ORIGINAL RESEARCH

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

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***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 (PL_{24}-AUC_{10} for PL chip; AR_{10}-AUC_{30} 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. PL_{24}-AUC_{10} levels were significantly lower in patients with such events than those without (P=0.002). Multiple logistic regression analyses showed association between low PL_{24}-AUC_{10} levels and periprocedural bleeding events (odds ratio, 2.71 [1.22–5.99]; P=0.01) and association between PL_{24}-AUC_{10} and periprocedural bleeding events in 176 patients of the femoral approach group (odds ratio, 2.88 [1.11–7.49]; P=0.03). However, PL_{24}-AUC_{10} levels in 127 patients of the radial approach group were not significantly different in patients with or without periprocedural bleeding events.

***Conclusions*—**PL_{24}-AUC_{10} 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

Periprocedural bleeding events are one of the most common complications after percutaneous coronary intervention (PCI), and patients with periprocedural bleeding have increased risks of readmission for treatment of recurrent bleeding, major adverse cardiovascular events, and all-cause mortality, compared with those without.[1–5] The incidence rate of periprocedural bleeding for PCI has been reduced by following various bleeding avoidance strategies, such as radial approach, vascular closure devices, and bivalirudin, but the incidence is still relatively high in some studies.[6–8] The incidence rates of major PCI-related periprocedural bleeding in Japanese patients with acute coronary syndrome were reported to be 4.8% for the femoral approach and 1.1% for the radial approach, and those for elective PCI for coronary artery disease (CAD) were reported to be 2.2% for the femoral approach and 0.2% for the radial approach.[9] Previous studies showed that patients' characteristics, clinical presentation, cardiac biomarkers, procedural characteristics, and the choice of antithrombotic therapies were significant periprocedural bleeding risk factors.[3,10] However, it is still unclear

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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 (AR_{10}-AUC_{30}) 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 AR_{10}-AUC_{30} level was a significant predictor of the efficacy of vitamin K antagonist and other direct oral anticoagulants.[14] We also reported that low AR_{10}-AUC_{30} 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 (PL_{24}-AUC_{10}) 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

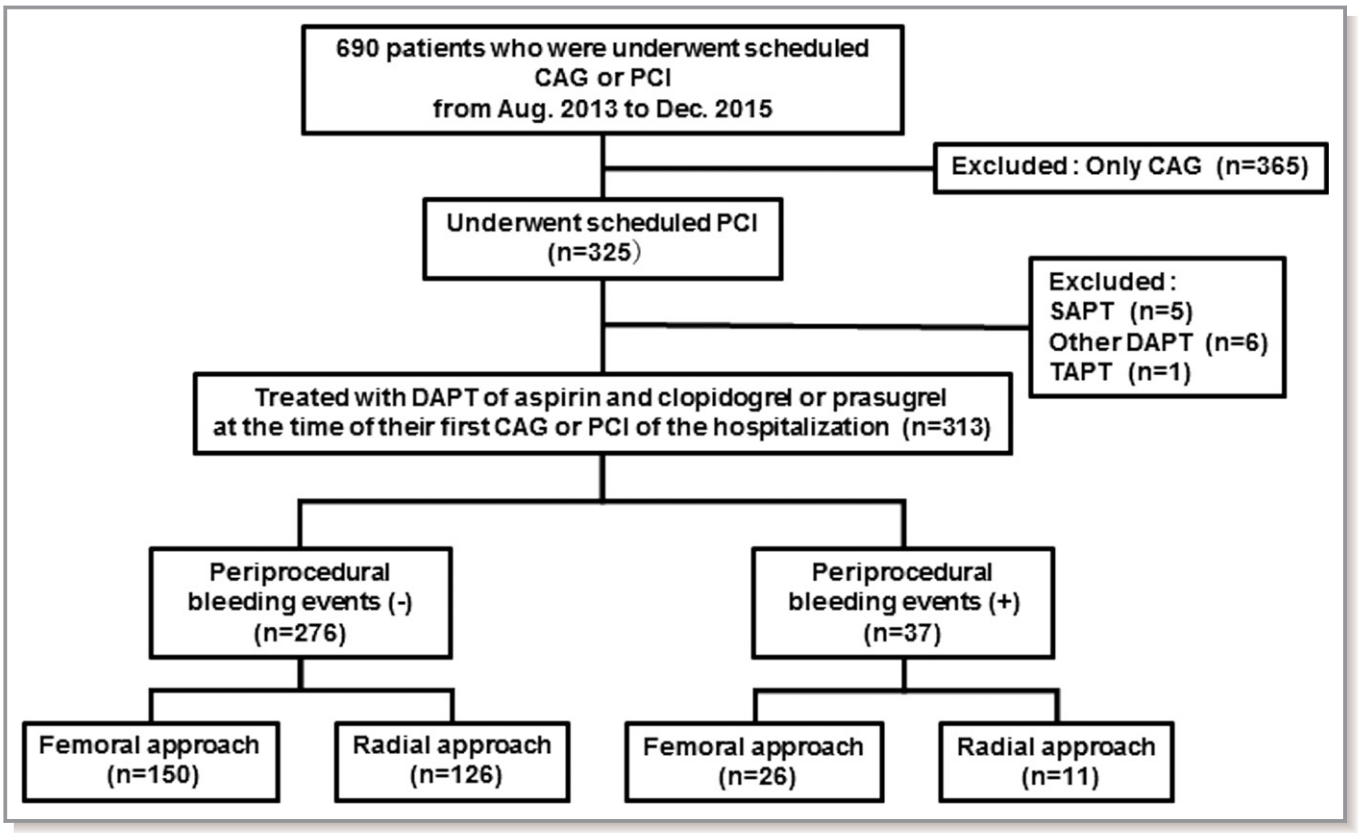

Figure 1. Patient selection process. CAG indicates coronary angiography; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy; TAPT, triple antiplatelet therapy.

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/m^2	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)	0.01
Dyslipidemia	256 (81.8)	229 (83.0)	27 (73.0)	0.1
Hypertension	270 (86.3)	238 (86.2)	32 (86.5)	0.9
CKD	142 (45.4)	126 (45.7)	16 (43.2)	0.7
Diabetes mellitus	178 (56.9)	163 (59.1)	15 (40.5)	0.03
Current smoking	43 (13.7)	41 (14.9)	2 (5.4)	0.1
FH of CAD	67 (21.4)	61 (22.1)	6 (16.2)	0.4
Hemoglobin, g/dL	13.0±1.8	13.1±1.8	12.6±1.6	0.1
Plt, $\times 10^3$	207±62	210±61	182±63	0.01
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	0.4
Nitrates	80 (25.6)	71 (25.7)	9 (24.3)	0.8
Statins	252 (80.5)	219 (79.3)	33 (89.2)	0.1
Beta-blockers	185 (59.1)	165 (59.8)	20 (54.1)	0.5
Ca-channel blockers	180 (57.5)	164 (59.4)	16 (43.2)	0.06
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)	0.4
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
PL_{24}-AUC_{10}	87.5 (39.7–159.7)	92.1 (50.2–164.7)	48.9 (18.2–114.8)	0.002
AR_{10}-AUC_{30}	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 PL_{24}-AUC_{10}, AR_{10}-AUC_{30}, and PRU. PL_{24}-AUC_{10}, AR_{10}-AUC_{30}, 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.

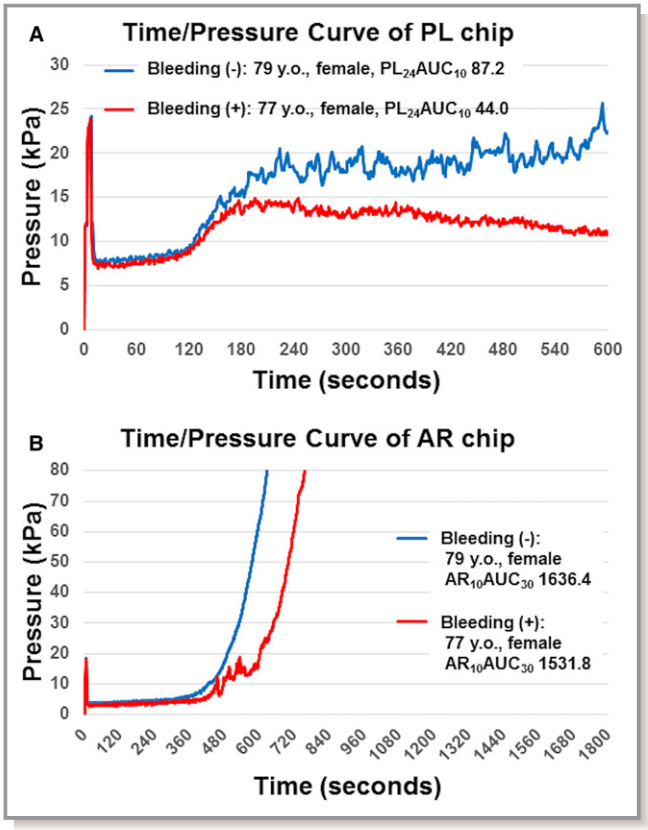

Figure 2. Representative time/pressure curves of T-TAS® of 2 patients without or with periprocedural bleeding events. A, PL chip; (B) AR chip. Thrombogenicity was evaluated by PL_{24}-AUC_{10}, which represents the area under the curve (AUC) in the first 10 minutes in the platelet chip tested at flow rate of 24 μL/min, and AR_{10}-AUC_{30}, which represents the AUC in the first 30 minutes in the atheroma chip tested at flow rate of 10 μL/min.

femoral vein by the 6-Fr sheath before treatment with unfractionated heparin at the time of the first coronary angiography or at the time of PCI. We measured PL_{24}-AUC_{10} and AR_{10}-AUC_{30} levels using T-TAS® (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®

Details of the method used for measurement of platelet thrombus formation by T-TAS® 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 flow rate of 24 μL^{-1}, corresponding to initial shear rates of 2000 s^{-1}. When reaction began, blood flew through the collagen-coated analytical path of the microchip. The analytical path held 25 capillary channels 40 μm wide×40 μm deep coated with type I collagen, and the small platelet aggregates gradually increased in size resulting in increased flow pressure. Flow pressure in the analytical path was measured continuously. We also measured the area under the curve (less than 60 kPa) of flow pressure for 10 minutes after the start of the assay. We described the area under the curve as PL_{24}-AUC_{10}, corresponding to a flow rate of 24 μL/min for the PL chip.

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 $CaCl_2$ and set into the reservoir. Blood was

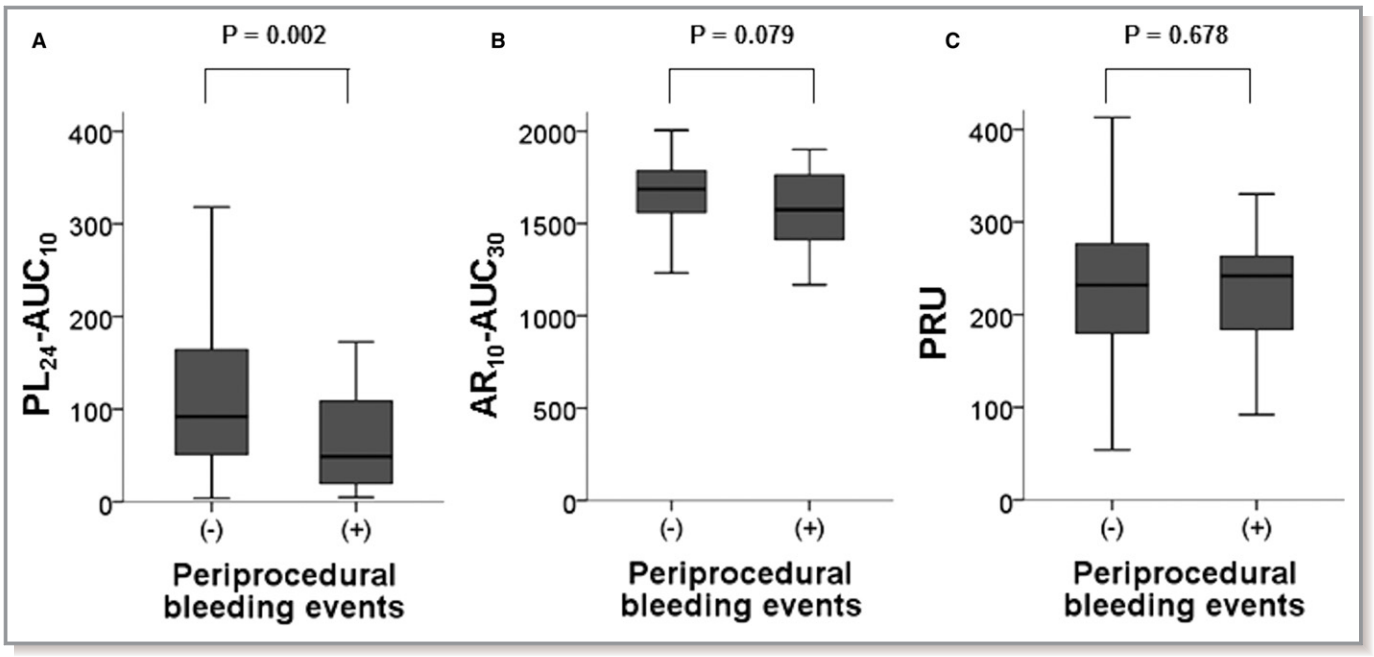

Figure 3. T-TAS® and VerifyNow parameters in patients with or without periprocedural bleeding events. A, PL_{24}-AUC_{10}; (B) AR_{10}-AUC_{30}; and (C) PRU. In these box-and-whisker plots, lines within the boxes represent median values; the upper and lower lines of the boxes represent the 25th and 75th percentiles, respectively; and the upper and lower bars outside the boxes represent the maximum and minimum values, respectively. PRU indicates P2Y12 reaction units.

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 AR_{10}-AUC_{30}).

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. PL_{24}-AUC_{10}, and AR_{10}-AUC_{30}, 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 χ^2 test for categorical data, and the *t* test for continuous variables, excluding PL_{24}-AUC_{10}, AR_{10}-AUC_{30}, 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 PL_{24}-AUC_{10}, AR_{10}-AUC_{30}, 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.[3,5,7,9,10] 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)		
	Events (−) n=150	Events (+) n=26	*P* Value	Events (−) n=126	Events (+) n=11	*P* Value
Age, y	70.9±9.5	75.2±7.5	0.01	70.0±10.6	76.6±6.1	0.005
Male sex	107 (71.3)	18 (69.2)	0.8	92 (73.6)	8 (72.7)	1.0
BMI, kg/m^2	23.9±3.7	21.7±3.5	0.007	24.4±1.9	20.8±2.6	0.001
History of PCI	64 (42.7)	11 (42.3)	0.9	57 (45.6)	6 (54.5)	0.5
OMI	44 (29.3)	11 (42.3)	0.1	42 (33.6)	4(36.4)	1.0
OCI	22 (14.7)	4 (15.4)	1.0	19 (15.2)	1 (9.1)	1.0
PAD	21 (14.0)	6 (23.1)	0.2	18 (14.4)	5 (45.5)	0.02
Dyslipidemia	122 (81.3)	20 (76.9)	0.5	106 (84.8)	7 (63.6)	0.09
Hypertension	129 (86.0)	23 (88.5)	1.0	109 (87.2)	9 (81.8)	0.6
CKD	64 (42.7)	13 (50.0)	0.4	61 (48.8)	3 (27.3)	0.1
Diabetes mellitus	94 (62.7)	12 (46.2)	0.1	68 (54.4)	3 (27.3)	0.08
Current smoking	22 (14.7)	2 (7.7)	0.5	19 (15.2)	0 (0.0)	0.3
FH of CAD	31 (20.7)	4 (15.4)	0.5	30 (24.0)	2 (18.2)	1.0
Hemoglobin, g/dL	13.0±1.7	12.9±1.5	0.6	13.1±1.9	11.9±1.7	0.04
Plt, $\times 10^3$	211±60	188±66	0.1	210±62	167±56	0.03
APTT, s	33.8±8.1	41.7±33.3	0.01	33.0±6.5	31.2±4.9	0.2
PT-INR	1.08±0.24	1.11±0.31	0.6	1.11±0.30	1.11±0.18	0.9
Ln BNP, pg/mL	3.80±1.13	3.96±1.27	0.5	3.84±1.21	4.05±0.94	0.5
EF, %	59.7±7.8	59.4±11.3	0.8	59.2±10.2	64.1±6.6	0.04
Nitrates	38 (25.3)	7 (26.9)	0.8	32 (25.6)	2 (18.2)	0.7
Statins	122 (81.3)	22 (84.6)	0.7	96 (76.8)	11 (100)	0.1
Beta-blockers	91 (60.7)	13 (50.0)	0.3	73 (58.4)	7 (63.6)	1.0
Ca-channel blockers	91 (60.7)	11 (42.3)	0.08	73 (58.4)	5 (45.5)	0.5
ACEI/ARB	90 (60.0)	15 (57.7)	0.8	79 (63.2)	7 (63.6)	1.0
PPI	97 (64.7)	17 (65.4)	0.9	86 (68.8)	9 (81.8)	0.5
Prasugrel	23 (15.3)	7 (26.9)	0.1	16 (12.8)	3 (27.3)	0.1
Anticoagulants	23 (15.2)	2 (7.7)	0.3	18 (14.4)	2 (18.2)	0.6
DAPT loading	64 (42.7)	10 (38.5)	0.8	65 (52.0)	5 (45.5)	0.6
Heparin (IU)	6780±1648	7154±1759	0.3	6734±1832	5500±1204	0.008
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	65 (52.0)	7 (63.6)	0.4
PL_{24}-AUC_{10}	107.4 (57.3–172.2)	48.9 (13.5–133.6)	0.004	83.8 (43.8–161.3)	60.3 (19.7–79.3)	0.2
AR_{10}-AUC_{30}	1687 (1565–1774)	1575 (1351–1752)	0.1	1683 (1553–1797)	1587 (1490–1772)	0.2
PRU	235 (182–283)	225 (159–256)	0.3	232 (175–274)	256 (217–270)	0.6

Data are mean±SD, or n (%) except for PL_{24}-AUC_{10}, AR_{10}-AUC_{30}, and PRU. PL_{24}-AUC_{10}, AR_{10}-AUC_{30}, 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.

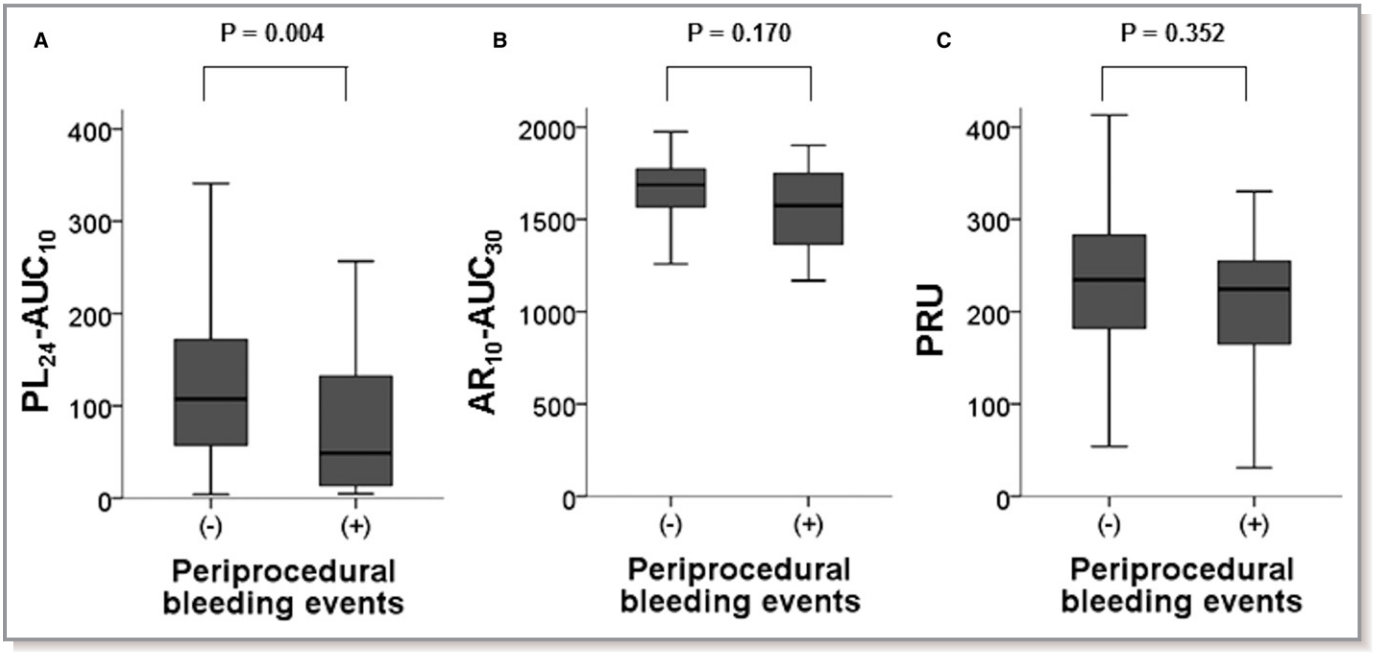

Figure 4. T-TAS® and VerifyNow parameters in patients with and without periprocedural bleeding events who underwent PCI through the femoral approach. A, PL_{24}-AUC_{10}; (B) AR_{10}-AUC_{30}; and (C) PRU. In these box-and-whisker plots, lines within the boxes represent median values; the upper and lower 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.

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.

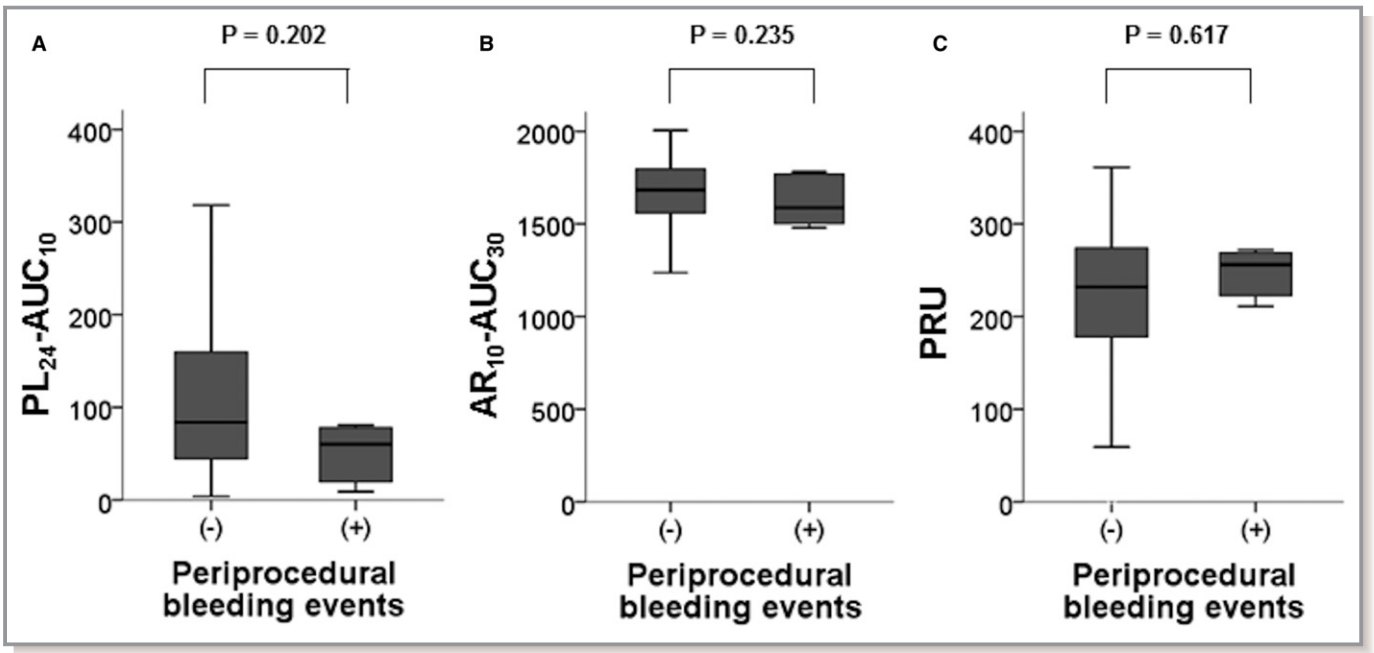

Figure 5. T-TAS® and VerifyNow parameters in patients with and without periprocedural bleeding events who underwent PCI through the radial approach. A, PL_{24}-AUC_{10}; (B) AR_{10}-AUC_{30}; and (C) PRU. In these box-and-whisker plots, lines within the boxes represent median values; the upper and lower 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

	Simple Regression Analysis	
	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
OCI	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†, >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 PL_{24}-AUC_{10}*	2.90	1.35–6.24
Low AR_{10}-AUC_{30}*	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 arterial disease; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; EF, ejection fraction; FH, family history; IU, international unit; OCI, 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.

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 PL_{24}-AUC_{10} for the PL chip and AR_{10}-AUC_{30} for the AR chip. Table 1 and Figure 3 summarize the main parameters of T-TAS® and VerifyNow. PL_{24}-AUC_{10} 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, AR_{10}-AUC_{30} (1575 [1400–1762] versus 1686 [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

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

	Model 1		Model 2		Model 3	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Low PL_{24}-AUC_{10}*	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.

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), PL_{24}-AUC_{10} 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, AR_{10}-AUC_{30} (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), PL_{24}-AUC_{10}, AR_{10}-AUC_{30}, and PRU levels were identical in patients with and without periprocedural bleeding events (PL_{24}-AUC_{10}: 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 legion, and low PL_{24}-AUC_{10} level correlated with periprocedural bleeding events. Multiple logistic regression analyses identified low PL_{24}-AUC_{10} 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 PL_{24}-AUC_{10} 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 PL_{24}-AUC_{10} 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.

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 PL_{24}-AUC_{10} 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/m^2	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, /10^3	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 PL_{24}-AUC_{10}*	2.98	1.18–7.56	2.84	0.72–11.21
Low AR_{10}-AUC_{30}*	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; OCI, old cerebral infarction; OMI, old myocardial infarction; OR, odds ratio; PAD, peripheral arterial diseasel; 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.

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

	Model 1		Model 2		Model 3	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Low PL_{24}-AUC_{10}*	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.

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,[14] the study subjects (atrial fibrillation versus CAD), blood flow conditions of the puncture site (vein versus artery), and type of antithrombotic therapy (anticoagulants versus antiplatelets) are different between 2 studies.

Several factors, including low BMI, old age, presence of PAD and diabetes mellitus, female sex, renal dysfunction, and procedural characteristics, have been identified as predictors of periprocedural bleeding events.[3,5,10,21–23] Furthermore, several studies described the association between platelet reactivity and bleeding events.[24,25] In 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.[24] Kim et al[25] 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 PL_{24}-AUC_{10} at the time of PCI were associated with periprocedural bleeding events in CAD patients. Further studies are needed to confirm the finding that PL_{24}-AUC_{10} 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 PL_{24}-AUC_{10} levels correlated with periprocedural bleeding events in CAD patients who underwent PCI, whereas in the radial approach group, low PL_{24}-AUC_{10} 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 PL_{24}-AUC_{10} 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 PL_{24}-AUC_{10} 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 PL_{24}-AUC_{10} 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

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 studies[26–28] reported no improvement in the clinical outcome of patients post-PCI by adjusting antiplatelet 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 antiplatelet 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 PL_{24}-AUC_{10} 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.

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Disclosures

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