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Research paper

Individual acute-phase bleeding and thrombotic risk balance assessment in patients undergoing percutaneous coronary intervention for acute myocardial infarction

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ABSTRACT

Background: Individualized treatment approach based on pre-procedural precise risk balance assessment between bleeding and thrombosis would be desirable for patients with myocardial infarction (MI) undergoing emergent percutaneous coronary intervention (PCI) in this ultra-short dual antiplatelet therapy era. We aimed to develop and validate a quick thrombosis/bleeding risk-balance assessment tool.
Methods: We developed and validated a novel thrombosis/bleeding risk-balance assessment tool using individual patient data from the prospective multicenter MI registry. Individual risks of thrombosis and bleeding within 7 days of the index PCI were estimated using a multinomial logistic regression model. The model was developed in the derivation cohort (4554 patients enrolled during 2003–2009) and validated in the validation cohort (2215 patients during 2010–2014).
Results: A total of 6769 patients (66 ± 12 years, 5175 men) were eligible in this analysis. Predictive performance of the multinomial logistic regression models for bleeding and thrombosis assessed by calibration plots was good both in the derivation and validation cohorts. The net predicted probability (NPP) was defined as predicted probability of bleeding event (%) – predicted probability of thrombotic event (%). The NPP successfully stratified patients into those with a higher risk of bleeding than thrombosis and those with a higher risk of thrombosis than bleeding. This finding was consistent between the derivation and validation cohorts.
Conclusions: We have established the risk balance assessment model for bleeding and thrombosis. Pre-procedural quick and precise assessment of the risk balance may help a decision making of procedural strategy and antithrombotic regimens in STEMI/non-STEMI patients undergoing PCI.

1. Introduction

Many recent trials suggested the short-dual antiplatelet therapy (DAPT) (1–3 months) is a treatment of choice for stable coronary disease [1–4]. However, thrombotic events remain to be an important concern of interventional cardiologists. The short DAPT strategy might not be

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readily applicable especially for acute coronary syndrome [5–7]. Physicians need to precisely assess the balance assessment between bleeding and thrombotic risk. Thrombotic risk and bleeding risks can be separately estimated with the risk prediction tools like Asian Dual antiplatelet therapy score (ADAPT score) and CREDO-Kyoto (Coronary Revascularization Demonstrating Outcome Study in Kyoto) score [8,9]. Two individual prediction models for bleeding and thrombotic events may work well for the prediction of each event. However, the multinomial logistic regression model will outperform the previous models created by the simple logistic regression analysis in terms of risk balance assessment as described later in detail.

Furthermore, these models can predict long-term (>1 year) bleeding and thrombotic risks. However, regardless of the patients' risk balance, patients are commonly treated with single antiplatelet after 1 year of index PCI. Bleeding and thrombotic events mainly occur in the acute phase, and the risks exponentially decrease over time [10]. Therefore, the assessment tool for short-term risk balance would be warranted to finetune the treatment strategy and further improve the clinical outcomes in acute phase.

In this study, we developed and validated an acute-phase thrombosis/bleeding risk-balance assessment tool for acute MI patients undergoing percutaneous coronary intervention (PCI) using the multinomial logistic regression model.

2. Materials and methods

2.1. Study population

This study is a post-hoc subanalysis of the Osaka Acute Coronary Insufficiency Study (OACIS) database (N = 12,093) (UMIN000004575). The OACIS is a prospective, multicenter cohort study designed to collect and analyze demographic, procedural and outcome data in patients with STEMI/NSTEMI at 25 collaborating hospitals with cardiac emergency units [11,12]. A diagnosis of acute MI was made if the patient fulfilled at least 2 of the following 3 criteria: (1) history of central chest pressure, pain, or tightness lasting ≥30 min, (2) typical ECG changes (i.e., ST-segment elevation ≥0.1 mV in 1 standard limb lead or 2 precordial leads, ST-segment depression ≥0.1 mV in 2 leads, abnormal Q waves, or T-wave inversion in 2 leads), and (3) a rise in serum creatinine phosphokinase concentration to more than twice the normal laboratory value [13,14]. The OACIS enrolled patients from 1998 to 2014 and followed them up until 2019. In this subanalysis, we used the data of patients who underwent emergent PCI within 24 h of hospitalization and had clinical outcome data available (Fig. 1). Further details are described in the supplemental file.

2.2. Study endpoints

The bleeding endpoint of the present study is major bleeding within 7 days of PCI. Major bleeding in the OACIS registry was defined as bleeding events fulfilling at least one of the followings: 1) hemoglobin drop ≥4 g/dL, 2) intracranial hemorrhage, 3) requiring surgical treatment, or 4) any transfusion. Major bleeding data was available only at 7-day follow-up, and data collection was done only during 2003–2014. The coronary thrombotic endpoint is any recurrent MI within 7 days of PCI. Any recurrent MI was defined as recurrence of MI regardless of lesion derived from the first culprit site [13]. Criteria for diagnosis of recurrent MI were identical to those used at the time of registration. MI data was collected during the entire study period (1998–2019). Information on clinical events was collected by local investigators when visiting outpatient clinics or through verbal or written contact with patients or family members.

2.3. PCI procedure and post-PCI medication

Details are described in the supplemental file.

2.4. Patient and public involvement

This research was conducted without patient involvement.

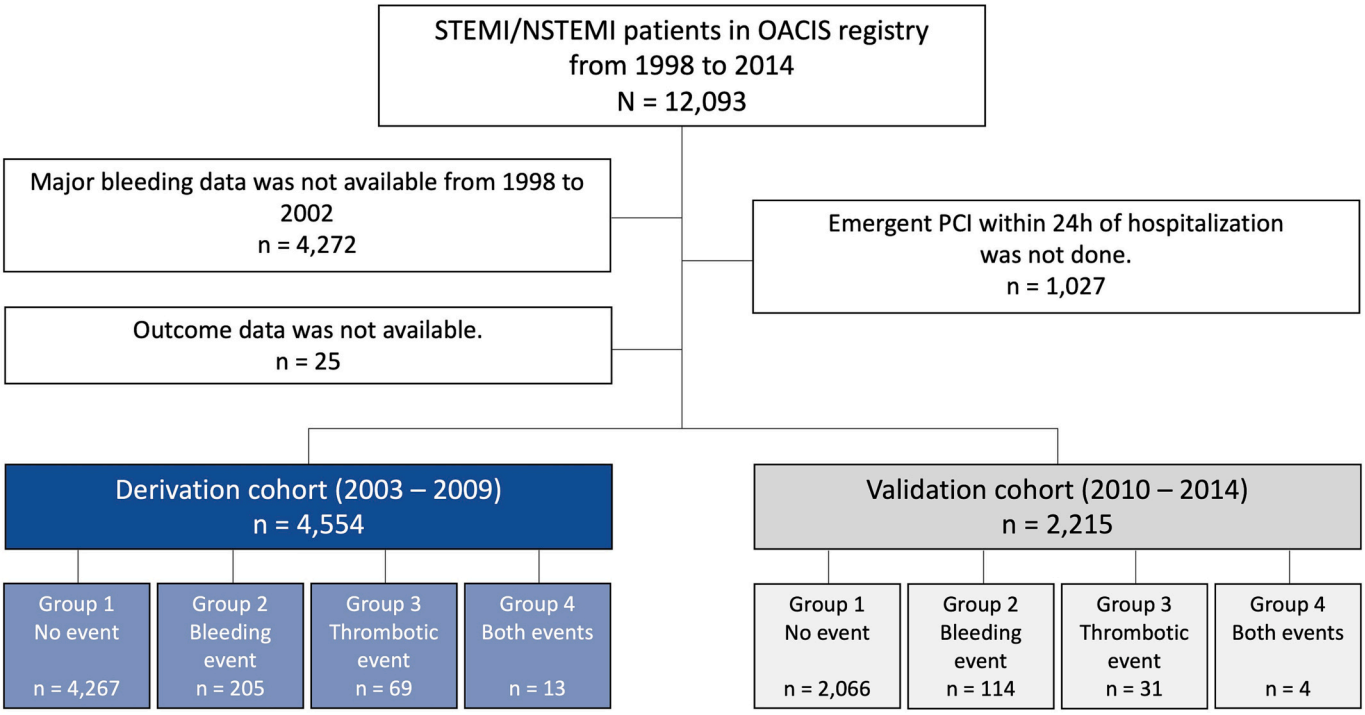

Fig. 1. Patient flowchart.
Abbreviations: ST/non-ST elevation myocardial infarction (STEMI/NSTEMI).

2.5. Statistical analysis

Full details of the statistical analysis are described in the supplemental file. All statistical analyses were performed with R software (version 4.0.5; R Foundation for Statistical Computing, Vienna, Austria). *P* value of <0.05 was considered statistically significant.

2.5.1. Multinomial logistic regression model

We used the multinomial logistic regression model to predict a probability of belonging to a category of interest. The dataset of the OACIS (2003–2014) was divided based on enrolment period into a derivation cohort to construct a prediction model and a validation cohort to assess the validity of the model. The derivation cohort consisted of patients enrolled between 2003 and 2009, whereas the validation cohort consisted of those enrolled between 2010 and 2014. This approach was selected because random sample splitting is not recommended to avoid overfitting the data, which should instead be subdivided based on a time period or geographical location [15].

The dependent variable of the present model was the group of clinical events. Patients were categorized into 4 groups according to the clinical event within 7 days of PCI: group 1) no event, group 2) bleeding event (patients who experienced major bleeding only), group 3) thrombotic event (patients who experienced. Any recurrent MI only), and group 4) both bleeding and thrombotic events (patients who experienced both major bleeding and any recurrent MI). Because we aimed to differentiate groups 2 (bleeding only) or 3 (thrombosis only) not only from group 1 (no event) but also from group 4 (both bleeding and thrombosis), we selected the multinomial logistic regression model rather than 2 individual binary logistic regression models for bleeding event and thrombotic event. The multinomial regression model can evaluate both events in a single model, which may take into an account unknown correlation between both events.

The independent variables used in this study are followings: age ≥ 75 years, female sex, diabetes mellitus, hypertension, anemia (hemoglobin level < 12 g/dL in women and < 13 g/dL in men according to the World Health Organization definition), creatinine clearance <60 mL/min, previous myocardial infarction or PCI, atrial fibrillation, and heart failure. These clinically relevant covariates were selected based on the previously reported Asian prediction scoring systems (ADAPT score and CREDO-Kyoto Score) and data availability in the current dataset [8,9]. The laboratory data were obtained on hospital admission before PCI. Atrial fibrillation was defined as atrial fibrillation detected by electrocardiogram on hospital admission. Heart failure was defined as that diagnosed within 1 week of hospital admission. The variables were included in the multinomial model all together in order to evaluate their bidirectional impacts both on bleeding and thrombotic events. Because the exclusion of cases with missing data can cause bias in this analysis and loss of power in detecting statistical differences, missing data were imputed by random forest imputation using the "missForest" package prior to the analysis. This multinomial regression model (multinom function in 'nnet' package) provides odds ratio for belonging to a particular group with reference to group 1 (no event group). Predicted probability of belonging to a particular group was calculated using the following formula:

$$P = \frac{1}{1 + e^{-(b_0 + b_1 x_1 + b_2 x_2 + \cdots + b_i x_i)}}$$

where *P* is the probability of being in a particular group; *e* is the base of the natural logarithm; x_i is the independent variable; b_0 is the coefficient on the constant term; b_i is the coefficient on the independent variable. Performance of the model was assessed for bleeding (group 2) and thrombotic event (group 3) groups individually, but not for both events group (group 4) because of the limited sample size of the group. Discriminative performance of the model was studied with the concordance (C) statistic, which is identical to the area under the receiver-operating characteristic curve. Predictive performance was assessed with calibration plots.

2.5.2. Risk balance calculator

We created the risk balance calculator, "OACIS Acute-phase Bleeding and Thrombotic Risk Balance Calculator". Readers can easily calculate the predicted risk probability of bleeding event, thrombosis, and both events with this calculator (Supplemental File). We defined the net predicted probability (NPP) as follows: predicted probability of bleeding event (%) – predicted probability of thrombotic event (%). Positive value of the NPP indicates that the predicted probability of bleeding event is higher than that of thrombotic event. Negative value of the NPP indicates that the predicted probability of thrombotic event is higher than that of bleeding event. The calculator provides treatment recommendation; bleeding risk-oriented strategy (NPP > 0 %) or thrombotic risk-oriented strategy (NPP < 0 %). Patients in the derivation cohort were divided into quintiles of NPP. In each quintile of NPP, observed event rates of bleeding event, thrombotic event, and both bleeding and thrombotic events were evaluated. The validation cohort was also divided into 5 groups based on the range of each quintile in the derivation cohort. Observed event rates of the clinical events were evaluated in these groups.

3. Results

3.1. Study subjects

Patient flowchart is presented in Fig. 1. A total of 12,093 patients (66 ± 12 years, 9096 males) were enrolled between 1998 and 2014 from 25 institutions. In this analysis, 6769 patients [66 ± 12 years, 5175 men (76.5 %), follow-up duration 1266 ± 748 days] were eligible. Event rates of bleeding, thrombosis, and both within 7 days of PCI were 4.7 % (319 patients), 1.5 % (100 patients), and 0.3 % (17 patients), respectively (Supplemental Fig. 1). The derivation and validation cohorts consisted of 4554 and 2215 patients, respectively. Both cohorts showed similar distribution of these clinical events (Supplemental Fig. 1).

3.2. Patient characteristics

Baseline characteristics of the patients stratified by the groups in the derivation and validation cohorts are tabulated in Tables 1 and 2, respectively. Patients in the group 2 (bleeding event group) were older, more likely to be female, had a higher prevalence of chronic kidney disease, cancer, and anemia. Patients in the group 3 (thrombotic event group) were less likely to be female, more frequently had a history of myocardial infarction or PCI, and less frequently had anemia.

3.3. Impact of the risk factors on bleeding and thrombotic events

Fig. 2 illustrates the impact of the risk factors on bleeding (group 2), thrombotic (group 3), or both events (group 4) within 7 days of PCI with reference to the no event group (group 1). The multinomial logistic regression model showed that age ≥ 75 years increased both bleeding event [Odds ratio (OR) 1.10; 95 % confidence interval (CI) 0.78–1.54] and thrombotic event (OR 1.86; 95%CI 1.03–3.37), but the impact was greater on thrombotic event than on bleeding event. Diabetes mellitus, hypertension, and atrial fibrillation had similar impact on bleeding and thrombosis. Female sex, anemia, and chronic kidney disease (creatinine clearance <60 mL/min) were all associated with increased bleeding risk and decreased thrombotic risk. Previous MI or PCI was associated with thrombotic event (OR 2.16; 95%CI 1.24–3.75). Heart failure had the greatest impact on both bleeding and thrombosis, but its impact was greater on bleeding rather (OR 4.21; 95%CI 3.11–5.69) than thrombosis (OR 1.86; 95%CI 1.26–3.59).

Table 1
Baseline characteristics in the derivation cohort.

	Group 1	Group 2	Group 3	Group 4		
	No event	Bleeding event	Thrombotic event	Both bleeding and thrombotic events	P value	Missing (%)
Number	4267	205	69	13		
Age	66.12 (11.78)	72.27 (11.72)	66.91 (13.04)	70.62 (10.15)	<0.001	0
Age ≥ 75 years	1075 (25.2)	95 (46.3)	23 (33.3)	4 (30.8)	<0.001	0
Female sex	1023 (24.0)	85 (41.5)	11 (15.9)	5 (38.5)	<0.001	0
Body mass index	23.89 (3.62)	22.05 (3.48)	23.26 (3.66)	22.38 (4.67)	<0.001	5.2
Patient history						
Diabetes mellitus	1408 (33.8)	77 (40.3)	25 (38.5)	5 (41.7)	0.228	2.6
Hypertension	2673 (64.4)	133 (68.6)	40 (61.5)	8 (66.7)	0.64	2.9
Dyslipidaemia	1930 (46.9)	49 (25.8)	34 (53.1)	6 (50.0)	<0.001	3.9
Smoking history	2593 (61.9)	85 (43.8)	40 (61.5)	8 (61.5)	<0.001	2.1
Cerebrovascular disease	401 (9.7)	22 (11.1)	9 (13.8)	2 (15.4)	0.547	2.7
Cancer	229 (5.5)	18 (9.0)	4 (6.2)	0 (0.0)	0.154	2.7
Previous MI or PCI	593 (14.2)	43 (21.5)	19 (29.2)	4 (30.8)	<0.001	2.1
ST elevation myocardial infarction	3628 (85.5)	166 (83.0)	61 (89.7)	11 (84.6)	0.578	0.7
Q wave myocardial infarction	2029 (48.0)	104 (52.0)	40 (58.8)	4 (30.8)	0.121	1.1
Culprit vessel						
Right coronary artery	1547 (36.9)	73 (36.3)	17 (24.6)	5 (45.5)	0.188	1.8
Left anterior descending artery	1987 (47.4)	88 (43.8)	44 (63.8)	4 (36.4)	0.029	1.8
Left circumflex artery	692 (16.5)	28 (13.9)	8 (11.6)	2 (18.2)	0.548	1.8
Left main trunk	75 (1.8)	27 (13.4)	2 (2.9)	1 (9.1)	<0.001	1.8
Killip classification III or IV	400 (9.4)	79 (38.5)	12 (17.4)	2 (15.4)	<0.001	0
Thrombolysis	188 (4.5)	15 (7.4)	11 (16.4)	2 (15.4)	<0.001	1.2
IABP	711 (16.7)	116 (56.6)	28 (40.6)	9 (69.2)	<0.001	0
PCPS	106 (2.5)	68 (33.2)	4 (5.8)	5 (38.5)	<0.001	0
Peak creatine kinase	2986.77 (2984.78)	5583.71 (7509.41)	3466.40 (3201.11)	6744.08 (8924.61)	<0.001	4.4
Peak creatine kinase myocardial band	281.67 (365.99)	422.95 (629.55)	335.48 (307.81)	361.16 (302.23)	<0.001	11
Atrial fibrillation	274 (6.5)	24 (11.9)	5 (7.4)	2 (15.4)	0.014	0.5
Creatinine clearance <60 mL/min	1466 (35.7)	133 (70.7)	24 (37.5)	5 (41.7)	<0.001	4
Anemia	736 (27.3)	83 (58.9)	8 (20.5)	4 (50.0)	<0.001	36.7
Heart failure	786 (18.4)	112 (54.6)	24 (34.8)	5 (38.5)	<0.001	0.1
Antiplatelets	4012 (98.8)	120 (95.2)	55 (91.7)	7 (87.5)	<0.001	6.6
Anticoagulants	656 (16.2)	22 (17.5)	18 (30.0)	2 (25.0)	0.032	6.6

Data are presented as number (percentage) or mean (standard deviation) with listwise deletion. Abbreviations: IABP, intra-aortic balloon pumping; MI, myocardial infarction; PCI, percutaneous coronary intervention; PCPS, percutaneous cardio-pulmonary support.

3.4. Predictive and discriminative performance of the multinomial model

Two case examples of risk balance assessment with the "OACIS Acute-phase Bleeding and Thrombotic Risk Balance Calculator" are shown in Fig. 3. Calibration plots for bleeding and thrombotic events are depicted in Supplemental Fig. 2. Predictive performance of the models for bleeding and thrombosis was good both in the derivation and validation cohorts. Discriminative performance of the models for bleeding showed fair discrimination: C statistic = 0.78 in the derivation cohort and 0.72 in the validation cohort [16]. Discriminative performance for thrombosis showed poor or failed to discriminate: C statistic = 0.67 in the derivation cohort and 0.59 in the validation cohort [16].

Patients with positive NPP (n = 3702) showed a higher bleeding event rate [195 (5.3 %)] than thrombotic event rate [48 (1.3 %)], while those with negative NPP (n = 852) showed a higher thrombotic event rate [21 (2.5 %)] than bleeding event rate [10 (1.2 %)] in the derivation cohort (Supplemental Table 1). These findings were consistent in the validation cohort as well (Supplemental Table 2).

We divided the patients into quintiles of NPP (Fig. 4). In the first quintile, as median value was negative, thrombotic event rate was higher than bleeding event rate. In the 2nd quintile, as the NPP was almost 0, event rate was similar between bleeding and thrombotic events. In the 3rd, 4th, and 5th quintiles, relative weight of bleeding event compared with thrombotic event got incrementally greater as the NPP got higher. The same findings were shown in the validation cohort.

4. Discussion

In this study, we established and validated the risk balance assessment tool for bleeding and thrombosis from the dataset of the real-world prospective STEMI/NSTEMI registry. The multinomial model successfully stratified patients with different thrombotic and bleeding risk balances. This analysis showed that majority of the PCI patients (80 %) had a neutral risk balance or a higher bleeding risk than thrombotic risk, whereas the patients with a higher thrombotic risk than bleeding risk is a minority (20 %).

Many recent randomized controlled trials assessing the safety of ultra-short dual antiplatelet therapy (DAPT) strategy have led many physicians to pay more careful attention on the risk assessment of bleeding events than they used to [4,17,18]. Nevertheless, thrombotic events remain to be important concern for interventionalists especially for PCI to MI lesions. There should be a cohort of those with a higher thrombotic risk than bleeding risk. In this short-DAPT era, however, such high-thrombotic risk patients are at a risk of being uniformly treated with short DAPT strategy. Because such patients are minority (one fifth of the whole population), interventionalists need to carefully identify them and treat appropriately. The established tool enables easy pre-procedural assessment and would help appropriate decision-making of the treatment strategy.

Several risk assessment tools have been published previously [8,9,19]. The most recent one was proposed by Urban et al. from the dataset of centers in Europe, the US, and Asia (N = 6641) [20]. Of note, their model was specific for high bleeding risk patients. This model also can provide trade-off assessment between bleeding and thrombotic events. Although the prediction tools previously reported worked well, MI patients were less represented in the studies from which these models derived. Since MI presentation itself is one of the strong predictors of thrombotic events and prompt risk balance assessment is essential for a decision making of appropriate treatment strategy during primary PCI, easy assessment tool specific for MI patients undergoing PCI would be warranted. We previously proposed the practical assessment method for the risk balance assessment using ARC-HBR criteria [21]. However, the

Table 2
Baseline characteristics in the validation cohort.

	Group 1	Group 2	Group 3	Group 4		
	No event	Bleeding event	Thrombotic event	Both bleeding and thrombotic events	P value	Missing (%)
Number	2066	114	31	4		
Age	66.36 (12.32)	69.23 (12.64)	67.03 (11.03)	54.75 (13.55)	0.023	0.1
Age ≥ 75 years	586 (28.4)	47 (41.2)	8 (25.8)	0 (0.0)	0.015	0.1
Female sex	434 (21.0)	31 (27.2)	4 (12.9)	0 (0.0)	0.183	0
Body mass index	24.10 (3.79)	23.81 (3.43)	24.61 (3.12)	29.95 (4.55)	0.113	4.3
Patient history						
Diabetes mellitus	656 (33.1)	37 (34.6)	9 (31.0)	3 (75.0)	0.347	4.2
Hypertension	1286 (65.1)	78 (71.6)	17 (63.0)	1 (25.0)	0.183	4.5
Dyslipidaemia	892 (45.7)	44 (41.5)	12 (44.4)	2 (50.0)	0.86	5.7
Smoking history	1288 (66.3)	61 (62.2)	25 (80.6)	3 (100.0)	0.164	6.3
Cerebrovascular disease	181 (9.5)	8 (7.6)	2 (6.5)	1 (25.0)	0.599	7.6
Cancer	162 (8.5)	16 (15.2)	1 (3.2)	0 (0.0)	0.064	7.6
Previous MI or PCI	250 (12.4)	12 (10.7)	3 (9.7)	0 (0.0)	0.787	2.7
ST elevation myocardial infarction	1748 (87.1)	77 (92.8)	26 (89.7)	3 (100.0)	0.401	4.2
Q wave myocardial infarction	752 (37.8)	35 (39.3)	7 (22.6)	1 (33.3)	0.369	4.7
Culprit vessel						
Right coronary artery	671 (36.0)	33 (30.8)	8 (25.8)	2 (50.0)	0.42	9.3
Left anterior descending artery	879 (47.1)	49 (45.8)	18 (58.1)	2 (50.0)	0.666	9.3
Left circumflex artery	296 (15.9)	12 (11.2)	3 (9.7)	0 (0.0)	0.358	9.3
Left main trunk	59 (3.2)	19 (17.8)	1 (3.2)	0 (0.0)	<0.001	9.3
Killip classification III or IV	243 (11.8)	77 (67.5)	3 (9.7)	3 (75.0)	<0.001	0
Thrombolysis	8 (0.4)	0 (0.0)	1 (3.3)	0 (0.0)	0.09	4.5
IABP	439 (21.2)	86 (75.4)	14 (45.2)	4 (100.0)	<0.001	0
PCPS	98 (4.7)	61 (53.5)	1 (3.2)	3 (75.0)	<0.001	0
Peak creatine kinase	2903.54 (3182.42)	7703.67 (12,295.63)	2896.14 (2275.93)	13,216.00 (7652.28)	<0.001	2.1
Peak creatine kinase myocardial band	286.31 (648.75)	515.90 (469.28)	438.91 (829.08)	794.35 (341.95)	0.001	2.2
Atrial fibrillation	134 (6.7)	11 (12.1)	1 (3.4)	0 (0.0)	0.196	3.8
Creatinine clearance <60 mL/min	730 (36.2)	55 (53.9)	9 (29.0)	1 (33.3)	0.003	2.9
Anemia	565 (27.4)	52 (45.6)	4 (12.9)	0 (0.0)	<0.001	0.2
Heart failure	392 (19.0)	66 (57.9)	11 (35.5)	2 (50.0)	<0.001	0
Antiplatelets	1863 (98.0)	57 (98.3)	28 (100.0)	2 (100.0)	0.889	10.2
Anticoagulants	238 (12.5)	17 (29.3)	3 (10.7)	0 (0.0)	0.002	10.2

Data are presented as number (percentage) or mean (standard deviation) with listwise deletion. Abbreviations: IABP, intra-aortic balloon pumping; MI, myocardial infarction; PCI, percutaneous coronary intervention; PCPS, percutaneous cardio-pulmonary support.

method was weighted relatively toward practical utility rather than predictive accuracy.

Compared with previous scoring systems, the present model has certain strengths. First, our derivation population only included STEMI/NSTEMI patients who received PCI. Given the higher thrombogenicity of MI lesions, unique assessment tool specific for MI would be required. Second, we developed the model with a multinomial logistic regression model, which can allow us to precisely focus on the balance between bleeding and thrombotic events. This cannot be achieved by a conventional binary logistic regression model. Group 1 and group 4 have a balanced risk, and therefore would not require specific care oriented either for bleeding or thrombotic risk. On the other hand, in the imbalanced groups (group 2 and group 3), either bleeding- or thrombosis-oriented treatment strategy may be desirable. The multinomial model enables the distinguishment between the balanced (group 1 and 4) and imbalanced groups (group 2 and 3). Third, predictive and discriminative power of the current model was comparable to the previous prediction scores. Lastly, NPP simply shows the absolute difference of incidence between bleeding and thrombotic events, and therefore simply suggest either bleeding-oriented or thrombosis-oriented strategy. PCI approach site and stent selection, periprocedural anticoagulation, indication of cardiopulmonary support device, and duration and type of DAPT may be decided based on this pre-PCI quick assessment. Nevertheless, any model for predicting the trade-off between thrombotic and bleeding events is highly dependent on the population where the model was created, the PCI procedures, the prescribed antiplatelet regimen, the event definitions, the duration of the study period, and the timing of risk assessment. Further prospective large-scale investigation is warranted to assess its clinical utility and validity in the up-to-date clinical practice, other regions, and other ethnicities.

4.1. Relative impact of risk factors on bleeding and thrombotic events

Another one of the strengths of the present analysis is that we evaluated the bidirectional impact of one independent variable in the same model. It is well known that there is an overlap in the risk factors for bleeding and thrombosis [22]. However, its bidirectional impact has not been specifically assessed so far. This study showed that age ≥ 75 years increases both bleeding event and thrombotic event but increases thrombotic risk more strongly. Diabetes mellitus has balanced impact on both risks. It was unexpected that hypertension decreased all events although not statistically significant. This finding was difficult to explain, but we speculate that this factor might be represented by the other factors like heart failure. Female sex, anemia, chronic kidney disease, and atrial fibrillation were all associated with increased bleeding risk and decreased thrombotic risk. Previous MI or PCI was the strong predictor for thrombotic event. Although total stent length ≥ 30 mm and minimum stent diameter < 3.0 mm are reported to be predictors for thrombosis, we could not include such stent information in the prediction model due to unavailability of the data [9]. However, the present model can in turn provide the risk balance information *before* PCI, and therefore PCI strategy can be guided by the information. Lastly, heart failure had the greatest impact on both bleeding and thrombosis, but its impact was greater on bleeding rather than thrombosis. For heart failure patients, bleeding risk rather than thrombotic risk should be carefully considered. Age ≥ 75 years and/or previous MI or PCI were prerequisite factors to be classified into the group with a higher thrombotic risk than bleeding risk. In other words, if a patient does not have any of these factors, the patient is likely to have a higher bleeding risk than thrombotic risk. This highly practical assessment may also be useful in our clinical practice.

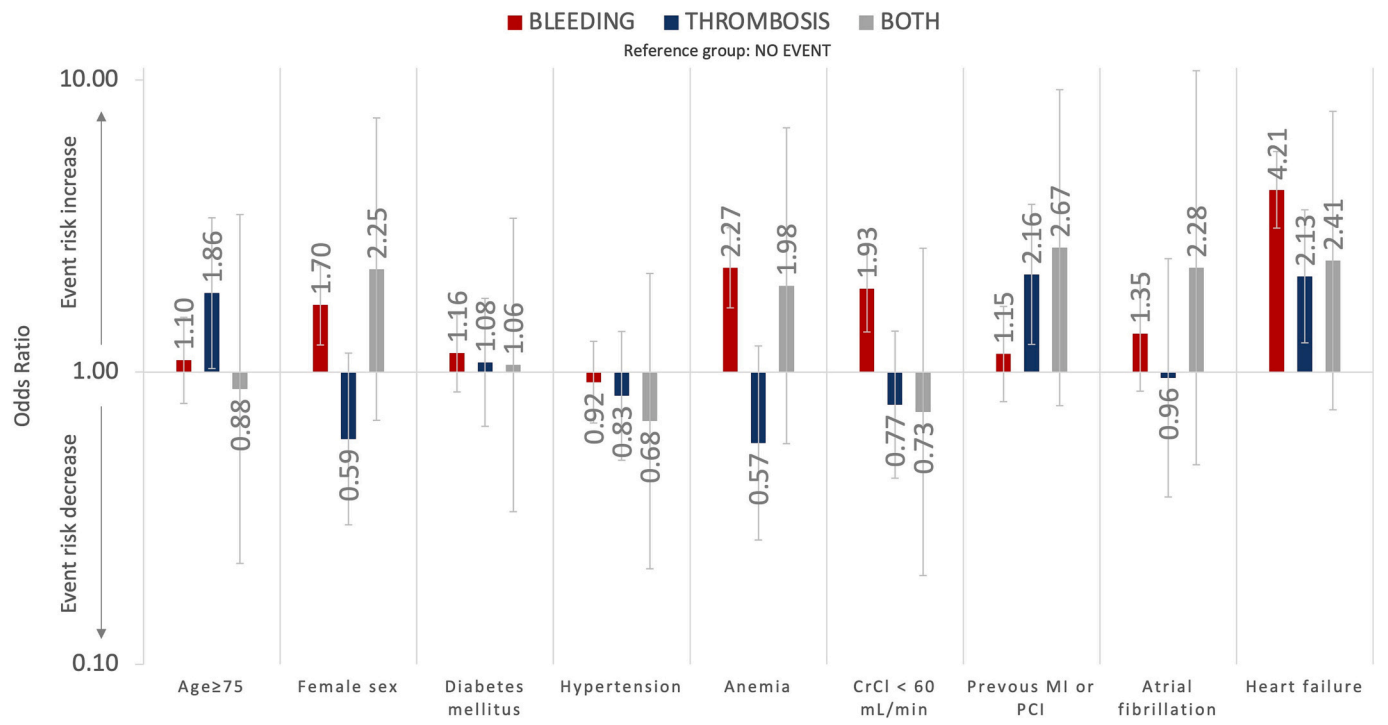

Fig. 2. Impact of risk factors on either bleeding, thrombosis, or both.
Vertical axis (logarithmic scale) indicates odds ratio (**red** for bleeding, **blue** for thrombosis, and **gray** for both events). Error bar means 95 % confidence interval of odds ratio. Upward bar graph indicates that the risk increases the event, whereas downward bar graph indicates that the risk decreases the event. Abbreviations: CrCl, creatinine clearance; MI, myocardial infarction; PCI, percutaneous coronary intervention. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.2. Study limitations

Several limitations should be acknowledged. First, we did not assess the long-term data due to the limited availability of bleeding event data. It would be, however, challenging to establish the best prediction model that can assess both short-term and long-term outcomes simultaneously because the clinical events of interest in this study are known to occur most frequently in the acute phase and exponentially decrease from the acute to the late phase [10]. Risk balance of the bleeding and thrombotic event may vary over time. It is reasonable to develop 2 different best models to predict short-term and long-term outcomes individually. This is a future topic of our investigations. Second, MI definition used in this registry was not in line with the current universal definition of MI, nor was major bleeding [17,23]. Thrombotic events in the present study indicate only recurrent MI but not other thrombotic events such as ischemic stroke or systemic embolism. As to major bleeding, site data was not available in this dataset. Third, the long enrollment period of 1998–2014 is of potential concern since pharmacologic practice and interventional technologies have evolved enormously in this period. Procedural changes, especially stent type (from bare metal stents to drug-eluting stents) and access site (from femoral to radial), may have strongly affected the event risk, but its data was not available in this dataset. Separation based on enrollment period might have confirmed the good performance of the established model (2003–2009) even in the up-to-date practice (2010–2014), which may compensate the limitation to a certain degree. Also, the similar event distribution between both cohorts (Supplemental Fig. 1) may support the validity of the analysis. However, further finetuning of the model with the recent clinical data would be desirable. Lastly, this study is the East-Asian registry, which would limit the generalizability of the current findings to other races and other regions.

5. Conclusions

In this short-DAPT era, patients with a higher thrombotic risk than bleeding risk should be carefully identified and treated appropriately, although such patients are minority (one fifth of the whole population). The quick assessment tool that we have established in this study can stratify patients with different thrombotic and bleeding risk balances. Pre-procedural quick and precise assessment of the risk balance may help a decision making of procedural strategy and antithrombotic regimens in STEMI/non-STEMI patients undergoing PCI.

Ethical statement

The OACIS enrolled patients from 1998 to 2014 and followed them up until 2019. The study is registered with the UMIN-CTR (University Hospital Medical Information Network Clinical Trials Registry) in Japan (ID: UMIN000004575). The study protocol complied with the Helsinki Declaration. The study was approved by Ethical Review Board of Osaka University Hospital (reference number: 14360) as sell as the institutional ethics committee of each participating institution.

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CRediT authorship contribution statement

Yohei Sotomi: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Visualization; Roles/Writing - original draft; Writing - review & editing.

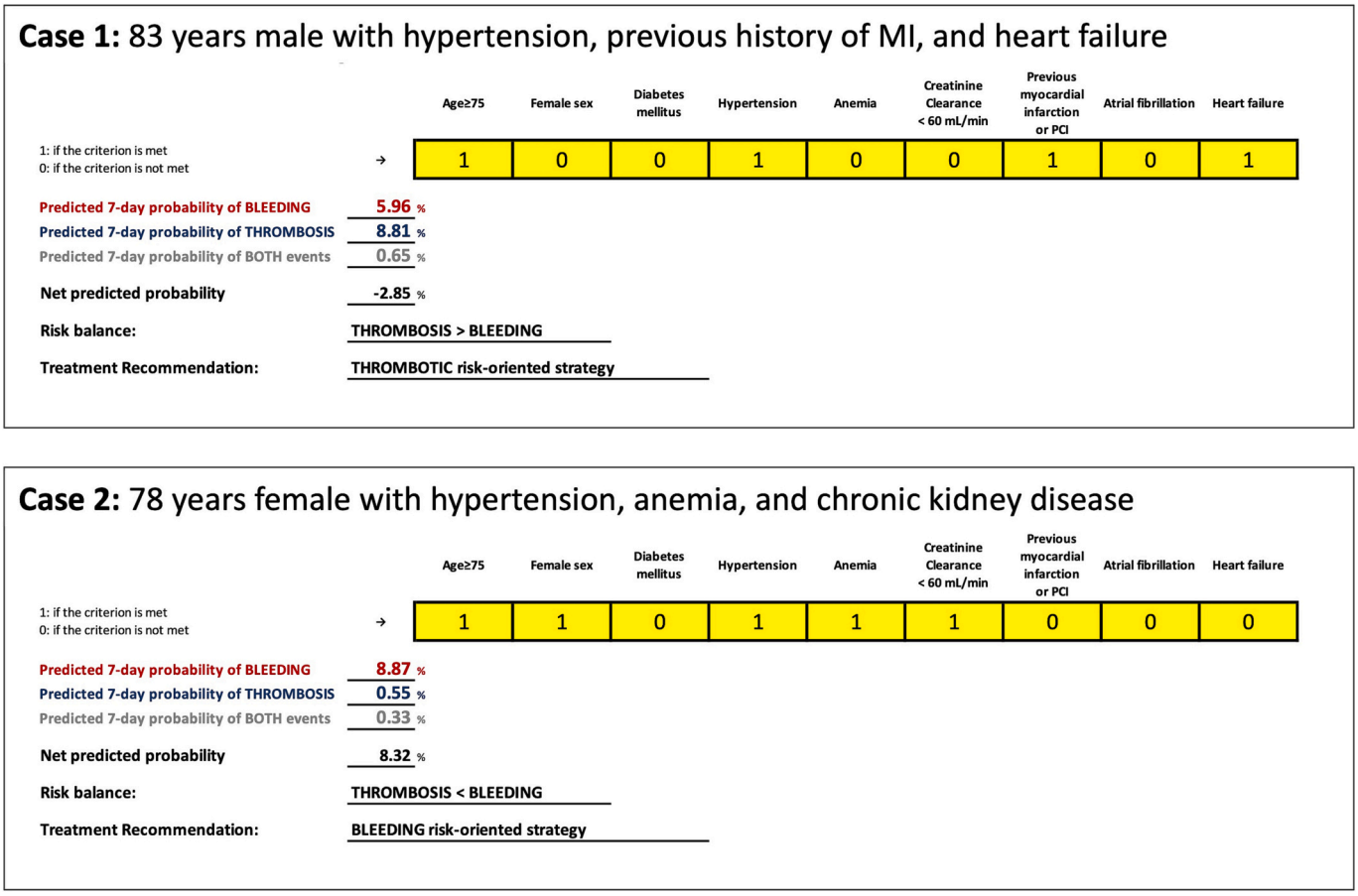

Fig. 3. Examples of risk balance assessment with the calculator.
We created the risk balance calculator, "OACIS Acute-phase Bleeding and Thrombotic Risk Balance Calculator". Readers can easily calculate the predicted risk probability of bleeding event, thrombosis, and both events with this calculator (Supplemental File). We defined the net predicted probability (NPP) as follows: predicted probability of bleeding event (%) – predicted probability of thrombotic event (%). Positive value of the NPP indicates that the predicted probability of bleeding event is higher than that of thrombotic event. Negative value of the NPP indicates that the predicted probability of thrombotic event is higher than that of bleeding event. Based on this risk balance assessment, the calculator provides treatment recommendation; bleeding risk-oriented strategy (NPP > 0 %) or thrombotic risk-oriented strategy (NPP < 0 %). Images of the calculator of 2 example cases are indicated. Users need to fill in only the yellow boxes. The calculator automatically provides predicted probabilities, risk balance and the treatment recommendation. **Case 1**: 83 years male with hypertension, previous history of myocardial infarction (MI), and heart failure shows a NPP of −2.85 %, and therefore, a higher risk of thrombosis than bleeding. Thrombotic risk-oriented treatment strategy would be recommended. **Case 2**: 78 years female with hypertension, anemia, and chronic kidney disease (creatinine clearance 48 mL/min) shows a NPP of 8.32 %, and therefore, a higher risk of bleeding than thrombosis. Bleeding risk-oriented treatment strategy would be recommended. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Y. Sotomi received research grants from Abbott Medical Japan and TOA EIYO, and speaker honoraria from Abbott Medical Japan, Boston Scientific Japan, TERUMO, Japan Lifeline, Biosensors, Medtronic, Daiichi-Sankyo, Bayer, Boehringer Ingelheim, and Bristol Myers Squibb, and is an endowed chair funded by TOA EIYO. H. Mizuno is an endowed chair

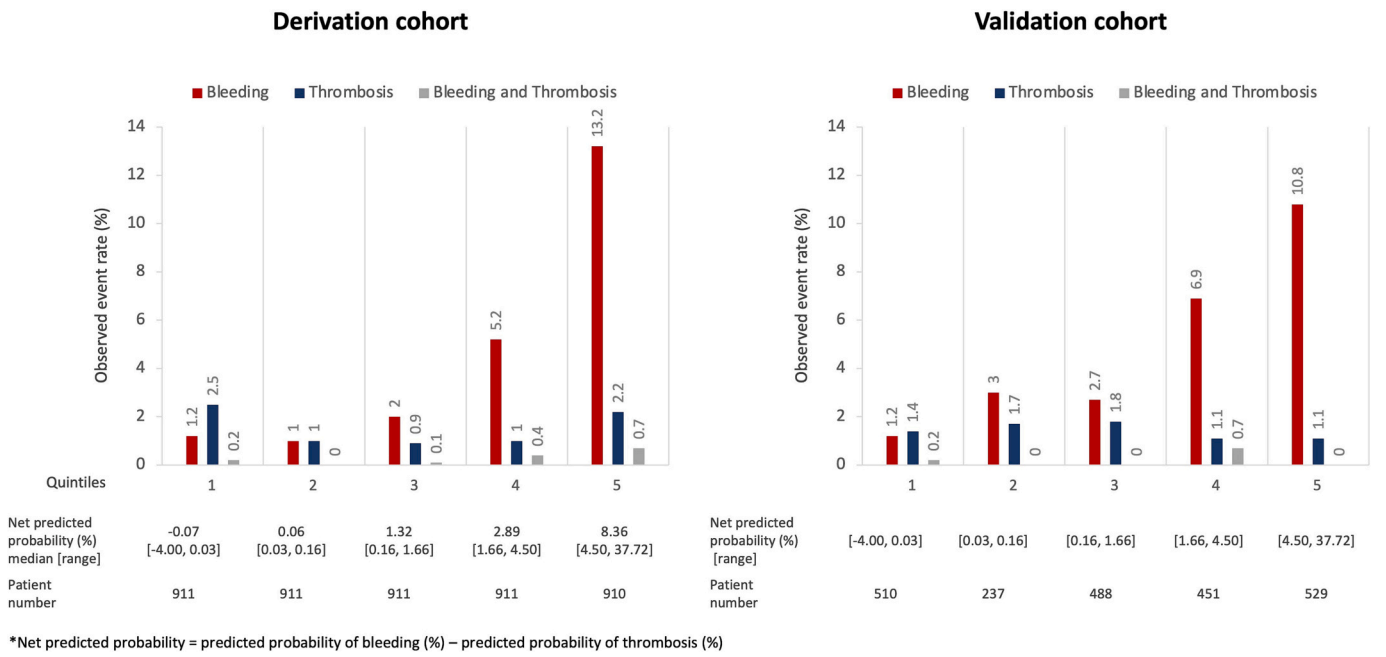

Fig. 4. Predictive performance of the prediction tool.
Patients in the derivation cohort were divided into quintiles of net predicted probability (NPP) (**left panel**). NPP was calculated as follows: predicted probability of bleeding event (%) – predicted probability of thrombotic event (%). Positive value of the NPP indicates that the predicted probability of bleeding event is higher than that of thrombotic event. Negative value of the NPP indicates that the predicted probability of thrombotic event is higher than that of bleeding event. In each quintile of NPP, observed event rates of bleeding event (red), thrombotic event (blue), and both bleeding and thrombotic events (gray) are presented as bar graphs. In the first quintile, as median value was negative, thrombotic event rate was higher than bleeding event rate. In the 2nd quintile, the NPP was almost 0, and event rate was similar between bleeding and thrombotic events. In the 3rd, 4th, and 5th quintiles, bleeding event rates compared with thrombotic event rates got incrementally higher as the NPP got higher. The same findings were shown in the validation cohort (**right panel**). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2023.100292.

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