A Novel Model for Prediction of Thromboembolic and Cardiovascular Events in Patients Without Atrial Fibrillation

Kamilla Steensig, MD[a,#], Kevin K W Olesen, MD[a,b,#], Morten Madsen, MSc[b], Troels Thim, MD, PhD[a], Lisette Okkels Jensen, MD, DMSc[c], Morten Würtz, MD, PhD[a], Steen Dalby Kristensen, MD, DMSc[a], Hans Erik Bøtker, MD, DMSc[a], Gregory Y H Lip, MD[d,e,f], John William Eikelboom, MD, PhD[g], and Michael Maeng, MD, PhD[a,*]

Patients without atrial fibrillation (AF) constitute approximately 75% of patients suffering thromboembolism and major adverse cardiovascular events (MACE), but evidence supporting risk stratification in these patients is sparse. We aimed to develop a risk prediction model for identification of patients without AF at high risk of first-time thromboembolic events. We included 72,381 coronary angiography patients without AF and without previous ischemic stroke or transient ischemic attack. The cohort was randomly divided into a derivation cohort (80%, n = 57,680) and a validation cohort (20%, n = 14,701). The primary thromboembolic end point was a composite of ischemic stroke, transient ischemic attack, and systemic embolism. MACE was defined as a composite of cardiac death, myocardial infarction, and ischemic stroke. The final model was compared with 2 validated clinical risk models ($CHADS_2$ and CHA_2DS_2-VASc). The risk prediction model assigned 1 point to heart failure, hypertension, diabetes mellitus, renal disease, age 65 to 74 years, active smoking, and multivessel obstructive coronary artery disease, and 2 points to age ≥75 years and peripheral artery disease. A C-index of 0.66 (95% CI 0.64 to 0.69) for prediction of the composite thromboembolic end point was found in the validation cohort, which was higher than for $CHADS_2$ (C-index 0.63 [95% CI 0.60 to 0.67]; p < 0.001) and CHA_2DS_2-VASc (C-index 0.64 [95% CI 0.62 to 0.67]; p = 0.034). The model also predicted MACE (C-index 0.71 [95% CI 0.69 to 0.73]). In conclusion it is possible to identify patients without AF at high risk of first-time thromboembolic events and MACE by use of a simple clinical prediction model. **(Am J Cardiol 2020;131:40−48)**

Patients without atrial fibrillation (AF) constitute approximately 75% of patients with thromboembolic events (TE: ischemic stroke, transient ischemic attack (TIA), and systemic embolism)[1] but evidence supporting risk stratification and prophylactic treatment in these patients is sparse. The latter may be explained by the lack of an intervention that, beyond treatment of hypertension and cholesterol, reduces TE risk in patients without AF. However, the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, that almost exclusively included patients without AF, showed that the combination of aspirin and low-dose rivaroxaban, compared with aspirin alone, reduced the relative risk of major adverse cardiovascular events (MACE) by 24% and stroke by 42%; the latter being the major driver of the reduced MACE rate.[2] Risc scores that can identify non-AF patients at high risk of TE, therefore have a new and important clinical relevance. Existing stroke risk scores such as $CHADS_2$ and CHA_2DS_2-VASc were developed for identification of AF patients at high risk of TE, but they also predict TE in patients without AF.[3−6] However, a dedicated prediction model for prediction of first-time TE in patients without AF may be superior to $CHADS_2$ and CHA_2DS_2-VASc and may potentially improve the identification of patients who will benefit from primary prevention. We developed a clinical prediction model for prediction of first-time TE and report the discrimination as well as calibration of this model among patients who underwent coronary angiography (CAG). Second, we compared the discriminatory ability of this new risk score with that of the $CHADS_2$ and CHA_2DS_2-VASc scores. Finally, we assessed the models' ability to predict MACE and mortality.

Methods

We conducted a population-based cohort study using Danish medical registries. Danish residents with a CAG registered in the Western Denmark Heart Registry

[a]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; [b]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [c]Department of Cardiology, Odense University Hospital, Odense, Denmark; [d]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark; [e]Liverpool Centre for Cardiovascular Science, Liverpool Heart and Chest Hospital, University of Liverpool, Liverpool, United Kingdom; [f]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; and [g]Division of Hematology & Thromboembolism, Department of Medicine, McMaster University, Ontario, Canada. Manuscript received March 14, 2020; revised manuscript received and accepted June 8, 2020.

This is an academic study funded by the Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark.

[#]Drs. Steensig and Olesen contributed equally to this manuscript.See page 47 for disclosure information.

*Corresponding author Tel: +45 26703237; fax: +45 78452260

E-mail address: michael.maeng@clin.au.dk (M. Maeng).

0002-9149/
https://doi.org/10.1016/j.amjcard.2020.06.031

(WDHR) between July 1, 2004 and December 31, 2012 were included.[7] In case of multiple CAGs during the study period, the first CAG was defined as index procedure.

The setting in Denmark is a tax-payer funded public national healthcare system, ensuring free access to healthcare for all Danish residents. At birth or upon immigration, each resident is assigned a unique 10-digit personal identifier, issued by the Danish Civil Registration System. This identifier is used throughout every regional and national registry and ensures accurate cross-linkage of healthcare information between registries which minimizes loss to follow-up.

The WDHR contains information about all cardiac procedures performed in Western Denmark since 1999 and covers a population of approximately 3.5 million inhabitants. The WDHR holds data on >240,000 CAGs, including details regarding presence and extent of coronary artery disease (CAD), procedural indication and priority, procedure related complications and patient characteristics.[7] Additional information concerning comorbidities was obtained from the Danish National Patient Registry (DNPR), which has recorded all hospital-based inpatient and outpatient diagnoses in Denmark since 1977. Causes of death were obtained from the Danish Register of Causes of Death, and medical information from the Danish National Database of Reimbursed Prescriptions, which contains data on all reimbursed prescriptions at Danish pharmacies since 2004.[8–10]

CAG was performed in 97,321 patients. We excluded patients <18 years (n = 33), patients with a previous diagnosis of AF in the DNPR (n = 13,226), patients treated with vitamin K-antagonists (n = 3,285) or direct anticoagulants (n = 48), patients with a diagnosis of ischemic stroke or TIA before or within 30 days after CAG (n = 6,162), and patients with <30 days of follow-up (n = 2,186).[8,9] International Classification of Diseases, Tenth Revision codes, and Anatomical Therapeutic Chemical codes used in covariate definitions are listed in Supplemental Table 1. Follow-up started 30 days after index CAG to account for immediate consequences of the CAG examination. We followed each patient using the DNPR to record the end points ischemic stroke, TIA, and systemic embolism. We examined available covariates considered clinically relevant, as described below.

Comorbidities registered before or within 30 days after index CAG were ascertained from the WDHR and the DNPR. We defined congestive heart failure as a diagnosis of congestive heart failure or left ventricular dysfunction registered in the DNPR, or a left ventricular ejection fraction ≤40% registered in the WDHR. Hypertension was defined as a diagnosis of hypertension registered in the DNPR or treatment with any antihypertensive drug according to the WDHR. Age and gender were obtained from WDHR, and the patients were divided into 3 age groups (<65 years, 65 to 74 years, and ≥75 years) according to age at index CAG. Moreover, body mass index was calculated from height and bodyweight as listed in the WDHR, and patients were categorized as underweight (≤18.5 kg/m^2), normal weight (18.5 to 25 kg/m^2), overweight (25 to 30 kg/m^2), or obese (≥30 kg/m^2).

We defined diabetes mellitus as the composite of 1) insulin treatment and/or oral antidiabetic medication use or non-pharmacological dietary treatment for diabetes registered in the WDHR, 2) redemption of ≥1 prescription(s) for antidiabetic medications in the Danish National Database of Reimbursed Prescriptions 6 month before CAG or within 30 days after CAG, or 3) a diagnosis of diabetes mellitus in the DNPR.

Peripheral artery disease (PAD) was defined as PAD and/or aortic plaque as registered in the DNPR. CAD was categorized as 0 vessel disease (VD), 1 VD, 2 VD, 3 VD, or diffuse VD. Obstructive multivessel disease was defined as obstructive VD (≥50% stenosis) in ≥2 coronary arteries, that is, 2 VD and 3 VD. Diffuse VD was defined as non-obstructive VD (<50% coronary stenosis) in ≥2 coronary arteries. Diagnoses of previous myocardial infarction were obtained through the DNPR. Smoking status was defined as active smoker or former/never smoker as listed in the WDHR. Moderate to severe renal disease was defined according to the Charlson Comorbidity Index as registered in the DNPR.[11]

The primary study end point was TE, a composite of ischemic stroke, TIA, and systemic embolism. The model was developed using TE as outcome. Study end points examined after model development were ischemic stroke alone, MACE (cardiac death, myocardial infarction, and ischemic stroke), and all-cause death. We used primary and secondary hospital discharge diagnoses registered in the DNPR. Follow-up started 30 days after CAG and continued until end point event, death, emigration, 5 years of follow-up, or end of follow up (December 31, 2012), whichever came first.

The study cohort was randomly divided into a derivation cohort representing 80% of the study population, and a validation cohort representing the remaining 20%. The model was designed in the derivation cohort and subsequently validated in the validation cohort. We used Pearson's chi-square test to assess any statistical difference of categorical baseline characteristics between the derivation cohort and the validation cohort. Years of follow-up and age did not follow a normal distribution in either cohort as illustrated by histogram and QQ-plot. Thus, the statistical differences between cohorts of follow-up and age as continuous variables were tested by the Mann-Whitney U test.

We constructed the model by performing separate univariate Cox regression analyses of all covariates in the derivation cohort using TE as outcome. Covariates with $p < 0.20$ were selected for further analyses and fitted into a multivariate Cox regression model.[12] Covariates not significantly contributing to the model ($p > 0.05$) were excluded.

We tested for interactions between covariates, and interaction terms were added to the model. We compared goodness of fit of the models with and without the interaction terms using likelihood ratio test. If $p < 0.05$, the interaction term was included in the model. To assess goodness of fit of the final model, Cox-Snell residuals were predicted and plotted against the cumulative hazards. To identify potential outliers, we estimated Martingale and deviance residuals. We assessed the Cox proportional hazard assumption, and finally we used Harrell's C-statistics to estimate model discrimination.

Weighted model: We assigned either 1 or 2 points to each covariate in the final model according to the

covariates' respective hazard ratios (HR). Covariates with a HR of 1.00 to 1.99 were assigned 1 point and HRs of 2.00 to 2.99 were assigned 2 points. Each patient's weighted risk score was then estimated. Due to low numbers of patients with high scores, patients with >4 points were classified as 1 group. The Cox proportional hazards assumption was tested in the weighted model, and Harrell's C-index was calculated to estimate discrimination.

Validation: In the validation cohort, we validated the weighted model by estimating the risk score for each patient. Patients with >4 points were grouped together. We estimated event rates per 100 person-years according to the number of points, and afterwards HRs were calculated using patients with 0 points as reference. Harrell's C-index was calculated in the validation cohort. Model calibration was graphically assessed by plotting observed versus predicted event probabilities over time stratified by the number of points according to the weighted model.

To assess the model's discrimination compared with other risk prediction scores, we calculated the $CHADS_2$ and CHA_2DS_2-VASc scores in the validation cohort. Subsequently, we estimated Harrell's C-indices of both risk prediction scores and calculated the absolute difference in C-index between the $CHADS_2$, the CHA_2DS_2-VASc, and our weighted model. We also constructed receiver operating characteristic curves for each of the 3 models among

Table 1
Baseline characteristics of the derivation cohort and the validation cohort

	Derivation cohort (n = 57,680)	Validation cohort (n = 14,701)	p-value*
Median years of follow-up (IQR)	3.7 years (1.8−5.0)	3.7 years (1.8−5.0)	0.39
Sex category			0.22
Male	36,005 (62%)	9,096 (62%)	
Median age (IQR)	64 years (55−72)	64 years (55−72)	0.35
Age category (years)			0.004
<65	30,538 (53%)	7,770 (53%)	
65−74	16,824 (29%)	4,147 (28%)	
≥75	10,318 (18%)	2,784 (19%)	
Smoking status			0.08
Never/former	35,555 (62%)	8,992 (61%)	
Active	16,790 (29%)	4,261 (29%)	
Missing	5,335 (9%)	1,448 (10%)	
Comorbidities			
Hypertension	31,607 (55%)	8,180 (56%)	0.07
Diabetes mellitus	8,597 (15%)	2,225 (15%)	0.48
Congestive heart failure	7,793 (14%)	1,962 (13%)	0.60
Previous myocardial infarction	20,053 (35%)	5,076 (35%)	0.59
Peripheral artery disease/aortic plaque	3,810 (7%)	999 (7%)	0.41
Renal disease	1,541 (3%)	429 (3%)	0.10
Body mass index (kg/m^2)			0.88
Underweight	706 (1%)	187 (1%)	
Normal	16,273 (28%)	4,182 (28%)	
Overweight	20,647 (36%)	5,258 (36%)	
Obese	20,054 (35%)	5,074 (35%)	
Medical treatment			
Aspirin	41,932 (73%)	10,652 (73%)	0.56
Statin	42,261 (73%)	10,800 (74%)	0.63
Beta-blocker	38,331 (67%)	9,725 (66%)	0.49
Angiotensin converting enzyme inhibitor	20,502 (36%)	5,182 (35%)	0.50
Angiotensin-II receptor inhibitor	8,744 (15%)	2,259 (15%)	0.53
Adenosine diphosphate inhibitor	16,277 (28%)	4,135 (28%)	0.83
Priority of coronary angiography			0.75
Acute	10,097 (18%)	2,540 (17%)	
Subacute	15,312 (27%)	3,936 (27%)	
Elective	32,270 (56%)	8,225 (56%)	
No. of coronary arteries narrowed			0.76
0	20,894 (36%)	5,367 (37%)	
Diffuse vessel disease	4,195 (7%)	1,046 (7%)	
1	15,582 (27%)	3,907 (27%)	
2	8,762 (15%)	2,257 (15%)	
3	8,247 (14%)	2,124 (14%)	
Obstructive multivessel disease (≥2 vessel disease)	17,009 (30%)	4,381 (30%)	

Data are numbers and percentages, n (%) unless otherwise stated.

* Categorical variables: Chi-square test. Follow-up and age as continuous variables: Mann-Whitney U test.

IQR = interquartile range.

patients without AF (Supplemental Figure 1). Moreover, the discrimination of the prediction model was also tested among CAG patients with AF and compared with the $CHADS_2$ and CHA_2DS_2-VASc scores among patients with AF (Supplemental Table 2).

In the validation cohort, we estimated event rates of ischemic stroke, MACE, and all-cause death stratified by number of points in the weighted model. Afterwards HR's were calculated using patients with 0 points as reference. Finally, Harrell's C-indices of ischemic stroke, MACE, and all-cause death were estimated. Analyses were performed using Stata/IC software version 15.1 (StataCorp, College station, Texas, USA).

The study complies with the Declaration of Helsinki and was approved by the Danish Data Protection Agency (record number 2015-57-0002, identification number AU420).

Results

Baseline characteristics and medication use are shown in Table 1. The study cohort comprised 72,381 patients, of which 57,680 were assigned to the derivation cohort and 14,701 to the validation cohort (Figure 1). Baseline characteristics were similar between the 2 cohorts, except for age category, which was statistically, but not clinically, different between cohorts (Table 1). There was no difference in age as a continuous variable.

Univariate analyses of all considered covariates and the initial multivariate analysis of all variables are presented in *Table 2*.

The final model included the following predictors of the composite end point: congestive heart failure, hypertension, age category, renal disease, PAD, smoking status (active smoking vs never/former smoking), obstructive coronary multivessel disease, and diabetes mellitus. Three interaction terms were included in the final model; diabetes/renal disease, hypertension/PAD, and age category/PAD. Harrell's C-index of the final unweighted model was 0.67 (95% CI 0.65 to 0.68).

Based on HRs in the final multivariate analysis, patients were assigned the following points for each risk factor: congestive heart failure (1 point), hypertension (1 point), age 65 to74 years (1 point), diabetes mellitus (1 point), smoking (1 point), PAD (2 points), age ≥75 years (2 points), renal disease (1 point), and obstructive coronary multivessel disease (1 point). The risk score thus was termed the CHADS-P_2A_2RC score (Table 2).

Event rates per 100 person-years and HRs increased with higher CHADS-P_2A_2RC scores (Table 3). In the validation cohort, 5,346 patients (36%) had a CHADS-P_2A_2RC score ≥3, which conferred a TE rate of >1 per 100 person-years

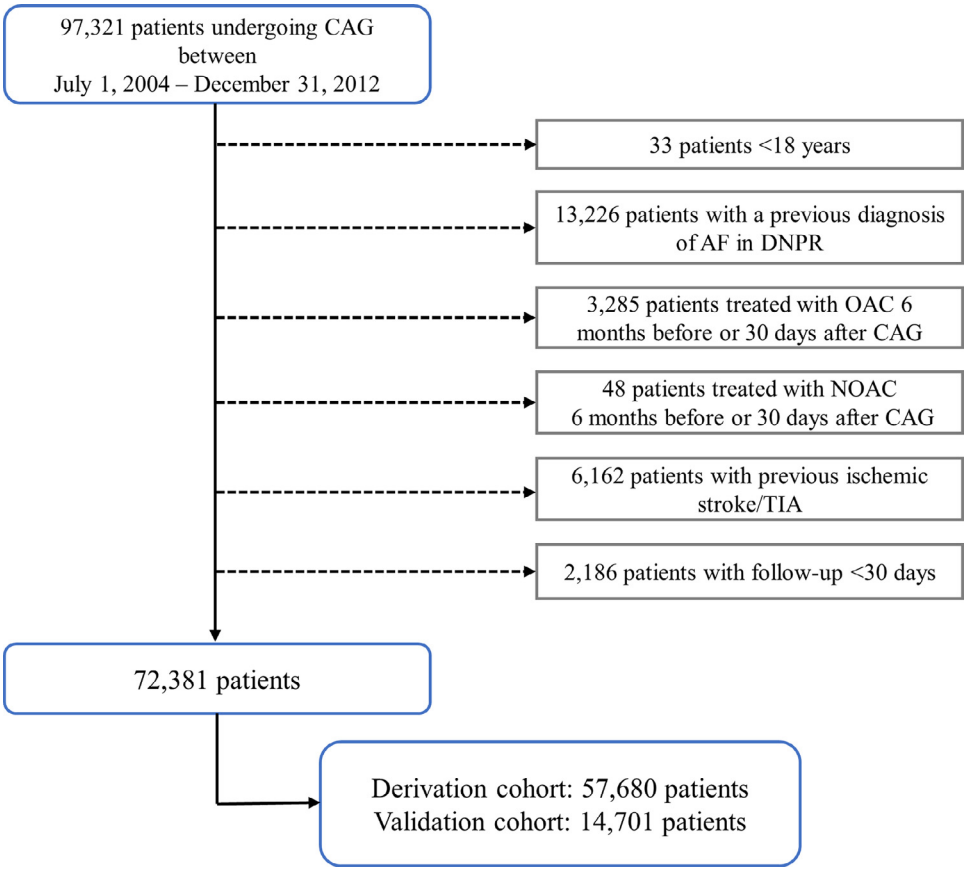

Figure 1. Patient flow chart. The flow chart illustrates the inclusion of 72,381 patients without atrial fibrillation or previous stroke examined by coronary angiography between July 1, 2004 and December 31, 2012, as registered in the Western Denmark Heart Registry.
AF = atrial fibrillation; CAG = coronary angiography; DNPR = Danish National Patient Registry; NOAC = Non-vitamin K antagonist oral anticoagulants; OAC = oral anticoagulant agents; TIA = transient ischemic attack.

Table 2
Univariate and multivariate analyses of potential risk factors associated with ischemic stroke, transient ischemic attack, and systemic embolism

Covariates	Univariate analyses		Primary multi variate analysis		Final multi variate analysis	Assigned points
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	
Sex category						
Male	1.05 (0.95−1.16)	0.308				
Age category (years)						
65−74	1.82 (1.63−2.04)	<0.001	1.71 (1.51−1.93)	<0.001	1.70 (1.49−1.93)	1
≥75	3.09 (2.76−3.46)	<0.001	2.83 (2.49−3.22)	<0.001	2.98 (2.60−3.41)	2
Body mass index						
Normal	0.99 (0.64−1.55)	0.979				
Overweight	0.95 (0.61−1.48)	0.818				
Obese	0.93 (0.60−1.45)	0.755				
Comorbidities						
Congestive heart failure	1.60 (1.42−1.80)	<0.001	1.32 (1.16−1.50)	<0.001	1.31 (1.15−1.49)	1
Hypertension	1.52 (1.38−1.67)	<0.001	1.29 (1.16−1.44)	<0.001	1.35 (1.20−1.51)	1
Peripheral artery disease	2.18 (1.89−2.52)	<0.001	1.62 (1.39−1.89)	<0.001	2.59 (1.81−3.70)	2
Renal disease	2.07 (1.64−2.60)	<0.001	1.74 (1.36−2.23)	<0.001	1.41 (1.01−1.98)	1
Myocardial infarction	1.16 (1.05−1.27)	0.003	0.99 (0.89−1.10)	0.788		
Diabetes mellitus	1.51 (1.35−1.70)	<0.001	1.32 (1.17−1.50)	<0.001	1.28 (1.12−1.46)	1
Coronary artery disease						
Obstructive multivessel disease (≥2 vessel disease)	1.61 (1.47−1.77)	<0.001	1.23 (1.10−1.36)	<0.001	1.22 (1.11−1.36)	1
Other						
Smoking	1.09 (0.98−1.20)	0.119	1.34 (1.20−1.49)	<0.001	1.33 (1.20−1.48)	1
Maximal score						11

Primary multivariate analysis: A primary multivariate Cox-regression analysis without interaction term. Final multivariate analysis: A multivariate Cox-regression including interaction terms (diabetes/renal disease, hypertension/peripheral artery disease, and peripheral artery disease/age category). All covariates considered clinically relevant were included in the univariate analyses, and all covariates with $p < 0.20$ were included in the primary multivariate analysis. In the univariate analysis of age category, patients <65 years were used as reference. In the univariate analysis of body mass index, underweight patients were used as reference. Coronary artery disease was compiled as obstructive multivessel disease (≥2 vessel disease). Before assigning points to the different variables, interaction analyses were performed. Each covariate was assigned 1 or 2 points according to their HR in the final multivariate analysis, which was performed in respect to the interactions.

CI = confidence interval; HR = hazard ratio.

Table 3
Clinical end points in relation to CHADS-P_2A_2RC score for 65,596 patients without atrial fibrillation or previous stroke, and with known smoking status A) The validation cohort (n = 13,253), B) The derivation cohort (n = 52,343). The clinical end point was a composite of ischemic stroke, transient ischemic attack, and systemic embolism.

A: The validation cohort				
CHADS-P_2A_2RC score (points)	Patients (n)	Events (n)	Rate per 100 person-years	HR (95% CI)
0	1,446	18	0.36 (0.23−0.57)	1 (reference)
1	3,148	56	0.53 (0.41−0.69)	1.46 (0.86−2.48)
2	3,313	78	0.71 (0.57−0.88)	1.95 (1.17−3.26)
3	2,679	107	1.28 (1.06−1.55)	3.54 (2.15−5.83)
4	1,581	81	1.70 (1.36−2.11)	4.66 (2.80−7.77)
>4	1,086	74	2.41 (1.92−3.02)	6.61 (3.95−11.06)
B: The derivation cohort				
CHADS-P_2A_2RC score (points)	Patients (n)	Events (n)	Rate per 100 person-years	HR (95% CI)
0	5,809	61	0.31 (0.24−0.39)	1 (reference)
1	12,754	250	0.58 0.51−0.65)	1.89 (1.43−2.50)
2	13,377	334	0.76 (0.68−0.84)	2.47 (1.88−3.24)
3	10,172	370	1.14 (1.03−1.26)	3.69 (2.82−4.84)
4	5,945	321	1.77 (1.59−1.97)	5.73 (4.36−7.54)
>4	4,286	274	2.37 (2.11−2.67)	7.61 (5.76−10.04)

Risk factors included in the CHADS-P_2A_2RC score: Congestive heart failure (1 point), hypertension, age 65−74 years (1 point), diabetes mellitus (1 point), smoking (1 point), peripheral artery disease (2 points), (1 point), age ≥75 years (2 points), renal disease (1 point), and obstructive coronary multivessel disease (1 point)

CI = confidence interval; HR = hazard ratio.

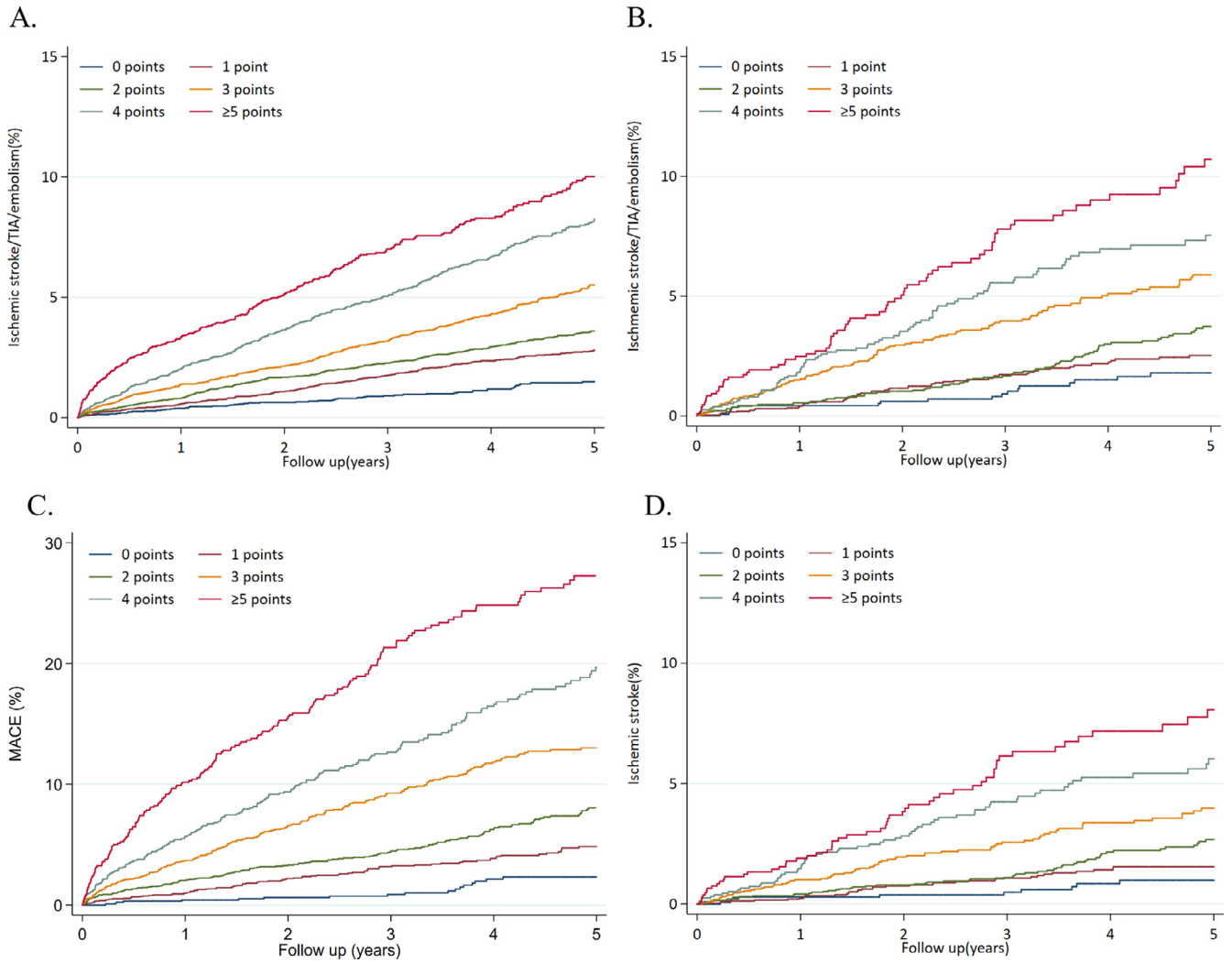

Figure 2. Cumulative incidence of end points in relation to CHADS-P_2A_2RC score.
(A) The composite thromboembolic end point (ischemic stroke, TIA and systemic embolism) in the derivation cohort (n = 57,680). *(B)* the composite thromboembolic end point in the validation cohort (n = 14,701). *(C)* MACE and *(D)* Ischemic stroke. All patients were registered in the Western Denmark Heart Registry after undergoing coronary angiography and were not previously diagnosed with atrial fibrillation or stroke/TIA.
MACE = major adverse cardiovascular events; TIA = transient ischemic attack.

(Figure 2). The CHADS-P_2A_2RC score performed similarly in the validation cohort (C-index 0.66, 95% CI 0.64 to 0.69). According to the calibration curves, showing the observed versus predicted event probabilities, the CHADS-P_2A_2RC score was well-calibrated in the validation cohort, displaying good fit between predicted and observed outcomes in each risk strata. Validation curves for TE are depicted in Figure 3 and validation curves for the secondary end points in Supplemental Figure 2.

C-indices of the $CHADS_2$ and CHA_2DS_2-VASc scores were 0.63 (95% CI 0.60 to 0.67) and 0.64 (95% CI 0.62 to 0.67), respectively. The C-index of the CHADS-P_2A_2RC score was higher than those of the $CHADS_2$ (Δ0.034, 95% CI 0.016 to 0.051, $p < 0.001$) and CHA_2DS_2-VASc (Δ0.018, 95% CI 0.001 to 0.035, p = 0.034) scores.

Event rates and HRs of ischemic stroke, MACE, and all-cause death were higher with increasing CHADS-P_2A_2RC scores (Table 4). C-index was 0.68 (95% CI 0.65 to 71) for ischemic stroke, 0.71 (95% CI 0.69 to 0.73) for MACE, and 0.72 (95% CI 0.70 to 0.73) for all-cause death.

Discussion

In this study we present a novel clinical prediction model intended for prediction of TE in patients without AF. This model has several important features. First, the CHADS-P_2A_2RC model was able to discriminate patients at different risks of TE. Second, the model proved to be well-calibrated in both high- and low-risk patients. Third, the CHADS-P_2A_2RC score also predicted ischemic stroke alone, MACE, and all-cause death, confirming its ability to identify, beyond TE, patients at risk of adverse cardiovascular events.[2] Fourth, the parameters included in the CHADS-P_2A_2RC score differed to some extent from the $CHADS_2$ and CHA_2DS_2-VASc scores, which were developed for patients with AF. Female sex was replaced by smoking, multivessel CAD was included, and PAD was included as

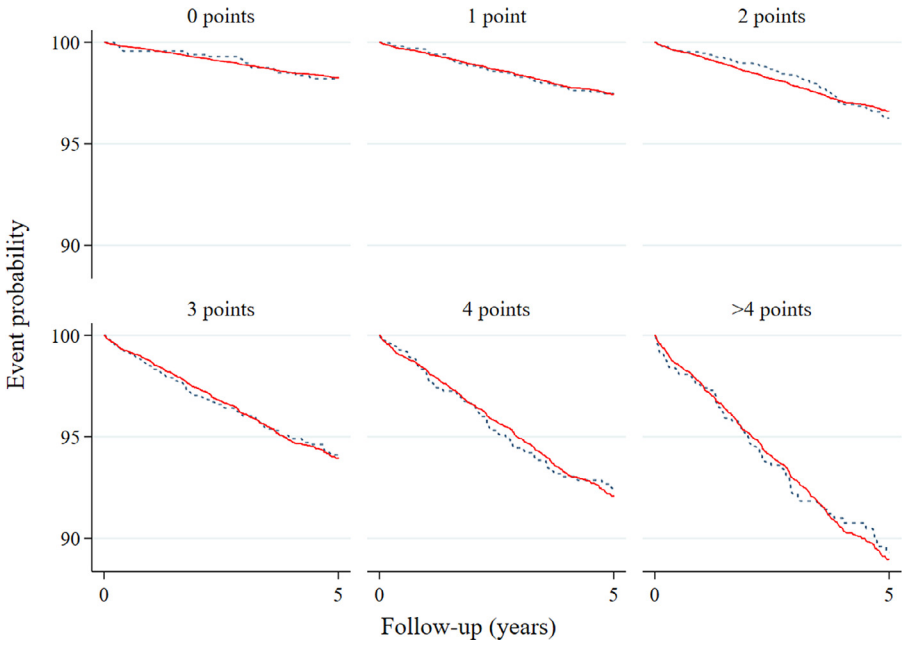

Figure 3. Calibration curves for the validation cohort. The red straight line represents the predicted probability, and the blue dotted line the observed probability of thromboembolic events (ischemic stroke, transient ischemic attack, and systemic embolism).

an independent parameter (as compared with part of the "V" for vascular components in CHA_2DS_2-VASc) with a weight of 2 points (as compared with 1 point in CHA_2DS_2-VASc). In this regard, it is also important that the $CHADS_2$ and CHA_2DS_2-VASc scores are used for identification of patients at low risk, and thus without indication for oral anticoagulant therapy, whereas the aim of the CHADS-P_2A_2RC score is to identify patients at high risk of ischemic stroke and MACE and whom may benefit from primary prophylaxis.

Approximately 75% of all TE are first-time events, which emphasizes the need for primary prevention strategies including clinical tools to identify patients at particular high risk of first-time TE.[13] Our primary TE end point included TIA for 2 reasons. First, TIA is a strong predictor of subsequent stroke and we therefore found it worth including in the primary end point. Secondly, there is a precedent for this TE definition in Danish registry-based studies on AF.[6,14–16] However, one may argue against TIA as part of the primary end point since TIA is a less reliable

Table 4
Rate of ischemic stroke, major adverse cardiovascular events, and all-cause death in the validation cohort

CHADS-P_2A_2RC score (points)	Events (n)	Rate per 100 person-years	HR (95% CI)
Ischemic stroke			
0	10	0.20 (0.11–0.37)	1 (reference)
1	35	0.33 (0.23–0.46)	1.64 (0.81–3.31)
2	56	0.51 (0.39–0.66)	2.52 (1.29–4.94)
3	71	0.84 (0.67–1.07)	4.20 (2.12–8.14)
4	64	1.33 (1.04–1.70)	6.59 (3.38–12.83)
>4	56	1.80 (1.39–2.34)	8.93 (4.55–17.50)
Major adverse cardiovascular events*			
0	18	0.44 (0.27–0.69)	1 (reference)
1	88	1.02 (0.82–1.25)	2.32 (1.40–3.86)
2	150	1.67 (1.42–1.96)	3.81 (2.34–6.21)
3	207	3.08 (2.69–3.53)	6.96 (4.30–11.27)
4	179	4.65 (4.01–5.38)	10.45 (6.44–16.97)
>4	187	7.45 (6.45–8.59)	16.67 (10.28–27.05)
All-cause death			
0	35	0.70 (0.50–0.97)	1 (reference)
1	104	0.97 (0.80–1.18)	1.39 (0.95–2.04)
2	188	1.68 (1.46–1.94)	2.40 (1.68–3.45)
3	287	3.36 (2.99–3.77)	4.79 (3.38–6.81)
4	280	5.70 (5.07–6.41)	8.12 (5.71–11.54)
>4	294	9.20 (8.21–10.32)	13.07 (9.21–18.56)

* End of inclusion December 1, 2011; end of follow-up December 31, 2011.
CI =confidence interval; HR = hazard ratio.

diagnosis than ischemic stroke based on the absence versus presence, respectively, of documented cerebral infarction. We therefore reported data for ischemic stroke alone as well as for MACE and all-cause death and found slightly higher C-indexes for these parameters than for TE. In the COMPASS trial, which had CAD as a major inclusion criterium, MACE was the primary end point. In this study, we included MACE as a secondary end point to document the potential of the CHADS-P_2A_2RC score to be used as tool for identifying patients with CAD and a high risk of MACE.

The CHADS-P_2A_2RC score can be used to identify patients at high risk of TE, ischemic stroke, MACE and all-cause death. Stroke is particularly important by being the fifth most frequent cause of death in the USA in 2016, and because stroke-related physical and/or cognitive deficits often reduce patients' quality of life and constitute a major health burden.[17] Among AF patients, protection against TE using oral anticoagulation is generally considered to outweigh the bleeding risk associated with anticoagulant treatment when the annual risk of TE exceeds 1%.[18–20] Therefore, AF patients with a CHA_2DS_2-VASc score of 1 are recommended to be considered prophylactic anticoagulant treatment, whereas patients with CHA_2DS_2-VASc $\geq$2 are candidates for prophylactic treatment in absence of a high bleeding risk according to both European and US guidelines.[18,20] However, along with other risk factors, AF should be considered a risk factor for TE rather its cause.[21] Consequently, patients without AF, but with aggregated risk factors, may have a similar or higher stroke risk than AF patients.

Except for hypertension, risk factors included in the CHADS-P_2A_2RC score were part of the inclusion criteria used in the randomized COMPASS trial, in which the vast majority of patients did not have AF. In the COMPASS trial, the combination of aspirin and low-dose rivaroxaban, as compared with aspirin alone, reduced the relative risk of MACE by 24% and stroke by 42%; the latter being the major driver of the reduced MACE rate.[2] The European Medicines Agency recently broadened the indication for rivaroxaban stating that combined therapy with aspirin and low-dose rivaroxaban is now indicated in high-risk patients.[22] Likewise, the US Federal Drug Agency stated that combined treatment is indicated in patients with CAD and PAD.[23] Considering these official statements, the CHADS-P_2A_2RC score offers a relatively simple tool to assist patients and clinicians in the shared decision-making process regarding dual pathway inhibition. Still, a specific cut-off for potential prophylactic treatment remains to be defined and will also depend on the individual patient's bleeding risk.

This is a hypothesis-generating registry-based cohort study based on patients who underwent CAG. All patient characteristics were obtained upon study initiation. Therefore, some patients' risk scores might have changed during follow-up.[24,25] Moreover, some patients might have been diagnosed with AF during follow-up leading to anticoagulant treatment initiation. Of note, patients' risk scores are more likely to increase than decrease over time, as most conditions are chronic. Smoking status was missing in 10% of the study population, and we might have underestimated the association between smoking and TE risk. Moreover, autopsy is no longer routinely performed in Denmark leading to potential underestimation of the number of fatal strokes. Finally, we did not have access to information about the presence of obstructive sleep apnea and patent foramen ovale, both of which are suggested risk factors for stroke.[13]

In conclusion, the CHADS-P_2A_2RC score is a novel clinical prediction model that predicts the risk of TE as well as ischemic stroke, MACE, and all-cause death among CAG patients without AF. The model discriminates between patients with low and high risk of TE and is well calibrated. The CHADS-P_2A_2RC score are thus able to identify patients with a high risk of adverse events in whom prophylactic stroke and MACE prevention may be considered.

Author contributions

Kamilla Steensig: Conceptualization, Methodology, Writing - Original Draft. **Kevin K W Olesen:** Conceptualization, Methodology, Software, Writing – Original Draft. **Morten Madsen:** Methodology, Software, Writing - Review & Editing. **Troels Thim:** Methodology, Writing - Review & Editing. **Lisette Okkels Jensen:** Writing - Review & Editing. **Morten Würtz:** Writing - Review & Editing. **Steen D Kristensen:** Writing - Review & Editing. **Hans Erik Bøtker:** Writing - Review & Editing. **Gregory Y H Lip:** Writing - Review & Editing. **John W Eikelboom:** Writing - Review & Editing. **Michael Maeng:** Conceptualization, Methodology, Writing - Review & Editing, Supervision.

Disclosures

The authors declare the following financial interests/personal relations which may be considered as potential competing interests:

KKWO has received speaking honoraria from Bayer. MW has received speaking honoraria or consultancy fees from Bayer, Boehringer Ingelheim, and BMS/Pfizer. MW has received speaking honoraria or consultancy fees from Bayer, Boehringer Ingelheim, and BMS/Pfizer. SDK has received lecture fees from Aspen, AstraZeneca, Bayer, Bristol-Myers Squibb /Pfizer, and Boehringer Ingelheim. GYHL is consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo, and speaker for Bayer, Bristol-Myers Squibb /Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally. JWE has received honoraria and research support from Bayer, Boehringer Ingelheim, BMS, Daiichi-Sankyo, Janssen, and Pfizer. He holds a mid-career award from the Heart and Stroke Foundation of Ontario and the Jack Hirsh/PHRI chair in thrombosis and atherosclerosis. MM has received lecture fees and consulting honoraria from Novo Nordisk, Bayer, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, MSD, and institutional research grants from Volcano (now Philips), Boston Scientific, Bayer, and Biosensors. KS, MoMa, TT, LOJ, and HEB have no disclosures in relation to this manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.06.031.

1. Christiansen CB, Gerds TA, Olesen JB, Kristensen SL, Lamberts M, Lip GY, Gislason GH, Kober L, Torp-Pedersen C. Atrial fibrillation and risk of stroke: a nationwide cohort study. *Europace* 2016;18:1689–1697.
2. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, Widimsky P, Hori M, Avezum A, Piegas LS, Branch KRH, Probstfield J, Bhatt DL, Zhu J, Liang Y, Maggioni AP, Lopez-Jaramillo P, O'Donnell M, Kakkar A, Fox KAA, Parkhomenko AN, Ertl G, Stork S, Keltai M, Ryden L, Pogosova N, Dans AL, Lanas F, Commerford PJ, Torp-Pedersen C, Guzik TJ, Verhamme PB, Vinereanu D, Kim JH, Tonkin AM, Lewis BS, Felix C, Yusoff K, Steg PG, Metsarinne KP, Cook Bruns N, Misselwitz F, Chen E, Leong D, Yusuf S. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *N Engl J Med* 2017;377:1319–1330.
3. Welles CC, Whooley MA, Na B, Ganz P, Schiller NB, Turakhia MP. The CHADS2 score predicts ischemic stroke in the absence of atrial fibrillation among subjects with coronary heart disease: data from the Heart and Soul Study. *Am Heart J* 2011;162:555–561.
4. Lip GY, Lin HJ, Chien KL, Hsu HC, Su TC, Chen MF, Lee YT. Comparative assessment of published atrial fibrillation stroke risk stratification schemes for predicting stroke, in a non-atrial fibrillation population: the Chin-Shan Community Cohort Study. *Int J Cardiol* 2013;168:414–419.
5. Mitchell LB, Southern DA, Galbraith D, Ghali WA, Knudtson M, Wilton SB. Prediction of stroke or TIA in patients without atrial fibrillation using $CHADS_2$ and CHA_2DS_2-VASc scores. *Heart* 2014;100:1524–1530.
6. Steensig K, Olesen KKW, Thim T, Nielsen JC, Madsen M, Jensen SE, Jensen LO, Kristensen SD, Lip GYH, Maeng M. Predicting stroke in patients without atrial fibrillation. *Eur J Clin Invest* 2019:e13103.
7. Schmidt M, Maeng M, Madsen M, Sørensen HT, Jensen LO, Jakobsen C-J. The Western Denmark Heart Registry: its influence on Cardiovascular Patient Care. *J Am Coll Cardiol* 2018;71:1259–1272.
8. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449–490.
9. Johannesdottir SA, Horvath-Puho E, Ehrenstein V, Schmidt M, Pedersen L, Sorensen HT. Existing data sources for clinical epidemiology: the Danish National Database of Reimbursed Prescriptions. *Clin Epidemiol* 2012;4:303–313.
10. Helweg-Larsen K. The Danish Register of Causes of Death. *Scand J Public Health* 2011;39:26–29.
11. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson Comorbidity Index predicted in-hospital mortality. *J Clin Epidemiol* 2004;57:1288–1294.
12. Hosmer DW, Lemeshow S, May S. *Applied Survival Analysis. Regression Modeling of Time-to-Event Data*. 2008.
13. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MS, Fornage M, Goldstein LB, Greenberg SM, Horvath SE, Iadecola C, Jauch EC, Moore WS, Wilson JA, American Heart Association Stroke Council, Council on Cardiovasc BC, Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MSV V, Fornage M, Goldstein LB, Greenberg SM, Horvath SE, Iadecola C, Jauch EC, Moore WS, Wilson JA, American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Functional Genomics and Translational Biology, Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;45:3754–5832.
14. Lip GYH, Skjoth F, Nielsen PB, Kjaeldgaard JN, Larsen TB. Effectiveness and safety of standard-dose Nonvitamin K antagonist oral anticoagulants and warfarin among patients with atrial fibrillation with a single stroke risk factor: a Nationwide Cohort Study. *JAMA Cardiol* 2017;2:872–881.
15. Olesen KKW, Steensig K, Madsen M, Thim T, Jensen LO, Raungaard B, Eikelboom J, Kristensen SD, Bøtker HE, Maeng M. Comparison of frequency of ischemic stroke in patients with versus without coronary heart disease and without atrial fibrillation. *Am J Cardiol* 2019;123:153–158.
16. Steensig K, Olesen KKW, Thim T, Nielsen JC, Jensen SE, Jensen LO, Kristensen SD, Bøtker HE, Lip GYH, Maeng M. Should the presence or extent of coronary artery disease be quantified in the CHA2DS2-VASc score in atrial fibrillation? A report from the Western Denmark Heart Registry. *Thromb Haemost* 2018;118:2162–2170.
17. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, OFlaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS, Virani SS, American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics - 2019 update: a report from the American Heart Association. *Circulation* 2019;135:e56–e528.
18. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. 2019 ACC / AHA / HRS GUIDELINE 2019 AHA / ACC / HRS focused update of the 2014 AHA / ACC / HRS guideline for the management of patients with atrial fibrillation task force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2019;74:104–132.
19. Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point the decision to anticoagulate patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes* 2011;4:14–21.
20. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Putte B Van, Vardas P, Agewall S, Camm J, Esquivias GB, Budts W, Carerj S, Casselman F, Coca A, Caterina R De, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GYH, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Gelder IC Van, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893–2962.
21. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke* 1991;22:312–318.
22. European Medicines Egency. Summary of opinion; Xarelto. Available at:https://www.ema.europa.eu/documents/smop/chmp-post-authorisation-summary-positive-opinion-xarelto-ii-58_en.pdf. Accessed March 3, 2020.
23. FDA. *Highlights of Prescribing Information*. Available at:https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202439s025lbl.pdf. Accessed March 3, 2020.
24. Chao TF, Lip GYH, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ, Chen SA. Relationship of aging and incident comorbidities to stroke risk in patients with atrial fibrillation. *J Am Coll Cardiol* 2018;71:122–132.
25. Yoon M, Yang P-S, Jang E, Yu HT, Kim T-H, Uhm J-S, Kim J-Y, Pak H-N, Lee M-H, Lip GYH, Joung B. Dynamic changes of CHA2DS2-VASc score and the risk of ischaemic stroke in asian patients with atrial fibrillation: a nationwide cohort study. *Thromb Haemost* 2018;118:1296–1304.