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Risk prediction score for clinical outcome in atrial fibrillation and stable coronary artery disease

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ABSTRACT

Objective Antithrombotic therapy is essential for patients with atrial fibrillation (AF) and stable coronary artery disease (CAD) because of the high risk of thrombosis, whereas a combination of antiplatelets and anticoagulants is associated with a high risk of bleeding. We sought to develop and validate a machine-learning-based model to predict future adverse events.

Methods Data from 2215 patients with AF and stable CAD enrolled in the Atrial Fibrillation and Ischaemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease trial were randomly assigned to the development and validation cohorts. Using the random survival forest (RSF) and Cox regression models, risk scores were developed for net adverse clinical events (NACE) defined as all-cause death, myocardial infarction, stroke or major bleeding.

Results Using variables selected by the Boruta algorithm, RSF and Cox models demonstrated acceptable discrimination and calibration in the validation cohort. Using the variables weighted by HR (age, sex, body mass index, systolic blood pressure, alcohol consumption, creatinine clearance, heart failure, diabetes, antiplatelet use and AF type), an integer-based risk score for NACE was developed and classified patients into three risk groups: low (0–4 points), intermediate (5–8) and high (≥9). In both cohorts, the integer-based risk score performed well, with acceptable discrimination (area under the curve 0.70 and 0.66, respectively) and calibration (p>0.40 for both). Decision curve analysis showed the superior net benefits of the risk score.

Conclusions This risk score can predict the risk of NACE in patients with AF and stable CAD.

Trial registration numbers UMIN000016612, NCT02642419.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A combination of antiplatelet and anticoagulant agents has been an essential antithrombotic therapy for patients suffering from atrial fibrillation (AF) and coronary artery disease (CAD); however, the persistent issue of bleeding complications associated with antithrombotic therapy remains a concern.

WHAT THIS STUDY ADDS

⇒ This subanalysis of the Atrial Fibrillation and Ischaemic Events With Rivaroxaban trial developed a machine-learning-based risk prediction model for net adverse clinical events in patients with AF and CAD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Managing the risk of both thromboembolic and bleeding events is crucial in the antithrombotic treatment of those patients. Using this risk score can prove beneficial in the decision-making process in clinical settings.

INTRODUCTION

Antiplatelet therapy is required for the secondary prevention of cardiovascular events in patients with coronary artery disease (CAD),[1–3] and anticoagulant therapy is essential for the prevention of thromboembolic events in patients with atrial fibrillation (AF).[4–6] A combination of antiplatelet and anticoagulant agents has been used in patients with AF and CAD; however, the high risk of antithrombotic therapy-related bleeding complications remains a problem. The AFIRE trial (Atrial Fibrillation and Ischaemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease) showed that rivaroxaban monotherapy was non-inferior in at reducing the risk of cardiovascular events or all-cause death and superior in at reducing the risk of major bleeding compared with a combination of rivaroxaban with a single antiplatelet drug in AF patients with stable CAD at ≥1 year after revascularisation or those with angiographically confirmed CAD not requiring revascularisation.[7]

Simple conventional risk scores, such as the $CHADS_2$,[8] CHA_2DS_2-VASc[9] or HAS-BLED[10]

scores, have been widely used to estimate the individual risk of thromboembolic or bleeding events in patients with AF. In addition, the $CHADS_2$ score is a useful prediction tool for cardiovascular or cerebrovascular events, even in CAD patients without AF.[11 12] However, subanalysis of the AFIRE trial demonstrated that patients with major bleeding had a high risk of subsequent major adverse cardiac and cerebrovascular events, especially within 30 days after major bleeding,[13] suggesting that a balanced risk assessment should be established to estimate the integrated risk of both thromboembolic and bleeding events in patients with AF and CAD.

To address this challenging issue, we conducted a post hoc analysis of the AFIRE trial to develop and validate a machine-learning-based risk prediction model for future net adverse clinical events (NACE) among patients with AF and stable CAD.

METHODS

Study design and study participants

This study was a post hoc analysis of the AFIRE trial, a multicentre, randomised, open-label, parallel-group trial. The detailed study design, protocol, and results of the primary analysis of the AFIRE trial have been reported previously.[7 14] Briefly, the AFIRE trial was conducted in 294 hospitals across Japan between 23 February 2015 and 30 September 2017 and included patients aged ≥20 years, diagnosed with AF with a $CHADS_2$ score ≥1 and stable CAD at ≥1 year after revascularisation or those with angiographically confirmed CAD not requiring revascularisation. Patients with a history of stent thrombosis, coexisting active cancer or poorly controlled hypertension were excluded in the trial. Patients were randomised in a 1:1 ratio to receive either rivaroxaban (10 mg once daily for patients with a creatinine clearance rate (CCR) of 15–49 mL/min or 15 mg once daily for patients with a CCR≥50 mL/min) alone or rivaroxaban plus an antiplatelet drug (either aspirin or $P2Y_{12}$ inhibitor). Patient follow-up was performed at baseline, 6 months and at the end of the trial, with additional follow-up for routine clinical care if needed. The study follow-up period was at least 24 months and up to 45 months.

The data were reviewed by an independent data and safety monitoring committee. In this post hoc analysis, 2215 patients in the modified intention-to-treat population from the AFIRE trial were analysed.

Outcome

The primary outcome of this study was NACE, consisting of all-cause death, myocardial infarction, stroke or major bleeding according to the criteria of the International Society on Thrombosis and Haemostasis.[15]

Candidate variables

After excluding of variables with >10% missing values and a correlation coefficient >0.7, 78 candidate variables at baseline were used to develop the risk prediction model as potential predictors of NACE (online supplemental table 1). Missing values were imputed by missForest,[16] which is a non-parametric imputation method using a random forest model that can learn non-linearity, easily handle mixed-type data and calculate out-of-bag errors.

Statistical analysis

Based on the outcome, study participants were randomly assigned to a development (50%) or validation (50%) dataset. The development dataset was further divided into two (a training or tuning set, each 50%) to tune the hyperparameters. Categorical variables are presented as frequencies and percentages, and continuous variables are presented as medians and IQR. Using only data from the development dataset, feature selection and relationship modelling for risk prediction model development were conducted (figure 1).

Feature selection

From all candidate variables, we further identified 13 predictors (age, sex, treatment randomisation, body mass index (BMI), systolic blood pressure, diastolic blood pressure, CCR, type of AF, alcohol consumption, diabetes mellitus, heart failure, prior stent implantation and prior coronary artery bypass grafting) using a feature selection method with the Boruta algorithm, which is a wrapper around a random forest classification algorithm that can provide a numerical estimate of the feature importance without tuning the parameters and removing the variables that are less relevant than random probes by a statistical test.[17]

Model development and evaluation

The relationships between the outcomes and variables selected by the Boruta algorithm were assessed using Cox proportional hazard (PH) models and random survival forest (RSF) models,[18] which is an ensemble tree-based classification method for the analysis of right-censored survival data. Each model was assessed based on Harrell's concordance index (C-index) for discrimination performance and the Brier score for both discrimination and calibration performance in the development and validation datasets.

Risk score development and validation

For clinical use, a simple integer-based risk score to predict the outcome was developed based on each variable's unadjusted HR, with statistical significance calculated from the Cox PH model in the development dataset. Continuous variables were categorised as follows: age (≥80 years, <80 years), BMI (<18.5, 18.5–25, ≥25), systolic blood pressure (<90, 90–140, ≥140), diastolic blood pressure (<60, 60–90, ≥90) and CCR (<30, 30–50, ≥50). The discrimination performance of the integer-based risk score was assessed using the area under the receiver operating characteristic curve (AUC-ROC) and its 95% CIs in the development and validation datasets. The calibration performance of the risk score was assessed using a calibration plot and Hosmer-Lemeshow test. Performance comparison of the new risk score with that of

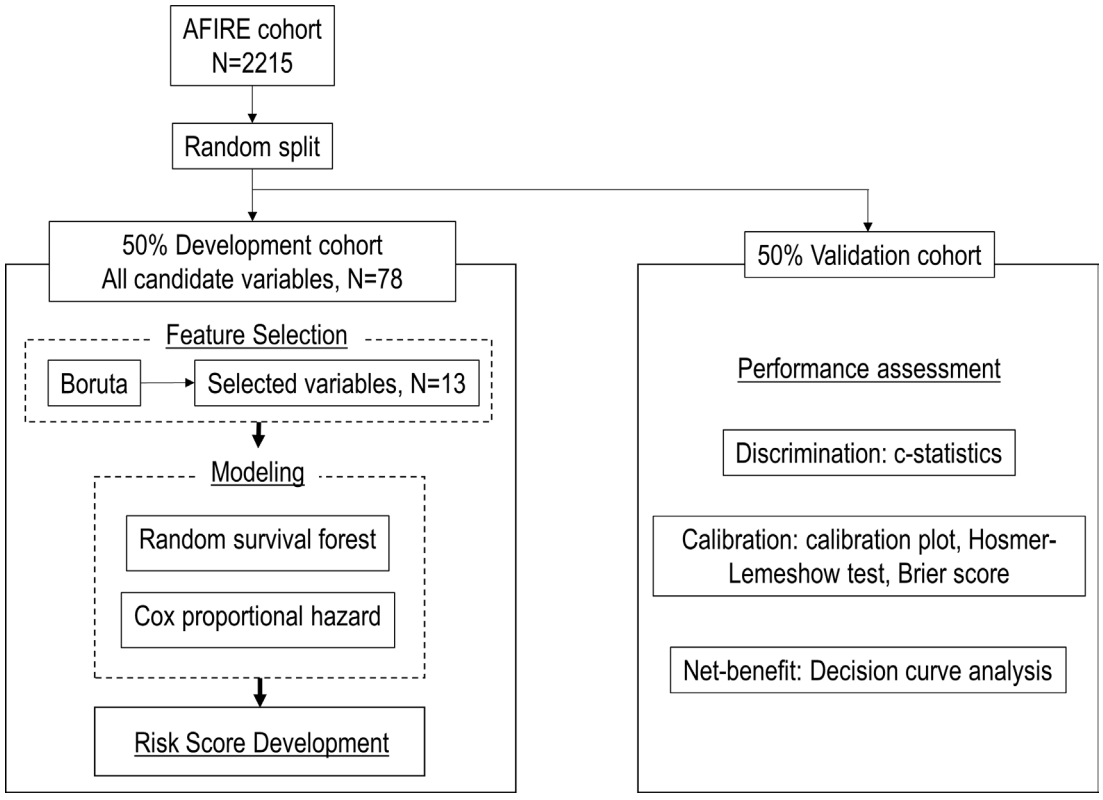

Figure 1 Study flow chart. Study design for the development and validation of the machine learning-based risk score model. AFIRE, Atrial Fibrillation and Ischaemic Events With Rivaroxaban.

conventional risk scores, such as the $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75 y, Diabetes mellitus, Stroke or TIA), CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 y, Diabetes mellitus, Stroke or TIA, Vascular disease, Age 65-74 y, Sex category [female]) and HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs) scores, was performed using ROC analysis, category and category-free net reclassification improvement, integrated discrimination improvement and decision curve analysis to indicate net benefit and clinical utility.[19–21]

Statistical analyses were performed using SPSS (V.23.0; IBM), R software, V.4.0.5 (The R Project for Statistical Computing) and Python (V.3.7.11, Python Software Foundation). Statistical significance was defined as a two-sided $p<0.05$.

RESULTS

Study participants

Among the 2215 patients in the AFIRE trial, 1107 were included in the development cohort (median (IQR) age, 75 (69–80) years; 870 (78.6%) males) and 1108 in the validation cohort (median (IQR) age, 75 (69, 80) years; 881 (79.5%) males). During a median (IQR) follow-up of 24.1 (17.3–31.5) months, 215 patients (9.7%) suffered NACE (107 and 108 in the development and validation cohorts, respectively). Patient characteristics for the development and validation cohorts are presented in table 1. There were no statistical differences in demographic and physiological findings, antithrombotic regimen, type of AF, comorbidities, medical history, or prior revascularisation between the cohorts, except for the location of the culprit lesion, interventions other than revascularisation and prior bleeding complications.

Performance of development models and integer-based risk score

The 13 Boruta algorithm-selected variables had high C-index of 0.706 and 0.667 in the development and validation cohorts, respectively, when used with the RSF model (online supplemental table 2). Using the same variables as the Cox PH model, the discrimination performance was acceptable (C-index of 0.680 and 0.650 in the development and validation cohorts, respectively). The RSF model had low Brier scores of 0.081 and 0.080 in the development and validation cohorts, respectively (online supplemental table 2), indicating good calibration. Similarly, the Cox PH model had low Brier scores of 0.079 and 0.081 in the development and validation cohorts, respectively.

The β-coefficients, HRs and 95% CIs for each of the selected variables calculated using the Cox PH model are presented in table 2. Using the variables with statistical significance, an integer-based risk score for NACE was created (figure 2); according to each variable's HR, a score for the risk of NACE was assigned (table 2). The new risk score model has a theoretical range of 0–23 and is divided into three risk groups: low (0–4 points),

Table 1 Clinical characteristics

Variables	Development cohort N=1107	Validation cohort N=1108	P value
Age, years	75 (69, 80)	75 (69, 80)	0.723
Male	870 (78.6)	881 (79.5)	0.594
BMI, kg/m^2	24.2 (22.2, 26.6)	24.2 (22.2, 26.5)	0.782
Systolic BP, mm Hg	126 (116, 136)	126 (116, 135)	0.722
Diastolic BP, mm Hg	70 (64, 78)	71 (64, 80)	0.350
Current smoker	149 (13.5)	143 (12.9)	0.700
Alcohol consumption			0.369
Daily	202 (18.2)	221 (19.9)	
Occasionally	361 (32.6)	374 (33.8)	
None	544 (49.1)	513 (46.3)	
Rivaroxaban monotherapy	549 (49.6)	558 (50.4)	0.718
Dose of rivaroxaban			0.459
10 mg/day	509 (46.0)	501 (45.2)	
15 mg/day	588 (53.1)	596 (53.8)	
Other	2 (0.2)	0 (0.0)	
Unknown	8 (0.7)	11 (1.0)	
Type of atrial fibrillation			0.337
Paroxysmal	571 (51.6)	605 (54.6)	
Persistent	172 (15.5)	167 (15.1)	
Permanent	364 (32.9)	336 (30.3)	
Hypertension	955 (86.3)	936 (84.5)	0.233
Diabetes mellitus	460 (41.6)	467 (42.1)	0.777
Dyslipidaemia	774 (69.9)	764 (69.0)	0.622
Angina pectoris	714 (64.5)	696 (62.8)	0.410
Heart failure	398 (36.0)	390 (35.2)	0.711
Liver dysfunction	19 (1.7)	22 (2.0)	0.638
Creatinine clearance	59.8 (45.7, 75.0)	58.7 (44.8, 74.0)	0.322
Haemorrhagic diathesis	17 (1.5)	15 (1.4)	0.720
Prior stroke	158 (14.3)	165 (14.9)	0.680
Transient ischaemic attack	23 (2.1)	25 (2.3)	0.773
Prior myocardial infarction	381 (34.4)	396 (35.7)	0.514
Prior PCI	779 (70.4)	785 (70.8)	0.805
Stent implantation	718 (64.9)	726 (65.5)	0.743
Type of stent			0.802
Drug-eluting	480/718 (66.9)	497/726 (68.5)	
Bare-metal	179/718 (24.9)	163/726 (22.5)	
Both types	27/718 (3.8)	28/726 (3.9)	
Unknown	32/718 (4.5)	38/726 (5.2)	
Cipher	86/718 (12.0)	88/726 (12.1)	
TAXUS	32/718 (4.5)	23/726 (3.2)	
Endeavour	23/718 (3.2)	29/726 (4.0)	
Xience	187/718 (26.0)	201/726 (27.7)	
Promus	103/718 (14.3)	112/726 (15.4)	
Nobori	46/718 (6.4)	38/726 (5.2)	

Continued

Table 1 Continued

Variables	Development cohort N=1107	Validation cohort N=1108	P value
Other	67/718 (9.3)	97/726 (13.4)	
Prior CABG	128 (11.6)	124 (11.2)	0.783
Location of culprit lesion			
Segment #1	113 (10.2)	127 (11.5)	0.342
Segment #2	134 (12.1)	123 (11.1)	0.461
Segment #3	111 (10.0)	106 (9.6)	0.716
Segment #4PD	20 (1.8)	33 (3.0)	0.071
Segment #4AV	24 (2.2)	36 (3.2)	0.117
Segment #5	15 (1.4)	31 (2.8)	0.017
Segment #6	251 (22.7)	258 (23.3)	0.732
Segment #7	253 (22.9)	298 (26.9)	0.028
Segment #8	17 (1.5)	34 (3.1)	0.016
Segment #9	43 (3.9)	37 (3.3)	0.492
Segment #10	2 (0.2)	4 (0.4)	0.687
Segment #11	77 (7.0)	71 (6.4)	0.606
Segment #12	44 (4.0)	29 (2.6)	0.074
Segment #13	117 (10.6)	125 (11.3)	0.591
Segment #14	34 (3.1)	34 (3.1)	0.997
Segment #15	15 (1.4)	10 (0.9)	0.313
Interventions other than PCI or CABG	120 (10.8)	158 (14.3)	0.015
Prior aortic aneurysm	46 (4.2)	30 (2.7)	0.061
Systemic embolism	5 (0.6)	6 (0.5)	0.764
Deep venous thrombosis	8 (0.7)	6 (0.5)	0.591
Pulmonary embolism	3 (0.3)	5 (0.5)	0.726
Peripheral artery disease	70 (6.3)	69 (6.2)	0.926
Other ischaemic disorder	87 (7.9)	104 (9.4)	0.200
Prior bleeding complication	37 (3.3)	22 (2.0)	0.047
Proton pomp inhibitor	670 (60.5)	687 (62.0)	0.475
NSAIDs	29 (2.6)	16 (1.4)	0.050

Data are presented as n (%) or median (IQR).
AV, atrioventricular branch; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; NSAIDs, nonsteroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention; PD, posterior descending branch.

intermediate (5–8 points) and high (≥9 points). The new risk score model demonstrated good discrimination with a C-index of 0.70 (95% CI 0.65 to 0.75; figure 3A) and acceptable calibration (Hosmer-Lemeshow test; χ^2 of 7.789, p=0.454; online supplemental figure 1a). The cumulative 3-year incidence of NACE increased in a graded fashion across the risk groups in the development cohort (figure 4A).

Validation and decision curve analysis of the integer-based risk score

In the validation cohort, the AUC of the new risk score was 0.66 (95% CI 0.60, 0.72; figure 3B) and the Hosmer-Lemeshow goodness-of-fit χ^2 was 3.417 (p=0.906; online supplemental figure 1), indicating moderate discrimination and acceptable calibration, respectively. The cumulative 3-year incidence of NACE also increased in a graded fashion across the three risk groups in the validation cohort (figure 4B). The AUC of conventional risk scores such as the $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores were 0.57 (95% CI 0.51 to 0.62), 0.57 (95% CI 0.51 to 0.62) and 0.51 (95% CI 0.46 to 0.57), respectively (online supplemental figure 2). Compared with these conventional risk scores, the discrimination performance of the new risk score was significantly higher (online supplemental figure 2 and online supplemental table 3). The decision curves for the new and conventional risk

Table 2 Cox proportional hazard parameter estimates and assigned score for the risk of NACE

Variables	β-estimate	HR (95% CI)	P value	Score
Age, years	0.044	1.05 (1.02 to 1.07)	0.001	
Elderly (age ≥80 years)	0.706	2.03 (1.37 to 3.00)	<0.001	2
Female	0.488	1.63 (1.08 to 2.46)	0.020	2
Combination with antiplatelet agents	0.392	1.48 (1.00 to 2.18)	0.047	1
BMI, kg/m^2	−0.068	0.93 (0.88 to 0.99)	0.020	
<18.5	1.062	2.89 (1.43 to 5.83)	0.003	3
≥18.5, <25	Ref	Ref	Ref	
≥25	−0.083	0.92 (0.61 to 1.38)	0.690	
Systolic BP, mm Hg	−0.013	0.99 (0.98 to 1.00)	0.042	
<90	1.540	4.66 (1.71 to 12.7)	0.003	4
≥90, <140	Ref	Ref	Ref	
≥140	−0.043	0.96 (0.58 to 1.58)	0.865	
Diastolic BP, mm Hg	−0.010	0.99 (0.97 to 1.01)	0.227	
<60	0.191	1.21 (0.73 to 2.02)	0.465	
≥60, <90	Ref	Ref	Ref	
≥90	−0.497	0.61 (0.22 to 1.66)	0.332	
Type of atrial fibrillation				
Paroxysmal	Ref	Ref	Ref	
Persistent	−0.035	0.97 (0.52 to 1.79)	0.912	
Permanent	0.469	1.60 (1.07 to 2.40)	0.023	2
No alcohol consumption	0.500	1.65 (1.04 to 2.62)	0.035	2
Diabetes mellitus	0.416	1.52 (1.04 to 2.22)	0.032	2
Heart failure	0.556	1.74 (1.19 to 2.55)	0.004	2
Prior stent implantation	0.226	1.25 (0.84 to 1.88)	0.273	
Prior CABG	−0.632	0.53 (0.25 to 1.14)	0.106	
Creatinine clearance	−0.018	0.98 (0.97 to 0.99)	<0.001	
≥50	Ref	Ref	Ref	
≥30, <50	0.612	1.84 (1.23 to 2.78)	0.003	2
<30	1.150	3.16 (1.67 to 5.96)	<0.001	3

BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; NACE, net adverse clinical event.

scores for predicting NACE in the validation cohort are shown in figure 5A. The new risk score had a greater net benefit, with threshold probabilities of 5%–25% than the conventional risk scores. A 10-fold cross-validated decision curve of the new risk score showed a similar standardised net benefit at each threshold probability (figure 5B), indicating the robustness of the results.

DISCUSSION

This post hoc analysis of the AFIRE trial demonstrated the development and validation of a machine-learning-based risk score that integrated easily available clinical and laboratory data to predict future adverse clinical events in patients with AF and stable CAD. Patients in the high-risk group had a 3-year NACE risk of approximately 40%. This risk score substantially improved the discriminatory ability and clinical usefulness of adverse clinical events compared with conventional risk scores. Antithrombotic therapy is needed for patients with AF and stable CAD because of the high risk of ischaemic and thrombotic events, whereas a combination of antiplatelet therapy with anticoagulants is associated with a high risk of bleeding events. Given this clinically unresolvable dilemma, this machine learning-based risk score is comprehensive, easily available and clinically useful for predicting future adverse events. Based on this risk score, clinicians should reconsider patient management, and close follow-up and cardiovascular healthcare should be provided to high-risk patients.

Machine learning has advantages in prediction model development compared with traditional statistical methods that focus on inference and do not require a

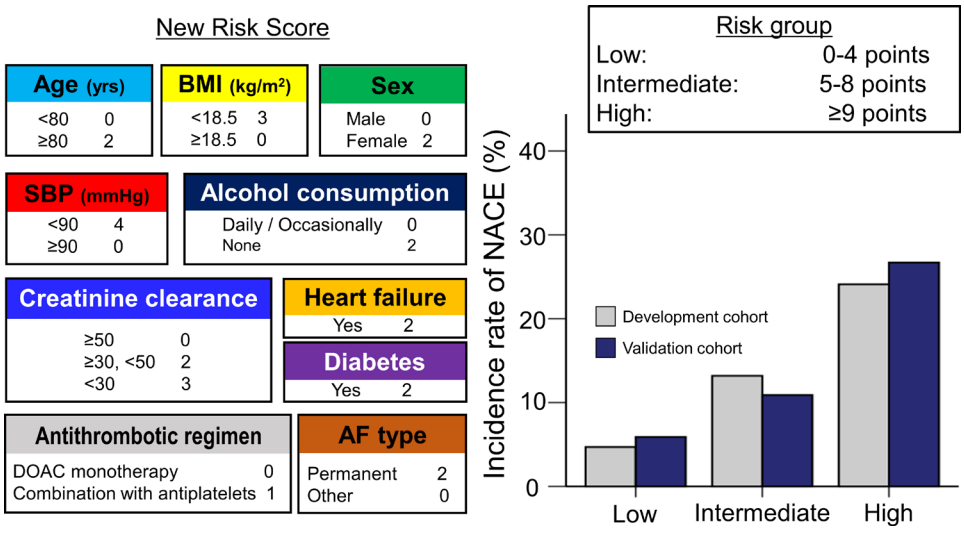

Figure 2 The machine learning-based New Risk Score for NACE incidence and the three risk groups. The bar graph shows the incidence rate of NACE among the three risk groups in the development and validation cohorts. AF, atrial fibrillation; BMI, body mass index; DOAC, direct oral anticoagulant; NACE, net adverse clinical event; SBP, systolic blood pressure.

prior assumption of causality in variable selection and modelling. Many machine-learning-based risk prediction models have been reported for the diagnosis and prognosis of patients with CAD[22–25] or AF,[26–28] whereas there has only been one previous report of a machine learning-based prediction model for CAD patients complicated with AF.[29] However, only one report showed a machine-learning prediction model for all-cause death among these patients. No established machine-learning-based risk score has been reported for the prediction of NACE combining thromboembolic events with bleeding events; therefore, this was the first study to develop a machine-learning-based risk prediction score for NACE with internal validation. In this study, we used the Boruta algorithm for variable selection and an RSF model in the development process of the prediction model, as well as the traditional Cox PH model for modelling and scoring. The Boruta algorithm is a novel feature selection algorithm to identify all relevant variables for outcomes and a wrapper built around a random forest classification algorithm, which can be performed quickly without tuning the parameters and provides a numerical estimate of feature importance.[17] RSF is a random forest method for the analysis of right-censored survival data[18] and can mathematically build binary recursive trees for all samples and obtain the maximal survival difference across daughter nodes with the application of bootstrap methods and the log-rank splitting rule.[30 31] Although traditional statistical methods for survival data, such as the Cox PH model, rely on restrictive assumptions such as PHs, machine-learning-based methods can manage large multidimensional datasets of right-censored survival data without the need for assumptions of parametric distributions, interaction between variables, linear relationships with outcome and overfitting of models. Therefore, to avoid these mathematical issues, machine-learning approaches may be able to predict complex clinical outcomes such as NACE more accurately. Moreover, the integer-based risk score created in this study would be easy to use in clinical practice because it does not require

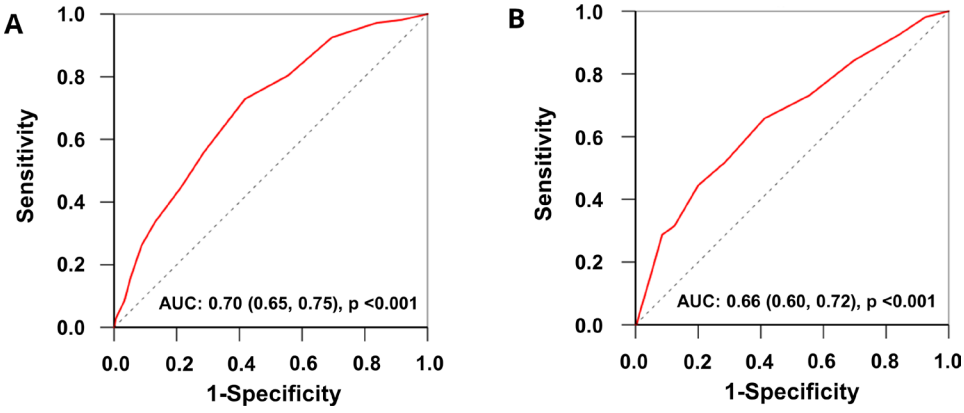

Figure 3 The ROC curves for the machine learning-based risk score for predicting NACE incidence. The AUC (95% CI) of the risk score in the (A) development and (B) validation cohorts is shown. AUC, area under the curve; NACE, net adverse clinical events; ROC, receiver operating curve.

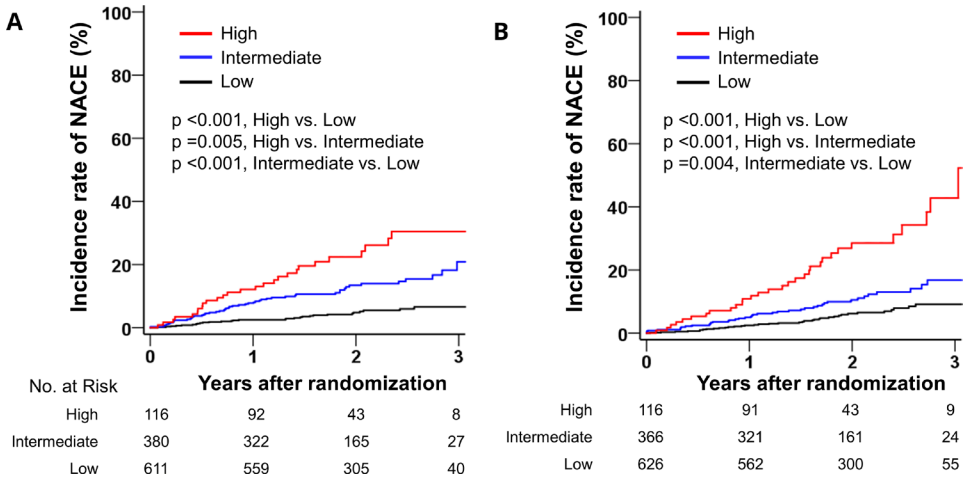

Figure 4 Kaplan-Meier curves of NACE according to the three risk groups. Patients with AF and stable CAD were stratified into three risk groups according to their risk score for NACE. Kaplan-Meier curves show the cumulative incidence of NACE among the three risk groups in the (A) development and (B) validation cohorts. AF, atrial fibrillation; CAD, coronary artery disease; NACE, net adverse clinical event.

nesting on a web-based platform or electronic medical record.

In patients with AF, the $CHADS_2$[8] and CHA_2DS_2-VASc scores[9] have been established as risk scores for thromboembolic events and the HAS-BLED score[10] as the risk score for major bleeding events. However, this study showed that these conventional risk scores did not have a good predictive performance for NACE in patients with AF and stable CAD. Here, we developed and validated a machine learning-based risk score for NACE in these patients, and the risk score had modest discrimination and good calibration with good reclassification improvement compared with conventional risk scores. One of the responsible factors may be that the variable selection of the integer-based risk score was conducted by combining machine learning (Boruta algorithm) and classical statistical (Cox PH) methods. The variables selected for the risk score in this study, such as older age, low BMI, female sex, CCR, heart failure, diabetes and combination with antiplatelets, were included in other traditional risk scores for the assessment of thrombotic and bleeding events.[10 32 33] Although most variables selected for the risk score can be interpreted and may be useful in understanding the underlying mechanism of clinical adverse events in patients with AF and stable CAD, the association between no alcohol consumption and high risk of NACE may be difficult to interpret. However, this can be explained by the following mechanism: among patients who do not have a drinking habit, some patients cannot consume alcohol because of decreased aldehyde dehydrogenase 2 (ALDH2) activity due to the ALDH2-deficient variant, which presents as alcohol flushing

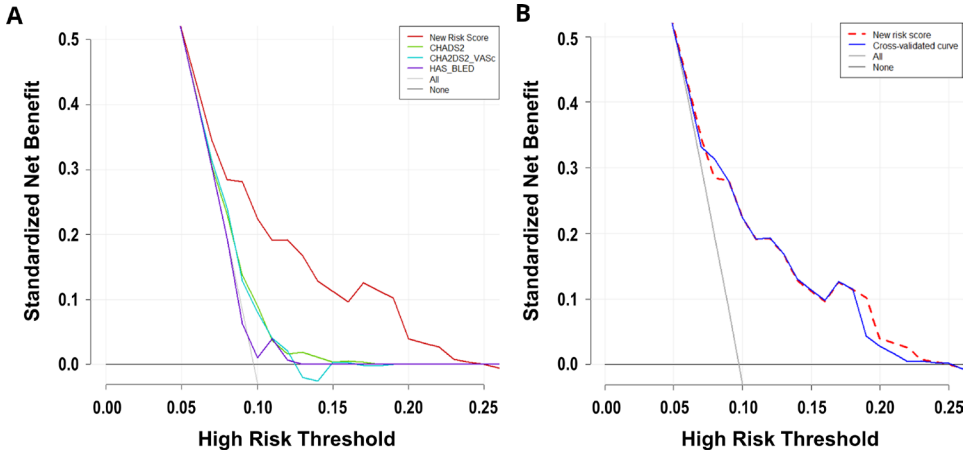

Figure 5 Decision curves for the new and conventional risk scores. (A) Decision curves for the new and conventional ($CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores) risk scores to predict NACE incidence in patients with AF and stable CAD. (B) A 10-fold cross-validated decision curve for the new risk score to obtain a bias-corrected decision curve. AF, atrial fibrillation; CAD, coronary artery disease; NACE, net adverse clinical event; $CHADS_2$, Congestive heart failure, Hypertension, Age ≥75 y, Diabetes mellitus, Stroke or TIA; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 y, Diabetes mellitus, Stroke or TIA, Vascular disease, Age 65-74 y, Sex category [female]; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs.

syndrome and is more common in East Asians than in other ethnic populations.[34–37] The ALDH2-deficient variant is a risk factor for ischaemic heart diseases, such as coronary spasms[38] and acute myocardial infarction.[39 40] Based on these findings, alcohol consumption may have been selected as a candidate risk prediction score for NACE in this study. This machine-learning-based risk score is easy to use because it is based on information that is easily available in clinical settings and does not require testing results or information that is difficult to obtain.

This study had several limitations. First, the study population was Japanese and received a rivaroxaban dose of 10 or 15 mg once daily approved by Japan, rather than the once-daily dose of 20 mg approved globally, which may have caused selection bias. Additionally, because the study population included only patients who met the eligibility criteria of the AFIRE trial, we did not verify that the results of this study are applicable to patients in a real-world setting. To confirm generalisability, the risk score should be validated in other ethnic populations or settings. Second, because relevant information, such as haemoglobin,[33] platelet count,[33] complex percutaneous coronary intervention[41] and control of chronic disease (diabetes mellitus and dyslipidaemia), was not captured in the AFIRE trial, the information was not included in the variable selection. Third, although discontinuation of antithrombotic therapy is a risk factor for thrombotic events, data for antithrombotic therapy adherence were not collected in the AFIRE trial and lack of data may have affected the results of this study.

In conclusion, this post hoc analysis of the AFIRE trial demonstrated the development and validation of a machine learning-based risk score that can predict future adverse clinical events in patients with AF and stable CAD. It is important to balance the risk of both thromboembolic and bleeding events in the antithrombotic management of these patients, and the application of this risk score can be useful for decision-making in clinical settings.

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Contributors All authors have contributed to this manuscript. MI, EN and SN performed the statistical analysis. HO, KoK and SY handled funding and supervision. KoK, SY, MA, JA, TM, MN, KaM, NH, KaK, AH, KuM and HO acquired the data. KoK, SY, MA, JA, TM, MN, KaM, NH, KaK, AH, KuM and HO conceived and designed the study. MI drafted the manuscript. KoK and KT made critical revisions of the manuscript for key intellectual content. KoK accpets full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests KoK reports remuneration for lectures from Bayer Yakuhin, Daiichi-Sankyo, Novartis Pharma AG and Otsuka Pharmaceutical; has received trust research/joint research funds from Bayer Yakuhin, and Daiichi-Sankyo; and has received scholarship funds from Abbott Medical. SY reports grants from Takeda Pharmaceutical, Abbott and Boston Scientific, and personal fees from Daiichi-Sankyo and Bristol Myers Squibb. MA reports grants from the Japan Agency for Medical Research and Development; personal fees from Bristol Myers Squibb and Nippon Boehringer Ingelheim; and grants and personal fees from Bayer Yakuhin and Daiichi-Sankyo. JA reports personal fees from Bayer Yakuhin and Sanofi and grants and personal fees from Daiichi-Sankyo. TM reports grants from the Japan Cardiovascular Research Foundation, and personal fees from Nippon Boehringer Ingelheim, Daiichi-Sankyo, AstraZeneca and Bayer Yakuhin. MN reports grants and personal fees from Bayer Yakuhin, Daiichi-Sankyo and Sanofi and personal fees from Bristol Myers Squibb and Nippon Boehringer Ingelheim. KaM reports personal fees from Amgen Astellas BioPharma, Astellas Pharma, MSD, Bayer Yakuhin, Sanofi, Takeda Pharmaceutical, Daiichi-Sankyo, Nippon Boehringer Ingelheim and Bristol Myers Squibb. NH reports grants and personal fees from Bayer Yakuhin, Nippon Boehringer Ingelheim and personal fees from Bristol Myers Squibb. KaK reports grants from the Japan Cardiovascular Research Foundation grants and personal fees from Bayer Yakuhin, Daiichi-Sankyo, Sanofi, MSD and AstraZeneca, and personal fees from Bristol Myers Squibb and Nippon Boehringer Ingelheim. AH reports grants and personal fees from Boston Scientific Japan, Otsuka Pharmaceutical, Sanofi, Astellas Pharma, Bristol Myers Squibb, Daiichi-Sankyo, Bayer Yakuhin, Fukuda Denshi, Abbott Japan, Japan Lifeline, Takeda Pharmaceutical and Sumitomo Dainippon Pharma, and personal fees from Toa Eiyo, Nippon Boehringer Ingelheim, Amgen Astellas BioPharma, and AstraZeneca. HO reports personal fees from Towa Pharmaceutical, Bristol Meyers Squibb, Pfizer, Toa Eiyo, Bayer Yakuhin, and Novartis Pharma. KT received significant research grant from AMI, Bayer Yakuhin, Bristol-Myers K.K., EA Pharma, Mochida Pharmaceutical, and scholarship fund from AMI, Bayer Yakuhin, Boehringer Ingelheim Japan, Chugai Pharmaceutical, Daiichi-Sankyo, Edwards Lifesciences Corporation, Johnson & Johnson K.K., Ono Pharmaceutical, Otsuka Pharmaceutical, Takeda Pharmaceutical, and honoraria from Amgen K.K., Bayer Yakuhin, Daiichi-Sankyo, Kowa Pharmaceutical, Novartis Pharma K.K., Otsuka Pharmaceutical, Pfizer Japan, and belongs to the endowed departments donated by Abbott Japan, Boston Scientific Japan K.K., Fides-one, GM Medical, ITI, Kaneka Medix, Nipro, Terumo, Abbott Medical, Cardinal Heaith Japan, Fukuda Denshi, Japan Lifeline, Medical Appliance, Medtoronic Japan.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and the trial was conducted in accordance with the Declaration of Helsinki and approved by the institutional review boards of the Kumamoto University Hospital (Rinri No.2547) and all participating institutions. The data were reviewed by an independent data and safety monitoring committee. In this post hoc analysis, 2215 patients in the modified intention-to-treat population from the AFIRE trial were analysed. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The data underlying this article will be shared on reasonable request to the corresponding author.

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SUPPLEMENTAL MATERIAL ONLINE CONTENTS

for Risk Prediction Score for Clinical Outcome in Atrial Fibrillation and Stable Coronary Artery Disease

Authors: Ishii et al.

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Supplementary Table 1. Variables available for the risk prediction model in AFIRE study

Variable Domain	Individual Variables
Demographic	**Age, sex, smoking history, alcohol drinking history**
Physiological Findings	Height, body weight, **body mass index, systolic blood pressure, diastolic blood pressure**
Clinical / Medical History	**Type of atrial fibrillation, allocated arm, History of hypertension, diabetes mellitus, dyslipidaemia, angina pectoris, heart failure, liver dysfunction, renal dysfunction, haemorrhagic diathesis, stroke, transient ischemic attack, myocardial infarction, aortic aneurysm, systemic embolism, deep venous thrombosis, pulmonary embolism, peripheral artery disease, other ischemic disorder, bleeding complication, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), and interventions other than PCI or CABG**

Laboratory	**Creatinine clearance**
Baseline Medication	**Rivaroxaban, warfarin, dabigatran, apixaban, edoxaban, other anti-coagulants, aspirin, clopidogrel, prasugrel, ticlopidine, ticagrelor, P2Y12 inhibitor, other antiplatelet drugs, dual antiplatelet therapy, dose of rivaroxaban, proton pump inhibitor, non-steroidal anti-inflammatory drugs**
Conventional Risk Score	$CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED
Coronary Angiographic Findings	**Bare metal stent, drug eluting stent, type of stent such as Cypher, TAXUS, Endeavor, Xience, Promus, Nobori, or other, culprit lesion of PCI according to AHA classification,** date of PCI

Bolded candidate variables had <10% missing data and were used to develop risk prediction models.

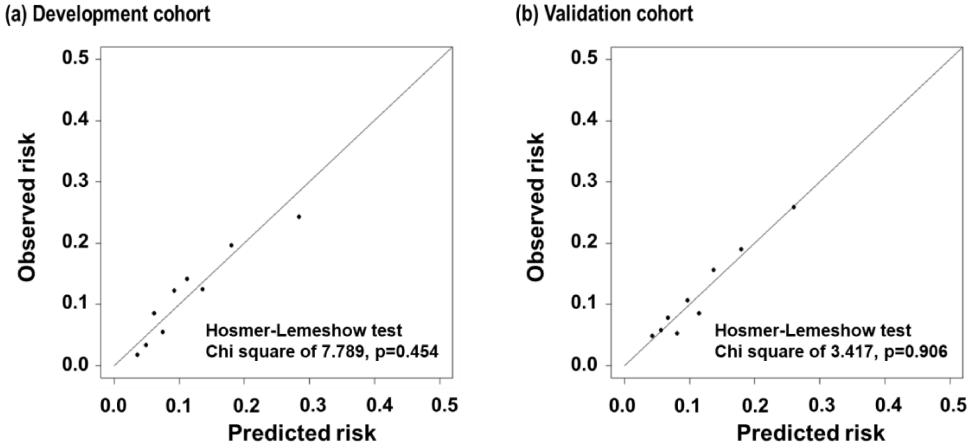
Supplementary Table 2. Discrimination and calibration of the random survival forest and Cox proportional hazard models

Variables	C-index	Brier score
Random survival forest model		
Development cohort	0.706	0.081
Validation cohort	0.667	0.080
Cox proportional hazard model		
Development cohort	0.680	0.079
Validation cohort	0.650	0.081

Supplementary Table 3. Discrimination and improvement indices for the new risk score compared to conventional risk scores

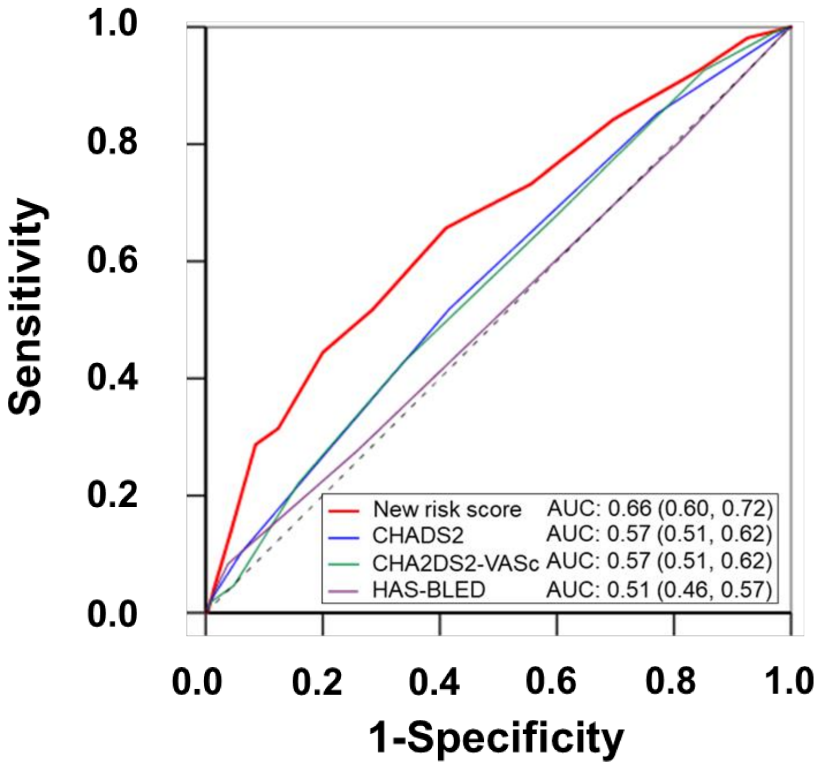
	Category free-NRI (95% CI), p-value	Categorical NRI (95% CI), p-value	IDI (95% CI), p-value
$CHADS_2$	0.429 (0.232, 0.625), p<0.001	0.130 (0.032, 0.228), p=0.010	0.029 (0.018,0.041), p<0.001
CHA_2DS_2-VASc	0.491 (0.297, 0.686), p<0.001	0.143 (0.043, 0.242), p=0.005	0.031 (0.019, 0.042), p<0.001
HAS-BLED	0.509 (0.318, 0.701), p<0.001	0.215 (0.088, 0.341), p<0.001	0.035 (0.021, 0.048), p<0.001

AUC, area under the curve; CI, confidence interval; NRI, net reclassification improvement; IDI, integrated discrimination improvement.



Supplementary Figure 1. Calibration plot of the new risk score for net adverse clinical events.

Calibration plot of the new machine-learning-based risk score using variables such as age, body mass index, sex, systolic blood pressure, alcohol consumption, creatinine clearance, heart failure, diabetes mellitus, antithrombotic regimen, and type of atrial fibrillation in the development (a) and validation (b) cohorts.



Supplementary Figure 2. Receiver operating characteristic curve for the new and conventional risk scores

Area under the receiver operating characteristic curve of the new machine-learning-based risk score and conventional risk scores such as the $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores.