level measured by T-TAS® is a potentially suitable index for the assessment of antiplatelet therapy in CAD patients.15

The present study was designed to determine the association of periprocedural bleeding events with platelet thrombus formation, which was estimated quantitatively by T-TAS®. Our results highlighted the utility of T-TAS® in predicting periprocedural bleeding in CAD patients undergoing PCI.

Methods

Study Population and Protocol

A total of 690 consecutive patients who underwent scheduled coronary angiography at Kumamoto University Hospital between September 2013 and March 2016 were screened in this study. Patients with end-stage renal dysfunction, and those with acute coronary syndrome, defined as acute myocardial infarction (with or without ECG evidence of ST-segment elevation), were not included in this screening. We excluded 365 patients who underwent coronary angiography only whereas the remaining 325 patients who underwent PCI were enrolled in this study. Of the latter group, we excluded patients on antiplatelet therapy other than dual antiplatelet therapy (DAPT) of aspirin and clopidogrel or prasugrel. The remaining 313 patients were the subjects of this study (Figure 1). Blood samples were obtained from the
Table 1. Clinical Characteristics of the Entire Study Population and Patients With and Without Periprocedural Bleeding Events

|                  | Baseline | Events (−) | Events (+) | P Value |
|------------------|----------|------------|------------|---------|
| n                | 313      | 276        | 37         |         |
| Age, y           | 71.1±9.8 | 70.5±10.0  | 75.6±7.0   | 0.003   |
| Male sex         | 226 (72.2)| 200 (72.5) | 26 (70.3)  | 0.7     |
| BMI, kg/m²       | 23.8±3.7 | 24.1±3.6   | 21.4±3.2   | <0.001  |
| History of PCI   | 139 (44.4)| 122 (44.2) | 17 (45.9)  | 0.8     |
| OMI              | 101 (32.3)| 86 (31.2)  | 15 (40.5)  | 0.2     |
| OCI              | 46 (14.7) | 41 (14.9)  | 5 (13.5)   | 0.8     |
| PAD              | 50 (16.0) | 39 (14.1)  | 11 (29.7)  |         |
| Dysplipidemia    | 256 (81.8)| 229 (83.0) | 27 (73.0)  |         |
| Hypertension     | 270 (86.3)| 238 (86.2)| 32 (86.5)  |         |
| CKD              | 142 (45.4)| 126 (45.7)| 16 (43.2)  |         |
| Diabetes mellitus| 178 (56.9)| 163 (59.1) | 15 (40.5)  |         |
| Current smoking  | 43 (13.7) | 41 (14.9)  | 2 (5.4)    |         |
| FH of CAD        | 67 (21.4) | 61 (22.1)  | 6 (16.2)   |         |
| Hemoglobin, g/dL | 13.0±1.8 | 13.1±1.8   | 12.6±1.6   |         |
| Plt, x 10^3      | 207±62   | 210±61     | 182±63     |         |
| APTT, s          | 34.0±12.0| 33.4±7.4   | 38.5±28.3  | 0.01    |
| PT-INR           | 1.10±0.27| 1.09±0.27  | 1.11±0.27  | 0.7     |
| Ln BNP, pg/mL    | 3.84±1.16| 3.82±1.16  | 3.98±1.17  | 0.4     |
| EF, %            | 59.7±9.1 | 59.5±9.0   | 60.8±10.3  |         |
| Nitrates         | 80 (25.6) | 71 (25.7)  | 9 (24.3)   | 0.8     |
| Statins          | 252 (80.5)| 219 (79.3)| 33 (89.2)  |         |
| Beta-blockers    | 185 (59.1)| 165 (59.8)| 20 (54.1)  |         |
| Ca-channel blockers| 180 (57.5)| 164 (59.4)| 16 (43.2)  |         |
| ACEI/ARB         | 191 (61.0)| 169 (61.2)| 22 (59.5)  | 0.8     |
| PPI              | 209 (66.8)| 183 (66.3)| 26 (70.3)  | 0.6     |
| Prasugrel        | 49 (15.7) | 39 (14.1)  | 10 (27.0)  | 0.04    |
| Anticoagulants   | 45 (14.4) | 41 (14.9)  | 4 (10.8)   | 0.5     |
| DAPT loading     | 144 (46.0)| 129 (46.7)| 15 (40.5)  |         |
| Heparin, IU      | 6747±1734| 6759±1731  | 6662±1771  | 0.7     |
| Femoral approach | 176 (56.2)| 150 (54.3)| 26 (70.3)  | 0.06    |
| Procedure duration, minute | 128±41 | 126±40   | 140±48    | 0.09    |
| ACC/AHA type B2/C| 224 (71.8)| 192 (69.8)| 32 (86.5)  | 0.03    |
| PL24-AUC10       | 87.5 (39.7–159.7)| 92.1 (60.2–164.7)| 48.9 (18.2–114.8) | 0.002  |
| AR10-AUC30       | 1678 (1531–1781)| 1686 (1559–1787)| 1575 (1400–1762) | 0.07    |
| PRU              | 234 (181–276)| 232.0 (179–277)| 242 (179–264) | 0.6     |

Data are mean±SD, or n (%), except for PL24-AUC10, AR10-AUC30, and PRU, which are expressed as median and quartile. ACC/AHA type B2/C indicates culprit lesion classified into type B2 or type C according to the American College of Cardiology/American Heart Association definition; ACEI, angiotensin-converting enzyme inhibitor; APTT, activated partial thromboplastin time; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; Ca, calcium; CAD, coronary artery disease; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; EF, ejection fraction; Events, periprocedural bleeding events; FH, family history; Heparin, the amount of unfractionated heparin used during PCI; IU, international unit; OCI, old cerebral infarction; OMI, old myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; Plt, platelet count; PPI, proton pump inhibitor; PRU, P2Y12 reaction units; PT-INR, prothrombin time/international normalized ratio.
femoral vein by the 6-Fr sheath before treatment with unfractionated heparin at the time of the first coronary angiography or PCI. We measured PL24-AUC10 and AR10-AUC30 levels using T-TAS/C226 (n = 311), and P2Y12 reaction units (PRU; n = 274) using VerifyNow (Ultegra rapid platelet function assay; Accumetrics Inc, San Diego, CA) systems.16,17 Patients were divided into 2 groups; those with and without periprocedural bleeding events (see below for definition of periprocedural bleeding events). Each group was also divided into 2 subgroups according to the approach site: femoral approach (n = 176) and radial approach (n = 137).

The study protocol was approved by the human ethics committee of Kumamoto University (Kumamoto, Japan) and informed consent was obtained from each patient or the family of the subject.

Details of DAPT

In the present study, all patients under analysis were being treated with aspirin and clopidogrel or prasugrel. All patients had been treated with 100 mg/day of aspirin from before admission. With regard to patients on clopidogrel, they had been treated with 75 mg/day of clopidogrel (representing the maintenance dose) from before admission or treated with 300 mg of clopidogrel as loading dose the night before their first coronary angiography or PCI. For patients on prasugrel, they had been treated with 3.75 mg/day of prasugrel (representing the maintenance dose used in Japan) from before the admission or treated with 20 mg of prasugrel (representing the loading dose in Japan) the night before their first coronary angiography or PCI.

Definition of Bleeding

All periprocedural bleeding events associated with arterial puncture site occurring on admission were recorded. A TR band (Terumo Corporation, Tokyo, Japan) for hemostasis was applied in patients who underwent puncture of the radial artery, whereas manual compression, Angio-Seal (St. Jude Medical, Inc, Saint Paul, MN), or Perclose ProGlide (Abbott Vascular Co, Abbott Park, IL), was used for vascular closure in patients who underwent puncture of the femoral artery. We defined periprocedural bleeding as a composite of the International Society on Thrombosis and Hemostasis major bleeding,18 access site hematoma required additional manual compression, and hematoma related with arteriovenous shunt or pseudoaneurysm.

Measurement of Thrombogenicity by T-TAS/C226

Details of the method used for measurement of platelet thrombus formation by T-TAS/C226 were reported previously.11,19 To monitor platelet thrombus formation, blood samples were collected into hirudine-anticoagulant tubes, then placed in a reservoir connected to a precision pump. In this study, we measured platelet thrombus formation at a flow rate of 24 µL/min, which represents the area under the curve (AUC) in the first 10 minutes in the platelet chip tested at flow rate of 10 µL/min.

For monitoring white thrombus formation, blood samples were collected into plastic tubes containing 3.2% sodium citrate. Citrated whole blood (480 µL) was mixed with 20 µL of 0.3 mol/L CaCl2 and set into the reservoir. Blood was
pushed into the analytical path, which contained a single capillary channel 300 μm wide × 80 μm deep coated with type I collagen plus tissue thromboplastin. White thrombus formation was monitored by flow pressure changes. The measurement was performed under a constant flow rate of 10 μL/min, corresponding to 600 s⁻¹ for the AR chip (described as AR₁₀-AUC₃₀).

Measurement of Residual Platelet Aggregation

PRU was measured using the VerifyNow system. Blood samples for the P2Y₁₂ cartridge were withdrawn into 1.8-mL blood collection tubes containing 3.2% sodium citrate. In this assay, fibrinogen-coated microparticles were used in the VerifyNow P2Y₁₂ cartridge to bind to available platelet receptors. The results were reported in PRU, which represented the amount of adenosine diphosphate-mediated aggregation specific to the platelet P2Y₁₂ receptor. PRU was determined based on the rate and extent of platelet reactivity in the adenosine diphosphate channel.

Statistical Analysis

Data are expressed as mean±SD. PL₂₄-AUC₁₀, and AR₁₀-AUC₃₀, and PRU are expressed as median and quartile values. Categorical data are presented as frequencies and percentages. We compared the baseline characteristics of patients with and without periprocedural bleeding events using the χ² test for categorical data, and the t test for continuous variables, excluding PL₂₄-AUC₁₀, AR₁₀-AUC₃₀, and PRU as appropriate. The Mann–Whitney U test was used for evaluation of the parameters of T-TAS® and VerifyNow systems. Associations between periprocedural bleeding events and PL₂₄-AUC₁₀, AR₁₀-AUC₃₀, PRU, and various clinical characteristics were analyzed by simple and multiple logistic regression analyses. Multiple regression analyses were performed by using 3 forced inclusion models, including several variables such as age, body mass index (BMI), sex, comorbidities, laboratory data, medication, and procedural characteristics, that were identified as predictors of periprocedural bleeding events in several studies. All statistical procedures were performed by using The Statistical Package for Social Sciences (version 23; IBM Corporation, Armonk, NY).

Results

Patient Characteristics and Frequency of Periprocedural Bleeding Events

Of the 325 study patients, we excluded 12 patients who received DAPT other than aspirin and clopidogrel or prasugrel. Five patients were treated with aspirin only. Six were under DAPT other than aspirin and clopidogrel or prasugrel. One
### Table 2. Clinical Characteristics According to Approach Site

|                   | Femoral Approach (n=176) | Radial Approach (n=137) | P Value |
|-------------------|--------------------------|-------------------------|---------|
|                   | Events (→) n=150         | Events (→) n=26         |         |
| Age, y            | 70.9±9.5                 | 75.2±7.5                | 0.01    |
| Male sex          | 107 (71.3)               | 18 (69.2)               | 0.8     |
| BMI, kg/m²        | 23.9±3.7                 | 21.7±3.5                | 0.007   |
| History of PCI    | 64 (42.7)                | 11 (42.3)               | 0.9     |
| OMI               | 44 (29.3)                | 11 (42.3)               | 0.1     |
| PAD               | 21 (14.0)                | 6 (23.1)                | 0.2     |
| Dyslipidemia      | 122 (81.3)               | 20 (76.9)               | 0.5     |
| Hypertension      | 129 (86.0)               | 23 (88.5)               | 1.0     |
| CKD               | 64 (42.7)                | 13 (50.0)               | 0.4     |
| Diabetes mellitus | 94 (62.7)                | 12 (46.2)               | 0.1     |
| Current smoking   | 22 (14.7)                | 4 (15.4)                | 1.0     |
| FH of CAD         | 31 (20.7)                | 4 (15.4)                | 0.5     |
| Hemoglobin, g/dL  | 13.0±1.7                 | 12.9±1.5                | 0.6     |
| Pt, x10³          | 211±60                   | 188±66                  | 0.1     |
| APTT, s           | 33.8±8.1                 | 41.7±33.3               | 0.01    |
| PT-INR            | 1.08±0.24                | 1.11±0.31               | 0.6     |
| Ln BNP, pg/mL     | 3.80±1.13                | 3.96±1.27               | 0.5     |
| EF, %             | 59.7±7.8                 | 59.4±11.3               | 0.8     |
| Statins           | 122 (81.3)               | 22 (84.6)               | 0.7     |
| Beta-blockers     | 91 (60.7)                | 13 (50.0)               | 0.3     |
| Ca-channel blockers| 91 (60.7)               | 11 (42.3)               | 0.08    |
| ACEI/ARB          | 90 (60.0)                | 15 (57.7)               | 0.8     |
| PPI               | 97 (64.7)                | 17 (65.4)               | 0.9     |
| Prasugrel         | 23 (15.3)                | 7 (26.9)                | 0.1     |
| Anticoagulants    | 23 (15.2)                | 2 (7.7)                 | 0.3     |
| DAPT loading      | 64 (42.7)                | 10 (38.5)               | 0.8     |
| Heparin (IU)      | 6780±1648                | 7154±1759               | 0.3     |
| Sheath size>7Fr   | 117 (78.0)               | 22 (84.6)               | 0.4     |
| Manual compression| 36 (26.3)                | 5 (21.7)                | 0.6     |
| Procedure duration, minute | 128±39 | 142±52 | 0.1 | 123±41 | 135±38 | 0.3 |
| ACC/AHA type B2/C | 127 (84.7)               | 25 (96.2)               | 0.2     |
| PL₂x₁₀·AUC₂₅₀   | 107.4 (57.3–172.2)       | 48.9 (13.5–133.6)       | 0.004   |
| AR₁₀·AUC₃₀₀      | 1687 (1565–1774)         | 1575 (1351–1572)        | 0.1     |
| PRU              | 235 (182–283)            | 225 (159–256)           | 0.3     |

Data are mean±SD, or n (%) except for PL₂x₁₀·AUC₂₅₀, AR₁₀·AUC₃₀₀, and PRU. PL₂x₁₀·AUC₂₅₀, AR₁₀·AUC₃₀₀, and PRU, which are expressed as median and quartile. ACC/AHA type B2/C indicates culprit lesion classified into type B2 or type C according to the American College of Cardiology/American Heart Association definition; ACEI, angiotensin-converting enzyme inhibitor; APTT, activated partial thromboplastin time; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; Ca, calcium; CAD, coronary artery disease; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; EF, ejection fraction; Events, periprocedural bleeding events; FH, family history; Heparin, the amount of unfractionated heparin used during PCI; IU, international unit; OCI, old cerebral infarction; OMI, old myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PII, platelet count; PPI, proton pump inhibitor; PRU, P2Y₁₂ reaction units; PT-INR, prothrombin time/international normalized ratio.
patient received triple antiplatelet therapy. Data of the remaining 313 patients who were on DAPT of aspirin and clopidogrel or prasugrel were analyzed. Patient characteristics are shown in Table 1. Of the 313 patients, 37 (11.8%) developed periprocedural bleeding events, whereas 276 (88.2%) did not suffer such events.

Figure 4. T-TAS® and VerifyNow parameters in patients with and without periprocedural bleeding events who underwent PCI through the femoral approach. A, PL24:AUC10; (B) AR10:AUC30; and (C) PRU. In these box-and-whisker plots, lines within the boxes represent median values; the upper and lower lines of the boxes represent the 25th and 75th percentiles, respectively; and the upper and lower bars outside the boxes represent the maximum and minimum values, respectively. PRU indicates P2Y12 reaction units.

Figure 5. T-TAS® and VerifyNow parameters in patients with and without periprocedural bleeding events who underwent PCI through the radial approach. A, PL24:AUC10; (B) AR10:AUC30; and (C) PRU. In these box-and-whisker plots, lines within the boxes represent median values; the upper and lower lines of the boxes represent the 25th and 75th percentiles, respectively; and the upper and lower bars outside the boxes represent the maximum and minimum values, respectively. PRU indicates P2Y12 reaction units.
Table 3. Results of Simple Regression Analysis for Factors That Correlate With Periprocedural Bleeding Events

| Parameter                                      | OR   | 95% CI  |
|------------------------------------------------|------|---------|
| Old age, >75 y                                 | 2.58 | 1.29–5.18|
| Male                                           | 0.90 | 0.42–1.91|
| Low BMI, <18                                   | 6.20 | 1.86–20.71|
| History of PCI                                 | 1.07 | 0.54–2.14|
| OMI                                            | 1.51 | 0.75–3.05|
| OCl                                            | 0.90 | 0.33–2.43|
| PAD                                            | 2.57 | 1.18–5.62|
| Dyslipidemia                                   | 0.55 | 0.25–1.22|
| Hypertension                                   | 1.02 | 0.38–2.79|
| CKD                                            | 0.91 | 0.45–1.81|
| Diabetes mellitus                              | 0.47 | 0.24–0.95|
| Current smoking                                | 0.33 | 0.08–1.42|
| FH of CAD                                      | 0.68 | 0.27–1.71|
| Hemoglobin, g/dL                               | 0.86 | 0.71–1.05|
| Plt, /10^3                                     | 0.99 | 0.99–1.00|
| APTT, s                                        | 1.02 | 1.00–1.04|
| PT-INR                                         | 1.24 | 0.37–4.14|
| Ln BNP, pg/mL                                  | 1.13 | 0.84–1.51|
| EF, %                                          | 1.02 | 0.98–1.06|
| Nitrates                                       | 0.93 | 0.42–2.06|
| Statins                                        | 2.15 | 0.73–6.31|
| Beta-blockers                                  | 0.79 | 0.40–1.58|
| Ca-channel blockers                            | 0.52 | 0.26–1.04|
| ACEI/ARB                                       | 0.93 | 0.46–1.87|
| PPI                                            | 1.20 | 0.57–2.54|
| Prasugrel                                      | 2.25 | 1.01–5.01|
| Anticoagulants                                 | 0.70 | 0.23–2.07|
| DAPT loading                                    | 0.78 | 0.39–1.56|
| High-dose heparin^1, >7000 IU                  | 1.03 | 0.47–2.23|
| Femoral approach                               | 1.99 | 0.94–4.18|
| Procedure duration, minute                     | 1.01 | 1.00–1.02|
| ACC/AHA type B2/C                              | 2.77 | 1.04–7.35|
| Low PL24-AUC10^*                               | 2.90 | 1.35–6.24|
| Low AR10–AUC30^*                               | 1.90 | 0.93–3.91|
| Low PRU^*                                      | 0.83 | 0.39–1.78|

ACC/AHA type B2/C indicates culprit lesion classified into type B2 or type C according to the American College of Cardiology/American Heart Association definition; ACEI, angiotensin-converting enzyme inhibitor; APTT, activated partial thromboplastin time; ARB, angiotensin receptor blocker; BMI, body mass index; Ca, calcium; CAD, cardiac artery disease; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; EF, ejection fraction; FH, family history; IU, international unit; OCl, old cerebral infarction; OMI, old myocardial infarction; OR, odds ratio; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; Plt, platelet count; PPI, proton pump inhibitor; PT-INR, prothrombin time/international normalized ratio.

^1 Data of this parameter were lower than the median value.

^2 Data of this parameter were higher than the median value.

Patients with periprocedural bleeding events were significantly older, not diabetic with peripheral arterial disease (PAD), and had lower BMI, platelet count and activated partial thromboplastin time, compared with those without. Furthermore, patients with periprocedural bleeding events were more often treated with prasugrel and had more complex culprit lesions classified into type B2 or type C lesion according to the American College of Cardiology/American Heart Association definition^20 than those without.

Among the 313 patients, 176 underwent PCI through the femoral artery. Of these, 150 (85.2%) did not suffer periprocedural bleeding events whereas 26 (14.8%) did. On the other hand, PCI was performed through the radial artery in 137 patients, and 11 (8.0%) developed periprocedural bleeding events, whereas 126 (92.0%) did not. In this study, 84 patients underwent PCIs through both the femoral and radial approaches; but these patients were included in the femoral group and did not develop periprocedural bleeding events associated with the radial approach.

Twelve (3.8%) patients developed major bleeding complications, defined as International Society on Thrombosis and Hemostasis major bleeding, and all underwent PCI through the femoral artery. They included 5 with retroperitoneal bleeding, 5 with major hematoma requiring ≥2 units of transfusion, 1 with pericardial effusion, and 1 required ≥2 units of transfusion attributed to bleeding from undetermined location. Other minor bleeding events occurred in 25 patients (8.0%), including minor hematoma requiring additional manual compression (n=17), minor bleeding requiring additional manual compression (n=5), arteriovenous shunt (n=1), and pseudoaneurysm (n=2). None of the patients suffered ≥2 bleeding events.

T-TAS® Parameters and PRU Levels in Each Group

Figure 2 shows representative time/pressure curve of T-TAS® data in patients with or without periprocedural bleeding events. We measured and evaluated the area under the curve of this time-pressure curve as PL24–AUC10 for the PL chip and AR10–AUC30 for the AR chip. Table 1 and Figure 3 summarize the main parameters of T-TAS® and VerifyNow. PL24–AUC10 levels were significantly lower in patients with periprocedural bleeding events than those without (48.9 [18.2–114.8] versus 92.1 [50.2–164.7]; P=0.002). However, AR10–AUC30 (1575 [1400–1762] versus 1685 [1559–1787]; P=0.07) and PRU levels (242 [179–264] versus 232 [179–277]; P=0.6) were not significantly different between the 2 groups.

Patient Characteristics According to Approach Site

Table 2 lists the clinical characteristics of patients of the femoral and radial approach groups. In the femoral approach...
group, patients with periprocedural bleeding events were significantly older, and had lower BMI and activated partial thromboplastin time, than those without. In the radial approach group, patients with periprocedural bleeding events were significantly older, had lower BMI, PAD, hemoglobin level, and platelet count, and had higher ejection fraction than those without. Furthermore, patients with periprocedural bleeding events were treated with smaller amount of unfractionated heparin than those without.

For the femoral approach group (Table 2 and Figure 4), PL24-AUC10 levels were significantly lower in patients with periprocedural bleeding events compared with those without (48.9 [13.5–133.6] versus 107.4 [57.3–172.2]; \( P = 0.004 \)). However, AR10-AUC30 (1575 [1351–1752] versus 1687 [1565–1774]; \( P = 0.1 \)) and PRU levels (224.5 [159–256] versus 235 [182–283]; \( P = 0.3 \)) were identical in the 2 groups.

For the radial approach group (Table 2 and Figure 5), PL24-AUC10, AR10-AUC30, and PRU levels were identical in patients with and without periprocedural bleeding events (PL24-AUC10: 60.3 [19.7–79.3] versus 83.8 [43.8–161.3]; \( P = 0.2 \); AR-AUC30: 1587 [1490–1772] versus 1683 [1553–1797]; \( P = 0.2 \); PRU: 256 [217–270] versus 232 [175–274]; \( P = 0.6 \)).

Predictors of Periprocedural Bleeding Events

Finally, we used logistic regression analyses to determine the factors that can predict periprocedural bleeding events. The result of simple regression analysis of the entire patients group is shown in Table 3. Simple logistic regression analysis demonstrated that old age, low BMI, PAD, diabetes mellitus, platelet counts, activated partial thromboplastin time, complex culprit lesion, and low PL24-AUC10 level correlated with periprocedural bleeding events. Multiple logistic regression analyses identified low PL24-AUC10 level as a significant predictor of periprocedural bleeding events in 3 forced inclusion models (Table 4), with a Hosmer–Lemeshow goodness-of-fit chi-square of 6.802 (\( P = 0.236 \)) in model 1, 5.068 (\( P = 0.750 \)) in model 2, and 9.840 (\( P = 0.276 \)) in model 3.

The results of simple regression analyses of subgroups are shown in Table 5. In the femoral approach group, simple logistic regression analysis demonstrated that activated partial thromboplastin time and low PL24-AUC10 level correlated with periprocedural bleeding events. In the radial approach group, simple logistic regression analysis demonstrated that old age, low BMI, and PAD were correlated with periprocedural bleeding events. Multiple logistic regression analyses using 3 forced inclusion models identified that only low PL24-AUC10 level was the significant predictor of periprocedural bleeding events of the femoral approach group in all 3 models (Table 6), with a Hosmer–Lemeshow goodness-of-fit chi-square of 1.806 (\( P = 0.614 \)) in model 1, 0.907 (\( P = 0.924 \)) in model 2, and 4.165 (\( P = 0.842 \)) in model 3. We did not perform multiple logistic regression analysis in the radial group because of the small number of periprocedural bleeding events.

Table 4. Results of Multiple Regression Analyses for Factors That Correlate With Periprocedural Bleeding Events

| Predictor                  | Model 1 OR (95% CI) | \( P \) Value | Model 2 OR (95% CI) | \( P \) Value | Model 3 OR (95% CI) | \( P \) Value |
|----------------------------|---------------------|---------------|---------------------|---------------|---------------------|---------------|
| Low PL24-AUC10\*           | 2.71 (1.22–5.99)    | 0.01          | 2.91 (1.30–6.50)    | 0.009         | 3.18 (1.43–7.06)    | 0.005         |
| Low BMI, <18               | 6.43 (1.76–23.46)   | 0.005         |                     |               |                     |               |
| Old age, >75 y             | 2.22 (1.06–4.66)    | 0.03          |                     |               |                     |               |
| Male                       | 1.40 (0.61–3.25)    | 0.4           |                     |               |                     |               |
| PAD                        |                     |               | 3.00 (1.32–6.82)    | 0.009         |                     |               |
| CKD                        |                     |               | 0.65 (0.31–1.38)    | 0.2           |                     |               |
| Hemoglobin, g/dL           | 0.94 (0.75–1.16)    | 0.5           |                     |               |                     |               |
| Prasugrel                  |                     |               | 1.98 (0.86–4.56)    | 0.1           |                     |               |
| Femoral approach           |                     |               | 2.01 (0.93–4.38)    | 0.07          |                     |               |
| Procedure duration         |                     |               | 1.01 (1.00–1.02)    | 0.04          |                     |               |

**BMI** indicates body mass index; **CKD**, chronic kidney disease; **OR** indicates odds ratio; **PAD**, peripheral arterial disease.

\*Data of this parameter were lower than the median value.

Discussion

In the present study, we investigated the association between T-TAS parameters and periprocedural bleeding events in CAD patients who underwent PCI. The main finding of this study is that low PL24-AUC10 level is a significant predictor of periprocedural bleeding events in CAD patients who undergo PCI by the femoral approach. To our best knowledge, this is...
Table 5. Results of Simple Regression Analyses for Factors That Correlate With Periprocedural Bleeding Events According to Approach Site

|                              | Femoral Approach | Radial Approach |
|------------------------------|------------------|-----------------|
|                              | OR   | 95% CI      | OR   | 95% CI      |
| Old age, >75 y               | 2.00 | 0.86–4.63   | 5.15 | 1.30–20.40  |
| Male                         | 0.90 | 0.37–2.24   | 0.95 | 0.24–3.78   |
| Low BMI, <18 kg/m²           | 3.27 | 0.76–14.07  | 27.78 | 2.29–336.36 |
| History of PCI               | 0.99 | 0.42–2.29   | 1.41 | 0.41–4.85   |
| OMI                          | 1.77 | 0.75–4.15   | 1.14 | 0.32–4.12   |
| OCI                          | 1.06 | 0.33–3.37   | 0.56 | 0.07–4.66   |
| PAD                          | 1.84 | 0.66–5.12   | 5.00 | 1.38–18.12  |
| Dyslipidemia                 | 0.77 | 0.28–2.08   | 0.31 | 0.08–1.17   |
| Hypertension                 | 1.25 | 0.34–4.53   | 0.70 | 0.14–3.53   |
| CKD                          | 1.34 | 0.58–3.09   | 0.39 | 0.10–1.53   |
| Diabetes mellitus            | 0.51 | 0.22–1.18   | 0.31 | 0.08–1.22   |
| Current smoking              | 0.49 | 0.11–2.20   | Not applicable |
| FH of CAD                    | 0.70 | 0.22–2.17   | 0.71 | 0.15–3.47   |
| Hemoglobin, g/dL             | 0.95 | 0.74–1.22   | 0.71 | 0.51–1.00   |
| Plt, /10³                    | 0.99 | 0.99–1.00   | 0.99 | 0.97–1.00   |
| APTT, s                      | 1.02 | 1.00–1.05   | 0.94 | 0.83–1.07   |
| PT-INR                       | 1.51 | 0.35–6.59   | 1.01 | 0.12–8.73   |
| Ln BNP, pg/mL                | 1.13 | 0.79–1.62   | 1.15 | 0.69–1.92   |
| EF, %                        | 1.00 | 0.95–1.05   | 1.09 | 0.98–1.22   |
| Nitrates                     | 1.09 | 0.42–2.78   | 0.63 | 0.13–3.05   |
| Statins                      | 1.26 | 0.40–3.95   | Not applicable |
| Beta-blockers                | 0.65 | 0.28–1.50   | 1.23 | 0.34–4.42   |
| Ca-channel blockers          | 0.48 | 0.20–1.11   | 0.61 | 0.18–2.09   |
| ACEI/ARB                     | 0.91 | 0.39–2.11   | 1.04 | 0.29–3.75   |
| PPI                          | 1.03 | 0.43–2.48   | 2.09 | 0.43–10.14  |
| Prasugrel                    | 2.03 | 0.77–5.39   | 2.58 | 0.62–10.74  |
| Anticoagulants               | 0.46 | 0.10–2.08   | 1.33 | 0.27–6.68   |
| DAPT loading                 | 0.84 | 0.36–1.97   | 0.78 | 0.23–2.70   |
| High-dose heparin, >7000 IU  | 1.69 | 0.71–4.03   | 1.02 | 0.42–2.45   |
| Sheath size 7Fr over         | 1.55 | 0.50–4.82   | Not applicable |
| Manual compression           | 0.80 | 0.27–2.25   | Not applicable |
| Procedure duration, minute   | 1.01 | 1.00–1.02   | 1.01 | 0.99–1.02   |
| ACC/AHA type B2/C            | 4.53 | 0.59–35.08  | 1.62 | 0.45–5.80   |
| Low PL24 ± AUC10*            | 2.98 | 1.18–7.56   | 2.84 | 0.72–11.21  |
| Low AR10 ± AUC20*            | 1.93 | 0.80–4.64   | 1.81 | 0.50–6.48   |
| Low PRU*                     | 0.97 | 0.40–2.43   | 0.31 | 0.06–1.58   |

ACC/AHA type B2/C indicates culprit lesion classified into type B2 or type C according to the American College of Cardiology/American Heart Association definition; ACEI, angiotensin-converting enzyme inhibitor; APTT, activated partial thromboplastin time; ARB, angiotensin receptor blocker; BMI, body mass index; Ca, calcium; CAD, cardiac arterial disease; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; EF, ejection fraction; FH, family history; IU, international unit; OI, old cerebral infarction; OMI, old myocardial infarction; OR, odds ratio; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; Plt, platelet count; PPI, proton pump inhibitor; PT-INR, prothrombin time/international normalized ratio.

*Data of this parameter were lower than the median value.
†Data of this parameter were higher than the median value.

DOI: 10.1161/JAHA.116.005283
the first report that describes the usefulness of T-TAS® for prediction of periprocedural bleeding events in CAD patients undergoing PCI. Although the concept of this study was similar to our previous report, the study subjects (atrial fibrillation versus CAD), blood flow conditions of the puncture site (vein versus artery), and type of antithrombotic therapy (antiplatelets versus anticoagulants) are different between 2 studies.

Several factors, including low BMI, age, presence of PAD and diabetes mellitus, female sex, renal dysfunction, and procedural characteristics, have been identified as predictors of periprocedural bleeding events. Furthermore, several studies described the association between platelet reactivity and bleeding events. In a subanalysis of the ADAPT-DES (Assessment of Dual AntiPlatelet Therapy With Drug-Eluting Stents) study, the lowest PRU quintile (PRU<95) was associated with significantly higher risk of clinically relevant bleeding compared with the other 4 groups. Kim et al tested the diagnostic utility of 3 conventional platelet-activity assays (light transmittance aggregometry, VerifyNow, and multiple electrode aggregometry) to define the predictive value of low platelet reactivity for bleeding within 1 year after stenting. They reported that only parameters measured by VerifyNow were independent predictors for bleeding events.

However, to our knowledge, there are no studies that examined the association between total antithrombotic effects of various antithrombotic agents and periprocedural bleeding events because of the difficulty in measuring total thrombogenicity affected by different pharmacological effects. In this study, we found that low levels of PL24-AUC10 at the time of PCI were associated with periprocedural bleeding events in CAD patients. Further studies are needed to confirm the finding that PL24-AUC10 measured by T-TAS® is a potentially useful predictor of periprocedural bleeding events post-PCI in patients with CAD.

In our study, the predictors of periprocedural bleeding events were different between the femoral and radial approach groups. In the femoral approach group, low PL24-AUC10 levels correlated with periprocedural bleeding events in CAD patients who underwent PCI, whereas in the radial approach group, low PL24-AUC10 levels did not correlate with periprocedural bleeding events. In the present study, we used a single standard device for compression in the radial approach group, whereas manual compression or vascular closure devices were used in the femoral approach group. Based on the small number of bleeding events, and no major bleeding events in the radial approach, it is possible that statistical power was not strong enough to select PL24-AUC10 level as a significant predictor of periprocedural bleeding events in the radial approach group. Furthermore, based on the same reasons, it is difficult to conclude that the radial approach is superior to the femoral approach with regard to periprocedural bleeding events.

Our study has several limitations. First, this study was performed in a single center with a relatively small study population. Further multiple center studies that include large numbers of subjects are needed to determine the true association between PL24-AUC10 levels and major periprocedural bleeding events. Second, the study included only a small group of patients who were treated with both antiplatelet and anticoagulant therapies. Further studies are needed to evaluate the association between periprocedural bleeding events and high-risk patients treated with both antiplatelet agents and anticoagulants. Third, we did not evaluate the association between T-TAS® parameters and long-term prognosis in the present study. We need to examine whether PL24-AUC10 levels measured by T-TAS® correlate with long-term bleeding or ischemic events in CAD patients.

Periprocedural bleeding events are associated with adverse clinical events post-PCI in patients with CAD.

**Table 6.** Results of Multiple Regression Analyses for Factors That Correlate With Periprocedural Bleeding Events in the Femoral Approach Group

| Parameter                  | Model 1 OR (95% CI) | P Value | Model 2 OR (95% CI) | P Value | Model 3 OR (95% CI) | P Value |
|----------------------------|---------------------|---------|---------------------|---------|---------------------|---------|
| Low PL24-AUC10*            | 2.88 (1.11–7.49)    | 0.03    | 3.11 (1.21–7.96)    | 0.01    | 4.24 (1.44–12.46)   | 0.009   |
| Male                       | 1.24 (0.46–3.34)    | 0.6     |                     |         |                     |         |
| Low BMI, <18               | 3.50 (0.77–15.85)   | 0.10    |                     |         |                     |         |
| PAD                        | 2.10 (0.72–6.13)    | 0.1     |                     |         |                     |         |
| CKD                        | 1.09 (0.45–2.62)    | 0.8     |                     |         |                     |         |
| Manual compression         |                     |         | 0.46 (0.14–1.59)    | 0.2     |                     |         |
| Procedure duration         | 1.02 (1.00–1.03)    | 0.009   |                     |         |                     |         |

BMI indicates body mass index; CKD, chronic kidney disease; OR, odds ratio; PAD, peripheral arterial disease.

*Data of this parameter were lower than the median value.
undergoing PCI. We might be able to reduce periprocedural bleeding events by detecting patients with high risk of periprocedural bleeding events by using T-TAS®. Previous studies26–28 reported no improvement in the clinical outcome of patients post-PCI by adjusting antithrombotic therapies using VerifyNow. If evidences for the association between parameters of T-TAS® and clinical events in CAD patients are accumulated, monitoring thrombogenicity to adjust antithrombotic therapy for each patient by using T-TAS® would improve the clinical outcome of patients with CAD undergoing PCI.

Conclusions
The results of the present study demonstrated that low PL24% AUC10 level measured by T-TAS® was a significant predictor of periprocedural bleeding events in CAD patients post-PCI, especially in patients who undergo PCI through the femoral approach. T-TAS® is potentially useful for the prediction of periprocedural bleeding events in CAD patients undergoing PCI.

Acknowledgments
We thank Kazuya Hosokawa and Tomoko Ohnishi from the Research Institute, Fujimori Kogyo Co, Yokohama, Kanagawa, Japan, for the excellent technical support in the operating T-TAS®. We also thank all paramedical staff and clinical secretaries for their kind support during this work.

Sources of Funding
This study was supported, in part, by grants-in-aid for Research Service (#15K09089) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Disclosures
None.

References
1. Kwok CS, Khan MA, Rao SV, Kinnaird TD, Sperrinn M, Buchan I, de Belder MA, Ludman PF, Nolan J, Loke YK, Mamas MA. Access and non-access site bleeding after percutaneous coronary intervention and risk of subsequent mortality and major adverse cardiovascular events: systematic review and meta-analysis. Circ Cardiovasc Interv. 2015;8:e001645.
2. Rao SV, Dai D, Subherwal S, Weintraub WS, Brindis RS, Messenger JC, Lopes RD, Peterson ED. Association between periprocedural bleeding and long-term outcomes following percutaneous coronary intervention in older patients. JACC Cardiovasc Interv. 2012;5:958–965.
3. Feit F, Voelz MD, Attubato MJ, Lincoff AM, Chew DP, Bittl JA, Topol EJ, Manoukian SV. Predictors and impact of major hemorrhage on mortality following percutaneous coronary intervention from the REPLACE-2 trial. Am J Cardiol. 2007;100:1364–1369.
4. Kwok CS, Rao SV, Myint PK, Keaveny B, Nolan J, Ludman PF, de Belder MA, Loke YK, Mamas MA. Major bleeding after percutaneous coronary intervention and risk of subsequent mortality: a systematic review and meta-analysis. Open Heart. 2014;1:e000021.
5. Kinnaird TD, Stable E, Mintz GS, Lee CW, Canos DA, Gevorkian N, Pinnow EE, Kent KM, Picard AD, Satler LF, Weisman NJ, Lindsay J, Fuchs S. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. Am J Cardiol. 2003;92:930–935.
6. Subherwal S, Peterson ED, Dai D, Thomas L, Messenger JC, Xian Y, Brindis RG, Feit F, Satler LF, Sperrinn M, Roet MT, Rao SV. Impact of drug-eluting stents on periprocedural bleeding events in CAD patients post-PCI by adjusting antithrombotic therapies using VerifyNow. J Am Coll Cardiol. 2012;59:1861–1869.
7. Vora AN, Rao SV. Bleeding complications after PCI and the role of transradial access. Curr Treat Options Cardiovasc Med. 2014;16:305.
8. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolosky E, Serebruany V, Valgimigli M, Vanneck P, Taggart D, Sabik JF, Cullip DE, Krakoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123:2736–2747.
9. Saito S, Isshiki T, Kimura T, Ogawa H, Yokoi H, Nishikawa M, Miyazaki S, Tanaka Y, Nakamura M. Impact of arterial access route on bleeding complications in Japanese patients undergoing percutaneous coronary intervention. Circ J. 2009;73:941–947.
10. Manoukian SV. Predictors and impact of bleeding complications in percutaneous coronary intervention, acute coronary syndromes, and ST-segment elevation myocardial infarction. Am J Cardiol. 2009;104:9c–15c.
11. Hosokawa K, Ohnishi T, Kondo T, Fukasawa M, Koide T, Maruyama I, Tanaka KA. A novel automated microchip flow-chamber system to quantitatively evaluate thrombus formation and antithrombotic agents under blood flow conditions. J Thromb Haemost. 2011;9:2029–2037.
12. Hosokawa K, Ohnishi T, Sameshima H, Miura N, Ito T, Koide T, Maruyama I. Analysing responses to aspirin and clopidogrel by measuring platelet thrombus formation under arterial flow conditions. Thromb Haemost. 2013;109:102–111.
13. Sueta D, Kaikita K, Okamoto N, Arima Y, Ishii M, Ito M, Oimatsu Y, Iwashita S, Takahashi A, Nakamura E, Hokimoto S, Mizuta H, Ogawa H. A novel quantitative assessment of whole blood thrombogenicity in patients treated with a non-vitamin K oral anticoagulant. Int J Cardiol. 2015;197:98–100.
14. Ito M, Kaikita K, Sueta D, Ishii M, Oimatsu Y, Arima Y, Iwashita S, Takahashi A, Hoshiyama T, Kanazawa H, Sakamoto K, Yamamoto E, Tsujita K, Yamamura M, Kojima S, Hokimoto S, Yamabe H, Ogawa H. Total thrombus-formation analysis system (T-TAS) can predict periprocedural bleeding events in patients undergoing catheter ablation for atrial fibrillation. J Am Heart Assoc. 2016;5:e002744. DOI: 10.1161/JAHA.115.002744.
15. Arima Y, Kaikita K, Ishii M, Ito M, Sueta D, Oimatsu Y, Sakamoto K, Tsujita K, Kojima S, Nagakawa K, Hokimoto S, Yamabe H, Ogawa H. Determination of platelet-derived thrombogenicity with the total thrombus-formation analysis system in coronary artery disease patients receiving antiplatelet therapy. J Thromb Haemost. 2016;14:850–859.
16. Kaikita K, Ono T, Iwashita S, Nakayama N, Sato K, Horio E, Nakamura S, Tsujita K, Tayama M, Sakamoto T, Nakao K, Oshima S, Sugiyama S, Ogawa H. Impact of CYP2C19 polymorphism on platelet function tests and coagulation and inflammatory biomarkers in patients undergoing percutaneous coronary intervention. J Atheroscler Thromb. 2014;21:64–76.
17. Ono T, Kaikita K, Hokimoto S, Iwashita S, Yamamoto K, Miyazaki Y, Horio E, Sato K, Tsujita K, Abe T, Deguchi M, Tayama S, Sumida H, Sugiyama S, Yamabe H, Nakamura S, Nakagawa K, Ogawa H. Determination of cut-off levels for on-clopidogrel platelet aggregation based on functional CYP2C19 gene variants in patients undergoing elective percutaneous coronary intervention. Thromb Res. 2011;128:e130–e136.
18. Schulman S, Angerus U, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in surgical patients. J Thromb Haemost. 2010;8:202–204.
19. Hosokawa K, Ohnishi T, Fukasawa M, Kondo T, Sameshima H, Koide T, Tanaka KA, Maruyama I. A microchip flow-chamber system for quantitative assessment of the platelet thrombus formation process. Microvasc Res. 2012;83:154–161.
20. Ryan TJ, Klocke FJ, Reynolds WA. Clinical competence in percutaneous transluminal coronary angioplasty. A statement for physicians from the ACP/ACC/AHA Task Force on Clinical Privileges in Cardiology. J Am Coll Cardiol. 1990;15:1469–74.
21. Delhaye C, Wakabayashi K, Maluenda G, Belle L, Ben-Dor I, Gonzalez MA, Gaglia MA Jr, Torguson R, Xue Z, Suddath WO, Satler LF, Kent KM, Lindsay J, Picard AD, Waksman R. Body mass index and bleeding complications after percutaneous coronary intervention: does bivalirudin make a difference? Am Heart J. 2010;159:1139–1146.
22. Alexander KP, Chen AY, Newby LK, Schwartz JB, Redberg RF, Hochman JS, Roe MT, Gibler WB, Ohman EM, Peterson ED. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) initiative. Circulation. 2006;114:1380–1387.

23. Maree AO, Margey RJ, Selzer F, Bajrangee A, Jneid H, Marroquin OC, Mulukutla SR, Laskey WK, Jacobs AK. Renal insufficiency, bleeding and prescription of discharge medication in patients undergoing percutaneous coronary intervention in the National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry. Cardiovasc Revasc Med. 2016;17:302–307.

24. Kirtane AJ, Parikh PB, Stuckey TD, Xu K, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann FJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Brodie BR, Mazzaferri EL Jr, Parvataneni R, Maehara A, Genereux P, Mehran R, Stone GW. Is there an ideal level of platelet P2Y12-receptor inhibition in patients undergoing percutaneous coronary intervention?: "Window" analysis from the ADAPT-DES Study (Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents). JACC Cardiovasc Interv. 2015;8:1978–1987.

25. Kim MH, Choi SY, An SY, Serebruany V. Validation of three platelet function tests for bleeding risk stratification during dual antiplatelet therapy following coronary interventions. Clin Cardiol. 2016;39:385–390.

26. Price MJ, Berger PB, Teiristein PS, Tanguay JF, Angiolillo DJ, Spriggs D, Puri S, Robbins M, Garratt KN, Bertrand OF, Stillabower ME, Aragon JR, Kandzari DE, Stenis CT, Lee MS, Manoukian SV, Cannon CP, Schork NJ, Topol EJ. Standard-vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. JAMA. 2011;305:1097–1105.

27. Collet JP, Cuisset T, Range G, Cayla G, Elhadad S, Pouillot C, Henry P, Motreff P, Carrie D, Boueri Z, Belle L, Van Belle E, Rousseau H, Aubry P, Monsegu J, Sabouret P, O'Connor SA, Abtan J, Kerneis M, Saint-Etienne C, Barthelemy O, Beygui F, Silvain J, Vicaut E, Montalescot G. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. N Engl J Med. 2012;367:2100–2109.

28. Cayla G, Cuisset T, Silvain J, Leclercq F, Manzo-Silberman S, Saint-Etienne C, Delarche N, Bellemain-Appaix A, Range G, El Mahmoud R, Carrie D, Belle L, Souteyrand G, Aubry P, Sabouret P, du Fretay XH, Beygui F, Bonnet JL, Lattuca B, Pouillot C, Varenne O, Boueri Z, Van Belle E, Henry P, Motreff P, Elhadad S, Salem JE, Abtan J, Rousseau H, Collet JP, Vicaut E, Montalescot G. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. Lancet. 2016;388:2015–2022.