

Prediction of Thrombotic and Bleeding Events After Percutaneous Coronary Intervention: CREDO-Kyoto Thrombotic and Bleeding Risk Scores

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Background—Prediction of thrombotic and bleeding risk is important to optimize antithrombotic therapy after percutaneous coronary intervention.

Methods and Results—We developed the prediction rules for thrombotic and bleeding events separately in Japanese patients. Derivation and validation cohorts consisted of 4778 patients from CREDO-Kyoto (Coronary Revascularization Demonstrating Outcome Study in Kyoto) registry cohort 2 and 4669 patients from RESET (Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent Trial) and NEXT (Nobori Biolimus-Eluting Versus Xience/Promus Everolimus-Eluting Stent Trial). Primary thrombotic and bleeding events were a composite of myocardial infarction, definite or probable stent thrombosis or ischemic stroke, and GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) moderate or severe bleeding. The prediction rule for thrombosis assigned 2 points for severe chronic kidney disease, atrial fibrillation, peripheral vascular disease, and anemia and 1 point for age ≥ 75 years, heart failure, diabetes mellitus, and chronic total occlusion. The prediction rule for bleeding assigned 2 points for thrombocytopenia, severe chronic kidney disease, peripheral vascular disease, and heart failure and 1 point for prior myocardial infarction, malignancy, and atrial fibrillation. In derivation and validation cohorts, area under the curve was 0.68 and 0.64, respectively, for thrombosis and 0.66 and 0.66, respectively, for bleeding. In the validation cohort, a high thrombosis risk score (≥ 4 , $n=682$) was associated with higher 3-year incidence of thrombotic events than a score that was intermediate (2–3, $n=1178$) or low (0–1, $n=2809$) (7.6%, 3.7%, versus 2.4%, respectively; $P<0.0001$). A high bleeding risk score (≥ 3 , $n=666$) was associated with higher incidence of bleeding than scores that were intermediate (1–2, $n=1802$) or low (0, $n=2201$) (8.8%, 4.1%, versus 2.3%, respectively; $P<0.0001$). Among 682 patients at high thrombotic risk, only 39 (5.7%) had low bleeding risk, whereas 401 (58.8%) had high bleeding risk with very high incidence of bleeding (11.6%).

Conclusions—CREDO-Kyoto thrombotic and bleeding risk scores demonstrated modest accuracy in stratifying thrombotic and bleeding risks; however, a large proportion of patients at high thrombotic risk also had high bleeding risk. (*J Am Heart Assoc.* 2018;7:e008708. DOI: 10.1161/JAHA.118.008708.)

Key Words: bleeding • coronary artery disease • thrombosis

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An accompanying Appendix S1 is available at <http://jaha.ahajournals.org/content/7/11/e008708/DC1/embed/inline-supplementary-material-1.pdf>

*A complete list of the CREDO-Kyoto PCI/CABG Registry Cohort 2, RESET, and NEXT trial investigators is provided in Appendix S1.

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Clinical Perspective

What Is New?

- CREDO-Kyoto (Coronary Revascularization Demonstrating Outcome Study in Kyoto) thrombotic and bleeding risk scores demonstrated modest accuracy in stratifying thrombotic risk and bleeding risk separately in the derivation and validation cohorts of Japanese patients.
- Reflecting the overlap of the risk predictors for thrombosis and bleeding, a large proportion of patients at high thrombotic risk also had high bleeding risk, and their bleeding event rate was very high.

What Are the Clinical Implications?

- Our results would provide clinicians determining treatment strategies for antithrombotic therapy with individual risks of thrombotic and bleeding events after percutaneous coronary intervention.
- Further studies are warranted to explore optimal antithrombotic therapy in the population at high thrombotic risk for which bleeding risk is also substantial.

Prolonged duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) was shown to significantly reduce the risk of myocardial infarction (MI) and stent thrombosis (ST) compared with aspirin monotherapy in the DAPT (Dual Antiplatelet Therapy) trial.¹ However, prolonged DAPT was also associated with higher risk of bleeding events and marginally higher mortality risk. In meta-analyses including the DAPT trial, risks of bleeding and mortality were significantly higher in the long DAPT group compared with the short DAPT group.^{2,3} These results suggest that predicting the risk of thrombotic and bleeding events is important for determining the intensity of antithrombotic therapy, including the duration of DAPT after PCI in individual patients. The DAPT score was developed to differentiate between ischemic high-risk patients and bleeding high-risk patients by using a single scoring system: within the DAPT study, it successfully identified those patients who could benefit from prolonged DAPT without excess bleeding risk.⁴ The DAPT study, however, excluded those patients who had bleeding events in the first year after PCI; therefore, the DAPT score can be applied only to those bleeding low-risk patients who could tolerate DAPT for 1 year after PCI. Risk prediction of thrombotic and bleeding events is more important just after PCI than after 1 year. Moreover, patients with high thrombotic risk were also reported to have high bleeding risk.⁵ It has not been yet adequately addressed whether the use of a single scoring system for evaluating both thrombotic and bleeding risk is superior to the use of scoring systems dedicated to evaluating thrombotic and bleeding risk separately.

We sought to develop the prediction rules for the thrombotic events and the bleeding events separately in a large Japanese observational database of patients undergoing first coronary revascularization and to validate the developed risk scores in another Japanese cohort.

Methods

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

We developed the 2 clinical prediction rules for thrombotic and bleeding events, named the CREDO-Kyoto (Coronary Revascularization Demonstrating Outcome Study in Kyoto) thrombotic risk score and the CREDO-Kyoto bleeding risk score.⁶

We identified the derivation cohort of 4778 patients treated by PCI with exclusive use of sirolimus-eluting stent from the CREDO-Kyoto PCI and coronary artery bypass grafting registry cohort 2, which is an investigator-initiated multicenter registry enrolling consecutive patients who underwent first coronary revascularization procedures among 26 centers in Japan between January 2005 and December 2007 (Figure 1A).⁷ The validation cohort consisted of 4669 patients treated with PCI with exclusive use of new-generation drug-eluting stents (DESs) from the RESET (Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent Trial), and NEXT (Nobori Biolimus-Eluting Versus Xience/Promus Everolimus-Eluting Stent Trial) studies (Figure 1B).^{8,9} RESET and NEXT are prospective, multicenter, randomized trials in Japan comparing new-generation everolimus-eluting stents with first-generation sirolimus-eluting stents and comparing new-generation biolimus-eluting stents with everolimus-eluting stents, respectively.^{8,9} The relevant review boards at all participating centers for each study approved each research protocol for the 3 studies. Because of retrospective enrollment, the requirement for written informed consent from patients was waived in the CREDO-Kyoto PCI and coronary artery bypass grafting registry cohort 2; however, we excluded those patients who refused participation in the study when contacted for follow-up. Written informed consent was obtained from all study patients in RESET and NEXT. We excluded those patients with in-hospital death, MI, ST, ischemic stroke, and bleeding during the index hospitalization because those in-hospital events were closely related to the index event and/or the index PCI and thus were not suitable for use in constructing the clinical prediction rules for long-term thrombotic and bleeding events.

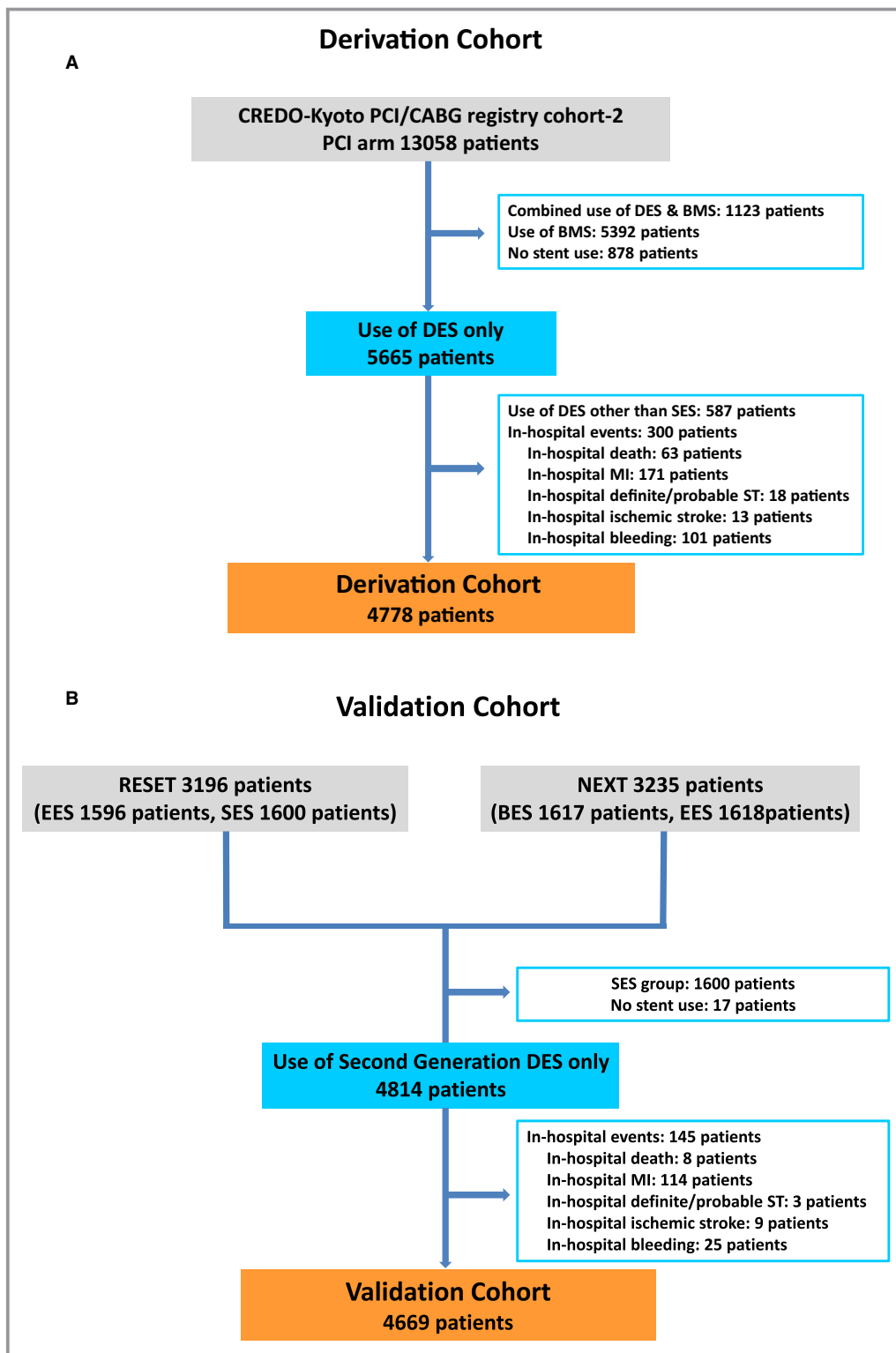


Figure 1. Study flow chart of the derivation cohort (A) and the validation cohort (B). BES indicates biolimus-eluting stent; BMS, bare metal stent; CABG, coronary artery bypass grafting; CREDO-Kyoto, Coronary Revascularization Demonstrating Outcome Study in Kyoto; DES, drug-eluting stent; EES, everolimus-eluting stent; MI, myocardial infarction; NEXT, Nobori Biolimus-Eluting Versus Xience/Promus Everolimus-Eluting Stent Trial; PCI, percutaneous coronary intervention; RESET, Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent Trial; SES, sirolimus-eluting stent; ST, stent thrombosis.

Table 1. Baseline Characteristics of Patients in the Derivation and Validation Cohort

	Derivation Cohort (n=4778)	Validation Cohort (n=4669)	P Value
Clinical characteristics			
Age, y	68.1±10.3	69.0±9.8	<0.0001
Age ≥75 y	1389 (29)	1474 (32)	0.008
Male	3447 (72)	3622 (78)	<0.0001
BMI	23.8±3.4	24.2±3.6	<0.0001
BMI <25.0	3083/4693 (66)	2903/4638 (63)	0.002
Acute myocardial infarction	733 (15)	251 (5.4)	<0.0001
Hypertension	3965 (83)	3770 (81)	0.005
Diabetes mellitus	1952 (41)	2136 (46)	<0.0001
On insulin therapy	499 (10)	493 (11)	0.86
Current smoking	1322 (28)	900 (19)	<0.0001
Heart failure	772 (16)	567 (12)	<0.0001
Multivessel disease	2762 (58)	2322 (50)	<0.0001
Prior MI	641 (13)	1329 (28)	<0.0001
Prior stroke	526 (11)	502 (11)	0.69
PVD	371 (7.8)	465 (10)	0.0002
Moderate CKD	1494/4728 (32)	1546/4644 (33)	0.08
Severe CKD	374/4728 (7.9)	371/4644 (8.0)	0.89
eGFR <30, not on dialysis	167/4728 (3.5)	106/4644 (2.3)	0.0003
Dialysis	207 (4.3)	265 (5.7)	0.003
AF	368 (7.7)	309 (6.6)	0.04
Anemia (Hb <11 g/dL)	517/4724 (11)	558/4656 (12)	0.11
Platelet count <100 000/μL	63/4750 (1.3)	77/4653 (1.7)	0.19
Cirrhosis	108 (2.3)	36 (0.8)	<0.0001
Malignancy	408 (8.5)	330 (7.1)	0.008
Procedural characteristics			
Number of target lesions	1.46±0.73	1.25±0.52	<0.0001
Target of LAD	3089 (65)	2268 (49)	<0.0001
Target of unprotected LMCA	149 (3.1)	128 (2.7)	0.28
Target of CTO	633 (13)	347 (7.4)	<0.0001
Target of bifurcation	1849 (39)	1087 (23)	<0.0001
Side-branch stenting	220 (4.6)	63 (1.4)	<0.0001
Total number of stents	1.87±1.18	1.55±0.81	<0.0001
Total stent length, mm	41.7±29.3	32.0±19.9	<0.0001
Total stent length ≥36 mm	2277 (48)	1555 (33)	<0.0001
Minimum stent size, mm	2.83±0.37	2.9±0.39	<0.0001
Minimum stent size <3.0 mm	2375 (50)	2212 (47)	0.02
Baseline medication			
Medication at hospital discharge			
Antiplatelet therapy			
Thienopyridine	4765 (99.7)	4646 (99.5)	0.08
Ticlopidine	4240 (89)	631 (14)	<0.0001

Continued

Table 1. Continued

	Derivation Cohort (n=4778)	Validation Cohort (n=4669)	P Value
Clopidogrel	517 (11)	3981 (86)	<0.0001
Aspirin	4714 (98.7)	4655 (99.7)	<0.0001
Cilostazole	711 (15)	279 (6.0)	<0.0001
Other medications			
Statins	2616 (55)	3569 (76)	<0.0001
Beta-blockers	1349 (28)	1742 (37)	<0.0001
ACE-I/ARB	2639 (55)	2877 (62)	<0.0001
Nitrates	1776 (37)	1198 (26)	<0.0001
Calcium channel blockers	2263 (47)	2080 (45)	0.006
Warfarin	389 (8.1)	354 (7.6)	0.31

Values are expressed as mean±SD or number (%). Patients with moderate CKD had eGFR ≥ 30 and <60 mL/min/1.73 m², and those with severe CKD were on dialysis or had eGFR <30 mL/min/1.73 m². ACE-I indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; CKD, chronic kidney disease; CTO, chronic total occlusion; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; LAD, left anterior descending coronary artery; LMCA, left main coronary artery; MI, myocardial infarction; PVD, peripheral vascular disease.

Definitions

The primary thrombotic event was defined as a composite of MI and definite or probable ST or ischemic stroke, and the primary bleeding event was defined as the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) moderate or severe bleeding. MI was adjudicated by the definition of ARTS (Arterial Revascularization Therapies Study) in CREDO-Kyoto PCI and coronary artery bypass grafting registry cohort 2 and by the definition of ARC (Academic Research Consortium) consensus criteria in RESET and NEXT.^{10,11} Both the ARTS and ARC definitions adopted the same criteria for spontaneous MI (biomarker elevation above the upper limit of normal). The present study evaluated post-discharge clinical outcomes after PCI, and the majority of adjudicated MIs were not procedure-related but rather spontaneous. The definitions for the outcomes other than MI were identical across the 3 studies. ST was defined according to the definition of the ARC.¹¹ Ischemic stroke during follow-up was defined as stroke requiring hospitalization with symptoms lasting >24 hours. Bleeding was defined according to the GUSTO classification.¹² All clinical events were adjudicated by the independent clinical event committees in each study.

Data Collection and Follow-up

In all 3 studies, demographic, angiographic, and procedural data were collected from hospital charts or databases at each participating center according to the definitions prespecified by the site investigators or by the experienced clinical research coordinators in the study management

center (Research Institute for Production Development, Kyoto, Japan). Follow-up data were obtained from hospital charts or by contacting patients or referring physicians with questions about vital status, subsequent hospitalization, and status of antiplatelet therapy. Persistent DAPT discontinuation was defined as withdrawal of either aspirin or thienopyridine lasting for at least 2 months.¹³ The follow-up duration was 5 years in the CREDO-Kyoto PCI and coronary artery bypass grafting registry cohort 2 and 3 years in RESET and NEXT.^{8,9,14} In the present analysis, follow-up was truncated at 3 years to standardize follow-up duration in both the derivation and validation cohorts.

Statistical Analyses

Categorical variables are expressed as number and percentage, and continuous variables are expressed as mean±SD. To compare the characteristics between cohorts, we used the χ^2 test for categorical variables and the Student *t* test or Wilcoxon rank sum test for continuous variables based on the distributions.

To develop clinical prediction rules, we first dichotomized the continuous variables to ensure that the final model did not contain any continuous variables, so clinicians could categorize patients by the presence or absence of a factor without performing any calculations. The cutoff values of age ≥ 75 years, body mass index <25.0 , hemoglobin <11 g/dL, and platelet count $<100\,000/\mu\text{L}$ were derived from the previous report.⁷ Patients with moderate and severe chronic kidney disease (CKD) were defined as those with an estimated glomerular filtration rate (eGFR) ≥ 30 and

Table 2. Univariate and Multivariate Analysis for Thrombotic and Bleeding Events in the Derivation Cohort

	Univariate	P Value	Multivariate		P Value	Score
	OR (95% CI)		OR (95% CI)	β Estimate		
Thrombotic risk score						
Age ≥75 y	1.84 (1.40–2.41)	<0.0001	1.71 (1.28–2.28)	0.536	0.0002	1
Male	1.04 (0.78–1.42)	0.78				
BMI <25.0	1.11 (0.84–1.47)	0.47				
Acute MI	1.15 (0.81–1.63)	0.46				
Hypertension	1.46 (0.99–2.22)	0.051				
Diabetes mellitus	1.58 (1.21–2.07)	0.0007	1.45 (1.1–1.91)	0.373	0.008	1
Current smoking	1.04 (0.77–1.38)	0.81				
Heart failure	2.34 (1.71–3.15)	<0.0001	1.6 (1.15–2.21)	0.467	0.005	1
Prior MI	1.38 (0.96–1.97)	0.08				
Prior stroke	1.90 (1.31–2.68)	0.0009				
PVD	2.08 (1.38–3.1)	0.0008	1.77 (1.18–2.67)	0.573	0.006	2
Moderate CKD	1.80 (1.34–2.41)	<0.0001				
Severe CKD	4.65 (3.12–6.83)	<0.0001	2.44 (1.6–3.71)	0.892	<0.0001	2
AF	2.13 (1.41–3.12)	0.0006	1.85 (1.22–2.8)	0.615	0.004	2
Anemia (Hb <11 g/dL)	3.17 (2.26–4.38)	<0.0001	1.77 (1.21–2.59)	0.57	0.003	2
Platelet count <100 000/μL	0.39 (0.02–1.78)	0.27				
Cirrhosis	1.63 (0.72–3.2)	0.22				
Malignancy	1.03 (0.62–1.63)	0.90				
Multivessel disease	1.44 (1.09–1.91)	0.009				
Target of LAD	1.22 (0.92–1.63)	0.17				
Target of unprotected LMCA	1.95 (1.01–3.45)	0.048				
Target of CTO	1.41 (0.99–2.0)	0.06	1.44 (1.0–2.07)	0.365	0.047	1
Target of bifurcation	0.79 (0.59–1.04)	0.09				
Side-branch stenting	0.78 (0.35–1.49)	0.47				
Total stent length ≥36 mm	1.37 (1.05–1.79)	0.02				
Minimum stent size <3.0 mm	1.09 (0.83–1.42)	0.54				
Bleeding risk score						
Age ≥75 y	1.49 (1.12–1.96)	0.007				
Male	1.19 (0.88–1.63)	0.27				
BMI <25.0	1.19 (0.9–1.6)	0.22				
Acute MI	0.88 (0.59–1.27)	0.49				
Hypertension	1.73 (1.16–2.7)	0.007				
Diabetes mellitus	1.44 (1.1–1.88)	0.008				
Current smoking	0.82 (0.60–1.11)	0.21				
Heart failure	2.75 (2.03–3.69)	<0.0001	2.13 (1.54–2.94)	0.754	<0.0001	2
Prior MI	2.06 (1.47–2.83)	<0.0001	1.68 (1.19–2.37)	0.519	0.003	1
Prior stroke	1.83 (1.26–2.59)	0.002				
PVD	2.83 (1.95–4.02)	<0.0001	2.61 (1.8–3.8)	0.961	<0.0001	2
Moderate CKD	1.46 (1.09–1.96)	0.01				
Severe CKD	3.94 (2.64–5.79)	<0.0001	2.65 (1.79–3.9)	0.973	<0.0001	2

Continued

Table 2. Continued

	Univariate	<i>P</i> Value	Multivariate		<i>P</i> Value	Score
	OR (95% CI)		OR (95% CI)	β Estimate		
AF	1.95 (1.27–2.88)	0.003	1.55 (1.01–2.38)	0.437	0.046	1
Warfarin	1.85 (1.22–2.72)	0.005				
Anemia (Hb <11 g/dL)	2.72 (1.92–3.80)	<0.0001				
Platelet count <100 000/ μ L	4.80 (2.24–9.37)	0.0002	2.76 (1.31–5.83)	1.016	0.008	2
Cirrhosis	1.84 (0.85–3.51)	0.11				
Malignancy	1.68 (1.1–2.49)	0.02	1.6 (1.05–2.43)	0.469	0.03	1

Patients with moderate CKD had eGFR ≥ 30 and < 60 mL/min/1.73 m², and those with severe CKD were on dialysis or had eGFR < 30 mL/min/1.73 m², respectively. BMI indicates body mass index; CI, confidence interval; CKD, chronic kidney disease; CTO, chronic total occlusion; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; LAD, left anterior descending coronary artery; LMCA, left main coronary artery; MI, myocardial infarction; OR, odds ratio; PVD, peripheral vascular disease.

< 60 mL/min per 1.73 m² and those with dialysis or eGFR < 30 mL/min per 1.73 m², respectively. Total stent length ≥ 36 mm and minimum stent size < 3.0 mm were determined by the Youden Index on receiver operating characteristic curves. We constructed univariate logistic regression models to assess the strength of the association between the 26 potential predictors and thrombotic events and between the 19 potential predictors and bleeding events in the derivation cohort. Missing values were considered null because the developed clinical prediction rules should allow risk prediction based on the available information for any patient with any missing or uncertain variables. Missing data were found for 85 patients (1.8%) regarding body mass index, for 50 patients (1.0%) regarding eGFR, for 54 patients (1.1%) regarding hemoglobin, and for 22 patients (0.5%) regarding platelet count in the derivation cohort and for 31 patients (0.7%) regarding body mass index, for 25 patients (0.5%) regarding eGFR, for 13 patients (0.3%) regarding hemoglobin, and for 16 patients (0.3%) regarding platelet count in the validation cohort. From clinical context, the missing data of each value were categorized as body mass index < 25.0 , eGFR ≥ 60 , hemoglobin ≥ 11.0 g/dL, and platelet count ≥ 100 000/ μ L, because physicians have to determine the likelihood of events in the future, even for patients with some missing data, by assuming no risk categories for variables with missing data. Variables found to be associated at $P < 0.10$ in the univariate logistic regression models were included in the multivariate models. We constructed multivariate logistic regression models to select variables associated with the thrombotic and bleeding events separately in the same derivation cohort. Applying the backward model selection procedure to eliminate the variables with higher P values, we finally constructed multivariate logistic regression models using those variables with $P < 0.05$ for each event. The results of the multivariate logistic regression models were then used to develop a clinical prediction

model.⁶ The β coefficient for each variable was divided by the smallest β coefficient and rounded to the nearest integer, which was used as the point for the variable. The risk score for an individual patient was determined by assigning points for each variable present and summing. The discriminatory performances of the models were assessed by receiver operating characteristic curve analysis in the derivation and validation cohorts.¹⁵ We calculated the area under the curve (AUC) of each model in the derivation and validation cohorts and compared the corresponding models between derivation and validation cohorts. The resulting continuous distribution of each risk score of all patients in the validation cohort was then stratified into 3 categories of scores according to the level of probability. The intermediate-risk group was determined so that incidence was similar to that of the entire validation cohort. Those patients with higher and lower risk scores than the those of the intermediate-risk group were classified as the high- and low-risk groups, respectively.

Cumulative incidence was estimated by the Kaplan–Meier method, and differences were assessed with the log-rank test for the 3 categorized risk groups. Statistical analyses were conducted by a physician (M.N.) and by a statistician (T.M.) with the use of JMP 10.0 and SAS 9.4 (SAS Institute) software. All statistical analyses were 2-tailed. $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

Because of the differences in the study design, baseline characteristics were significantly different in several aspects between the derivation and validation cohorts. Regarding clinical characteristics, patients in the derivation cohort were younger and had lower body mass indexes than those in the

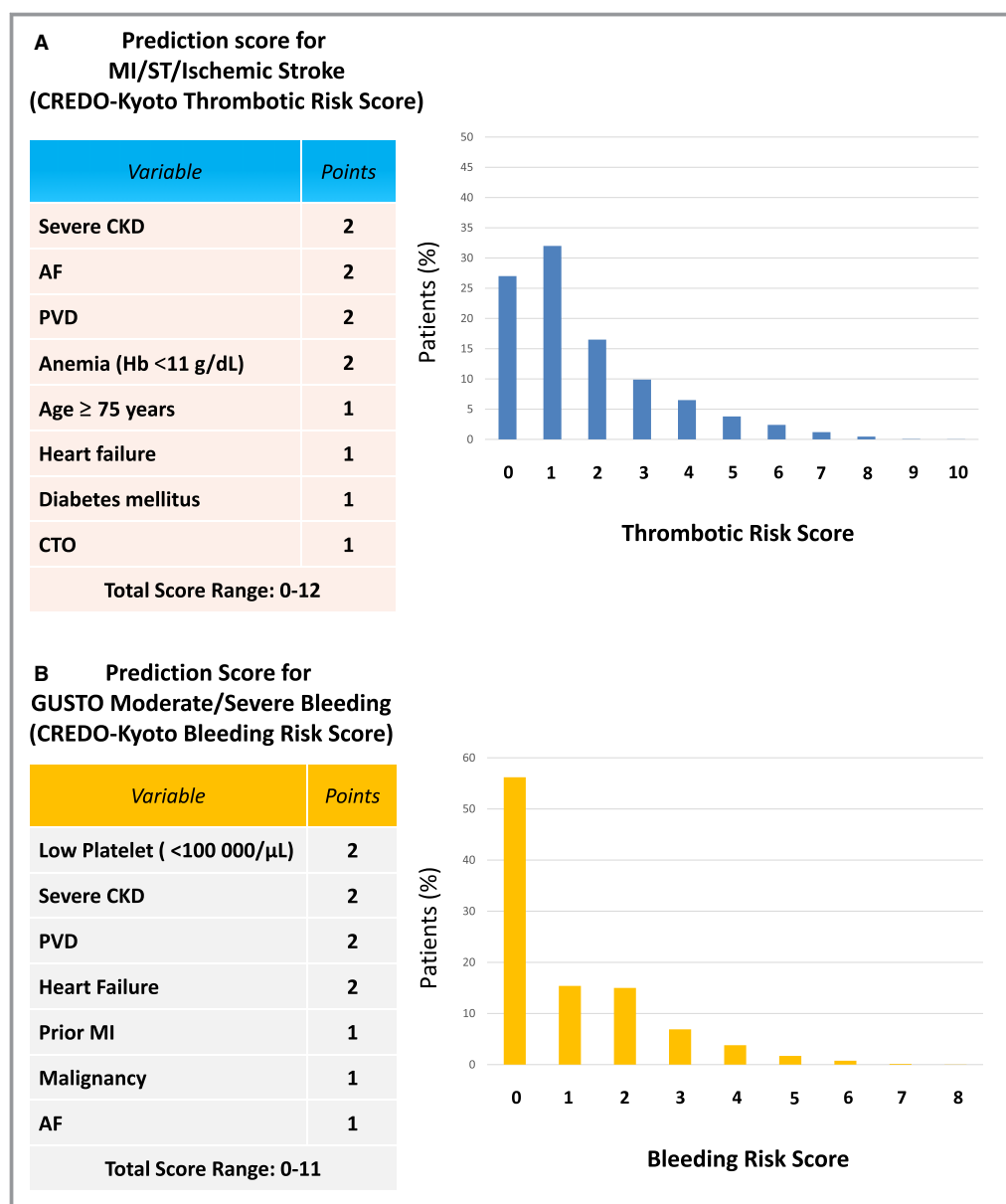


Figure 2. Elements and distribution of the prediction scores. A, Thrombotic risk score in the derivation cohort. B, Bleeding risk score in the derivation cohort. Severe CKD indicates those with dialysis or estimated glomerular filtration rate <30 mL/min per 1.73m². For the web calculator, see <http://www.seiken-j.or.jp/CREDO-Kyoto.risk.score/>.²⁶ AF indicates atrial fibrillation; CKD, chronic kidney disease; CREDO-Kyoto, Coronary Revascularization Demonstrating Outcome Study in Kyoto; CTO, chronic total occlusion; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; Hb, hemoglobin; MI, myocardial infarction; PVD, peripheral vascular disease; ST, definite or probable stent thrombosis.

validation cohort. Acute MI, hypertension, current smoking, heart failure, multivessel disease, and atrial fibrillation (AF) were more often found in the derivation cohort, whereas male sex, diabetes mellitus, prior MI, peripheral vascular disease (PVD), and dialysis were more prevalent in the validation cohort. Regarding procedural characteristics, the derivation cohort included more target lesions, longer total

stent length, and smaller minimum stent size than the validation cohort. Left anterior descending coronary artery, chronic total occlusion, and bifurcation lesions were more prevalent in the derivation cohort than in the validation cohort. The prevalence of statin use was significantly lower in the derivation cohort than in the validation cohort (Table 1).

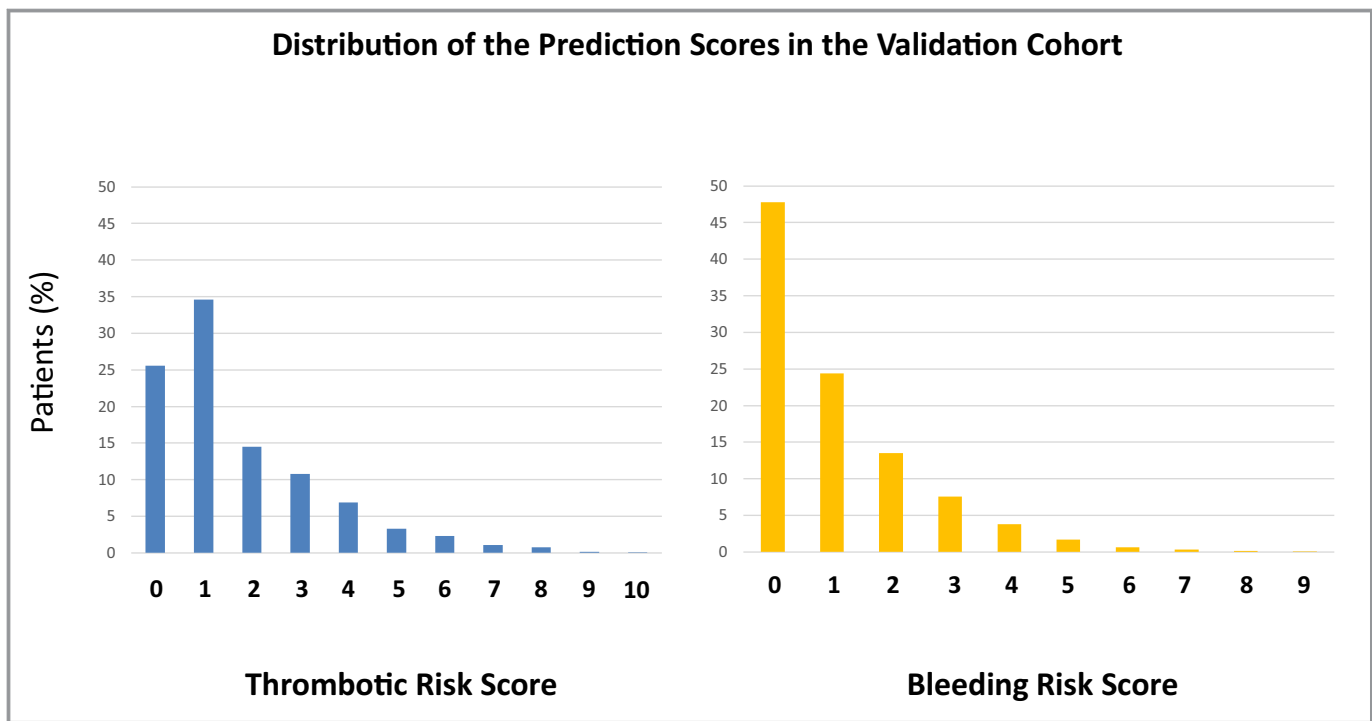


Figure 3. Distribution of the prediction scores in the validation cohort.

Thrombotic Risk Score

The prediction rule for the thrombotic risk assigned 2 points for severe CKD, AF, PVD, and anemia and 1 point for age ≥ 75 years, heart failure, diabetes mellitus, and chronic total occlusion (Table 2). The thrombotic risk score ranged from 0 to 12, with peaks at 1 point in the derivation and validation cohorts (Figures 2A and 3). Distribution of the thrombotic risk score categories was comparable in both the derivation and validation cohorts, with the majority of patients in the low thrombotic risk category (Table 3). Patients were classified by thrombotic risk score as *high*, *intermediate*, and *low*: High was ≥ 4 points (derivation cohort: $n=693$, 14.5%; validation cohort: $n=682$, 14.6%), intermediate was 2–3 points (derivation cohort: $n=1263$, 26.4%; validation cohort: $n=1178$, 25.2%), and low was 0–1 point (derivation cohort: $n=2822$ patients, 59.1%; validation cohort: $n=2809$, 60.2%).

The AUC for the thrombotic risk score was 0.68 in the derivation cohort and 0.64 in the validation cohort (Figure 4). The CREDO-Kyoto thrombotic risk score was validated with modest accuracy in the validation cohort without significant difference in the AUC between the derivation and validation cohorts ($P=0.23$). Calibration of the model was tested on the entire cohort and proved satisfactory (Figure 5A).

Bleeding Risk Score

The prediction rule for the bleeding risk assigned 2 points for thrombocytopenia, severe CKD, PVD, and heart failure and 1

point for prior MI, malignancy, and AF (Table 2). The variables incorporated in the bleeding risk score had considerable overlap with those incorporated in the thrombotic risk score (severe CKD, AF, PVD, and heart failure). The bleeding risk score ranged from 0 to 11, with the peak at 0 points in the derivation and validation cohorts (Figures 2B and 3). The distribution of the bleeding risk score categories was comparable in the derivation and validation cohorts, with the majority of patients in the low bleeding risk category (Table 3). Patients were classified by thrombotic risk score as *high*, *intermediate*, and *low*: High was ≥ 3 points (derivation cohort: $n=638$, 13.4%; validation cohort: $n=666$, 14.3%), intermediate was 1–2 points (derivation cohort: $n=1455$, 30.5%; validation cohort: $n=1802$, 38.6%), and low was 0 points (derivation cohort: $n=2685$, 56.2%; validation cohort: $n=2201$, 47.1%).

The AUC for the bleeding risk score was 0.66 in the derivation cohort and 0.66 in the validation cohort (Figure 4). The CREDO-Kyoto bleeding risk score was also validated with modest accuracy in the validation cohort without significant difference in AUC between the derivation and validation cohorts ($P=0.96$). Calibration of the model was tested on the entire cohort and proved satisfactory (Figure 5B).

Clinical Outcomes Over 3 Years in the Derivation and Validation Cohorts

In the derivation cohort, primary thrombotic and bleeding events occurred in 230 patients (5.0%) and in 229 patients (5.0%), respectively, over 3 years. Patients with high

Table 3. Cumulative 3-Year Incidences of Events According to the Thrombotic and Bleeding Risk Categories in the Derivation and Validation Cohorts

	Thrombotic Risk Score			P Value	Bleeding Risk Score			P Value
	Low	Intermediate	High		Low	Intermediate	High	
Derivation cohort, n	2822	1263	693		2685	1455	638	
MI, ST, or ischemic stroke	86 (3.1)	70 (5.8)	74 (11.8)	<0.0001	92 (3.5)	83 (5.9)	55 (9.7)	<0.0001
MI	40 (1.5)	20 (1.7)	23 (3.8)	0.0003	40 (1.5)	22 (1.6)	21 (3.8)	0.0007
ST	23 (0.8)	10 (0.8)	11 (1.8)	0.06	22 (0.9)	12 (0.9)	10 (1.8)	0.08
Ischemic stroke	47 (1.7)	51 (4.3)	51 (8.1)	<0.0001	51 (2.0)	64 (4.6)	34 (6.0)	<0.0001
GUSTO moderate/severe bleeding	89 (3.2)	67 (5.6)	73 (11.6)	<0.0001	84 (3.2)	68 (4.9)	77 (13.5)	<0.0001
GUSTO severe bleeding	44 (1.6)	25 (2.1)	33 (5.3)	<0.0001	42 (1.6)	26 (1.9)	34 (6.0)	<0.0001
Death	91 (3.3)	100 (8.0)	179 (26.3)	<0.0001	77 (2.9)	129 (9.0)	164 (26.2)	<0.0001
Cardiac death	32 (1.2)	38 (3.1)	73 (11.7)	<0.0001	22 (0.8)	55 (3.9)	66 (11.4)	<0.0001
Noncardiac death	59 (2.1)	62 (5.1)	106 (16.5)	<0.0001	55 (2.1)	74 (5.3)	98 (16.7)	<0.0001
Persistent DAPT discontinuation	1386 (50.2)	599 (49.5)	331 (53.6)	0.53	1288 (49.1)	722 (51.9)	306 (53.1)	0.24
Validation cohort, n	2809	1178	682		2201	1802	666	
MI, ST, or ischemic stroke	66 (2.4)	42 (3.7)	48 (7.6)	<0.0001	48 (2.2)	65 (3.7)	43 (7.1)	<0.0001
MI	30 (1.1)	18 (1.6)	24 (3.8)	<0.0001	20 (0.9)	32 (1.8)	20 (3.3)	0.0001
ST	5 (0.2)	5 (0.5)	6 (0.9)	0.01	4 (0.2)	7 (0.4)	5 (0.8)	0.06
Ischemic stroke	36 (1.3)	26 (2.3)	24 (3.8)	<0.0001	29 (1.4)	34 (2.0)	23 (3.8)	0.0004
GUSTO moderate/severe bleeding	57 (2.1)	55 (4.8)	62 (9.9)	<0.0001	49 (2.3)	72 (4.1)	54 (8.8)	<0.0001
GUSTO severe bleeding	37 (1.4)	40 (3.5)	41 (6.5)	<0.0001	36 (1.7)	43 (2.5)	39 (6.3)	<0.0001
Death	86 (3.1)	97 (8.4)	124 (18.4)	<0.0001	79 (3.6)	112 (6.3)	116 (17.6)	<0.0001
Cardiac death	25 (0.9)	29 (2.6)	54 (8.3)	<0.0001	21 (1.0)	35 (2.0)	52 (8.2)	<0.0001
Noncardiac death	61 (2.2)	68 (6.0)	70 (11.0)	<0.0001	58 (2.7)	77 (4.4)	64 (10.2)	<0.0001
Persistent DAPT discontinuation	1116 (40.8)	449 (39.9)	250 (41.0)	0.9	899 (42.0)	673 (38.7)	243 (41.0)	0.1

Data reflect patients with the event (cumulative incidence) and are shown as n (%). DAPT indicates dual antiplatelet therapy; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; MI, myocardial infarction; ST, definite or probable stent thrombosis.

thrombotic risk scores in the derivation cohort had higher cumulative 3-year incidence of primary thrombotic events compared with those with intermediate and low thrombotic risk scores (11.8%, 5.8%, and 3.1%; $P<0.0001$; Figures 6A and 7A). Patients with high bleeding scores in the derivation cohort had higher cumulative 3-year incidence of primary bleeding events compared with those with intermediate and low bleeding risk scores (13.5%, 4.9%, and 3.2%; $P<0.0001$; Figures 6B and 7B). In the validation cohort, primary thrombotic and bleeding events occurred in 156 patients (3.5%) and 175 patients (3.9%), respectively. In the validation cohort, there also was an incremental increase in the cumulative 3-year incidence of primary thrombotic events with higher thrombotic risk scores (7.6%, 3.7%, and 2.4%, respectively; $P<0.0001$; Figures 6A and 7C) and an incremental increase in the cumulative 3-year incidence of primary bleeding events with higher bleeding risk scores (8.8%, 4.1%, and 2.3%, respectively; $P<0.0001$; Figures 6B and 7D), although the absolute event rates in the

validation cohort were lower than those in the derivation cohort (Figure 6).

There was close correlation of thrombotic and bleeding risk. In both the derivation and validation cohorts, the bleeding event rate was also markedly higher in patients with high thrombotic risk scores (Table 3, and Figure 6C). Among 693 and 682 patients with high thrombotic risk scores in the derivation and validation cohorts, respectively, 408 (58.9%) and 401 (58.8%), respectively, also had high bleeding risk scores; both the bleeding and mortality rates for these patients were extremely high (Figure 8, and Table 4). Only 35 patients (5.1%) and 39 patients (5.7%) in the derivation and validation cohorts, respectively, had low bleeding risk scores among those with high thrombotic risk scores (Figure 8). Among those with low thrombotic risk scores, the vast majority had low bleeding risk scores (Figure 8). An incremental increase in the incidence of primary thrombotic and bleeding events were observed with higher bleeding risk scores in patients with high thrombotic risk scores (Figure 9).

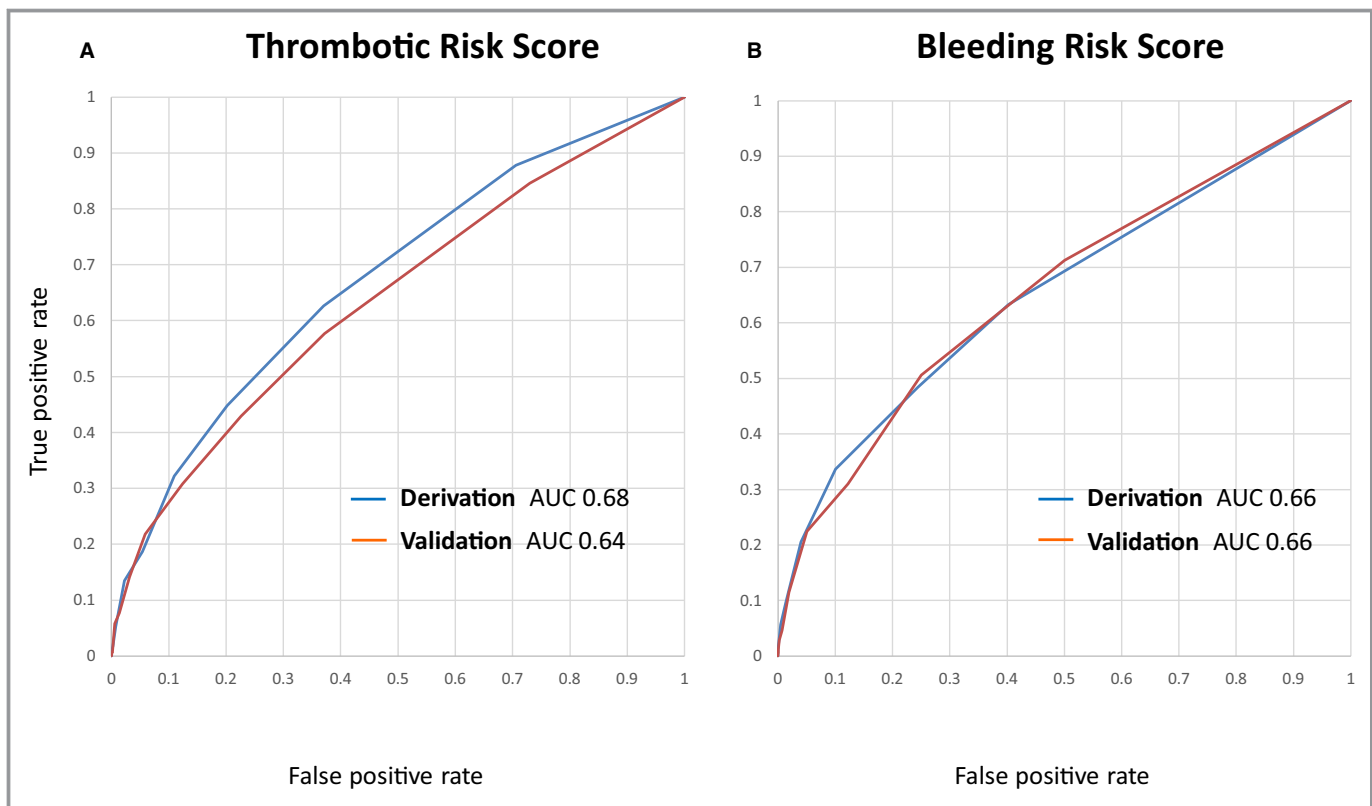


Figure 4. A, AUC for the thrombotic risk score in the derivation and validation cohorts. There was no significant difference between the derivation and validation cohorts ($P=0.23$). B, AUC for the bleeding risk score in the derivation and the validation cohorts. There was no significant difference between the derivation and validation cohorts ($P=0.96$). AUC indicates area under the curve; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; MI, myocardial infarction; ST, definite or probable stent thrombosis.

The cumulative incidence of persistent DAPT discontinuation was not significantly different, regardless of the thrombotic and bleeding risk score categories in both the derivation and validation cohorts (Table 3 and Figure 10).

Discussion

The main findings of this study were as follows. First, the CREDO-Kyoto thrombotic and bleeding risk scores demonstrated modest accuracy in stratifying thrombotic and bleeding risk separately in the derivation and validation cohorts from Japanese PCI studies. Second, reflecting the overlap of the risk predictors for thrombosis and bleeding, a large proportion of patients with high thrombotic risk also had high bleeding risk, and the bleeding event rate among those patients was very high.

Several thrombotic and bleeding risk scores have been reported previously. A thrombotic risk score was proposed in the DAPT trial, the PARIS (Patterns of Non-Adherence to Dual

Anti-Platelet Regimen in Stented Patients) registry, and TRA 2°P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events—Thrombolysis in Myocardial Infarction 50) trial.^{4,16,17} CKD, PVD, age, heart failure, and diabetes mellitus were the common independent predictors for thrombotic events in the previous studies and in the present study.^{4,16,17} In the PARIS registry, the procedural parameters were not included for derivation of the thrombotic score.¹⁶ However, in a pooled analysis of 6 randomized trials investigating DAPT durations after PCI, long-term DAPT compared with short-term DAPT yielded significant reductions in major adverse cardiac events in the complex PCI group but not in the non-complex PCI group, suggesting that it would be important to include procedural complexity for deriving the thrombotic risk score.¹⁸ AF was a characteristic thrombotic risk factor in the current study. Ischemic stroke is included as a thrombotic event in this study and could be the major reason for the emergence of AF as an independent risk factor for thrombotic events. In the DAPT trial and PARIS registry, thrombotic events were defined as the composite of ST or MI, whereas TRA 2°P-

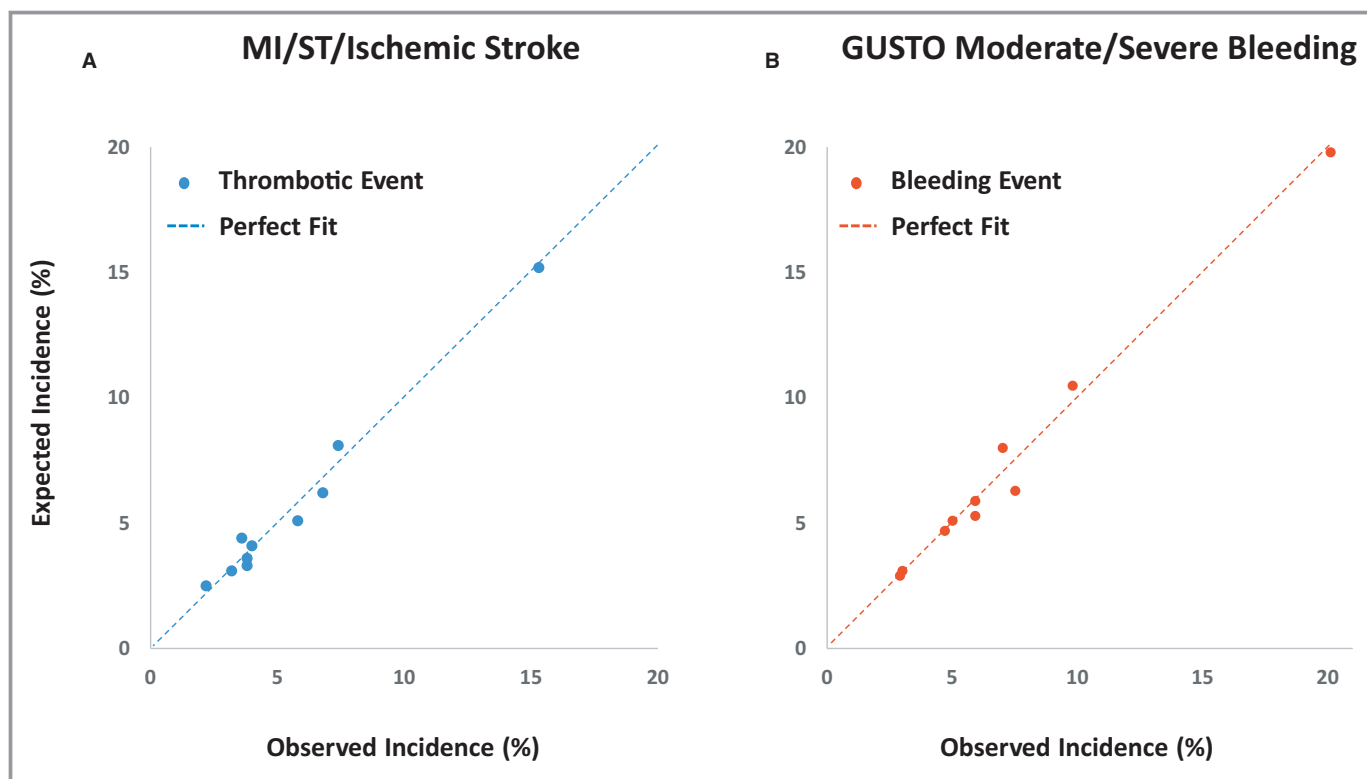


Figure 5. Observed vs predicted incidence of thrombotic and bleeding events. Scatterplot allowing a visual assessment of the linearity of increasing event rates across risk groups. The straight dashed diagonal line represents perfect calibration, and deviations from this line represent over- and underprediction of actual risk. A, MI, ST, and ischemic stroke. B, GUSTO moderate/severe bleeding. GUSTO indicates Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; MI, myocardial infarction; ST, definite or probable stent thrombosis.

TIMI 50 included ischemic stroke as a thrombotic event.^{4,16,17} Inclusion of ischemic stroke as a component of the thrombotic composite end point would be appropriate because ischemic stroke is clinically as important as MI and is a target of more intensive antithrombotic therapy in patients who underwent PCI.

Bleeding risk score is established in the DAPT study, the PRECISE-DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) study, the PARIS registry, ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents), HORIZON AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction), and CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA [American College of Cardiology/American Heart Association] Guidelines) trials.^{4,5,16,19–21} CKD, PVD, heart failure, and use of anticoagulation (or AF) were the common independent predictors for bleeding events in the previous studies and in the present study.^{4,5,16,19–21} In the present study, thrombocytopenia (platelet count <100 000/ μ L) emerged as an independent risk factor for

bleeding events, although it was not evaluated in the previous reports.^{19–21} The differences of independent predictors of thrombotic and bleeding events across studies might be due to the differences in race, study design, and patient population, although the risk factors identified in the present study were generally consistent with those in the previous studies. The present prediction rules assessing thrombotic and bleeding risks demonstrated modest accuracy in the derivation and validation cohorts, with AUCs in the range of 0.6 to 0.75, which was regarded as helpful discrimination in the clinical prediction models.²² Similar AUCs were reported in the DAPT and PARIS studies.^{4,16} Discussing the superiority of one risk score over another is beyond the scope of this study. Nevertheless, it would be preferable to use risk scores derived in the population with same or similar ethnic and/or geographic characteristics as the patient.

More intensive antithrombotic therapy should be recommended based on the balance between thrombotic risk and bleeding risk in individual patients. The cumulative incidence of persistent DAPT discontinuation in the present study, however, was not different regardless of the thrombotic and bleeding risk

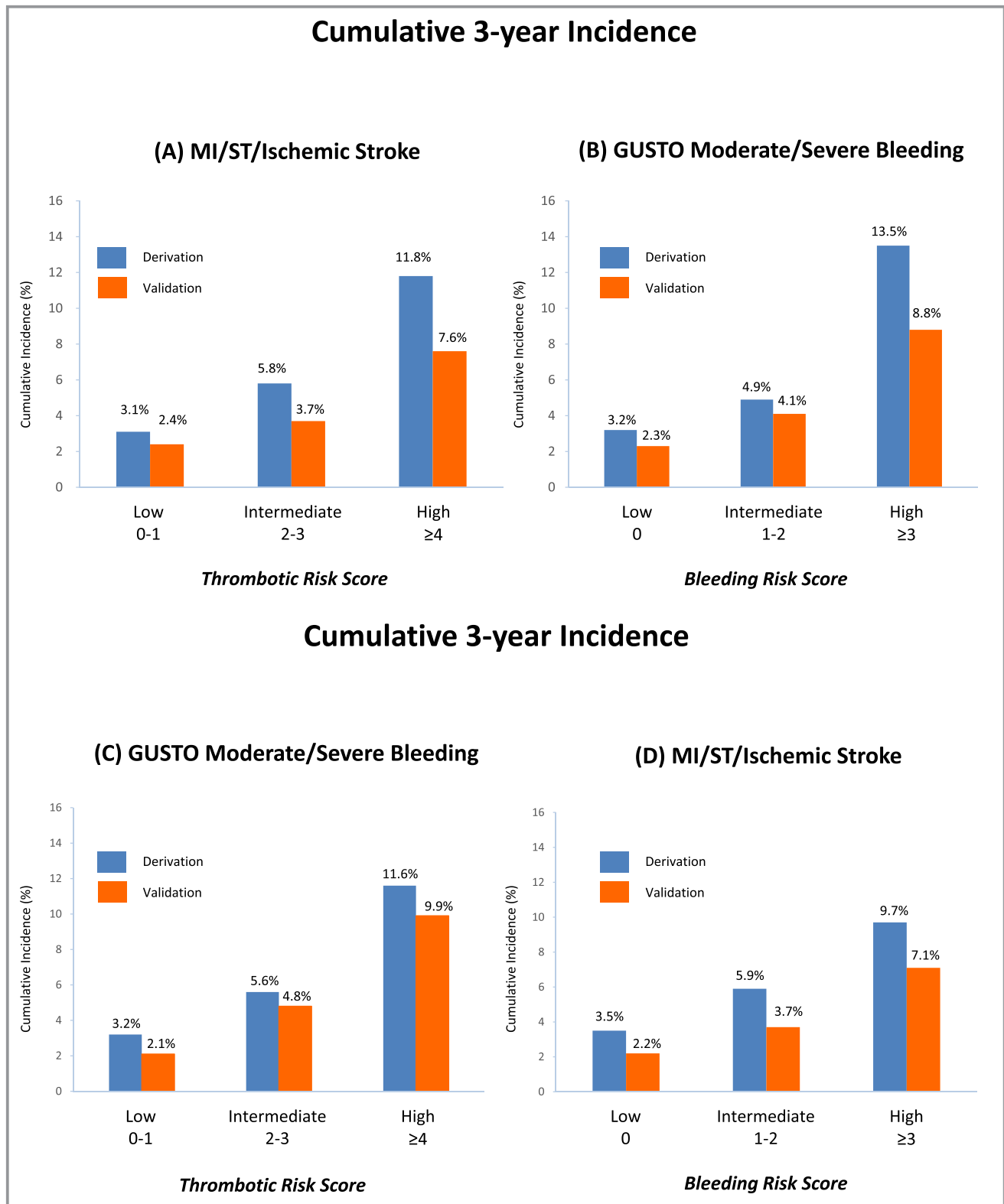


Figure 6. Cumulative 3-year incidence of thrombotic and bleeding events in the derivation and validation cohorts. A, MI, ST, and ischemic stroke according to the thrombotic risk score categories. B, GUSTO moderate/severe bleeding according to the bleeding risk score categories. C, GUSTO moderate/severe bleeding according to the thrombotic risk score categories. D, MI, ST, and ischemic stroke according to the bleeding risk score categories. GUSTO indicates Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; MI, myocardial infarction; ST, definite or probable stent thrombosis.

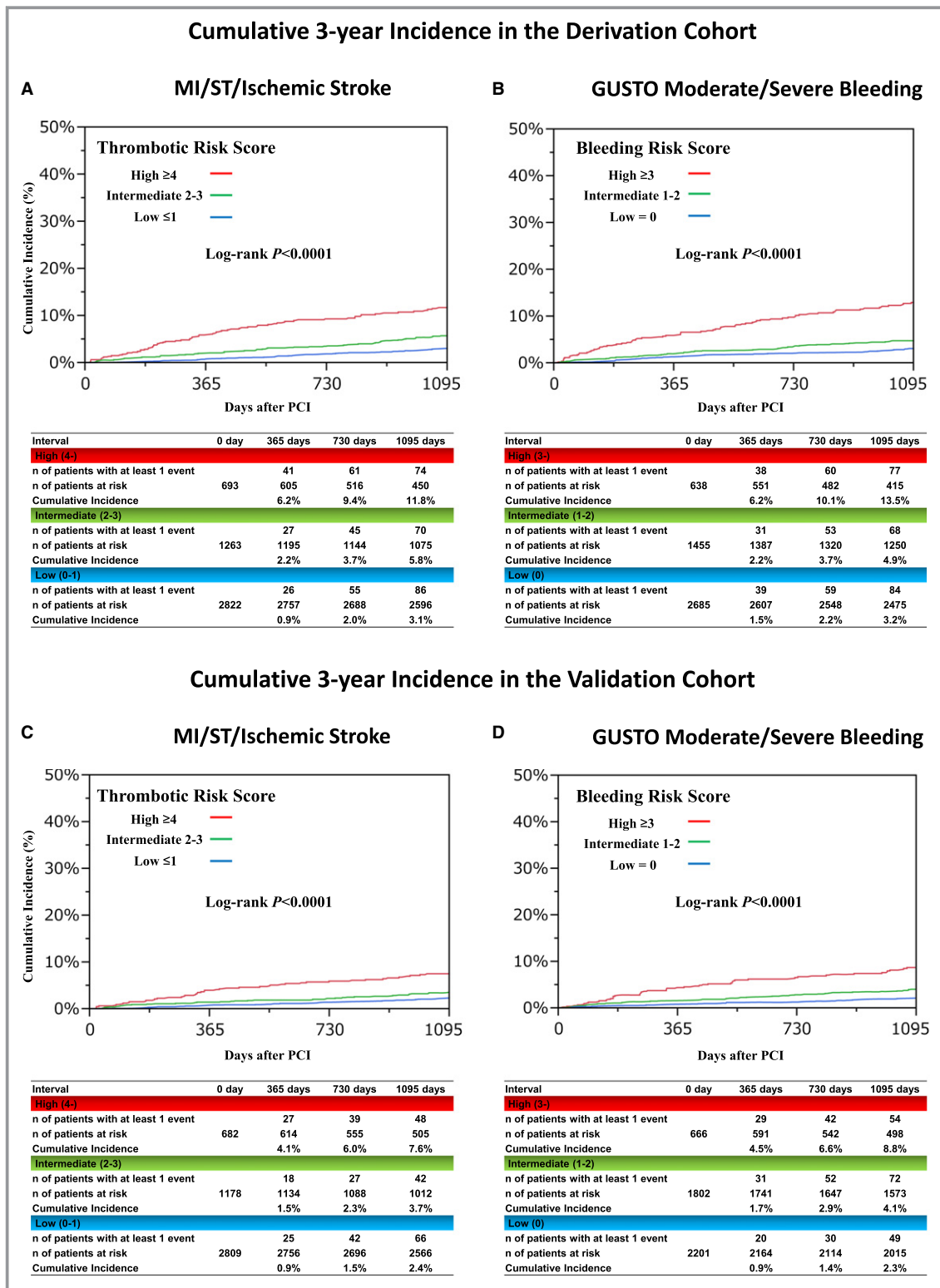


Figure 7. A, Cumulative 3-year incidence of MI, ST, and ischemic stroke according to the thrombotic risk score categories in the derivation cohort. B, Cumulative 3-year incidence of GUSTO moderate/severe bleeding according to the bleeding risk score categories in the derivation cohort. C, Cumulative 3-year incidence of MI, ST, and ischemic stroke according to the thrombotic risk score categories in the validation cohort. D, Cumulative 3-year incidence of GUSTO moderate/severe bleeding according to the bleeding risk score categories in the validation cohorts. GUSTO indicates Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; MI, myocardial infarction; PCI, percutaneous coronary intervention; ST, definite or probable stent thrombosis.

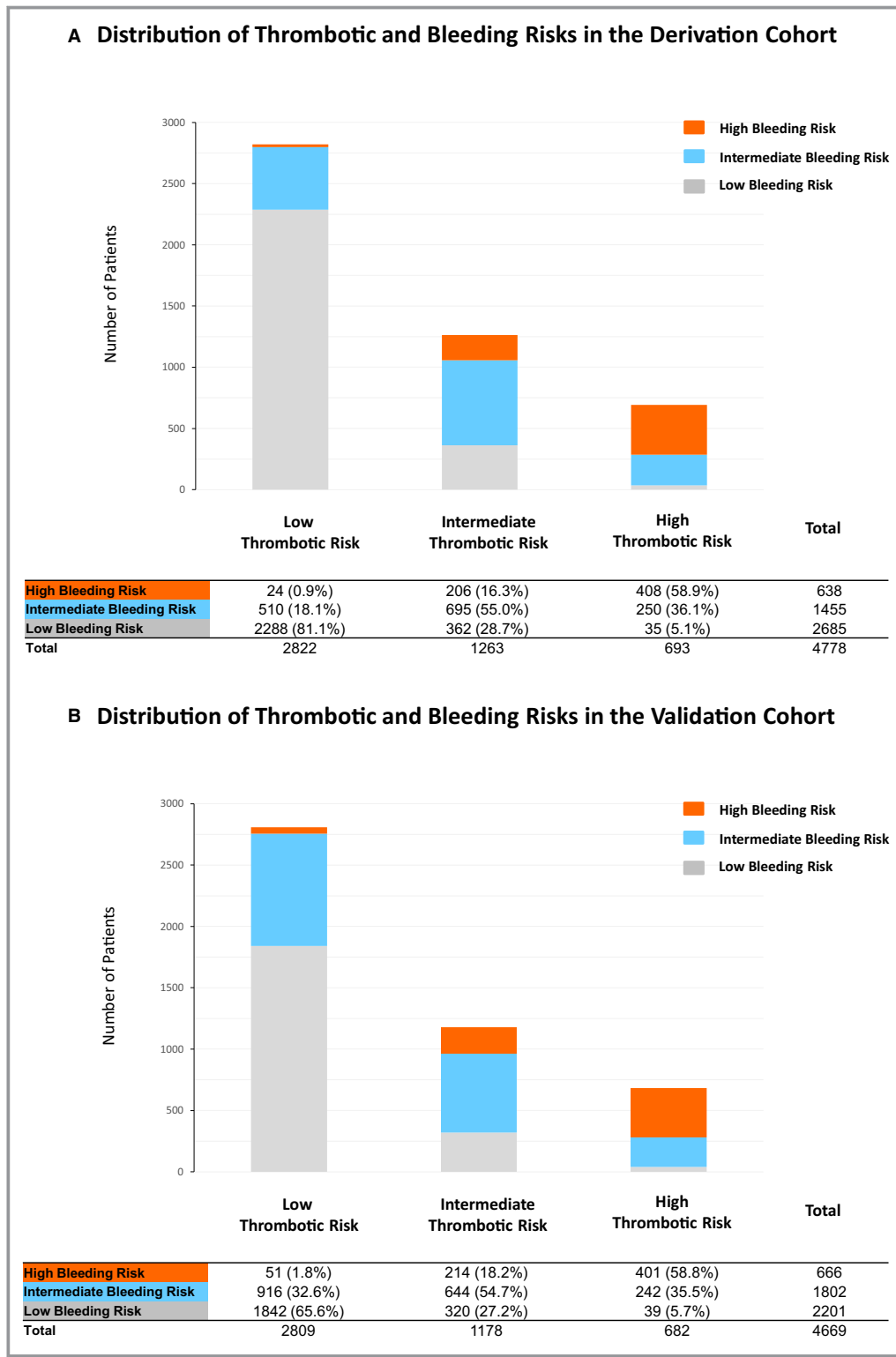


Figure 8. Distribution of the bleeding risk score categories according to the thrombotic risk score categories in the derivation cohort (A) and the validation cohort (B).

score categories, suggesting that appropriate risk stratification was not performed in determining DAPT duration after PCI. Shorter DAPT duration in patients with high bleeding risk might have substantially reduced bleeding events.

There was substantial overlap of the predictors between the thrombotic and bleeding risk scores in this study. CKD, AF, PVD, and heart failure emerged as the common predictors for both thrombotic and bleeding events. Similar

Table 4. Cumulative 3-Year Incidence of Events Considering Both the Thrombotic and Bleeding Risk Scores in the Derivation and Validation Cohorts

	Bleeding Risk Score (Incidence)			P Value
	Low	Intermediate	High	
Derivation cohort				
Low thrombotic risk score, n	2288	510	24	
MI, ST, or ischemic stroke	69 (3.1)	17 (3.4)	0 (0)	0.66
GUSTO moderate/severe bleeding	63 (2.8)	23 (4.6)	3 (14.3)	0.001
GUSTO severe bleeding	34 (1.5)	9 (1.8)	1 (4.2)	0.44
Death	52 (2.3)	34 (6.7)	5 (21.4)	<0.0001
Intermediate thrombotic risk score, n	362	695	206	
MI, ST, or ischemic stroke	21 (6.0)	39 (5.9)	10 (5.2)	0.93
GUSTO moderate/severe bleeding	20 (5.7)	26 (3.9)	21 (10.9)	0.0008
GUSTO severe bleeding	8 (2.3)	7 (1.1)	10 (5.2)	0.002
Death	19 (5.3)	51 (7.5)	30 (14.7)	0.0003
High thrombotic risk score, n	35	250	408	
MI, ST, or ischemic stroke	2 (5.9)	27 (11.3)	45 (12.7)	0.66
GUSTO moderate/severe bleeding	1 (3.0)	19 (8.1)	53 (14.7)	0.02
GUSTO severe bleeding	0 (0)	10 (4.2)	23 (6.5)	0.22
Death	6 (17.9)	44 (17.7)	129 (32.2)	0.0001
Validation cohort				
Low thrombotic risk score, n	1842	916	51	
MI, ST, or ischemic stroke	35 (1.9)	31 (3.5)	0 (0)	0.03
GUSTO moderate/severe bleeding	32 (1.8)	25 (2.8)	0 (0)	0.13
GUSTO severe bleeding	24 (1.3)	13 (1.5)	0 (0)	0.69
Death	47 (2.6)	35 (3.9)	4 (7.8)	0.02
Intermediate thrombotic risk score, n	320	644	214	
MI, ST, or ischemic stroke	12 (3.9)	21 (3.4)	9 (4.5)	0.75
GUSTO moderate/severe bleeding	13 (4.2)	30 (4.8)	12 (5.9)	0.63
GUSTO severe bleeding	9 (3.0)	20 (3.2)	11 (5.5)	0.24
Death	26 (8.3)	44 (6.9)	27 (12.7)	0.02
High thrombotic risk score, n	39	242	401	
MI, ST, or ischemic stroke	1 (2.6)	13 (5.6)	34 (9.4)	0.13
GUSTO moderate/severe bleeding	3 (8.0)	17 (7.5)	42 (11.6)	0.23
GUSTO severe bleeding	3 (8.0)	10 (4.5)	28 (7.7)	0.24
Death	6 (16.1)	33 (13.8)	85 (21.4)	0.04

Data are shown as n (%). GUSTO indicates Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; MI, myocardial infarction; ST, definite or probable stent thrombosis.

results were also seen in the previous studies.^{4,16} Reflecting the overlap of the risk predictors, a large proportion of patients with high thrombotic risk also had high bleeding risk, and more intensive antithrombotic therapy would be contraindicated for those patients. Consequently, it would not be sufficient just to stratify thrombotic risk only when

considering more intensive antithrombotic therapy. It might be reasonable to evaluate bleeding risk initially to determine the intensity of antithrombotic therapy or the duration of DAPT, as indicated in the 2017 European Society of Cardiology guidelines.²³ Further studies are warranted to explore the optimal antithrombotic therapy in the population

Cumulative 3-year Incidence in Patients with High Thrombotic Score

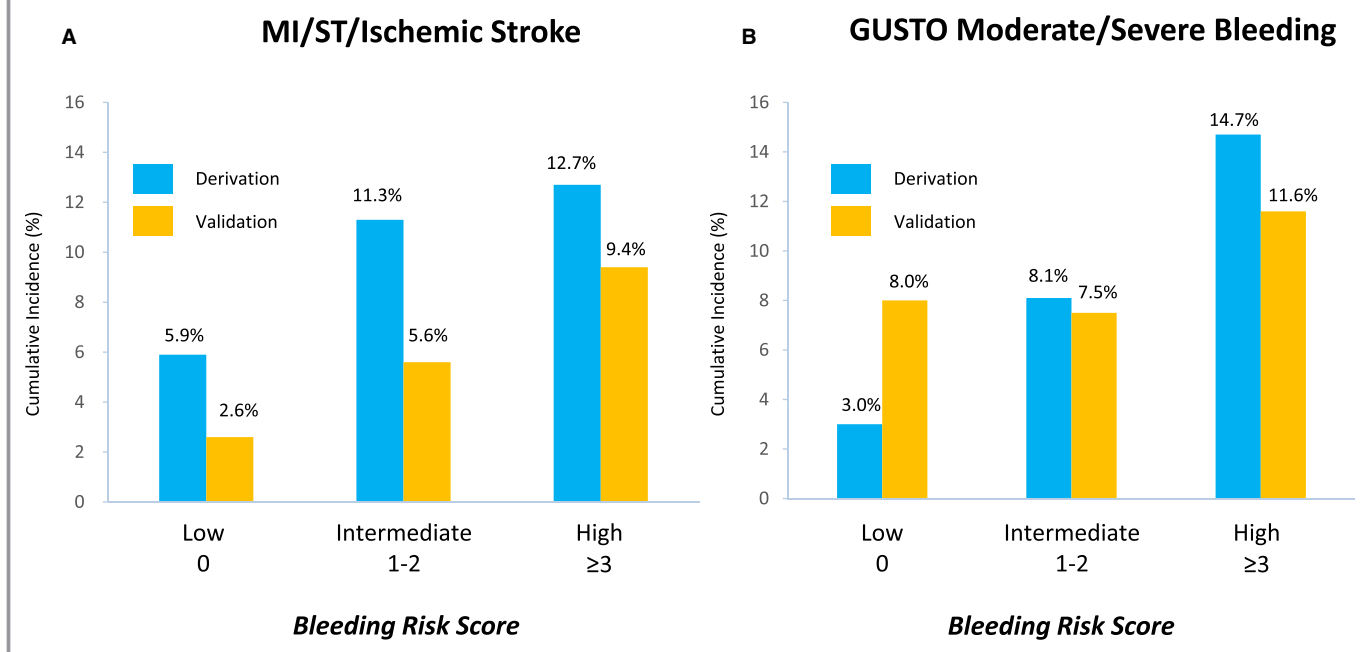


Figure 9. Cumulative 3-year incidence of thrombotic and bleeding events in patients with high thrombotic scores in the derivation and validation cohorts. A, MI, ST, and ischemic stroke according to the bleeding risk score categories. B, GUSTO moderate/severe bleeding according to the bleeding risk score categories. GUSTO indicates Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; MI, myocardial infarction; ST, definite or probable stent thrombosis.

with high thrombotic risk for whom bleeding risk is also substantial.

Study Limitations

Some limitations to our study should be considered. First, we did not have information on previous history of ST or bleeding events, which could be strongly associated with very high risk for thrombotic or bleeding events, respectively. Second, patients in the validation cohort were derived from randomized controlled trials; therefore, the types of patients included in the validation cohort would be different from those in clinical practice. There is also the chance that some patients might have been included in both the derivation and validation cohorts, because the validation cohort allowed enrollment of those patients with previous PCI. However, the enrollment periods of the 3 studies did not overlap; therefore, there was no possibility of including the same index PCI in different cohorts. Third, the prediction rules were derived from a population treated with early generation DESs, which are no longer used in current clinical practice; however, the

prediction rules were validated in a population treated with the currently used new-generation DESs. Consequently, the differences in the types of DES would not have affected the predictors for thrombosis and bleeding after PCI. Finally, the present study results were based on the patient characteristics and clinical outcomes of Japanese patients. We should be very cautious in extrapolating these results outside Japan. We recently conducted an external validation study for the DAPT score, demonstrating that it could differentiate patients with high ischemic risk from those with high bleeding risk in a Japanese population²⁴; however, the thrombotic event rate was much lower in our validation study in Japanese patients than in the DAPT study. East Asian patients have been reported to have a lower rate of thrombotic events after PCI compared with Western patients.²⁵ The distribution of bleeding risk scores among the patients with high thrombotic risk might be different in a Western population compared with the participants in the present Japanese study and would have important implications for patients selection for intensive antithrombotic therapy after PCI.

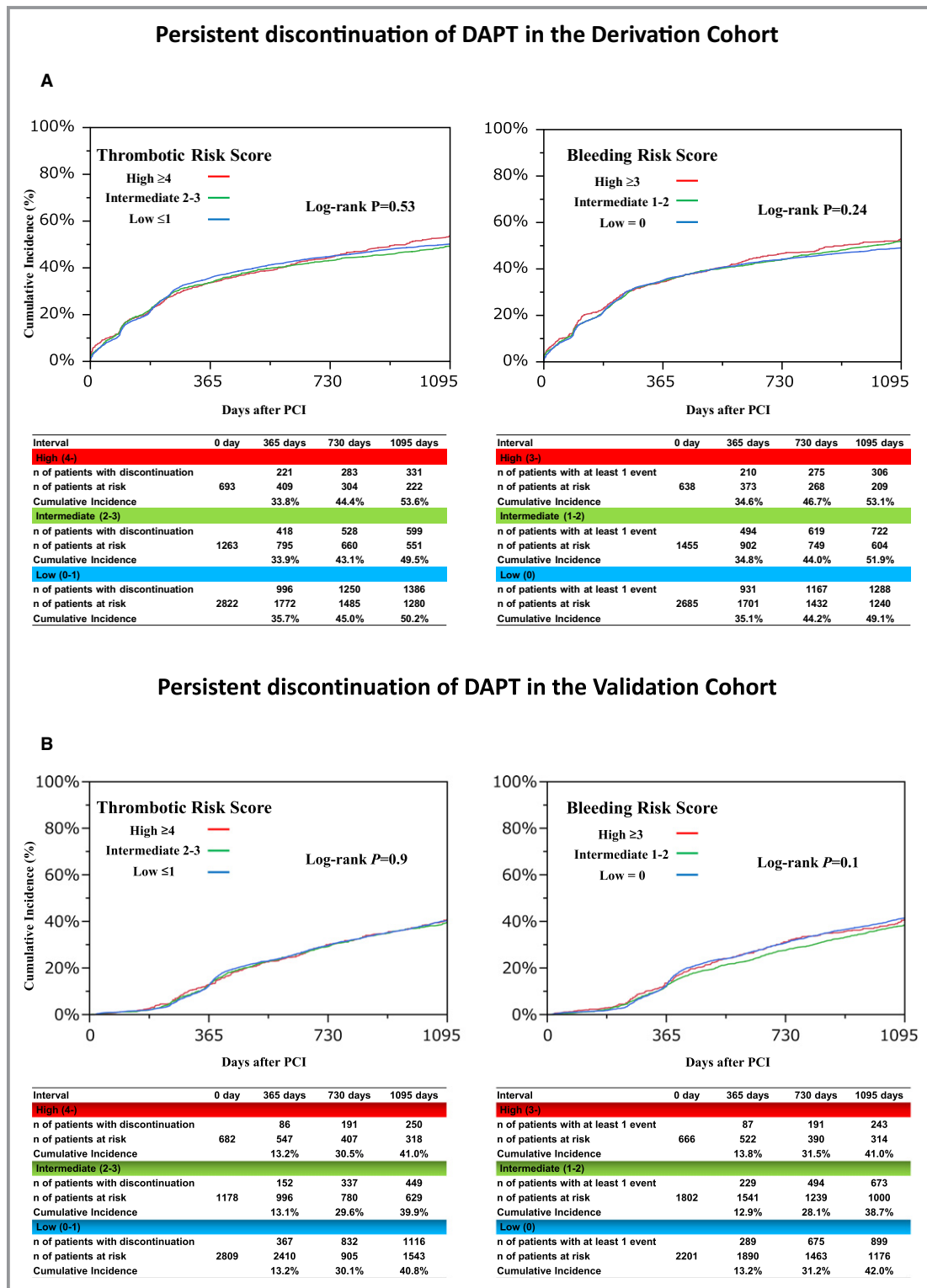


Figure 10. Persistent discontinuation of DAPT according to the risk score categories in the derivation cohort (A) and the validation cohort (B). DAPT indicates dual antiplatelet therapy; PCI, percutaneous coronary intervention.

Conclusions

The CREDO-Kyoto thrombotic and bleeding risk scores demonstrated modest accuracy in stratifying thrombotic and bleeding risk separately in the derivation and validation cohorts from

Japanese PCI studies. Reflecting the overlap of the risk predictors for thrombosis and bleeding, a large proportion of the patients with high thrombotic risk also had high bleeding risk, and the bleeding event rate for those patients was very high.

Acknowledgments

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Disclosures

None.

References

- Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*. 2014;371:2155–2166.
- Palmerini T, Benedetto U, Bacchi-Reggiani L, Della Riva D, Biondi-Zoccai G, Feres F, Abizaid A, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Genereux P, Bhatt DL, Orlandi C, De Servi S, Petrou M, Rapezzi C, Stone GW. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. *Lancet*. 2015;385:2371–2382.
- Toyota T, Shiomi H, Morimoto T, Natsuaki M, Kimura T. Short versus prolonged dual antiplatelet therapy (DAPT) duration after coronary stent implantation: a comparison between the DAPT study and 9 other trials evaluating DAPT duration. *PLoS One*. 2017;12:e0174502.
- Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, Spertus JA, Steg PG, Cutlip DE, Rinaldi MJ, Camenzind E, Wijns W, Apruzzese PK, Song Y, Massaro JM, Mauri L. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA*. 2016;315:1735–1749.
- Costa F, van Klaveren D, James S, Heg D, Raber L, Feres F, Pilgrim T, Hong MK, Kim HS, Colombo A, Steg PG, Zanchin T, Palmerini T, Wallentin L, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet*. 2017;389:1025–1034.
- Tu JV, Naylor CD. Clinical prediction rules. *J Clin Epidemiol*. 1997;50:743–744.
- Kimura T, Morimoto T, Furukawa Y, Nakagawa Y, Kadota K, Iwabuchi M, Shizuta S, Shiomi H, Tada T, Tazaki J, Kato Y, Hayano M, Abe M, Tamura T, Shirohara M, Miki S, Matsuda M, Takahashi M, Ishii K, Tanaka M, Aoyama T, Doi O, Hattori R, Tatami R, Suwa S, Takizawa A, Takatsu Y, Kato H, Takeda T, Lee JD, Nohara R, Ogawa H, Tei C, Horie M, Kambara H, Fujiwara H, Mitsudo K, Nobuyoshi M, Kita T. Long-term safety and efficacy of sirolimus-eluting stents versus bare-metal stents in real world clinical practice in Japan. *Cardiovasc Interv Ther*. 2011;26:234–245.
- Kimura T, Morimoto T, Natsuaki M, Shiomi H, Igarashi K, Kadota K, Tanabe K, Morino Y, Akasaka T, Takatsu Y, Nishikawa H, Yamamoto Y, Nakagawa Y, Hayashi Y, Iwabuchi M, Umeda H, Kawai K, Okada H, Kimura K, Simonton CA, Kozuma K. Comparison of everolimus-eluting and sirolimus-eluting coronary stents: 1-year outcomes from the randomized evaluation of sirolimus-eluting versus everolimus-eluting stent trial (RESET). *Circulation*. 2012;126:1225–1236.
- Natsuaki M, Kozuma K, Morimoto T, Kadota K, Muramatsu T, Nakagawa Y, Akasaka T, Igarashi K, Tanabe K, Morino Y, Ishikawa T, Nishikawa H, Awata M, Abe M, Okada H, Takatsu Y, Ogata N, Kimura K, Urasawa K, Tarutani Y, Shiode N, Kimura T. Biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent: a randomized, controlled, noninferiority trial. *J Am Coll Cardiol*. 2013;62:181–190.
- Serruys PW, Ong AT, van Herwerden LA, Sousa JE, Jatene A, Bonnier JJ, Schonberger JP, Buller N, Bonser R, Disco C, Backx B, Hugenholtz PG, Firth BG, Unger F. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the arterial revascularization therapies study (ARTS) randomized trial. *J Am Coll Cardiol*. 2005;46:575–581.
- Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med*. 2007;356:1020–1029.
- The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med*. 1993;329:673–682.
- Kimura T, Morimoto T, Nakagawa Y, Tamura T, Kadota K, Yasumoto H, Nishikawa H, Hiasa Y, Muramatsu T, Meguro T, Inoue N, Honda H, Hayashi Y, Miyazaki S, Oshima S, Honda T, Shiode N, Namura M, Sone T, Nobuyoshi M, Kita T, Mitsudo K. Antiplatelet therapy and stent thrombosis after sirolimus-eluting stent implantation. *Circulation*. 2009;119:987–995.
- Natsuaki M, Morimoto T, Furukawa Y, Nakagawa Y, Kadota K, Yamaji K, Ando K, Shizuta S, Shiomi H, Tada T, Tazaki J, Kato Y, Hayano M, Abe M, Tamura T, Shirohara M, Miki S, Matsuda M, Takahashi M, Ishii K, Tanaka M, Aoyama T, Doi O, Hattori R, Kato M, Suwa S, Takizawa A, Takatsu Y, Shinoda E, Eizawa H, Takeda T, Lee JD, Inoko M, Ogawa H, Hamasaki S, Horie M, Nohara R, Kambara H, Fujiwara H, Mitsudo K, Nobuyoshi M, Kita T, Kimura T. Late adverse events after implantation of sirolimus-eluting stent and bare-metal stent: long-term (5–7 years) follow-up of the Coronary Revascularization Demonstrating Outcome study-Kyoto registry Cohort-2. *Circ Cardiovasc Interv*. 2014;7:168–179.
- Metz CE. Basic principles of ROC analysis. *Semin Nucl Med*. 1978;8:283–298.
- Baber U, Mehran R, Giustino G, Cohen DJ, Henry TD, Sartori S, Ariti C, Litherland C, Dangas G, Gibson CM, Krucoff MW, Moliterno DJ, Kirtane AJ, Stone GW, Colombo A, Chieffo A, Kini AS, Witzeneichler B, Weisz G, Steg PG, Pocock S. Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from PARIS. *J Am Coll Cardiol*. 2016;67:2224–2234.
- Bohula EA, Bonaca MP, Braunwald E, Aylward PE, Corbalan R, De Ferrari GM, He P, Lewis BS, Merlini PA, Murphy SA, Sabatine MS, Scirica BM, Morrow DA. Atherothrombotic risk stratification and the efficacy and safety of vorapaxar in patients with stable ischemic heart disease and previous myocardial infarction. *Circulation*. 2016;134:304–313.
- Giustino G, Chieffo A, Palmerini T, Valgimigli M, Feres F, Abizaid A, Costa RA, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Gilard M, Morice MC, Sawaya F, Sardella G, Genereux P, Redfors B, Leon MB, Bhatt DL, Stone GW, Colombo A. Efficacy and safety of dual antiplatelet therapy after complex PCI. *J Am Coll Cardiol*. 2016;68:1851–1864.
- Genereux P, Giustino G, Witzeneichler B, Weisz G, Stuckey TD, Rinaldi MJ, Neumann FJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Yadav M, Francese DP, Palmerini T, Kirtane AJ, Litherland C, Mehran R, Stone GW. Incidence, predictors, and impact of post-discharge bleeding after percutaneous coronary intervention. *J Am Coll Cardiol*. 2015;66:1036–1045.
- Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, Parise H, Fahy M, Manoukian SV, Feit F, Ohman ME, Witzeneichler B, Guagliumi G, Lansky AJ, Stone GW. A risk score to predict bleeding in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2010;55:2556–2566.
- Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, Wang TY, Glibler WB, Ohman EM, Roe MT, Pollack CV Jr, Peterson ED, Alexander KP. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines) bleeding score. *Circulation*. 2009;119:1873–1882.
- Alba A, Agoritsas T, Walsh M, Hanna S, Iorio A, Devereaux PJ, McGinn T, Guyatt G. Discrimination and calibration of clinical prediction models. Users' guides to the medical literature. *JAMA*. 2017;318:1377–1384.
- Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jørgensen A, Juni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN. 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;39:213–260.
- Yoshikawa Y, Shiomi H, Watanabe H, Natsuaki M, Kondo H, Tamura T, Nakagawa Y, Morimoto T, Kimura T. Validating utility of DAPT score in a large pooled cohort from three Japanese PCI studies. *Circulation*. 2018;137:551–562.
- Levine GN, Jeong YH, Goto S, Anderson JL, Huo Y, Mega JL, Taubert K, Smith SC Jr. Expert consensus document: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. *Nat Rev Cardiol*. 2014;11:597–606.
- <http://www.seiken-j.or.jp/CREDO-Kyoto.risk.score/>

SUPPLEMENTAL MATERIAL

Appendix

List of the participating centers and the investigators

List A. CREDO-Kyoto registry cohort-2

Kyoto University Hospital: Takeshi Kimura

Kishiwada City Hospital: Mitsuo Matsuda, Hirokazu Mitsuoka

Tenri Hospital: Yoshihisa Nakagawa

Hyogo Prefectural Amagasaki Hospital: Hisayoshi Fujiwara, Yoshiki Takatsu, Ryoji Taniguchi

Kitano Hospital: Ryuji Nohara

Koto Memorial Hospital: Tomoyuki Murakami, Teruki Takeda

Kokura Memorial Hospital: Masakiyo Nobuyoshi, Masashi Iwabuchi

Maizuru Kyosai Hospital: Ryoza Tatami

Nara Hospital, Kinki University Faculty of Medicine: Manabu Shirotani

Kobe City Medical Center General Hospital: Toru Kita, Yutaka Furukawa, Natsuhiko Ehara

Nishi-Kobe Medical Center: Hiroshi Kato, Hiroshi Eizawa

Kansai Denryoku Hospital: Katsuhisa Ishii

Osaka Red Cross Hospital: Masaru Tanaka

University of Fukui Hospital: Jong-Dae Lee, Akira Nakano

Shizuoka City Shizuoka Hospital: Akinori Takizawa

Hamamatsu Rosai Hospital: Masaaki Takahashi

Shiga University of Medical Science Hospital: Minoru Horie, Hiroyuki Takashima

Japanese Red Cross Wakayama Medical Center: Takashi Tamura

Shimabara Hospital: Mamoru Takahashi

Kagoshima University Medical and Dental Hospital: Chuwa Tei, Shuichi Hamasaki

Shizuoka General Hospital: Hirofumi Kambara, Osamu Doi, Satoshi Kaburagi

Kurashiki Central Hospital: Kazuaki Mitsudo, Kazushige Kadota

Mitsubishi Kyoto Hospital: Shinji Miki, Tetsu Mizoguchi

Kumamoto University Hospital: Hisao Ogawa, Seigo Sugiyama

Shimada Municipal Hospital: Ryuichi Hattori, Takeshi Aoyama, Makoto Araki

Juntendo University Shizuoka Hospital: Satoru Suwa

List B. RESET Trial

Caress Sapporo Tokeidai Memorial Hospital: Kazushi Urasawa, Ryoji Koshida

Teine Keijinkai Hospital: Mitsugu Hirokami

Cardio-vascular Center Hokkaido Ohno Hospital: Takehiro Yamashita, Masato Nagashima

Caress Sapporo Hokko Memorial Hospital: Yoichi Nozaki

Hokkaido Social Insurance Hospital: Keiichi Igarashi, Jungo Furuya

Aomori Prefectural Central Hospital: Fuminobu Yoshimachi, Yukinori Sakamoto

Iwate Prefectural Central Hospital: Akihiro Nakamura, Shigefumi Fukui

Iwate Medical University Hospital: Tomonori Itoh

Sendai Kosuei Hospital: Naoto Inoue, Kaname Takizawa

Tohoku Kousei Nenkin Hospital: Yoshiaki Katahira, Takao Nakano

Sendai Open Hospital: Atsushi Kato

Iwaki Kyoritsu General Hospital: Yoshito Yamamoto, Tomohiro Tada

Fukushima Medical University Hospital: Yasuchika Takeishi, Kazuhiko Nakazato

Hoshi General Hospital: Mikihiro Kijima, Yuichi Ujiie

Ohta Nishinouchi Hospital: Nobuo Komatsu, Goro Ishida

Saiseikai Kurihashi Hospital: Yoshimi Ota, Atsushi Honda

Saitama Cardiovascular And Respiratory Center: Makoto Muto, Tetsuya Ishikawa

Dokkyo Medical University Koshigaya Hospital: Takaaki Komatsu

Jikei University Kashiwa Hospital: Mitsuyuki Shimizu, Yoshiki Uehara

Juntendo University Hospital: Hiroyuki Daida, Katsumi Miyauchi

Sakakibara Memorial Hospital: Tetsuya Sumiyoshi, Ryuta Asano

NTT Medical Center Tokyo: Masao Yamasaki

The Cardiovascular Institute Hospital: Junji Yajima, Ryuichi Funada

Mitsui Memorial Hospital: Kengo Tanabe, Masanori Taniwaki

Tokyo Medical University Hospital: Nobuhiro Tanaka, Masashi Ogawa

Teikyo University Hospital: Akiyoshi Miyazawa, Ken Kozuma, Nobuaki Suzuki

Tokyo Women's Medical University Hospital: Nobuhisa Hagiwara, Fumiaki Mori

The Jikei University Hospital: Takayuki Ogawa, Kazuo Ogawa

Juntendo University Nerima Hospital: Masataka Sumiyoshi, Shinya Okazaki

Tokyo Metropolitan Hiroo General Hospital: Tamotsu Tejima, Yasuhiro Tanabe

St. Luke's International Hospital: Yutaro Nishi

Itabashi Chuo General Hospital: Hiroshi Ohta

Saiseikai Yokohama-city Eastern Hospital: Toshiya Muramatsu, Hiroshi Ishimori

Yokohama Rosai Hospital: Kenichi Kato, Kazuhiko Yumoto

Tokai University Hospital: Yoshihiro Morino

Yokohama City University Medical Center: Kazuo Kimura, Kiyoshi Hibi

Kitasato University Hospital: Taiki Tojo, Takao Shimohama

Kanazawa Cardiovascular Hospital: Masanobu Namura, Yuki Horita

University of Fukui Hospital: Jong-Dae Lee, Akira Nakano

Fukui Cardio Vascular Center: Sumio Mizuno, Katsushi Misawa

Juntendo University Shizuoka Hospital: Satoru Suwa

Shizuoka City Shizuoka Hospital: Tomoya Onodera, Ryosuke Takeuchi

Shizuoka General Hospital: Osamu Doi, Satoshi Kaburagi

Okamura Memorial Hospital: Yasuhiro Tarutani

Seirei Hamamatsu General Hospital: Hisayuki Okada

Hamamatsu Medical Center: Masakazu Kobayashi, Yohei Takayama

Toyohashi Heart Center: Takahiko Suzuki, Masashi Kimura

Aichi Medical University Hospital: Takayuki Ito, Hiroaki Takashima

Tosei General Hospital: Hiroshi Asano

Nagoya Daini Red Cross Hospital: Haruo Hirayama, Mamoru Nanasato, Yasushi Tatematsu

Toyota Memorial Hospital: Hisashi Umeda

Nagoya Kyoritsu Hospital: Toru Aoyama

Fujita Health University Hospital: Yukio Ozaki, Hiroyuki Naruse

Matsusaka Chuo General Hospital: Masatoshi Miyahara

Nagai Hospital: Kozo Hoshino

Mie University Hospital: Takashi Tanigawa

Mie Heart Center: Hideo Nishikawa, Hiroyuki Suzuki

Yokkaichi Social Insurance Hospital: Masaki Kawamura

Koto Memorial Hospital: Teruki Takeda

Shiga University of Medical Science Hospital: Takashi Yamamoto

Kyoto University Hospital: Takeshi Kimura, Hiroki Shiomi

Mitsubishi Kyoto Hospital: Shinji Miki, Tetsu Mizoguchi

National Hospital Organization Kyoto Medical Center: Mitsuru Abe

Kyoto Second Red Cross Hospital: Hiroshi Fujita

Sakurabashi Watanabe Hospital: Kenji Fujii

Osaka City General Hospital: Akira Itoh, Kazuhiro Osawa

Osaka Saiseikai Noe Hospital: Shunsuke Take, Shiho Koyama

Osaka City University Hospital: Minoru Yoshiyama, Satoshi Nishimura

Osaka Red Cross Hospital: Tsukasa Inada, Fujio Hayashi

National Cerebral and Cardiovascular Center: Hiroshi Nonogi, Eiji Tada

Sumitomo Hospital: Yuji Yasuga, Nobuhiro Mitsusada

Higashisumiyoshi Morimoto Hospital: Yuji Sakanoue

Kansai Denryoku Hospital: Katsuhisa Ishii, Kazuaki Kataoka

Kobe City Medical Center General Hospital: Makoto Kinoshita

Kobe University Hospital: Junya Shite, Hirotoshi Hariki

Kansai Rosai Hospital: Masaaki Uematsu, Masaki Awata

Hyogo Prefectural Amagasaki Hospital: Yoshiki Takatsu, Ryoji Taniguchi

Hyogo College of Medicine Hospital: Motomaru Masutani

Tenri Hospital: Yoshihisa Nakagawa, Hirokazu Kondo

Nara Medical University Hospital: Shiro Uemura, Kenichi Ishigami

Japanese Red Cross Society Wakayama Medical Center: Takashi Tamura, Hiroki Sakamoto

Wakayama Medical University Hospital: Takashi Akasaka, Hironori Kitabata

Tottori University Hospital: Masahiko Kato, Yoshiyuki Furuse

Matsue Red Cross Hospital: Kinya Shiota, Asao Mimura

The Sakakibara Heart Institute of Okayama: Keizou Yamamoto, Hiroyuki Takinami

Kurashiki Central Hospital: Kazushige Kadota, Hiroyuki Tanaka

Kawasaki Medical School Hospital: Hiroyuki Okura, Yoji Neishi

Okayama University Hospital: Hiroshi Ito, Yoshiki Hata

Hiroshima City Hospital: Masaharu Ishihara, Kazuoki Dai

Fukuyama Cardiovascular Hospital: Seiichi Haruta, Hideo Takebayashi

Tsuchiya General Hospital: Mamoru Toyofuku

Chikamori Hospital: Kazuya Kawai, Shuichi Seki

University Of Occupational And Environmental Health Japan: Shinjo Sonoda, Yoshitaka

Muraoka

Kurume University Hospital: Takafumi Ueno, Seiji Kanaya

Kokura Memorial Hospital: Masashi Iwabuchi, Shinichi Shirai

Kouseikai Hospital: Yoshihiro Iwasaki

Saiseikai Kumamoto Hospital: Koichi Nakao

Kumamoto Rousai Hospital: Toshiyuki Matsumura, Sei Nakata

Miyazaki Medical Association Hospital: Yoshisato Shibata, Nehiro Kuriyama

Kagoshima Medical Center: Hitoshi Nakashima, Yasuhisa Iriki

List C. NEXT Trial

Caress Sapporo Tokeidai Memorial Hospital: Kazushi Urasawa, Ryoji Koshida

Oji General Hospital: Katsuhisa Ishii, Nobuo Kato

Hokkaido Junkanki Hospital: Daisuke Hotta, Masaru Yamaki

Teine Keijinkai Hospital: Mitsugu Hirokami

Cardio-vascular Center Hokkaido Ohno Hospital: Takehiro Yamashita, Masato Nagashima

Caress Sapporo Hokko Memorial Hospital: Yoichi Nozaki

Japan Community Health Care Organization Hokkaido Hospital: Keiichi Igarashi, Jungo Furuya

Aomori Prefectural Central Hospital: Fuminobu Yoshimachi, Dai Miura, Yoshihisa Aida,

Yukinori Sakamoto, Atsushi Konta

Iwate Prefectural Central Hospital: Akihiro Nakamura, Shigefumi Fukui, Sohta Nakajima

Iwate Medical University Hospital: Tetsuya Fusazaki

Tohoku Pharmaceutical University Hospital: Yoshiaki Katahira, Takao Nakano

Sendai Open Hospital: Atsushi Kato, Toru Takii

Iwaki Kyoritsu General Hospital: Yoshito Yamamoto, Tomohiro Tada

Fukushima Medical University Hospital: Yasuchika Takeishi, Kazuhiko Nakazato

Saiseikai Kurihashi Hospital: Yoshimi Ota, Atsushi Honda

Saitama Cardiovascular and Respiratory Center: Tetsuya Ishikawa, Takuro Fujii

Dokkyo Medical University Koshigaya Hospital: Takaaki Komatsu

New Tokyo Hospital: Sunao Nakamura, Naoyuki Kurita

Juntendo University Hospital: Hiroyuki Daida, Katsumi Miyauchi

Sakakibara Memorial Hospital: Itaru Takamisawa

NTT Medical Center Tokyo: Masao Yamasaki

The Cardiovascular Institute Hospital: Junji Yajima, Shingo Tanaka, Ryuichi Funada, Nobuhiro

Murata

Mitsui Memorial Hospital: Kengo Tanabe, Yoshifumi Nakajima

Tokyo Medical University Hospital: Nobuhiro Tanaka, Masashi Ogawa, Naotaka Murata

Teikyo University Hospital: Ken Kozuma, Nobuaki Suzuki

Tokyo Women's Medical University Hospital: Nobuhisa Hagiwara, Fumiaki Mori, Junichi

Yamaguchi

Juntendo University Nerima Hospital: Masataka Sumiyoshi, Kenji Inoue, Shinya Okazaki

Itabashi Chuo Medical Center: Hiroshi Ohta

Saiseikai Yokohama-city Eastern Hospital: Toshiya Muramatsu, Hiroshi Ishimori

Kanto Rosai Hospital: Atsuo Namiki

Yokohama Rosai Hospital: Kenichi Kato, Kazuhiko Yumoto

Tokai University Hospital: Nobuhiko Ogata, Shou Torii

Yokohama City University Medical Center: Kazuo Kimura, Kiyoshi Hibi

Kitasato University Hospital: Taiki Tojo, Takao Shimohama

Kanazawa Cardiovascular Hospital: Masanobu Namura, Yuki Horita

University of Fukui Hospital: Jong-Dae Lee, Hiroyasu Uzui, Akira Nakano

Fukui Cardiovascular Center: Sumio Mizuno, Katsushi Misawa

Ogaki Municipal Hospital: Hiroaki Mukawa, Yohei Shibata, Kazushi Terada

Juntendo University Shizuoka Hospital: Satoru Suwa

Shizuoka General Hospital: Osamu Doi, Hideaki Moriwaki, Hiroki Sakamoto

Okamura Memorial Hospital: Yasuhiro Tarutani

Seirei Hamamatsu General Hospital: Hisayuki Okada

Hamamatsu Medical Center: Masakazu Kobayashi, Terumori Sato, Yohei Takayama

Aichi Medical University Hospital: Hiroaki Takashima, Takayuki Ito, Amano Tetsuya

Tosei General Hospital: Masayoshi Ajioka, Yosuke Murase, Yusuke Sakamoto

Toyota Memorial Hospital: Hisashi Umeda, Kazutaka Hayashi

Fujita Health University Hospital: Yukio Ozaki, Hiroyuki Naruse

Japanese Red Cross Nagoya Daini Hospital: Haruo Hirayama, Yasushi Tatematsu, Hiroki Kamiya

Chubu Rosai Hospital: Tetsuya Amano, Tomohiro Yoshida, Tadayuki Uetani

Nagai Hospital: Kozo Hoshino

Mie University Hospital: Takashi Tanigawa, Toshiki Sawai

Mie Heart Center: Hideo Nishikawa, Hiroyuki Suzuki

Japan Community Health Care Organization Yokkaichi Hazu Medical Center: Masaki Kawamura,

Takashi Yamanaka

Koto Memorial Hospital: Teruki Takeda

Shiga University of Medical Science Hospital: Takashi Yamamoto

Kyoto University Hospital: Takeshi Kimura, Masahiro Natsuaki, Hou Heigen, Hirotooshi

Watanabe

Mitsubishi Kyoto Hospital: Shinji Miki, Tetsu Mizoguchi, Masashi Kato

National Hospital Organization Kyoto Medical Center: Masaharu Akao, Mitsuru Abe

Kyoto Second Red Cross Hospital: Hiroshi Fujita

Osaka University Hospital: Shinsuke Nanto, Masahiro Kumada, Kouichi Tachibana, Keita

Okayama

Sakurabashi Watanabe Hospital: Kenshi Fujii

Osaka City General Hospital: Akira Itoh, Takahiro Naruko, Kei Yunoki

Osaka Saiseikai Noe Hospital: Shunsuke Take, Yoshihiro Kato, Shiho Koyama

Osaka City University Hospital: Takao Hasegawa, Tomokazu Iguchi

Osaka Red Cross Hospital: Tsukasa Inada, Fujio Hayashi

National Cerebral and Cardiovascular Center Hospital: Hiroki Sakamoto, Satoshi Yasuda

Sumitomo Hospital: Yuji Yasuga, Nobuhiro Mitsusada

Higashisumiyoshi Morimoto Hospital: Yuji Sakanoue

Bell Land General Hospital: Toru Kataoka

Kobe City Medical Center General Hospital: Natsuhiko Ehara

Kobe University Hospital: Toshihiro Shinke, Takumi Inoue, Junya Shite, Akihide Konishi

Kansai Rosai Hospital: Masaki Awata, Takayuki Ishihara

Hyogo Prefectural Amagasaki Hospital: Yoshiki Takatsu, Ryoji Taniguchi

Hyogo College of Medicine Hospital: Motomaru Masutani, Masaharu Ishihara

Tenri Hospital: Yoshihisa Nakagawa, Toshihiro Tamura

Japanese Red Cross Society Wakayama Medical Center: Takashi Tamura, Yuichi Kawase,

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Wakayama Medical University Hospital: Takashi Akasaka, Yasushi Ino, Hironori Kitabata

Tottori University Hospital: Masahiko Kato, Yoshiyuki Furuse

Matsue Red Cross Hospital: Kinya Shirota

The Sakakibara Heart Institute of Okayama: Atsushi Hirohata, Eiki Hirose

Kurashiki Central Hospital: Kazushige Kadota, Seiji Habara

Kawasaki Medical School Hospital: Hiroyuki Okura, Yoji Neishi

Hiroshima City Hospital: Masaharu Ishihara, Yasuharu Nakama

Fukuyama Cardiovascular Hospital: Hideo Takebayashi, Kenji Goto

Tsuchiya General Hospital: Nobuo Shiode, Masaya Otsuka, Mamoru Toyofuku

Iwakuni Clinical Center: Satoru Sakuragi

Chikamori Hospital: Kazuya Kawai, Shuichi Seki

University of Occupational and Environmental Health Japan: Shinjo Sonoda, Yoshitaka Muraoka

Fukuoka Wajiro Hospital: Taro Saito, Yoritaka Otsuka

Kurume University Hospital: Takafumi Ueno, Yoshiaki Mitsutake, Hidetoshi Chibana

Kokura Memorial Hospital: Masashi Iwabuchi, Shinichi Shirai

Kouseikai Hospital: Yoshihiro Iwasaki, Masahiko Ishizaki

Saiseikai Kumamoto Hospital: Koichi Nakao, Shinzo Miyamoto

National Hospital Organization Kumamoto Medical Center: Kazuteru Fujimoto

Kumamoto Rousai Hospital: Toshiyuki Matsumura, Takuo Tsurugi

Miyazaki Medical Association Hospital: Yoshisato Shibata, Nehiro Kuriyama

Tenyokai Central Hospital: Hiroshi Yamaguchi, Junichiro Takaoka, Nobuhiko Atsuchi

National Hospital Organization Kagoshima Medical Center: Hitoshi Nakashima, Tetsuro Kataoka,

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