Prognostic Value of the Pattern of Non-Adherence to Anti-Platelet Regimen in Stented Patients (PARIS) Bleeding Risk Score for Long-Term Mortality After Percutaneous Coronary Intervention

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Summary

The Patterns of non-Adherence to Anti-Platelet Regimen in Stented Patients (PARIS) bleeding risk score has been proposed to predict the risk of bleeding events after percutaneous coronary intervention (PCI). However, the prognostic value of the PARIS bleeding risk score for long term all-cause mortality, cardiac mortality and hospitalization due to heart failure has not yet been evaluated. Therefore, the aim of the present study was to evaluate the prognostic value of the PARIS bleeding risk score for all-cause and cardiac mortalities and hospitalization due to heart failure after PCI. Consecutive 1061 patients who had undergone PCI were divided into 3 groups based on the PARIS bleeding risk score; low (n = 112), intermediate (n = 419) and high-risk groups (n = 530). We prospectively followed up the 3 groups for all-cause and cardiac mortalities and hospitalization due to heart failure. Kaplan-Meier analysis revealed that all of the outcomes were highest in the high-risk group among the 3 groups (P < 0.001, P < 0.001 and P < 0.001 respectively). Multivariable Cox proportional hazard analysis, adjusted for confounding factors, revealed that all-cause mortality of the intermediate or high-risk groups was higher than those of the low-risk group (adjusted hazard ratio 6.06 and 12.50, P = 0.013 and P < 0.001, respectively). The PARIS bleeding risk score is a significant indicator of prognosis for all-cause mortality in patients after PCI.

Key words: Coronary artery disease, Prognosis, Risk stratification tool, Cardiac death, All cause death, Hospitalization due to heart failure

Percutaneous coronary intervention (PCI) is a reliable and effective therapeutic option for patients with coronary artery disease (CAD), and has become one of the most widely applied treatments in present-day cardiology. Accurate prediction of adverse events after the PCIs is a feature of contemporary societal guidelines, because the magnitude of risk can aid in therapy selection and form the basis for a precise preprocedural informed consent practice.1-3)

Using dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor inhibitor in patients who have undergone PCIs could reduce the risk for ischemic cardiovascular events. However, this regimen might increase the risk of bleeding.4) Bleeding not only prolongs hospitalization duration and increases the cost of treatment, but also significantly increases the risk for adverse cardiovascular events, including death.5)

The Pattern of non-Adherence to Anti-Platelet Regimen in Stented Patients (PARIS) bleeding risk score6) is a useful tool for predicting the risks of bleeding events in patients who have undergone PCIs. In addition to bleeding events, cardiac death is a more serious cardiovascular event that should be considered after PCI. However, the prognostic value of the PARIS bleeding risk score for all-cause and cardiac mortalities and hospitalization due to heart failure has not yet been evaluated. Therefore, the aim of this study was to evaluate the ability of the PARIS bleeding risk score for predicting all-cause and cardiac mortalities and hospitalization due to heart failure in patients after PCIs.

Methods

Subjects and study protocol: This was an observational study that enrolled a total of 1061 patients who underwent PCI due to stable angina pectoris or acute coronary syndrome (ACS) at Fukushima Medical University Hospital between January 2010 and May 2018. The diagnosis of stable angina pectoris and ACS was made by several cardiologists based on the definition in the cardiovascular
The PARIS bleeding risk score in the present study was calculated according to the risk score for major bleeding events from PARIS.6 The PARIS bleeding score consisted of 6 risk factors: age, body mass index, current smoker, anemia, creatinine clearance < 60 mL/minute, and triple anti-thrombotic therapy at discharge. We added 0 to 4 points depending on age, 0 or 2 points depending on BMI, 0 or 2 points depending on smoking habit, 0 or 3 points depending on anemia, 2 points if creatinine clearance less was than 60 mL/minute, and 2 points if triple therapy was prescribed at discharge.

The range of integer scores was 0 to 14. We divided the patients into 3 groups based on their PARIS bleeding risk score; low (PARIS bleeding risk score < 3, n = 112), intermediate (PARIS bleeding risk score 4-7, n = 419), and high-risk groups (PARIS bleeding risk score ≥ 8, n = 530). We compared the clinical features, laboratory data and parameters of echocardiography, as well as the characteristics of lesions, among the 3 groups.

The patients were followed up until April 2020 for all-cause death, cardiac death, hospitalization due to heart failure, and bleeding events. All-cause death included cardiac death and death from respiratory failure, infection, sepsis, cancer, renal failure, stroke, digestive hemorrhage, and others. Cardiac death was confirmed by independent experienced cardiologists as death either from worsened heart failure, ventricular fibrillation documented by electrocardiography or implantable devices, sudden cardiac death, or acute coronary syndrome. Bleeding events were defined as Bleeding Academic Research Consortium (BARC) 2, 3 and 5.5 Status and dates of death were obtained from the patients’ medical records, the attending physicians at the referring hospital, or the patients or the patients’ families via telephone. Physicians other than attending physicians, who were blinded to the analyses of this study, conducted an investigation. Survival time was calculated from the date of PCI until the date of death. We were able to follow-up all patients, and written informed consent was obtained from all of them. The study protocol was approved by the Ethics Committee of Fukushima Medical University, and was carried out in accordance with the principles outlined in the Declaration of Helsinki. Reporting of the study conforms to Strengthening the Reporting of Observational Studies in Epidemiology along with references to Strengthening the Reporting of Observational Studies in Epidemiology and the broader Enhancing the Quality and Transparency of Health Research guidelines.15

Comorbidities and previous history: Comorbidities were assessed by attending physicians. A smoker was defined as a patient with a current smoking habit or a habit that had been discontinued ≤ 6 months before hospitalization. Hypertension was defined as the recent use of antihypertensive drugs, a systolic blood pressure of ≥ 140 mmHg, and/or a diastolic pressure of ≥ 90 mmHg. Diabetes was defined as the recent use of insulin or antidiabetic drugs, a fasting blood glucose value of ≥ 126 mg/dL, and/or a hemoglobin A1c value of ≥ 6.5%. Dyslipidemia was defined as the recent use of cholesterol-lowering drugs, a triglyceride value of ≥ 150 mg/dL, a low-density lipoprotein (LDL) cholesterol value of ≥ 140 mg/dL, and/or a high-density lipoprotein (HDL) cholesterol value of < 40 mg/dL. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) of < 60 mL/minute/1.73 m² according to the Modification of Diet in Renal Disease formula.11 Anemia was defined as a hemoglobin level of < 12.0 g/dL in females and < 13.0 g/dL in males.12 Atrial fibrillation was identified by an electrocardiogram performed during hospitalization and/or from medical records. The diagnosis of heart failure (HF) was made by several cardiologists based on the guidelines.13

Laboratory data and echocardiography: Blood samples were obtained at admission. Echocardiography was performed using standard techniques by experienced echocardiographers who were blinded to the study. The echocardiographic parameters investigated left ventricular ejection fraction (LVEF) using the modified Simpson’s biplane method. All measurements were performed using ultrasound systems (ACUSON Sequoia, Siemens Medical Solutions USA, Inc, Mountain View, CA, USA).

Lesions and therapies: Multivessel disease is defined as significant stenosis (> 75%) in two or more major coronary arteries (of ≥ 2.5 mm diameter).14 Since the present study was an observational cohort study, revascularization strategy by PCI and optimal medical therapy were selected at each physician’s discretion. Unless serious bleeding complications occurred, the duration of the dual antiplatelet therapy (DAPT) periods was 3 months after bare-metal stent implantation and one year after drug-eluting stent (DES) implantation, regardless of anticoagulation therapy. After that, an aspirin or a P2Y12 inhibitor monotherapy was continued. Triple therapy is defined as the prescription of both DAPT and oral anticoagulants.

Statistical analysis: Statistical analysis was performed using SPSS version 25.0 (SPSS, Armonk, NY, USA). In all analyses, P < 0.05 was taken to indicate statistical significance. Quantitative variables are presented as the mean ± SD. The categorical variables are expressed as numbers and percentages, and the chi-square test was used for comparisons. The Kaplan-Meier method was used for presenting the mortality, with the log-rank test. The prognostic value of the PARIS bleeding risk score was tested by both univariate and multivariate Cox proportional hazard analyses. In the multivariate Cox proportional hazard analyses, the PARIS bleeding risk score was forcedly entered, and thereafter adjusted for clinical factors that were significantly different among the 3 groups in the univariate models, and not included in the criteria of the PARIS bleeding risk score.

Results

Clinical characteristics: The 1061 patients in the study population included 834 men (78.6%) and had a mean age of 68.8 years. Comparisons of clinical characteristics in the low, intermediate, and high-PARIS bleeding risk score groups are shown in Table I. Over 50% of the study population had a PARIS bleeding score of ≥ 8, and were therefore classified as being at high risk of bleeding. The high-risk group was significantly older and had higher prevalences of smokers, previous coronary artery bypass grafting, anemia, CKD, dialysis, peripheral artery disease,
## Table I. Baseline Characteristics of Patients According to PARIS Bleeding Risk Score

|                                | Total  | Low-risk group | Intermediate-risk group | High-risk group | P-value |
|--------------------------------|--------|----------------|------------------------|----------------|---------|
| PARIS bleeding risk score      | 7.4 ± 3.0 | 2.4 ± 0.6 | 5.5 ± 1.0 | 10.0 ± 1.6 | < 0.001 |
| Age, years                     | 68.8 ± 11.3 | 56.4 ± 10.6 | 65.6 ± 10.4 | 73.9 ± 9.0 | < 0.001 |
| Male                           | 834 (78.6%) | 93 (83.0%) | 335 (80.0%) | 406 (76.6%) | 0.221  |
| Body mass index, kg/m²         | 24.2 ± 3.6 | 27.6 ± 2.8 | 24.8 ± 3.6 | 22.9 ± 3.2 | < 0.001 |
| Smoking                        | 702 (66.7%) | 57 (52.3%) | 276 (66.8%) | 369 (69.6%) | 0.002  |
| History of PCI                 | 180 (17.0%) | 14 (12.5%) | 72 (17.2%) | 94 (17.7%) | 0.402  |
| History of CABG                | 37 (3.5%) | 0 (0%) | 10 (2.4%) | 27 (5.1%) | 0.008  |
| History of OMI                 | 89 (8.4%) | 9 (8.0%) | 32 (7.6%) | 48 (9.1%) | 0.728  |
| Co-morbidities                 |        |                |                |                |         |
| Hypertension                   | 902 (85.7%) | 96 (88.1%) | 348 (84.3%) | 458 (86.4%) | 0.491  |
| Diabetes mellitus              | 447 (41.9%) | 41 (37.0%) | 158 (37.4%) | 248 (46.5%) | 0.009  |
| Non-insulin-treated            | 476 (44.9%) | 54 (48.2%) | 203 (48.4%) | 219 (41.3%) |         |
| Insulin-treated                | 65 (6.1%) | 5 (4.6%) | 13 (3.3%) | 48 (9.1%) | 0.009  |
| Dyslipidemia                   | 972 (92.5%) | 108 (99.1%) | 395 (95.6%) | 469 (87.7%) | < 0.001 |
| Anemia                         | 483 (45.9%) | 2 (1.8%) | 49 (11.9%) | 334 (62.1%) | < 0.001 |
| Chronic kidney disease         | 461 (43.8%) | 3 (0.2%) | 99 (24.0%) | 362 (67.7%) | < 0.001 |
| Dialysis                       | 62 (5.9%) | 0 (0%) | 11 (2.7%) | 51 (9.6%) | < 0.001 |
| Peripheral artery disease      | 132 (12.5%) | 4 (3.7%) | 34 (8.2%) | 94 (17.7%) | < 0.001 |
| Heart failure                  | 204 (19.2%) | 4 (3.6%) | 68 (16.2%) | 132 (24.9%) | < 0.001 |
| Atrial fibrillation            | 160 (15.2%) | 8 (7.3%) | 38 (9.2%) | 114 (21.6%) | < 0.001 |
| Clinical presentations         |        |                |                |                | 0.327  |
| Stable angina pectoris         | 535 (50.4%) | 49 (43.8%) | 215 (51.3%) | 271 (51.1%) |         |
| Acute coronary syndrome        | 526 (49.6%) | 63 (56.3%) | 204 (48.7%) | 259 (48.9%) |         |
| Multivessel disease            | 517 (48.7%) | 43 (38.4%) | 186 (44.4%) | 288 (54.3%) | 0.001  |
| Target lesion                  |        |                |                |                | 0.014  |
| RCA                            | 340 (32.0%) | 38 (33.9%) | 124 (29.6%) | 178 (33.6%) |         |
| LAD                            | 492 (46.4%) | 60 (53.6%) | 198 (47.3%) | 234 (44.2%) |         |
| LCX                            | 189 (17.8%) | 11 (9.8%) | 85 (20.3%) | 93 (17.5%) |         |
| LMT                            | 36 (3.4%) | 2 (1.8%) | 12 (2.9%) | 22 (4.2%) |         |
| Graft                          | 3 (0.3%) | 0 | 0 | 3 (0.6%) |         |
| Laboratory data                |        |                |                |                |         |
| White blood cell, ×10⁹/uL       | 8.2 ± 3.6 | 9.2 ± 3.9 | 8.2 ± 3.4 | 8.0 ± 3.6 | 0.009  |
| Hemoglobin, g/dL               | 13.2 ± 1.9 | 14.7 ± 1.2 | 14.0 ± 1.5 | 12.2 ± 1.8 | < 0.001 |
| eGFR, mL/minute/1.73 m²        | 64.0 ± 24.4 | 79.2 ± 17.1 | 72.5 ± 20.0 | 53.9 ± 24.8 | < 0.001 |
| Albumin, g/dL                  | 3.8 ± 0.5 | 4.1 ± 0.3 | 4.0 ± 0.4 | 3.7 ± 0.5 | < 0.001 |
| LDL cholesterol, mg/dL         | 105.5 ± 35.7 | 121.8 ± 44.9 | 107.9 ± 35.2 | 99.9 ± 32.6 | < 0.001 |
| HDL cholesterol, mg/dL         | 49.6 ± 18.8 | 46.8 ± 11.2 | 52.1 ± 21.2 | 48.0 ± 17.7 | 0.020  |
| Triglycerides, mg/dL           | 139.1 ± 116.2 | 159.6 ± 93.5 | 152.3 ± 152.9 | 123.5 ± 76.4 | 0.004  |
| HbA1c, %                       | 6.1 ± 0.0 | 6.3 ± 1.2 | 6.2 ± 1.0 | 6.1 ± 1.0 | 0.188  |
| Echocardiography               |        |                |                |                |         |
| LVEF, %                        | 56.3 ± 12.0 | 56.8 ± 10.7 | 57.6 ± 11.4 | 55.1 ± 12.7 | 0.022  |
| Procedural characteristics     |        |                |                |                |         |
| BMS                            | 128 (12.1%) | 18 (16.1%) | 47 (11.2%) | 63 (49.2%) | 0.369  |
| DES                            | 820 (77.3%) | 81 (72.3%) | 328 (78.3%) | 411 (77.5%) | 0.401  |
| DCB                            | 18 (1.7%) | 1 (0.9%) | 6 (1.4%) | 11 (2.1%) | 0.587  |
| POBA                           | 63 (5.9%) | 7 (6.3%) | 25 (6.0%) | 31 (5.8%) | 0.986  |
| Medications                    |        |                |                |                |         |
| β-blockers                     | 670 (63.1%) | 72 (66.1%) | 259 (62.7%) | 337 (64.1%) | 0.791  |
| RAS inhibitors                 | 797 (75.8%) | 89 (81.7%) | 301 (72.9%) | 407 (76.9%) | 0.115  |
| Statins                        | 879 (83.6%) | 106 (97.2%) | 377 (91.3%) | 396 (74.9%) | < 0.001 |
| Proton pump inhibitors         | 792 (75.4%) | 75 (68.8%) | 300 (72.6%) | 417 (78.8%) | 0.022  |
| Triple therapy at discharge    | 120 (11.3%) | 1 (0.9%) | 33 (7.9%) | 86 (16.2%) | < 0.001 |

BMS indicates bare metal stent; CABG, coronary artery bypass grafting; DCB, drug coated balloon; DES, drug eluting stent; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LDL, low density lipoprotein; LMT, left main trunk; LVEF, left ventricular ejection fraction; OMI, old myocardial infarction; PARIS, the patterns of non-adherence to anti-platelet regimen in stented patients; PCI, percutaneous coronary intervention; POBA, plain old balloon angioplasty; and RCA, right coronary artery.

history of HF, and atrial fibrillation. Moreover, the high-risk group had a lower body mass index and lower prevalence of dyslipidemia, and lower levels of white blood cells, hemoglobin, eGFR, albumin, LDL cholesterol, HDL.
cholesterol, triglycerides and LVEF. Regarding medications, in the high-risk group, significantly fewer patients were prescribed statins and more patients were prescribed triple anti-thrombotic therapy at discharge.

Follow-up: During the follow-up period (mean 1809 days), there were 205 all-cause deaths, including 64 cardiac deaths, 100 hospitalizations due to heart failure and 73 bleeding events. The 64 cardiac deaths included 48 deaths from heart failure, 10 deaths from acute myocardial infarction, and 6 deaths from ventricular arrhythmia. The 73 bleeding events included 49 gastrointestinal hemorrhage, 9 intracranial hemorrhage, 6 nasal bleeding, 5 puncture site bleeding, 2 hematuria, and 2 pulmonary hemorrhages. In the Kaplan-Meier analysis, as shown in the Figure, all of the outcomes were highest in the high-risk group among the 3 groups ($P < 0.001$, $P < 0.001$, $P < 0.001$, respectively).

Cox proportional hazard regression analysis: The Cox proportional hazard analyses of the association of the PARIS bleeding score, which are presented as categorical variables (groups), with all-cause and cardiac mortalities, hospitalization due to heart failure and bleeding events are presented in Table II-V. The PARIS bleeding risk score was revealed to be an independent prognostic factor and the Cox proportional hazard analysis demonstrated that the intermediate or high-risk group had higher risk of all-cause mortality compared with the low-risk group (hazard ratio 6.06, 95% confidence intervals 1.47-25.01, $P = 0.013$, and hazard ratio 12.50, 95% confidence intervals 3.07-50.91, $P < 0.001$, respectively). The Cox proportional hazard analysis demonstrated that the high-risk group had higher risk of hospitalization due to heart failure and bleeding events compared with the low-risk group (hazard ratio 12.50, 95% confidence intervals 1.71-90.94, $P = 0.013$, and hazard ratio 7.86, 95% confidence intervals 1.06-57.94, $P = 0.043$, respectively).

Moreover, we performed the Cox proportional hazard analyses of the association of the PARIS bleeding score, which are presented as continuous variables (per 1-point increase), with all-cause and cardiac mortalities, hospitalization due to heart failure and bleeding events as sensitivity analyses (Supplemental Table). In the multivariable Cox proportional hazard analysis, a high PARIS bleeding score was determined to be an independent predictor of all-cause and cardiac mortalities, hospitalization due to heart failure and bleeding events in patients after PCI, after adjusting for other confounding factors (hazard ratio 1.18 per 1-point increase, 95% confidence intervals 1.10-1.26, $P < 0.001$, hazard ratio 1.14 per 1-point increase, 95% confidence intervals 1.02-1.28, $P = 0.021$, hazard ra-
## Prognostic Value of PARIS Score for Mortality

### Table II. Cox Proportional Hazard Model of PARIS Bleeding Score for All-Cause Mortality

| Variable                              | Univariate analysis | Multivariate analysis* |
|---------------------------------------|---------------------|------------------------|
|                                       | Hazard ratio        | 95% CI                 | P value    | Hazard ratio | 95% CI | P value    |
| PARIS bleeding score                   |                     |                        |            |              |        |            |
| Low-risk group                         | Reference           |                        |            | Reference    |        |            |
| Intermediate-risk group                | 6.82                | 1.65 – 28.11           | 0.008      | 6.06         | 1.47 – 25.01 | 0.013    |
| High-risk group                        | 20.15               | 4.99 – 81.31           | < 0.001    | 12.50        | 3.07 – 50.91 | < 0.001  |
| Age (per 1 year increase)             | 1.06                | 1.04 – 1.07            | < 0.001    |              |        |            |
| Male                                  | 0.90                | 0.70 – 1.36            | 0.902      |              |        |            |
| Body mass index (per 1 kg/m² increase)| 0.88                | 0.84 – 0.92            | < 0.001    |              |        |            |
| Smoking                               | 0.97                | 0.72 – 1.29            | 0.851      |              |        |            |
| History of CABG                       | 0.70                | 0.52 – 0.95            | 0.026      | 0.72         | 0.38 – 1.36 | 0.317    |
| Hypertension                          | 0.83                | 0.54 – 1.29            | 0.419      |              |        |            |
| Diabetes mellitus                     | 1.13                | 0.86 – 1.49            | 0.359      |              |        |            |
| Anemia                                | 3.58                | 2.62 – 4.89            | < 0.001    |              |        |            |
| Chronic kidney disease                | 2.65                | 1.99 – 3.52            | < 0.001    |              |        |            |
| Dialysis                              | 3.45                | 2.32 – 5.11            | < 0.001    |              |        |            |
| Peripheral artery disease             | 1.76                | 1.24 – 2.50            | 0.001      | 1.31         | 0.91 – 1.88 | 0.145    |
| Heart failure                         | 3.03                | 2.29 – 4.01            | < 0.001    | 7.35         | 3.98 – 13.57 | < 0.001  |
| Atrial fibrillation                   | 2.06                | 1.50 – 2.84            | < 0.001    | 1.31         | 0.93 – 1.85 | 0.117    |
| Acute coronary syndrome               | 1.14                | 0.86 – 1.50            | 0.339      |              |        |            |
| Multivessel disease                   | 1.54                | 1.16 – 2.04            | 0.002      | 1.29         | 0.97 – 1.72 | 0.079    |
| LVEF (per 1% increase)                | 0.97                | 0.95 – 0.98            | < 0.001    | 0.98         | 0.97 – 0.99 | 0.007    |
| β-blockers                            | 1.28                | 0.95 – 1.73            | 0.094      |              |        |            |
| RAS inhibitors                        | 0.92                | 0.67 – 1.28            | 0.649      |              |        |            |
| Statins                               | 0.29                | 0.21 – 0.39            | < 0.001    | 0.43         | 0.32 – 0.59 | < 0.001  |

*In the multivariate analysis, PARIS bleeding score was forcedly entered, and thereafter adjusted for history of CABG, peripheral artery disease, heart failure, atrial fibrillation, multivessel disease, LVEF and statins with the forced entry method. CABG indicates coronary artery bypass grafting; CI, confidence interval; LVEF, left ventricular ejection fraction; PARIS, the patterns of non-adherence to anti-platelet regimen in stented patients; and RAS, renin-angiotensin-aldosterone system.

### Table III. Cox Proportional Hazard Model of PARIS Bleeding Score for Cardiac Mortality

| Variable                              | Univariate analysis | Multivariate analysis* |
|---------------------------------------|---------------------|------------------------|
|                                       | Hazard ratio        | 95% CI                 | P value    | Hazard ratio | 95% CI | P value    |
| PARIS bleeding score                   |                     |                        |            |              |        |            |
| Low-risk group                         | Reference           |                        |            | Reference    |        |            |
| Intermediate-risk group                | 4.03                | 0.53 – 30.66           | 0.178      | 3.61         | 0.47 – 27.57 | 0.215    |
| High-risk group                        | 12.24               | 1.69 – 88.71           | 0.013      | 5.63         | 0.75 – 41.98 | 0.092    |
| Age (per 1 year increase)             | 1.04                | 1.01 – 1.06            | 0.001      |              |        |            |
| Male                                  | 1.07                | 0.58 – 1.97            | 0.814      |              |        |            |
| Body mass index (per 1 kg/m² increase)| 0.85                | 0.79 – 0.92            | < 0.001    |              |        |            |
| Smoking                               | 1.16                | 0.68 – 1.99            | 0.579      |              |        |            |
| History of CABG                       | 0.67                | 0.40 – 1.11            | 0.124      |              |        |            |
| Hypertension                          | 0.60                | 0.30 – 1.19            | 0.145      |              |        |            |
| Diabetes mellitus                     | 1.17                | 0.71 – 1.92            | 0.524      |              |        |            |
| Anemia                                | 3.20                | 1.86 – 5.53            | < 0.001    |              |        |            |
| Chronic kidney disease                | 3.04                | 1.80 – 5.14            | < 0.001    |              |        |            |
| Dialysis                              | 3.73                | 1.90 – 7.34            | < 0.001    |              |        |            |
| Peripheral artery disease             | 2.06                | 1.14 – 3.74            | 0.016      | 1.64         | 0.89 – 3.02 | 0.108    |
| Heart failure                         | 2.21                | 1.31 – 3.73            | 0.003      | 20.20        | 9.66 – 42.23 | < 0.001  |
| Atrial fibrillation                   | 2.45                | 1.42 – 4.22            | 0.001      | 1.22         | 0.68 – 2.19 | 0.496    |
| Acute coronary syndrome               | 0.92                | 0.56 – 1.51            | 0.754      |              |        |            |
| Multivessel disease                   | 2.46                | 1.44 – 4.21            | 0.001      | 1.67         | 0.95 – 2.94 | 0.074    |
| LVEF (per 1% increase)                | 0.94                | 0.93 – 0.96            | < 0.001    | 0.96         | 0.94 – 0.98 | < 0.001  |
| β-blockers                            | 2.02                | 1.12 – 3.66            | 0.019      | 1.26         | 0.66 – 2.40 | 0.465    |
| RAS inhibitors                        | 1.14                | 0.62 – 2.10            | 0.659      |              |        |            |
| Statins                               | 0.26                | 0.15 – 0.44            | < 0.001    | 0.50         | 0.29 – 0.86 | 0.014    |

*In the multivariate analysis, PARIS bleeding score was forcedly entered, and thereafter adjusted for peripheral artery disease, heart failure, atrial fibrillation, multivessel disease, LVEF, β-blockers and statins with the forced entry method. CABG indicates coronary artery bypass grafting; CI, confidence interval; LVEF, left ventricular ejection fraction; PARIS, the patterns of non-adherence to anti-platelet regimen in stented patients; and RAS, renin-angiotensin-aldosterone system.
## Table IV. Cox Proportional Hazard Model of PARIS Bleeding Score for Hospitalization Due the Heart Failure

| Variable                                | Univariate analysis | Multivariate analysis* | Hazard ratio | 95% CI      | P value | Hazard ratio | 95% CI      | P value |
|-----------------------------------------|---------------------|------------------------|--------------|-------------|---------|--------------|-------------|---------|
| PARIS bleeding score                    |                     |                        |              |             |         |              |             |         |
| Low-risk group                          | Reference           |                        |              |             |         |              |             |         |
| Intermediate-risk group                 | 5.67                | 0.76 – 42.29           | 0.090        | 5.73        | 0.76 – 42.81 | 0.089 |
| High-risk group                         | 21.74               | 2.98 – 154.45          | 0.002        | 12.50       | 1.71 – 90.94 | 0.013 |
| Age (per 1 year increase)              | 1.05                | 1.03 – 1.07            | < 0.001      |             |         |              |             |         |
| Male                                    | 0.68                | 0.44 – 1.05            | 0.007        |             |         |              |             |         |
| Body mass index (per 1 kg/m² increase) | 0.89                | 0.84 – 0.94            | < 0.001      |             |         |              |             |         |
| Smoking                                 | 0.73                | 0.49 – 1.09            | 0.133        |             |         |              |             |         |
| History of CABG                         | 0.33                | 0.16 – 0.69            | 0.003        | 0.55        | 0.25 – 1.22 | 0.147 |
| Hypertension                            | 0.85                | 0.42 – 1.69            | 0.645        |             |         |              |             |         |
| Diabetes mellitus                       | 1.43                | 0.95 – 2.15            | 0.084        |             |         |              |             |         |
| Anemia                                  | 3.56                | 2.28 – 5.58            | < 0.001      |             |         |              |             |         |
| Chronic kidney disease                  | 5.55                | 3.43 – 9.00            | < 0.001      |             |         |              |             |         |
| Dialysis                                | 1.69                | 0.79 – 3.38            | 0.181        |             |         |              |             |         |
| Peripheral artery disease               | 2.24                | 1.39 – 3.61            | < 0.001      | 1.43        | 0.86 – 2.40 | 0.167 |
| Heart failure                           | 22.92               | 10.43 – 50.37          | < 0.001      | 7.54        | 3.25 – 17.48 | < 0.001 |
| Atrial fibrillation                     | 3.10                | 2.06 – 4.69            | < 0.001      | 1.82        | 1.18 – 2.82 | 0.006 |
| Acute coronary syndrome                 | 1.11                | 0.75 – 1.64            | 0.600        |             |         |              |             |         |
| Multivessel disease                     | 1.66                | 1.10 – 2.50            | 0.015        | 1.27        | 0.83 – 1.96 | 0.265 |
| LVEF (per 1% increase)                  | 0.95                | 0.94 – 0.96            | < 0.001      | 0.97        | 0.96 – 0.99 | 0.003 |
| β-blockers                              | 2.01                | 1.23 – 3.29            | 0.005        | 1.35        | 0.79 – 2.29 | 0.265 |
| RAS inhibitors                          | 1.17                | 0.71 – 1.93            | 0.531        |             |         |              |             |         |
| Statins                                 | 0.36                | 0.23 – 0.56            | < 0.001      | 0.53        | 0.34 – 0.85 | 0.009 |

*In the multivariate analysis, PARIS bleeding score was forcedly entered, and thereafter adjusted for history of CABG, peripheral artery disease, heart failure, atrial fibrillation, multivessel disease, LVEF, β-blockers and statins with the forced entry method. CABG indicates coronary artery bypass grafting; CI, confidence interval; LVEF, left ventricular ejection fraction; PARIS, the patterns of non-adherence to anti-platelet regimen in stented patients; and RAS, renin-angiotensin-aldosterone system.

## Table V. Cox Proportional Hazard Model of PARIS Bleeding Score for Bleeding Events

| Variable                                | Univariate analysis | Multivariate analysis* | Hazard ratio | 95% CI      | P value | Hazard ratio | 95% CI      | P value |
|-----------------------------------------|---------------------|------------------------|--------------|-------------|---------|--------------|-------------|---------|
| PARIS bleeding score                    |                     |                        |              |             |         |              |             |         |
| Low-risk group                          | Reference           |                        |              |             |         |              |             |         |
| Intermediate-risk group                 | 5.82                | 0.78 – 43.40           | 0.086        | 4.93        | 0.65 – 37.00 | 0.120 |
| High-risk group                         | 13.26               | 1.83 – 95.98           | 0.010        | 7.86        | 1.06 – 57.94 | 0.043 |
| Age (per 1 year increase)              | 1.02                | 1.00 – 1.05            | 0.015        |             |         |              |             |         |
| Male                                    | 1.15                | 0.64 – 2.06            | 0.635        |             |         |              |             |         |
| Body mass index (per 1 kg/m² increase) | 0.90                | 0.84 – 0.97            | 0.006        |             |         |              |             |         |
| Smoking                                 | 0.97                | 0.59 – 1.59            | 0.921        |             |         |              |             |         |
| History of CABG                         | 0.34                | 0.15 – 0.79            | 0.013        | 0.36        | 0.15 – 0.89 | 0.028 |
| Hypertension                            | 0.67                | 0.35 – 1.29            | 0.237        |             |         |              |             |         |
| Diabetes mellitus                       | 0.87                | 0.55 – 1.38            | 0.567        |             |         |              |             |         |
| Anemia                                  | 3.31                | 1.98 – 5.55            | < 0.001      |             |         |              |             |         |
| Chronic kidney disease                  | 2.04                | 1.27 – 3.26            | 0.003        |             |         |              |             |         |
| Dialysis                                | 3.92                | 2.10 – 7.29            | < 0.001      |             |         |              |             |         |
| Peripheral artery disease               | 1.05                | 0.52 – 2.11            | 0.883        |             |         |              |             |         |
| Heart failure                           | 2.50                | 1.55 – 4.04            | < 0.001      | 2.05        | 0.60 – 6.97 | 0.250 |
| Atrial fibrillation                     | 2.11                | 1.23 – 3.60            | 0.006        | 1.50        | 0.85 – 2.63 | 0.153 |
| Acute coronary syndrome                 | 1.68                | 1.05 – 2.70            | 0.029        | 2.19        | 1.31 – 3.66 | 0.003 |
| Multivessel disease                     | 1.60                | 1.00 – 2.56            | 0.049        | 1.53        | 0.94 – 2.47 | 0.081 |
| LVEF (per 1% increase)                  | 0.97                | 0.95 – 0.99            | 0.033        | 0.98        | 0.97 – 1.00 | 0.238 |
| β-blockers                              | 1.73                | 1.01 – 2.95            | 0.043        | 1.37        | 0.78 – 2.41 | 0.271 |
| RAS inhibitors                          | 0.90                | 0.52 – 1.53            | 0.706        |             |         |              |             |         |
| Statins                                 | 0.26                | 0.16 – 0.44            | < 0.001      | 0.32        | 0.19 – 0.54 | < 0.001 |

*In the multivariate analysis, PARIS bleeding score was forcedly entered, and thereafter adjusted for history of CABG, heart failure, atrial fibrillation, acute coronary syndrome, multivessel disease, LVEF, β-blockers and statins with the forced entry method. CABG indicates coronary artery bypass grafting; CI, confidence interval; LVEF, left ventricular ejection fraction; PARIS, the patterns of non-adherence to anti-platelet regimen in stented patients; and RAS, renin-angiotensin-aldosterone system.
Discussion

In this study of 1061 patients who underwent PCIs, we studied the predictive value of the PARIS bleeding risk score for all-cause mortality. To the best of our knowledge, the present study is the first to show that long-term all-cause mortality was significantly higher in patients who underwent PCIs with a high PARIS bleeding score than in those with a low score, regardless of other co-morbidities and previous history.

Our results indicate that the risk stratification of the PARIS bleeding risk score could be used to identify those with high risk of death among patients who had undergone PCIs, which is an important value for clinical practice. Identifying these high-risk patients using the PARIS bleeding risk score may help clinicians to strengthen monitoring and treatment, in order to decrease the incidence of adverse events following PCI.

The PARIS bleeding risk score was first described in the 2017 DAPT guidelines, and was reported to be a useful score for predicting the risks of major bleeding events after PCIs. It was important to show the usefulness of the PARIS bleeding risk score for predicting bleeding events in the present study, since the score had never been validated in East-Asian populations. In previous studies, other clinical scores that predict bleeding events after PCI were evaluated in the real world, for different populations, different end points, or different follow-up durations. However, to the best of our knowledge, the PARIS bleeding risk score has not yet been evaluated from the perspective of its predictive value for mortality. Death is obviously the most serious event after PCIs, and it is necessary to identify patients at high risk of death. The content of the PARIS bleeding score is relatively simple and easy to calculate in order not to use angiographical information. Physicians can apply the PARIS bleeding score not only to estimate the risk of major bleeding, but also to evaluate the risk of death for patients after PCIs.

A possible reason why the PARIS bleeding risk score can also predict mortality might be due to the configuration factors used, such as age, body mass index, current smoking, anemia, decreased creatinine clearance rate, and therapy on discharge. These predictors have already reported to be risk factors for poor prognosis in patients with coronary heart disease. Furthermore, bleeding has been reported to be closely associated with mortality after DES implantation. The association between death and bleeding episodes after PCIs might be due to hypotension, anemia, the adverse effects of blood product transfusion, ineffective oxygen delivery, vasoconstriction, platelet dysfunction, or the discontinuation and/or reversal of essential antithrombotic or antiplatelet therapy in some patients.

Until the present time, the risk stratification scores for coronary heart disease, including the Global Registry of Acute Coronary Events score and Thrombolysis in Myocardial Infarction score have been used in ACS patients to estimate mortality for a short period. The overall National Cardiovascular Data Registry model was reported to have a good predictive ability for predicting 30-day mortality in patients after PCIs, however, no long-term follow-up results were reported. Therefore, the present study has the advantages of enrolling all patients who underwent PCI and an extended clinical follow-up.

Our study findings indicate the clinical value of the PARIS bleeding risk score, as well as the possibility for its use in a wide range of applications.

Study limitations: There are several limitations in the present study. First, as a prospective observational cohort study of a single center with a relatively small number of patients, the study may be somewhat underpowered. Second, we used only variables at hospitalization, without taking into consideration changes in medical parameters and post-discharge treatment. Therefore, the present results should only be viewed as preliminary, and thus further studies with a larger population are needed.

Conclusions

In patients with PCIs, a high PARIS bleeding risk score was associated with higher long-term all-cause mortality. Therefore, the PARIS bleeding risk score could be useful not only for the risk stratification of bleeding events after PCIs, but also for predicting all-cause mortality in patients after PCIs.

Disclosure

Conflicts of interest: The authors declare that there are no conflicts of interest.

Data availability: Individual deidentified participant data will not be shared.

References

1. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014; 35: 2541-619.
2. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 130: e344-426.
3. Filh SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 130: 1749-67.
4. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014; 371: 2155-66.
5. Kim YH, Lee JY, Ahn JM, et al. Impact of bleeding on subsequent early and late mortality after drug-eluting stent implantation. JACC Cardiovasc Interv 2011; 4: 423-31.

6. Baber U, Mehran R, Giustino G, et al. Coronary Thrombosis and Major Bleeding After PCI With Drug-Eluting Stents: Risk Scores From PARIS. J Am Coll Cardiol 2016; 67: 2224-34.

7. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol 2000; 36: 970-1062.

8. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012; 33: 2569-619.

9. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011; 123: 2736-47.

10. von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Bmj 2007; 335: 806-8.

11. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006; 145: 247-54.

12. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016; 18: 891-975.

13. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129-200.

14. Cui K, Lyu S, Song X, et al. Long-Term Safety and Efficacy of Staged Percutaneous Coronary Intervention for Patients with ST-Segment Elevation Myocardial Infarction and Multivessel Coronary Disease. Am J Cardiol 2019; 124: 334-42.

15. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018; 39: 213-60.

16. Ando T, Nakazato K, Kimishima Y, et al. The clinical value of the PRECISE-DAPT score in predicting long-term prognosis in patients with acute myocardial infarction. Int J Cardiol Heart Vasc 2020; 29: 100552.

17. Tanaka S, Sakata R, Marui A, et al. Predicting long-term mortality after first coronary revascularization: - the Kyoto model -. Circ J 2012; 76: 328-34.

18. Nammas W, Kiviiniemi T, Schlitt A, et al. Value of DAPT score to predict adverse outcome in patients with atrial fibrillation undergoing percutaneous coronary intervention: A post-hoc analysis from the AFCAS registry. Int J Cardiol 2018; 253: 35-9.

19. Généreux P, Giustino G, Witzenbichler B, et al. Incidence, Predictors, and Impact of Post-Discharge Bleeding After Percutaneous Coronary Intervention. J Am Coll Cardiol 2015; 66: 1036-45.

20. Ndrepepa G, Fusaro M, Cassese S, et al. Relation of body mass index to bleeding during percutaneous coronary interventions. Am J Cardiol 2015; 115: 434-40.

21. Ma WQ, Wang Y, Sun XJ, et al. Impact of smoking on all-cause mortality and cardiovascular events in patients after coronary revascularization with a percutaneous coronary intervention or coronary artery bypass graft: a systematic review and meta-analysis. Coron Artery Dis 2019; 30: 367-76.

22. Lee PC, Kini AS, Ahsan C, et al. Anemia is an independent predictor of mortality after percutaneous coronary intervention. J Am Coll Cardiol 2004; 44: 541-6.

23. Voelzt MD, Patel AD, Feit F, et al. Effect of anemia on hemorrhagic complications and mortality following percutaneous coronary intervention. Am J Cardiol 2007; 99: 1513-7.

24. Kwok CS, Tiong D, Pradhan A, et al. Meta-Analysis of the Prognostic Impact of Anemia in Patients Undergoing Percutaneous Coronary Intervention. Am J Cardiol 2016; 118: 610-20.

25. Cai Q, Mukku VK, Ahmad M. Coronary artery disease in patients with chronic kidney disease: a clinical update. Curr Cardiol Rev 2013; 9: 331-9.

26. Lee JM, Kang J, Lee E, et al. Chronic Kidney Disease in the Second-Generation Drug-Eluting Stent Era: Pooled Analysis of the Korean Multicenter Drug-Eluting Stent Registry. JACC Cardiovasc Interv 2016; 9: 2097-109.

27. Wang TY, Xiao L, Alexander KP, et al. Antiplatelet therapy use after discharge among acute myocardial infarction patients with in-hospital bleeding. Circulation 2008; 118: 2139-45.

28. Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). Bmj 2006; 333: 1091.

29. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med 2003; 163: 2345-53.

30. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. Jama 2000; 284: 835-42.

31. Peterson ED, Dai D, DeLong ER, et al. Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588,398 procedures in the National Cardiovascular Data Registry. J Am Coll Cardiol 2010; 55: 1923-32.

Supplemental Files
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