Impact of PARIS and CREDO-Kyoto thrombotic and bleeding risk scores on clinical outcomes in patients with acute myocardial infarction

（急性心筋梗塞における PARIS,CREDO-Kyoto 血栓および出血リスクスコアの検討）

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Short title: Impact of PARIS and CREDO-Kyoto risk scores

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ABSTRACT

Background: The PARIS and CREDO-Kyoto risk scores were developed to identify patients at risks of thrombotic and bleeding events individually. However, these scores have not been well validated in different cohorts.

Methods and Results: This bi-center registry enrolled 905 patients with acute MI undergoing primary PCI. Patients were divided into 3 groups according to the PARIS and CREDO-Kyoto thrombotic and bleeding risk scores. The study endpoints included ischemic (cardiovascular death, recurrent MI, and ischemic stroke) and major bleeding (Bleeding Academic Research Consortium type 3 or 5) events. Of 905 patients, 230 (25%) and 219 (24%) had high thrombotic and bleeding risks with the PARIS scores, while 78 (9%) and 50 (6%) patients did with the CREDO-Kyoto scores. According to the 2 scores, more than 50% of patients with high bleeding risk had concomitant high thrombotic risk. During the mean follow-up period of 714 days, 163 (18.0%) and 95 (10.5%) patients had ischemic and bleeding events. Both PARIS and CREDO-Kyoto scores were significantly associated with ischemic and bleeding events after primary PCI. For ischemic events, the CREDO-Kyoto rather than PARIS thrombotic risk score had better diagnostic ability.

Conclusions: In the present Japanese cohort of acute MI patients undergoing contemporary primary PCI, the PARIS and CREDO-Kyoto thrombotic and bleeding risk scores were discriminative for predicting ischemic and bleeding events.

Key words: risk score; acute myocardial infarction; percutaneous coronary intervention

Introduction

Primary percutaneous coronary intervention (PCI) for patients suffering from acute myocardial infraction (MI) reduces subsequent cardiac events and improves clinical outcomes, and has become a standard-of-care procedure.[1] In patients undergoing PCI, previous studies have shown that both ischemic and bleeding events had a significant impact on mortality in a similar magnitude.[2-4] Recent guidelines recommend risk assessment for both ischemic and bleeding events, and several risk predicting models have been proposed.[5,6] Although the DAPT (Dual Antiplatelet Therapy) and PRECISE-DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) scores are guideline-recommended risk scoring systems, they were developed to guide DAPT duration after PCI and thus do not have capability to evaluate ischemic and bleeding risks individually.[7,8] In this context, the PARIS (Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients) and CREDO-Kyoto (Coronary Revascularization Demonstrating Outcome Study in Kyoto) scores were developed from Western and Japanese PCI populations, both of which include thrombotic and bleeding risk scores respectively.[9,10] However, these scores have not been well validated in a different cohort, especially in patient with acute MI. In the present study, we aimed to evaluate the predictive ability of PARIS and CREDO-Kyoto thrombotic and bleeding risk scores in patients with acute MI undergoing contemporary primary PCI.

Methods

Study Design and Population

This was a retrospective, bi-center, observational study. Between January 2012 and December 2018, a total of 942 patients with acute MI underwent primary PCI at 2 tertiary centers, Chiba University Hospital and Eastern Chiba Medical Center. Acute MI was defined based on the fourth universal definition of MI.[11] Patients with ST-segment elevation MI and non ST-segment

elevation MI were both included. Primary PCI was done in all patients included in the present study according to local standard practice. Patients received DAPT before or at the time of PCI, and the use of intracoronary imaging and contemporary drug-eluting stents were mostly preferred.[12-15] The major exclusion criteria were duplicated patients (n=31), failed PCI (n=4), and no stent implantation (n=2). Thus, 905 patients with acute MI undergoing primary PCI with coronary stenting were included. All participants provided written informed consent for the PCI procedure, and informed consent for the present study was obtained in the form of opt-out. This study was approved by the ethical committee of Chiba University Hospital and Eastern Chiba Medical Center, and was performed in accordance with the Declaration of Helsinki.

PARIS and CREDO-Kyoto Risk Scores

Thrombotic and bleeding risks were assessed by the PARIS and CREDO-Kyoto risk scores, as previously reported (Table 1).[9,10] In brief, the PARIS thrombotic and bleeding risk scores include 6 components in each. Diabetes, acute coronary syndrome presentation, current smoking, renal impairment, prior PCI, and a history of coronary artery bypass grafting are listed as the thrombotic risk score, while the bleeding risk score consists of age, body mass index, current smoking, anemia, renal impairment, and triple therapy (DAPT plus oral anticoagulation) on discharge.[9] On the other hand, the CREDO-Kyoto thrombotic and bleeding risk scores include 8 and 7 items respectively. Renal impairment, atrial fibrillation, peripheral artery disease, anemia, age, heart failure, diabetes, and chronic total occlusion are the components of the thrombotic risk score, whereas the bleeding risk score is composed of low platelet counts, renal impairment, peripheral artery disease, heart failure, prior MI, malignancy, and atrial fibrillation.[10] Patients were divided into low, intermediate, and high thrombotic and bleeding risks according to the thresholds (Table 1).[9,10]

Follow-Up and Study Endpoint

Follow-up data were ascertained from medical records at Chiba University Hospital and Eastern Chiba Medical Center. Guideline recommended DAPT for 12 months in patients with acute MI, although medical treatment was left to the discretion of treating physicians. The primary endpoint of the present study included both ischemic (cardiovascular death, recurrent MI, and ischemic stroke) and bleeding (Bleeding Academic Research Consortium type 3 or 5) events. These events were adjudicated based on the consensus documents.[11,16,17]

Statistical Analysis

Statistical analysis was performed with JMP Pro 15.0.0 (SAS Institute, Cary, USA). All data are expressed as mean ± standard deviation or frequency (%). The Kaplan-Meier analysis was employed to calculate the time to clinical endpoints, and the log-rank test was applied to compare between-group differences. Ischemic and bleeding event rates were also evaluated with landmark analysis using the date of discharge as landmark, excluding patients who died during the index hospitalization. The receiver operating characteristics (ROC) curve analysis was conducted on the ischemic and bleeding events. The area under the curve (AUC) of the ROC curve was compared using the Delong method. A two-sided p value <0.05 was considered statistically significant.

Results

Table 2 and S1 list baseline patient and procedural characteristics. The PARIS thrombotic and bleeding risk scores divided patients into the low, intermediate, and high risks in 207 (23%), 468 (52%), and 230 (25%) and in 233 (26%), 453 (50%), and 219 (24%). The CREDO-Kyoto score determined the low, intermediate, and high thrombotic and bleeding risk groups in 658 (73%), 169 (19%), and 78 (9%) and in 691 (76%), 164 (18%), and 50 (6%), respectively (Figure

1). More than half of patients with high bleeding risk had concomitant high thrombotic risk evaluated with both PARIS and CREDO-Kyoto risk scores (Figure 1). The PARIS and CREDO-Kyoto scores were often discordant. For instance, among patients with high PARIS bleeding risk, 58% were classified as low bleeding risk by the CREDO-Kyoto score (Figure 2).

During the mean follow-up period of 714±710 days, 163 (18.0%) and 95 (10.5%) patients had ischemic and bleeding events (Table 3). Gastrointestinal (35%), vascular (access-site) (26%), and cerebral (11%) bleedings are the frequent types of major bleeding events. Both PARIS and CREDO-Kyoto thrombotic and bleeding risk scores were significantly associated with ischemic and bleeding events (Table S2 and Figure 3 and 4). There were no significant differences between low and intermediate risk groups in ischemic and bleeding events in PARIS risk scores (Figure 3 and 4). A landmark analysis after discharge showed similar results, but the PARIS thrombotic risk score was not significantly associated with ischemic events after discharge (Figure S1). In the ROC curve analysis, the PARIS (AUC 0.56, $p=0.002$) and CREDO-Kyoto (AUC 0.65, $p<0.001$) thrombotic risk scores predicted ischemic events. The CREDO-Kyoto rather than PARID thrombotic risk score had a better diagnostic ability ($p<0.001$) (Figure 5). Both PARIS (AUC 0.62, $p<0.001$) and CREDO-Kyoto (AUC 0.63, $p<0.001$) bleeding risk scores were predictive for bleeding events, with no between-group difference ($p=0.69$) (Figure 5).

Discussion

The present study demonstrated that in patients with acute MI undergoing contemporary primary PCI, the PARIS risk score determined approximately one-quarter of patients as having high thrombotic and bleeding risks, whereas the CREDO-Kyoto score only classified less than 10% of patients as high thrombotic and bleeding risk groups. According to the 2 scores, more than half of patients with high bleeding risk had concomitant high thrombotic risk in this

Japanese cohort. With different components, the PARIS and CREDO-Kyoto scores were often discordant. Although both PARIS and CREDO-Kyoto risk scores were predictive for ischemic and bleeding events, the CREDO-Kyoto scores were more discriminative especially for ischemic events.

Ischemic and Bleeding Risks

Clinical outcomes in patients with acute MI has considerably improved in the few decades, however, MI remains one of the leading causes of morbidity and mortality worldwide.[18,19] Recent nationwide registry data clearly showed that during the last 20 years, the introduction of invasive and more intense antithrombotic treatment has been associated with a substantial reduction of ischemic events and mortality but an increase in bleeding events following MI.[20] It is well known that both ischemic and bleeding events after MI are strongly linked with subsequent mortality.[2-4] For instance, in a large-scale retrospective cohort (n=32906), major bleedings were associated with an increased risk of death in patients undergoing PCI (adjusted hazard ratio 1.61, 95% confidence interval 1.30-2.00), similar to that after an MI (adjusted hazard ratio 1.91, 95% confidence interval 1.62-2.25).[4] Therefore, recent guidelines recommend risk assessment from the viewpoint of both ischemic and bleeding events,[5,6] which may be useful for guiding patient care and antithrombotic therapy.

PARIS and CREDO-Kyoto Risk Scores

The DAPT and PRECISE-DAPT scores are the recommended risk scoring systems by current international guidelines.[5,6] However, these scores were exclusively developed to guide the duration of DAPT after PCI, and therefore are not able to assess ischemic and bleeding risks individually.[7,8] The PARIS risk scores were developed from a prospective, multicenter observational study of patients undergoing PCI in the United States and European countries, in

which only 8% of patients with acute MI were included. From the derivation cohort, 6 items were identified as factors associated with thrombotic and bleeding events, respectively (Table 1). In the original paper of PARIS, patients at high bleeding risk accounted for less than 10% of a total cohort, in which nearly 40% of patients were classified as concomitant high thrombotic risk.[9] The CREDO-Kyoto risk scores were generated from a Japanese cohort of 4778 participants treated by PCI with first generation sirolimus-eluting stent including 15% of acute MI patients, in which 8 and 7 items were identified as significant factors associated with thrombotic and bleeding events (Table 1). According to the CREDO-Kyoto scores, patients were at high bleeding risk in 13% in the original derivation cohort, of whom 59% had a concomitant high thrombotic risk.[10] Patients at high bleeding risk accounted for 24% and 6% of the present MI cohort assessed by the PARIS and CREDO-Kyoto scores against 9% and 13% in the original reports, indicating that different risk scores in different populations determine patient risks differently. Nevertheless, the present study reinforces the fact that patients at high bleeding risk are likely to have concomitant high thrombotic risk. Both PARIS and CREDO-Kyoto risk scores were validated with another cohort in the original papers, although they have not been well investigated by different study groups.

In the present study, the PARIS and CREDO-Kyoto thrombotic and bleeding risk scores were both predictive for subsequent ischemic and bleeding events after MI, suggesting the usefulness of these scores in patients with acute MI for the risk stratification. Interestingly, the CREDO-Kyoto thrombotic score had a higher AUC than the PARIS thrombotic risk score for ischemic events, and the CREDO-Kyoto rather than PARIS risk scores were more discriminative especially in low and intermediate risk groups. Given that CREDO-Kyoto scores were derived from a Japanese cohort as well as the present study, the racial difference may play an important role in predicting ischemic and bleeding risks. Only a few similar components such as diabetes and renal impairment are included between PARIS and CREDO-Kyoto risk

scores, and the majority of items are discordant, illustrating the significant differences in the two risk scores from Western and Eastern countries. It should be also noted that the CREDO-Kyoto rather than PARIS risk scores found the fewer number of patients at high thrombotic/bleeding risks. A sub-analysis of the ReCre8 trial recently investigated the diagnostic ability of PARIS and CREDO-Kyoto scores, and found high PARIS thrombotic and bleeding risks in 15% and 8%, and high CREDO-Kyoto thrombotic and bleeding risks in 5% and 6%.[21] This sub-analysis showed that discriminative capability of PARIS thrombotic and bleeding risk scores evaluated with AUC was marginal (0.59 and 0.55), while CREDO-Kyoto thrombotic and bleeding risk scores displayed moderate discrimination (0.68 and 0.67). Although the ReCre8 was a device-specific randomized trial and employed specific antithrombotic regimen in which troponin-negative patients received dual antiplatelet therapy for only 1 month, the overall results may be in line with our study. Further studies are warranted to confirm our results and to clarify whether risk score-based patient care can improve clinical outcomes, in large-scale prospective cohorts.[22-25]

Study Limitations

Some limitations to our study should be considered. This was a retrospective study, and the sample size was modest. Medical treatment was left to treating physicians, and antithrombotic regimens (e.g. duration of dual antiplatelet therapy) might have affected the results. Since the PARIS and CREDO-Kyoto scores can determine thrombotic and bleeding risks individually, these 2 risk scores were evaluated in the present study. However, the impact of different risk predicting models (e.g. Academic Research Consortium definition of High Bleeding Risk) is unknown.[26-29] In addition, while the present study suggested the possible superiority of CREDO-Kyoto score over the PARIS score, real-world data from Western countries to validate the CREDO-Kyoto risk scores are needed.

Conclusions

The PARIS and CREDO-Kyoto thrombotic and bleeding risk scores were demonstrated as significantly predictive scoring systems in patients with acute MI undergoing primary PCI. In this contemporary dataset in Japan, patients at high bleeding risk had concomitant high thrombotic risk in more than 50%. The 2 different risk scores often determined patient risks differently. The CREDO-Kyoto rather than PARIS risk scores might be more discriminative in the present cohort, suggesting the racial differences in scoring systems.

Sources of Funding

None

Data Availability

The data will not be shared.

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Table 1. PARIS and CREDO-Kyoto Thrombotic and Bleeding Risk Scores

	PARIS risk score		CREDO-Kyoto risk score	
	Thrombotic	Bleeding	Thrombotic	Bleeding
Number of items	6	6	8	7
Components and assigned scores	DM (1 or 3); ACS (1 or 2); Current smoking (1); CCr <60 ml/min (2); Prior PCI (2); Prior CABG (2)	Age (1, 2, 3, or 4); BMI <25 or ≥35 (2); Current smoking (2); Anemia (3); CCr <60 ml/min (2); TT on discharge (2)	CKD (2); AF (2); PAD (2); Anemia (2); Age (1); HF (1); DM (1); CTO (1)	Low platelet (2); CKD (2); PAD (2); HF (2); Prior MI (1); Malignancy (1); AF (1)
Cut-off value	Low (0-2), intermediate (3-4), and high (5-10)	Low (0-3), intermediate (4-7), and high (8-14)	Low (0-1), intermediate (2-3), and high (4-12)	Low (0), intermediate (1-2), and high (3-11)

ACS, acute coronary syndrome; AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; CCr, creatinine clearance; CKD, chronic kidney disease; CTO, chronic total occlusion; DM, diabetes mellitus; HF, heart failure, MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TT, triple therapy.

Table 2. Baseline Characteristics

Variable	All (n=905)
Age (years)	66.8±12.1
Men	700 (77%)
Body mass index (kg/m^2)	24.1±3.6
Hypertension	607 (67%)
Diabetes mellitus	340 (38%)
Dyslipidemia	550 (61%)
Current smoker	311 (34%)
Prior MI	54 (6%)
Prior PCI	76 (8%)
Prior CABG	16 (2%)
Prior heart failure	17 (2%)
Atrial fibrillation	56 (6%)
Peripheral artery disease	18 (2%)
Malignancy	53 (6%)
eGFR (ml/min/1.73 m^2)	64.3±23.8
Hemoglobin (g/dl)	13.8±2.2
Platelet count (×10^9/l)	22.8±7.7
Type of MI	
STEMI	616 (68%)
NSTEMI	289 (32%)
Killip class on admission	
I	600 (66%)
II	74 (8%)
III	57 (6%)
IV	174 (19%)
Cardiac arrest on admission	122 (13%)
Medications at discharge	
Antithrombotic treatment	
DAPT	828 (91%)

Triple therapy	58 (6%)
Aspirin	859 (95%)
P2Y12 inhibitor	855 (94%)
Clopidogrel	441 (52%)
Prasugrel	412 (48%)
Ticlopidine	2 (0.2%)
Oral anticoagulant	99 (11%)
β-blocker	648 (72%)
ACE-I or ARB	716 (79%)
Calcium channel blocker	188 (21%)
Diuretic	187 (21%)
Statin	772 (85%)
Culprit vessel	
RCA	269 (30%)
LMT/LAD	460 (51%)
LCX	145 (16%)
Undetermined	31 (3%)
Chronic total occlusion	24 (3%)
Access site	
Radial artery	775 (86%)
Femoral artery	110 (12%)
Brachial artery	20 (2%)
Mechanical circulatory support	
IABP	106 (12%)
ECMO	55 (6%)
IVUS	876 (97%)
Drug-eluting stent	823 (91%)

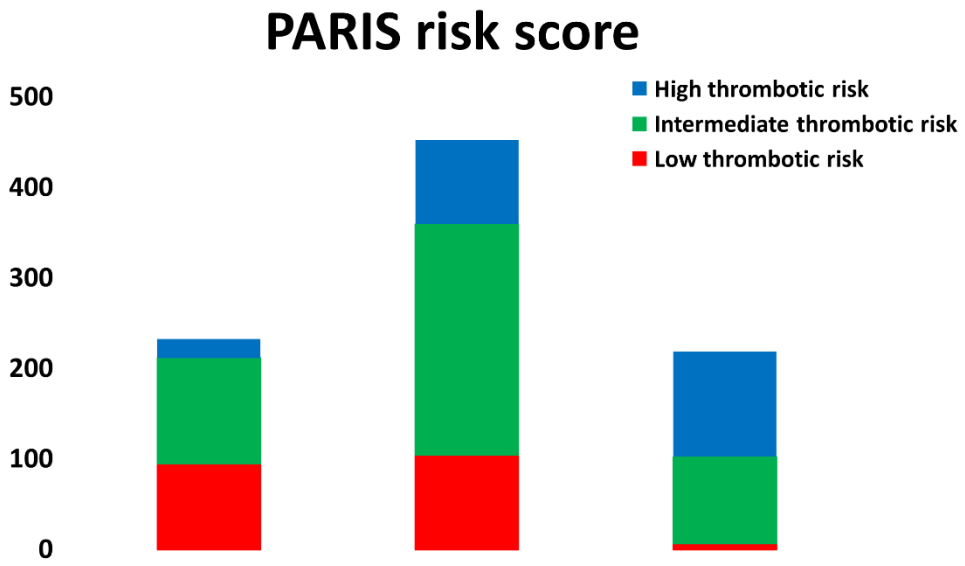
Values are mean ± standard deviation or n (%). ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pumping; IVUS, intravascular ultrasound; LAD, left anterior descending artery; LCX, left circumflex; LMT, left main trunk; MI, myocardial infarction; NSTEMI, non ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right

coronary artery; STEMI, ST-segment elevation myocardial infarction.

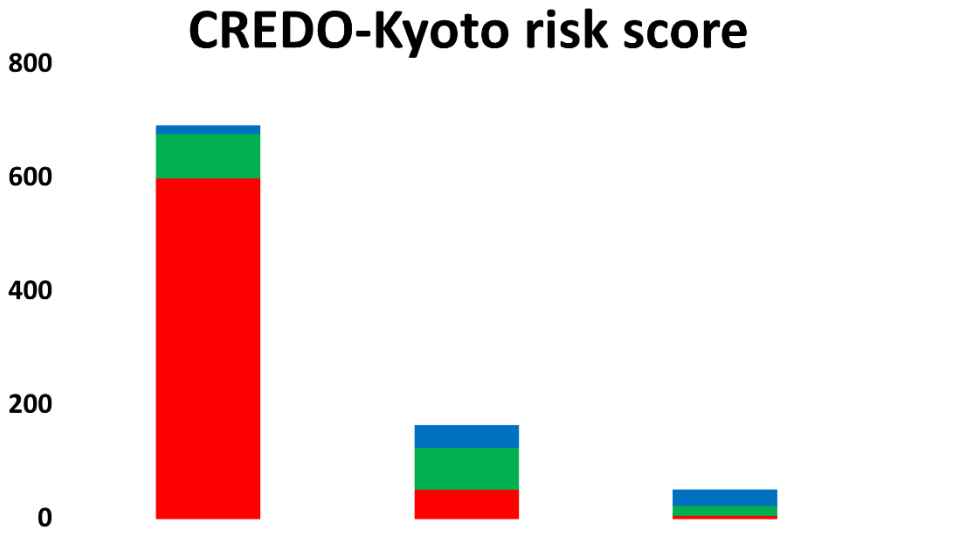
Table 3. Clinical Outcomes

Variable	All (n=905)
Ischemic events	163 (18.0%)
Cardiovascular death	105 (11.6%)
Recurrent MI	40 (4.4%)
Ischemic stroke	36 (4.0%)
Bleeding events	95 (10.5%)
BARC 3	87 (9.6%)
BARC 5	8 (0.9%)

BARC, Bleeding Academic Research Consortium; MI, myocardial infarction.

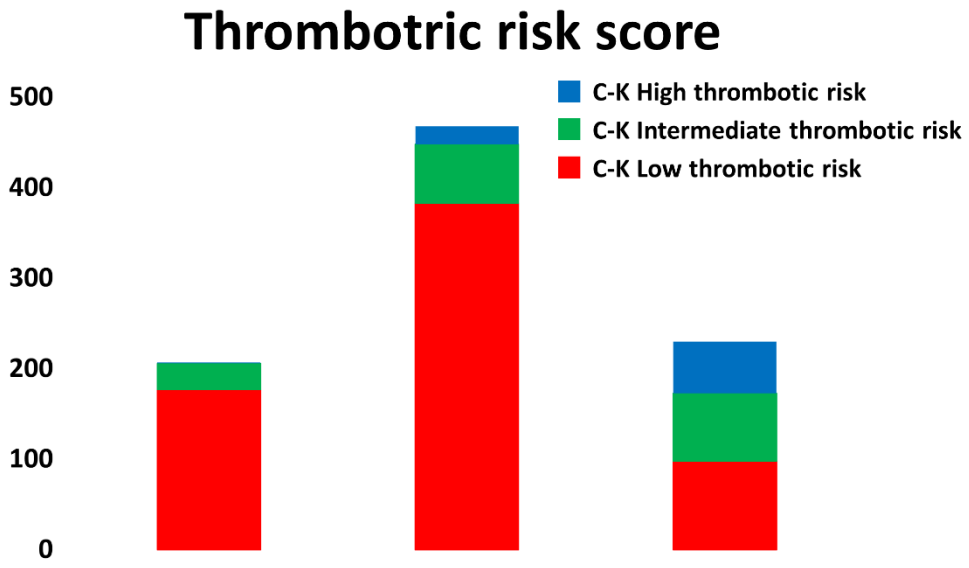


	Low bleeding risk	Intermediate bleeding risk	High bleeding risk	Total
High thrombotic risk	21	93	116	230
Intermediate thrombotic risk	117	255	96	468
Low thrombotic risk	95	105	7	207
Total	233	453	219	905

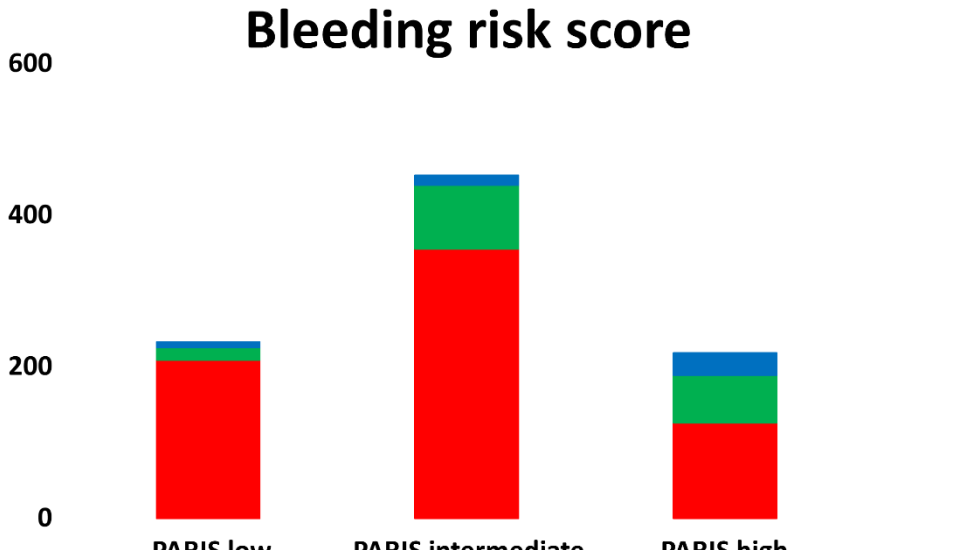


	Low bleeding risk	Intermediate bleeding risk	High bleeding risk	Total
High thrombotic risk	13	38	27	78
Intermediate thrombotic risk	78	74	17	169
Low thrombotic risk	600	52	6	658
Total	691	164	50	905

Figure 1. Distribution of the thrombotic risk score categories according to the bleeding risk score categories.



	PARIS low thrombotic risk	PARIS intermediate thrombotic risk	PARIS high thrombotic risk	Total
C-K High thrombotic risk	1	20	57	78
C-K Intermediate thrombotic risk	29	65	75	169
C-K Low thrombotic risk	177	388	98	658
Total	207	468	230	905



	PARIS low bleeding risk	PARIS intermediate bleeding risk	PARIS high bleeding risk	Total
C-K High bleeding risk	7	13	30	50
C-K Intermediate bleeding risk	17	84	63	164
C-K Low bleeding risk	209	356	126	691
Total	233	453	219	905

Figure 2. Distribution of the PARIS and CREDO-Kyoto (C-K) risk score categories in thrombotic and bleeding risks.

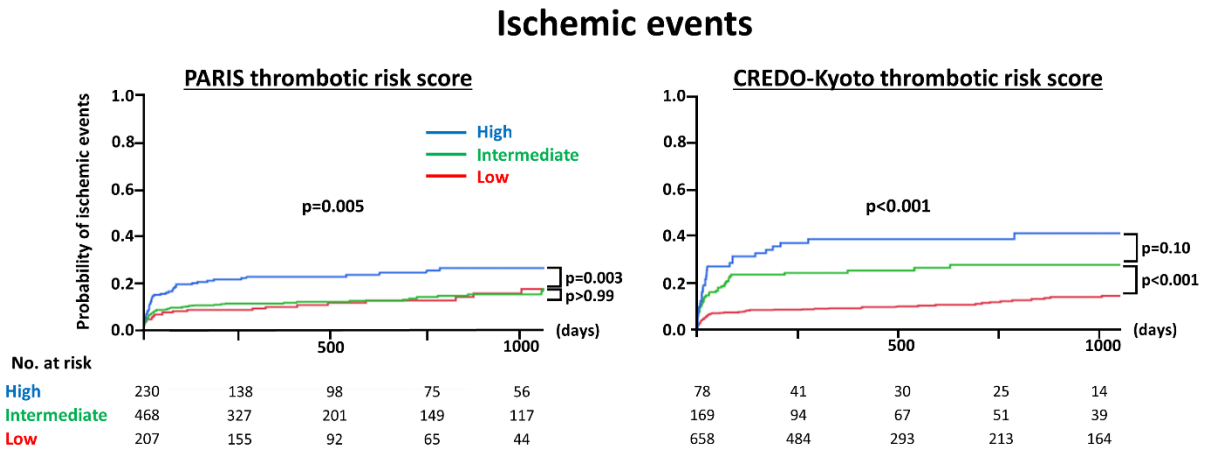


Figure 3. Cumulative incidence of ischemic events according to the PARIS and CREDO-Kyoto risk score categories. Ischemic events were defined as a composite of cardiovascular death, recurrent myocardial infarction, and ischemic stroke.

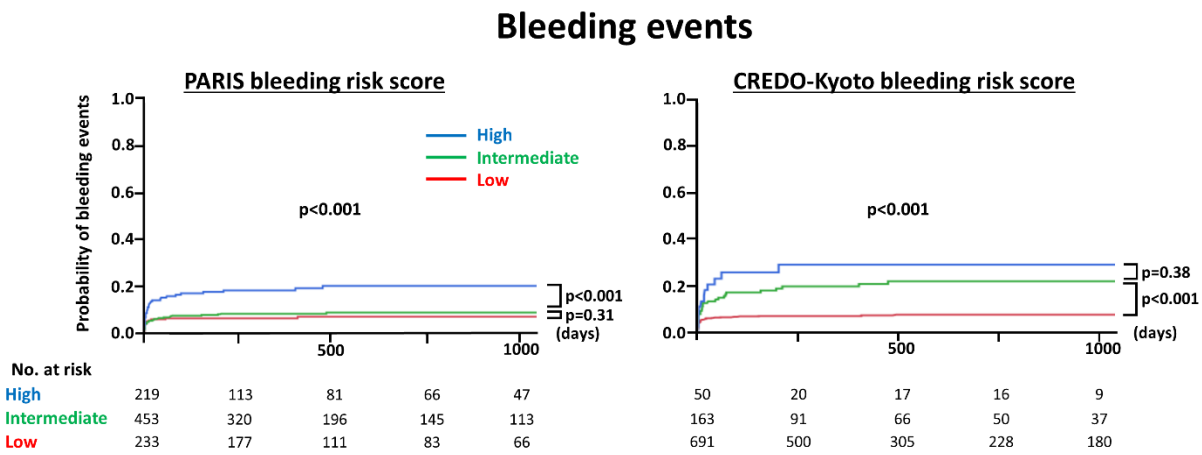


Figure 4. Cumulative incidence of major bleeding events according to the PARIS and CREDO-Kyoto risk score categories. Major bleedings were defined as Bleeding Academic Research Consortium type 3 or 5 events.

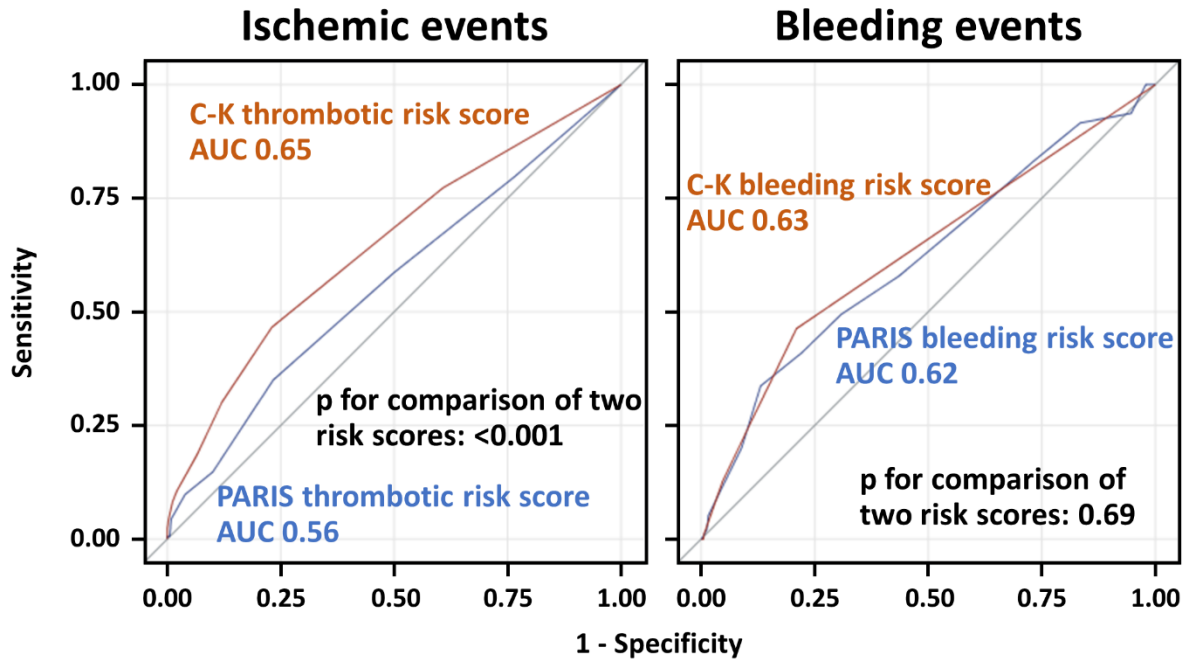


Figure 5. The receiver operating characteristics curve analysis for ischemic and bleeding events with area under the curve comparisons of PARIS and CREDO-Kyoto (C-K) risk scores.

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