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Establishment and Verification of a Nomogram for Predicting the Probability of New-Onset Atrial Fibrillation After Dual-Chamber Pacemaker Implantation

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Abstract

Background: This study aims to establish and validate a nomogram as a predictive model in patients with new-onset atrial fibrillation (AF) after dual-chamber cardiac implantable electronic device (pacemaker) implantation.

Methods: A total of 1120 Chinese patients with new-onset AF after pacemaker implantation were included in this retrospective study. Patients had AF of at least 180/minute lasting 5 minutes or longer, detected by atrial lead and recorded at least 3 months after implantation. Patients with previous atrial tachyarrhythmias before device implantation were excluded. A total of 276 patients were ultimately enrolled, with 51 patients in the AF group and 225 patients in the non-AF group. Least absolute shrinkage and selection operator (LASSO) method was used to determine the best predictors. Through multivariate logistic regression analysis, a nomogram was drawn as a predictive model. Concordance index, calibration plot, and decision curve analyses were applied to evaluate model discrimination, calibration, and clinical applicability. Internal verification was performed using a bootstrap method.

Results: The LASSO method regression analysis found that variables including peripheral arterial disease, atrial pacing-ventricular pacing of at least 50%, atrial sense–ventricular sense of at least 50%, increased left atrium diameter, and age were important predictors of developing AF. In multivariate logistic regression, peripheral arterial disease, atrial pacing-ventricular pacing of at least 50%, and age were found to be independent predictors of new-onset AF.

Conclusion: This nomogram may help physicians identify patients at high risk of new-onset AF after pacemaker implantation at an early stage in a Chinese population.

Keywords: Pacemaker, artificial; atrial fibrillation; nomograms

Introduction

Atrial fibrillation (AF) is the most common arrythmia in adults older than 40 years.[1] Stroke is the most serious complication of AF and can triple the mortality rate in patients with AF. Each year, 16.9 million people worldwide experience stroke. The causes remain unexplained for approximately 20% to 40% of strokes.[2] Between 10% and 30% of these unexplained stroke cases may be the result of a missed AF diagnosis.[3-5] Cardiac implantable electronic device–detected AF (CIED-AF), which is a type of subclinical atrial fibrillation (SCAF), has attracted much attention in recent years, as it can increase the detection rate of AF episodes. Although different from clinical AF, SCAF, which often manifests as asymptomatic AF, has a strong predictive effect on clinical AF.[6] Subclinical AF occurs frequently in older people. Cardiac implantable electronic devices help detect CIED-AF.[7] The detected increase in AF load may lead to increased ischemic stroke, heart failure (HF), and

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mortality.[8-10] Identifying patients with CIEDs at high risk of new-onset AF is important to prevent adverse clinical outcomes. The current diagnosis of AF relies mainly on clinical symptoms, electrocardiography, and other detection methods. However, AF is often paroxysmal and asymptomatic, which makes early effective and accurate detection of AF difficult. Therefore, establishment of an SCAF prediction model may help clinicians make effective interventions and have good therapeutic effect.

Age is a frequently reported independent predictor of CIED-AF.[7,11] Some studies have also found that conditions such as hypertension, HF, and cerebral microvascular disease; $CHADS_2$ (congestive HF, hypertension, age ≥75 years, and diabetes mellitus, stroke) and CHA_2DS_2-VASc (congestive HF, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65-74 years, sex category) scores; echocardiographic indicators including left atrial (LA) diameter and LA volume index; and pacemaker parameters such as ventricular pacing ratio may be predictors of CIED-AF.[10-14] However, their effectiveness in predicting the risk of CIED-AF is still controversial. Currently, there are no predictive tools to integrate and analyze the risk factors affecting CIED-AF.

Nomogram is a prognostic model that describes statistics in a graphical manner through biological clinical variables. It is a tool for prediction based on statistical data obtained from patients with diseases with identical characteristics. Each variable in the nomogram is given a value that represents its prognostic significance. Individualized risk can be estimated according to the patients' different clinical characteristics. The cumulative scores of all variables are matched with the result scale, and a value is obtained to estimate the specific results.[15-17] Compared with other predictive tools, nomogram is most accurate and has superior discriminative capability in predicting results.[18] As an important tool for guiding modern medical decisions, nomogram has been widely used in the fields such as surgery, cancer, and myocardial infarction.[19-21] No previous research to date has reported use of nomogram as a predictive model for prediction of CIED-AF occurrence.

The purpose of this study was to identify independent predictors and establish a nomogram based on parameter integration to predict the probability of new-onset AF in patients after dual-chamber pacemaker implantation. The goal of this model is to help clinicians identify high-risk patients, control risk factors, and select reasonable treatment options for these patients.

Abbreviations and Acronyms

ABI	ankle-brachial index
AF	atrial fibrillation
AP	atrial pacing
CIED	cardiac implantable electronic device
CIED-AF	cardiac implantable electronic device–detected atrial fibrillation
C-index	concordance index
HF	heart failure
LA	left atrial
LASSO	least absolute shrinkage and selection operator
OR	odds ratio
PAD	peripheral arterial disease
SCAF	subclinical atrial fibrillation
VP	ventricular pacing
VS	ventricular sense

Patients and Methods

Patient Selection

To evaluate the predictive ability and discrimination performance of nomograms, bootstrap verification (1000 bootstrap samples) was performed to calculate the concordance index (C-index). Patients with new-onset AF after CIED implantation[7] at the cardiovascular department of Sir Run Run Shaw Hospital in Hangzhou, China, from January 1, 2017, to December 31, 2018, were included in the study. Patients were excluded if they had a history of AF or atrial flutter or other persistent supraventricular tachycardia lasting more than 5 minutes as confirmed by previous examination or if they had a history of cardiac surgery for congenital heart disease, valvular heart disease, or myocardial infarction. Patients were also excluded if they had an implanted single-chamber pacemaker, implantable cardioverter-defibrillator, or cardiac resynchronization therapy-defibrillator/pacemaker or if they had undergone replacement of a CIED. Patients were divided into 2 groups based on whether new-onset AF was detected after pacemaker implantation (new-onset AF and non-AF groups). The inclusion and exclusion criteria are shown in Table I.[22]

Data Collection

The following medical data were obtained from electronic medical records based on relevant demographic, clinical, and laboratory features. These features consist of general information, history, auxiliary examination,

TABLE I. Key Inclusion and Exclusion Criteria

Inclusion criteria
1. Age ≥18 y
2. Underwent dual-chamber pacemaker implantation because of sick sinus node syndrome and/or atrioventricular block according to the guideline's class I and IIa recommendation[22]
3. Underwent dual-chamber pacemaker implantation at Sir Run Run Shaw Hospital between January 2017 and December 2018
4. Regularly participated in outpatient follow-up for >1 y after pacemaker implantation
Exclusion criteria
1. History of atrial fibrillation, atrial flutter, or other persistent supraventricular tachycardia lasting >5 min confirmed by previous examination (eg, body surface 12-lead electrocardiogram, telemetry equipment, dynamic electrocardiogram)[a]
2. Had already received an implanted single-chamber pacemaker, implantable cardioverter-defibrillator, or cardiac resynchronization therapy-defibrillator/pacemaker or had undergone replacement of a cardiovascular implanted electronic devices
3. History of cardiac surgery for congenital heart disease, valvular heart disease, or myocardial infarction[a]
4. History of severe infection, hyperthyroidism, cardiomyopathy, valvular heart disease, or severe arrhythmia[a]
5. Incomplete clinical data
6. Follow-up period <1 y or loss of follow-up

[a] Patients with these histories were excluded regardless of the event's time frame.

echocardiographic parameters, medication administration record, and pacemaker parameters. General information included age, sex, body mass index, and smoking and drinking status. Medical history included congestive HF, hypertension, coronary heart disease, peripheral arterial disease (PAD), diabetes, hyperlipidemia, cerebrovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease. Peripheral arterial disease was previously diagnosis according to ankle-brachial index (ABI) of 0.9 or less, ABI of 1.4 or greater, or imaging evidence combined with clinical manifestations. Congestive HF was defined by moderate to severe systolic left ventricular dysfunction, left ventricular ejection fraction of 40% or less, or receiving medication to relieve symptoms of HF. Hypertension was defined by systolic blood pressure of 140 mm Hg or greater and/or diastolic blood pressure of 90 mm Hg or greater as measured 3 times in the same patient on different days or if the patient had a history of using antihypertensive drugs to control blood pressure. Diabetes was diagnosed according to fasting venous plasma glucose concentration of at least 7.0 mmol/L (126 mg/dL), random vein plasma glucose concentration of at least 11.1 mmol/L (200 mg/dL), or positive glucose tolerance test vein plasma glucose concentration of at least 11.1 mmol/L 2 hours after oral administration of 75 g of glucose and/or the use of insulin or oral hypoglycemic drugs. If a patient met any 1 of the 3 criteria, all 3 measurements were duplicated the following day. Coronary heart disease included patients with known but untreated disease and those being treated with antiplatelet aggregation drugs and lipid-lowering drugs. Diagnosis of cerebrovascular disease was made according to the corresponding neurological symptoms and signs and from imaging evidence. The attack lasted more than 24 hours. Chronic kidney disease was diagnosed as basic kidney disease lasting more than 3 months with an estimated glomerular filtration rate less than or equal to 60 mL/min/1.73 m^2. Chronic obstructive pulmonary disease was diagnosed according to a history of more than 2 years of cough, expectoration, asthma, and other respiratory symptoms, as well as lung function test airflow limitation (forced expiratory volume in 1 second/forced vital capacity <70%). Auxiliary examination included N-terminal prohormone of brain natriuretic peptide, estimated glomerular filtration rate, blood urea nitrogen, and high-sensitivity C-reactive protein. Echocardiographic parameters included left ventricular ejection fraction and LA diameter. Increased LA diameter was defined as 40 mm or greater for men and 38 mm or greater for women by echocardiography.[23] Prior medication administration records included angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists, b-blockers, calcium channel blockers, lipid-lowering drugs, diuretics, and antiplatelet drugs. Pacemaker parameters included pacemaker manufacturer, type of electrode, and mode setting. $CHADS_2$ and CHA_2DS_2-VASc scores were also included. The

nominal pacemaker setting for paced atrioventricular intervals/sensed atrioventricular intervals delay is 180/150 ms with the atrioventricular interval optimization function on.

The primary outcome was new-onset AF (atrial rate ≥180 bpm detected by atrial lead) with duration of at least 5 minutes occurring at least 3 months after CIED implantation. Confirmation of AF diagnosis must have been made by at least 1 clinician, and CIED-AF was diagnosed according to guidelines from the European Society of Cardiology.[24] Patients were followed up regularly at 1, 3, 6, 9, and 12 months after implantation. During follow-up, pacemaker parameters were recorded.

All participants provided written consent before entering the study. The study was approved by the medical ethics committees of Sir Run Run Shaw Hospital, affiliated with the Medical School of Zhejiang University, with the ethics approval No. keyan20180106-10.

Statistical Analysis

Data were analyzed using SPSS 25.0 software and R software version 3.6.0 (http://www.r-project.org). Categorical variables were compared by χ^2 test and expressed as a number and percentage. Continuous variables with a normal distribution were compared by *t* test and expressed as mean (SD). Continuous variables with nonnormal distribution were compared by Mann-Whitney U test and expressed as median (IQR).

The least absolute shrinkage and selection operator (LASSO) regression method for reducing high-dimensional data was applied to select the best predictor for new-onset AF in patients after dual-chamber pacemaker implantation. The LASSO regression was performed using the "glmnet" package of R software. Cross-validation was used to determine the adjustment parameter (λ) suitable for LASSO regression. The principle is that the sum of the absolute values of the negative log likelihood ratios must be smaller than the adjustment parameter λ. If λ is large, it has no effect on the estimated regression parameters, but as λ decreases, some coefficients may decrease to 0. Therefore, λ was chosen with the smallest cross-validation error. Finally, the model was refitted by using all the observed values and the selected λ. Most coefficients were reduced to 0, and the remaining nonzero coefficient variables were risk factors selected by LASSO. Subsequently, after combined consideration with the clinical significance of the variables, LASSO regression results, and sample size, final variables included in the model were determined.

The binary classification logistic regression was used to construct a prediction model. In logistic regression, the association between independent variables and clinical events was determined by 95% CI, odds ratio (OR), and *P* value. $P < .05$ was considered statistically significant.

Based on binary classification logistic regression, a nomogram was established to predict the probability of new-onset AF in patients with dual-chamber pacemakers. To evaluate the accuracy and discriminative ability of the nomogram, the C-index was calculated and a calibration curve constructed. The "rmda" package decision curve analysis chart in R software was used to quantify the net benefit under different threshold probabilities in patients with new-onset AF after dual-chamber pacemaker implantation to determine the clinical utility of the nomogram. Lift verification (1000 bootstrap samples) was applied for internal verification of the model.

Results

Clinical Characteristics of the Study Cohort

The primary cohort included 1120 patients who underwent surgery for electronic device implantation in the cardiology department of Sir Run Run Shaw Hospital between January 2017 and December 2018. After screening according to the inclusion and exclusion criteria, 276 patients were ultimately enrolled, including 51 patients with new-onset AF and 225 patients without AF. Nineteen patients had incomplete medical records, 60 patients had irregular outpatient visits and lack of follow-up data, and 3 patients died within 1 year of follow-up, for a total of 82 patients who were excluded because of incomplete data or loss to follow-up (Fig. 1).

Patients were followed up for a mean period of approximately 23.44 months. New-onset AF was detected in 51 patients (18.7%) after double-chamber pacemaker implantation, and 225 patients did not develop AF. The follow-up time for patients with new-onset AF was longer (23.5 months vs 21.0 months). The clinical characteristics between the 2 groups were compared, and the results showed a significant difference in age ($P = .012$) and history of PAD ($P < .001$). The average age of patients with new-onset AF was 72.9 years, which was significantly older than the non-AF group (68.8 years old). The incidence of PAD was significantly higher in the new-onset AF group than in the non-AF

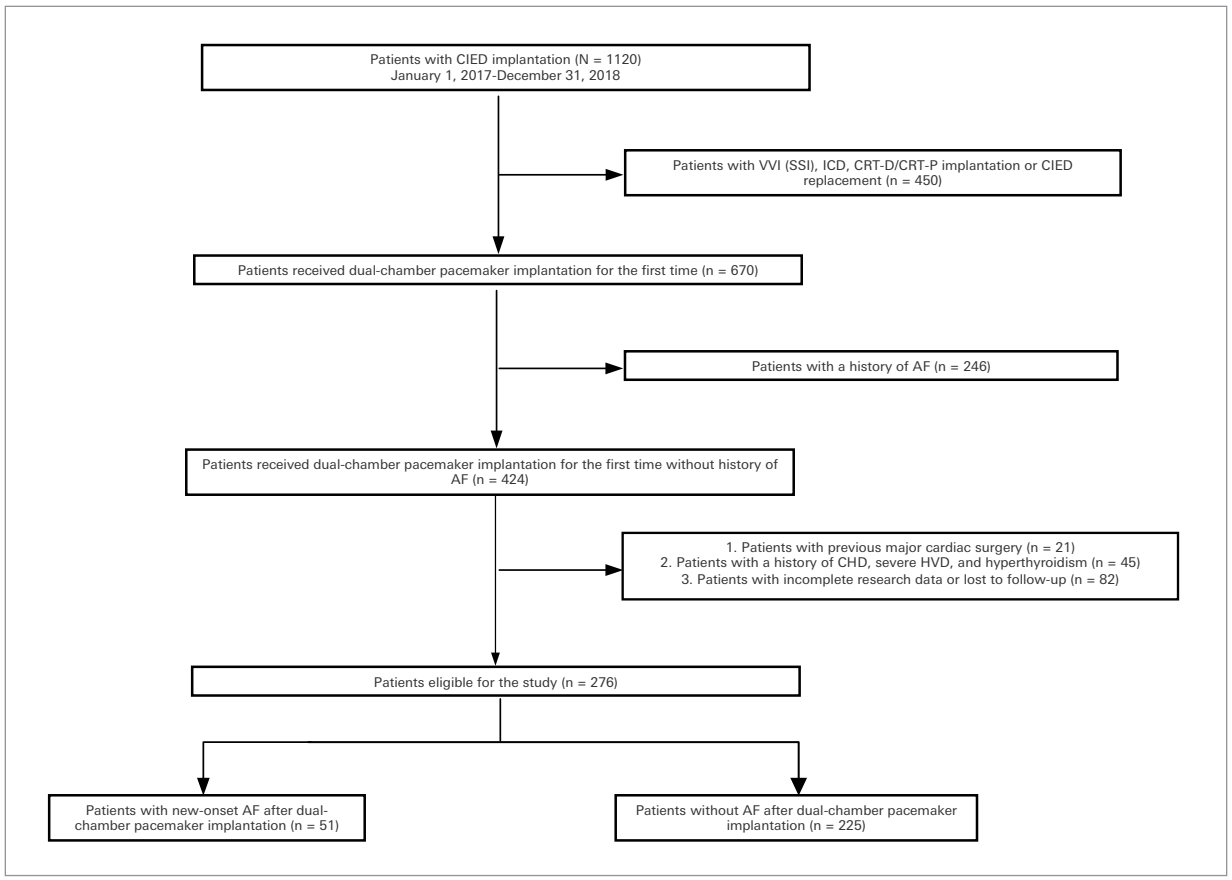

Fig. 1. Screening flow chart with inclusion and exclusion criteria.

AF, atrial fibrillation; CHD, coronary heart disease; CIED, cardiac implantable electronic device; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; HVD, heart valve disease; ICD, implantable cardioverter-defibrillator; SSI, single-chamber pacing and single-chamber sensing with inhibition; VVI, ventricular pacing and ventricular sensing with inhibition.

group (17.6% vs 4%). There were also significant differences in the pacing pattern between the 2 groups. In the group of patients with new-onset AF, atrial pacing (AP)–ventricular pacing (VP) ≥50% accounted for 19.6% of cases, which was higher than 8.0% in the group without AF (P = .014). Atrial pacing ≥50% and atrial sense (AS)–ventricular sense (VS) ≥50% were also statistically different between the 2 groups, with P values of .048 and .037, respectively. The percentage of AS-VS ≥50% in the new-onset AF group was 17.6%, and in the group without new-onset AF, the percentage was 32.4%. Thus, it was found that the population with less AS-VS ≥50% (which indicated a greater percentage of AP and/or VP) was more prone to new-onset AF. There was a negative correlation between AS-VS ≥50% and risk of new-onset AF. There were no significant differences between the 2 groups in sex, body mass index, or history of hypertension, diabetes, coronary heart disease, HF, and drug use. Descriptive statistics of the patients in this study are shown in Table II.

Feature Selection

The 28 independent variables assessed in this study were selected by the LASSO regression algorithm. When the most suitable tuning parameter λ was 0.036, the partial likelihood deviation reached the minimum value (Fig. 2A). At that time, 5 nonzero coefficient variables were retained in the LASSO analysis (Fig. 2B). The variable with the most predictive accuracy was PAD, followed by AP-VP ≥50%, AS-VS ≥50%, LA diameter, and age.

TABLE II. Patient Clinical Characteristics[a]

Variable	New-onset AF (n = 51)	No AF (n = 225)	*P* value
Age, mean (SD), y	72.92 (1.2)	68.8 (0.73)	.012
Male	33 (64.7)	122 (54.2)	.173
BMI, mean (SD), kg/m^2	23.76 (3.61)	23.85 (3.52)	.880
Smoke	12 (24)	49 (22.0)	.756
Consume alcohol	8 (15.7)	40 (17.9	.703
CHF	6 (11.8)	14 (6.2)	.168
Hypertension	35 (68.6)	151 (67.1)	.835
CHD	13 (25.5)	41 (18.2)	.237
PAD	9 (17.6)	9 (4.0)	<.001
TIA	7 (13.7)	17 (7.6)	.158
Diabetes	12 (23.5)	41 (18.2)	.385
Chronic kidney disease	5 (9.8)	31 (13.8)	.447
Hyperlipidemia	19 (37.3)	58 (25.8)	.099
COPD	1 (2.0)	14 (6.2)	.225
ACEIs/angiotensin II receptor antagonists	20 (39.2)	64 (28.4)	.131
β-Blockers	8 (15.7)	20 (8.9)	.147
Calcium channel blockers	23 (45.1)	80 (35.6)	.203
Lipid-lowering drugs	24 (47.1)	75 (33.3)	.065
Diuretics	9 (17.6)	24 (10.7)	.165
Antiplatelets	17 (33.3)	66 (29.3)	.574
Reason for pacemaker implantation			.124
Sick sinus syndrome	20 (39.2)	120 (53.3)	
AV block	26 (51.0)	94 (41.8)	
Sick sinus syndrome and AV block	5 (9.8)	11 (4.9)	
Atrial active electrode	26 (56.5)	130 (60.5)	.621
Ventricular active electrode	43 (95.6)	205 (96.2)	.828
Echocardiographic parameters			
LVEF <55%	4 (7.8)	9 (4.0)	.242
Increased LA diameter	19 (37.3)	55 (24.4)	.062
Laboratory parameters			
N-terminal pro-brain natriuretic peptide, median (IQR), pg/mL	273.0 (131.0-466.0)	198 (81.5-535.0)	.316
eGFR, mL/min/1.73 m^2			.402
0-29	1 (2.0)	4 (1.8)	
30-59	6 (11.8)	31 (13.8)	
60-89	29 (56.9)	99 (44.0)	
≥90	15 (29.4)	91 (40.4)	
CRP, median (IQR), mg/L	1.4 (0.5-4.0)	1.4 (0.5-3.1)	.661
BUN, mean (SD), mg/L	5.58 (1.43)	5.97 (2.09)	.217
Pacemaker parameters			
AP ≥50%	25 (49.0)	77 (34.2)	.048
VP ≥50%	26 (51.0)	84 (37.3)	.072
AP-VP ≥50%	10 (19.6)	18 (8.0)	.014
AP-VS ≥50%	11 (21.6)	49 (21.8)	.974
AS-VP ≥50%	13 (26.0)	59 (26.2)	.974
AS-VS ≥50%	9 (17.6)	73 (32.4)	.037
$CHADS_2$ ≥2	27 (52.9)	88 (39.1)	.070
CHA_2DS_2-VASc ≥2	45 (88.2)	171 (76.0)	.056
Follow-up time, median (IQR), mo	23.5 (19.2-32.1)	21.0 (16.5-29.4)	.008

ACEI, angiotensin-converting enzyme inhibitor; AP, atrial pacing; AP-VS, atrial sense–ventricular pacing; AP-VP, atrial pacing–ventricular pacing; AS-VS, atrial sense–ventricular sense; AS-VP, atrial sense–ventricular pacing; BMI, body mass index; BUN, blood urea nitrogen; CHA_2DS_2-VASc, CHF, hypertension, age ≥75 years, diabetes mellitus, stroke or TIA, vascular disease, age 65-74 years, sex category; $CHADS_2$, CHF, hypertension, age, ≥75 years diabetes, stroke; CHD, coronary heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LA, left atrial; LVEF, Left ventricular ejection fraction; PAD, peripheral artery disease; TIA, transient ischemic attack; VP, ventricular pacing.

[a] Data are presented as No. (%), unless otherwise noted. $P < .05$ was considered statistically significant.

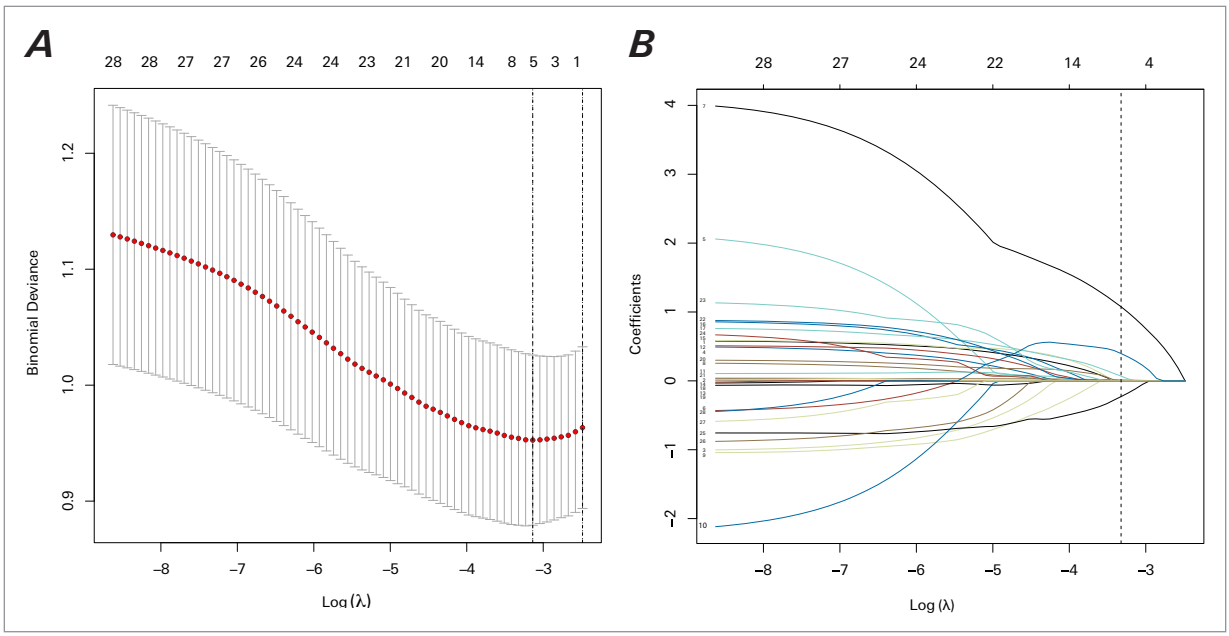

Fig. 2. Graphs show the selection of predictors using LASSO regression. The variable with the most predictive accuracy was peripheral artery disease, followed by atrial pacing–ventricular pacing of at least 50%, atrial sense–ventricular sense of at least 50%, increased left atrial diameter, and age. **A)** Cross-validation by the minimum parameters was used to determine the best parameters in the LASSO model. The 28 independent variables were selected using the LASSO regression algorithm. When the most suitable tuning parameter λ was 0.036, the partial likelihood deviation reached the minimum value. The 2 vertical dashed lines represent the lines with lowest error (left) and the fewest features (right). **B)** An effective diagram of curves generated by 28 features of LASSO coefficient. Five nonzero coefficient variables were retained in the LASSO analysis. The vertical dashed line represents the selected independent variable when λ as 0.036 is intercepted.

LASSO, least absolute shrinkage and selection operator.

TABLE III. Predictors of New-Onset AF in Patients With Dual-Chamber Pacemaker Implantation by Multifactor Logistic Regression

Intercept and variable	β	Prediction model, OR (95% CI)	*P* value[a]
Intercept	−4.57	0.010 (0.001-0.112)	<.001
Age	.037	1.037 (1.004-1.072)	.029
PAD	1.82	1.812 (0.917-3.585)	<.001
AP-VP ≥50%	1.10	3.006 (1.242-7.279)	.015
Increased LA diameter	.595	1.812 (0.916-3.585)	.088

AF, atrial fibrillation; AP-VP, atrial pacing-ventricular pacing, β, regression coefficient; LA, left atrial; OR, odds ratio; PAD, peripheral artery disease.

[a] $P < .05$ was considered statistically significant.

Nomogram Construction and Performance

After combined analysis of the variables' clinical significance and LASSO regression results and after further assessment of whether the variables were colinear and crossover, 4 variables were used for logistic regression as initial independent variables: PAD, AP-VP ≥50%, increased LA diameter, and age. Logistic regression results showed that PAD (OR, 1.812 [95% CI, 0.917-3.585]; $P < .001$), AP-VP ≥50% (OR, 3.006 [95% CI, 1.242-7.279]; $P = .015$), and age (OR, 1.037 [95% CI, 1.004-1.072]; $P = .029$) were independent predictors (Table III). The predictive factors obtained above were integrated into a model through R language, and the results were visualized with a nomogram (Fig. 3).

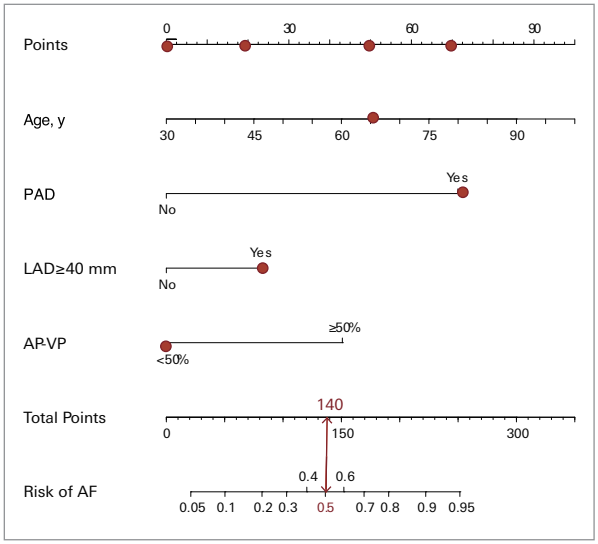

Fig. 3 This sample nomogram for calculating the risk of new-onset AF after dual-chamber pacemaker implantation takes a 65-year-old male patient with PAD as an example. The 65 years in the age line corresponds to a score of 50 in the points line, and the presence of PAD corresponds to a score of 70. If LAD is 42 mm, the corresponding score is 20. If AP-VP less than 50% is detected, the corresponding score is 0. The above-described scores are cumulative, so the total score for this patient is 140 points (50 + 70 + 20 + 0). Therefore, when a vertical line is drawn from the total score axis to the risk of new-onset AF axis, the result shows that the risk of new-onset AF is 50%.

AF, atrial fibrillation; AP-VP, atrial pacing–ventricular pacing; LAD, left atrial diameter; PAD, peripheral artery disease; .

Nomogram Example

Taking a 65-year-old male patient with a dual-chamber pacemaker and PAD as an example (Fig. 3), 65 years in the age line corresponds to a score of 50 in the points line, and the presence of PAD corresponds to a score of 70. If the patient is admitted to the hospital with an echocardiogram indicating an increased LA diameter of 42 mm, the corresponding score is 20. If AP-VP <50% is detected during pacemaker program-control follow-up, the corresponding score is 0. The above-mentioned scores are cumulative, so the total score for this patient is 140 points (50 + 70 + 20 + 0). Therefore, when a vertical line is drawn from the total score axis to the risk of new-onset AF axis, the result shows that the risk of new-onset AF is 50% (Fig. 3).

Verification of the Nomogram

The C-index for nomogram prediction was 0.726 (95% CI, 0.717-0.735) for the cohort (Fig. 4A), or 0.727 (95% CI, 0.651-0.800) through bootstrapping validation. The calibration curve of the nomogram for the risk of new-onset AF in patients with a dual-chamber pacemaker indicated that the predictions were highly consistent with the observed results. The above-described data showed that the model had good predictive ability (Fig. 4B).

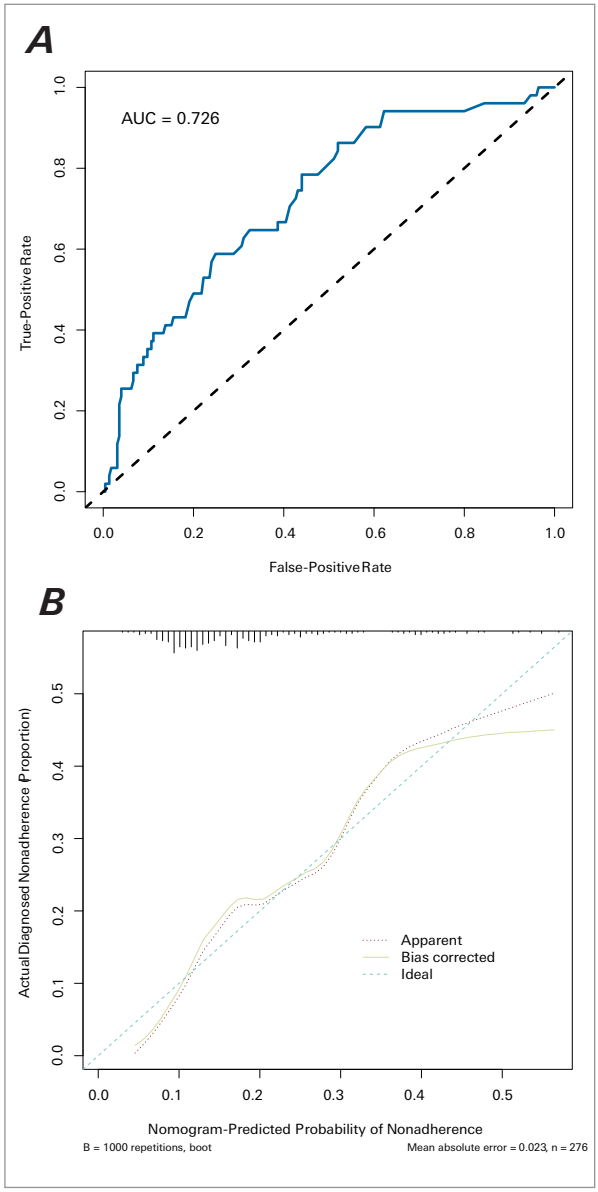

Fig. 4 Evaluation of the discrimination and consistency of the predictive model of new-onset AF after dual-chamber pacemaker implantation, including **A**) receiver operating characteristic curve and **B**) calibration curve of the predictive model. Bootstrap verification (1000 bootstrap samples) was performed to calculate the concordance index. The x-axis represents predicted risk of new-onset AF, the y-axis represents actual risk of new-onset AF, the diagonal dashed lines represent the ideal model predictions, the solid lines represent the nomogram performance, and the diagonal dotted line indicates the ideal prediction.

AF, atrial fibrillation; AUC, area under the curve.

Clinical Value of the Nomogram

The clinical decision curve is a new method to evaluate the clinical application value of the predictive model. The decision curve analysis of the nomogram is presented in Figure 5. The nomogram predictive model established in this study had a higher clinical net benefit than the single-factor model of AP-VP ≥50% or increase in LA diameter. Therefore, the decision curve analysis confirmed the net benefits of the predictive nomogram.

Discussion

Cardiac implantable electronic device–detected AF is reported to be closely associated with stroke and HF.[8,25] Whether the risk of CIED-AF is the same as for clinically observed AF is still controversial. Currently, there are no published guidelines or clinical trials to help clinicians make an evidence-based clinical decision for the prevention of CIED-AF.[26] Also, there is no generally accepted predictive model of new-onset AF for patients with an implanted pacemaker. In this study, the authors aimed to establish and validate a predictive nomogram for predicting the risk of developing new-onset AF in patients with CIEDs. Considering that pacemaker implantation may induce surgery-related AF, combined with previous literature, AF recorded by pacemaker at least 3 months after implantation was chosen as the outcome event of this study.

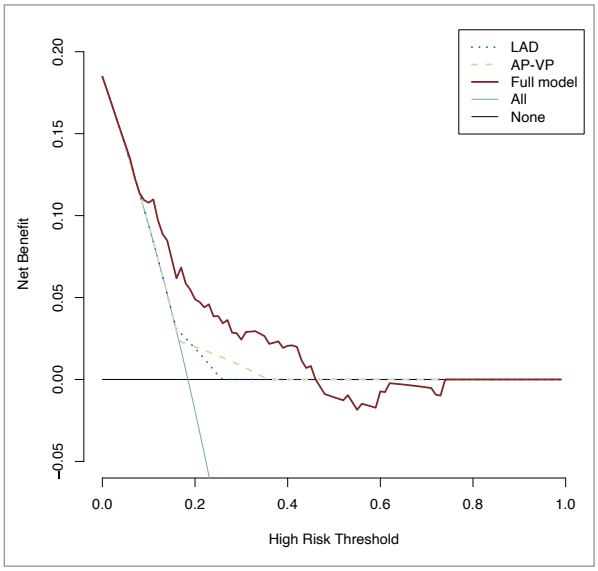

Fig. 5 Clinical decision curve of a predictive model of new-onset AF after dual-chamber pacemaker implantation. The x-axis represents the threshold probability, the y-axis represents the net benefit, the red line represents the nomogram of new-onset AF after dual-chamber pacemaker implantation, the purple dotted line represents the LA diameter single-factor predictive model, the green dashed line represents the AP-VP ≥50% univariate predictive model, the solid light-gray line represents patients with new AF after dual-chamber pacemaker implantation, and the solid dark-gray line represents patients without AF.

AF, atrial fibrillation; AP-VP, atrial pacing–ventricular pacing; LA, left atrial; LAD, left anterior descending artery.

It was reported that approximately 13% to 35% of patients with CIEDs may experience new-onset AF.[13,25,27] In this study, the incidence of new-onset AF after dual-chamber pacemaker implantation was 18.7%, which was consistent with previous studies. The differences in the incidence of AF from various studies may be the result of differences in research backgrounds and methods of diagnosing AF. In addition, some studies did not exclude patients with a history of AF.

In this study, multivariate logistic regression analysis results revealed that PAD, AP-VP ≥50%, and age were independent predictors of new-onset AF after dual-chamber pacemaker implantation. Although LA diameter was not an independent predictor, LA diameter did play an important role in the progress of new-onset AF. This study used the LASSO method, a data dimensionality reduction method, which is suitable for the regression of large groups of clinical factors, selects variables for the sample data, and extracts the most important predictors by compressing the original coefficients to avoid overfitting.

Atrial fibrillation is more common in patients with PAD than in the general population.[28,29] Data from the Reduction of Atherothrombosis for Continued Health (REACH) Registry indicated a high prevalence of PAD coexisting with AF.[30] The 2 diseases have common risk factors and epidemiological characteristics, and the coexistence of these conditions significantly increases the risk of major adverse events (including stroke, myocardial infarction, cardiovascular death, and all-cause death).[22,31] In an observational study based on global risk assessment of AF in older women, Perez et al[32] found that PAD was independently associated with a high incidence of AF. The Multi-Ethnic Study of Atherosclerosis[33] and Cardiovascular Health Study[34] also confirmed this relationship. The authors found that PAD remained an independent risk factor for AF after adjusting for factors such as age, sex, ethnicity, and cardiovascular disease. In addition, studies have shown that the risk of AF increases as the value of the ABI decreased.[33,35] Bekwelem et al[36] found that the relationship

between PAD and AF may be mainly related to traditional atherosclerotic risk factors. Atherosclerosis and AF have several similar risk factors and have both been associated with elevated levels of proinflammatory cytokines, endothelial dysfunction, and platelet-mediated thrombosis.[37-39] Theses common risk factors may explain why PAD was observed as a risk factor of CIED-AF in this study.

Previous studies have shown a linear increase in the cumulative percentage of VP and the risk of AF.[40,41] Cheung et al[13] studied patients with different indications for dual-chamber pacemaker implantation and found that in patients with sinus node dysfunction and a dual-chamber pacemaker, cumulative VP ≥50% is related to the elevated occurrence risk of AF by 2-fold. In combination with previous studies, it was speculated that AP-VP pacing may enhance myocardial cell extension, atrial fibrosis, and destruction of intercellular coupling, thereby promoting the remodeling of the atrium. In addition, right ventricular pacing may lead to mechanical desynchronization of the heart. This desynchronization will impair left ventricular function, change hemodynamics, gradually increase LA pressure, and further promote atrial myocyte electrical remodeling, which may cause CIED-AF.[42-45]

Consistent with previous studies, the findings of this study revealed that advanced age could contribute to the development of new-onset AF.[7] Several possible mechanisms may explain the relationship between AF and age. Atrial fibrosis, which is an important structural basis for AF, increases with ages.[46,47] This may be one of the causes of AF in older adult patients with dual-chamber pacemakers. In addition, 1 study found that aging may be the most important risk factor affecting the stability of the cardiovascular internal environment.[48]

This study also indicated that increased LA diameter could contribute to the development of new-onset AF.[49] The following mechanisms may explain the relationship between increased LA diameter and new-onset AF. On one hand, CIED implantation may directly induce cardiac fibrosis and atrial expansion, which lead to cardiac remodeling and reentry loop formation and, eventually, to AF. On the other hand, CIED implantation may trigger tachycardia, which may promote atrial contraction dysfunction and induce atrial dilation.[50] Atrial dilation promotes atrial remodeling and atrial fibrosis by increasing the diastolic length of atrial muscle cells, which triggers AF.[51]

To the authors' knowledge, this is the first study to establish a nomogram-illustrated model to evaluate the risk of new-onset AF after CIED implantation in a Chinese population. This nomogram may be a convenient tool for clinicians to identify patients at high risk for new-onset AF early after dual-chamber pacemaker implantation. Early recognition of patients at high risk for new-onset AF may be helpful for AF prevention management and prognosis improvement. By applying the nomogram, the risk factors can be controlled, thus reducing the incidence of new-onset AF. The probabilities derived from the nomogram can also be used prospectively to evaluate the effects and outcomes of long-term primary prevention for patients at high risk for developing AF after dual-chamber pacemaker implantation. In addition, some scholars believe that SCAF may be the direct cause of stroke, whereas others consider SCAF to be only a risk factor for stroke. Being able to assess the risk of AF through the nomogram may allow clinicians to enhance the frequency of programmed follow-up for high-risk patients to reduce the rate of missed diagnosis. More timely information on the occurrence of SCAF and its complications (eg, stroke and HF) can be provided, and potential mechanisms can be further revealed.

This study had several limitations. First, the data were collected retrospectively in a single center, and the sample size was small. The included independent variables cannot completely cover all AF risk factors. As a result, the predictive power of the model was limited. Second, categorical variables were used to build a line chart to ensure that the nomogram is an easy-to-use clinical tool. Compared with the use of continuous variables, this simplicity may partially sacrifice the effectiveness of prognostic risk prediction.[52] Third, this study used self-service internal verification. Although this is an acceptable method of negotiating chart development and verification, external validation is still needed to test its versatility. Fourth, there may be inadequate detection conditions for the variables involved in this study. For example, not every patient was tested for ABI after admission, which may lead to a missed PAD diagnosis in some patients. In addition, LA examination only involved LA diameter. Including LA volume and LA function measurements may make the predictive model more accurate. Therefore, further research is needed to supplement the follow-up information, increase the sample size, and select more independent variables to reflect the risk of new-onset AF after pacemaker implantation. This will help to improve the predictive ability of the model.

Conclusion

In conclusion, the authors established and validated an original nomogram that can be conveniently used to identify the risk of new-onset AF in patients after dual-chamber pacemaker implantation in a Chinese population. The proposed nomogram incorporating PAD, AP-VP ≥50%, age, and increased LA diameter may be a valuable tool for clinicians in making decisions and implementing interventions with clinical practical utility.

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References

1. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation.* 2004;110(9):1042-1046. doi:10.1161/01.CIR.0000140263.20897.42
2. Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet.* 2014;383(9913):245-254. doi:10.1016/s0140-6736(13)61953-4
3. Sanna T, Diener HC, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med.* 2014;370(26):2478-2486. doi:10.1056/NEJMoa1313600
4. Brachmann J, Morillo CA, Sanna T, et al. Uncovering atrial fibrillation beyond short-term monitoring in cryptogenic stroke patients: three-year results from the cryptogenic stroke and underlying atrial fibrillation trial. *Circ Arrhythm Electrophysiol.* 2016;9(1):e003333. doi:10.1161/CIRCEP.115.003333
5. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med.* 2014;370(26):2467-2477. doi:10.1056/NEJMoa1311376
6. Mahajan R, Perera T, Elliott AD, et al. Subclinical device-detected atrial fibrillation and stroke risk: a systematic review and meta-analysis. *Eur Heart J.* 2018;39(16):1407-1415. doi:10.1093/eurheartj/ehx731
7. Boriani G, Glotzer TV, Ziegler PD, et al. Detection of new atrial fibrillation in patients with cardiac implanted electronic devices and factors associated with transition to higher device-detected atrial fibrillation burden. *Heart Rhythm.* 2018;15(3):376-383. doi:10.1016/j.hrthm.2017.11.007
8. Wong JA, Conen D, Van Gelder IC, et al. Progression of device-detected subclinical atrial fibrillation and the risk of heart failure. *J Am Coll Cardiol.* 2018;71(23):2603-2611. doi:10.1016/j.jacc.2018.03.519
9. Van Gelder IC, Healey JS, Crijns H, et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. *Eur Heart J.* 2017;38(17):1339-1344. doi:10.1093/eurheartj/ehx042
10. Nishinarita R, Niwano S, Fukaya H, et al. Burden of implanted-device-detected atrial high-rate episode is associated with future heart failure events—clinical significance of asymptomatic atrial fibrillation in patients with implantable cardiac electronic devices. *Circ J.* 2019;83(4):736-742. doi:10.1253/circj.CJ-18-1130
11. Ogino Y, Ishikawa T, Ishigami T, et al. Characteristics and prognosis of pacemaker-identified new-onset atrial fibrillation in Japanese people. *Circ J.* 2017;81(6):794-798. doi:10.1253/circj.CJ-16-1018
12. Israel C, Kitsiou A, Kalyani M, et al. Detection of atrial fibrillation in patients with embolic stroke of undetermined source by prolonged monitoring with implantable loop recorders. *Thromb Haemost.* 2017;117(10):1962-1969. doi:10.1160/TH17-02-0072
13. Cheung JW, Keating RJ, Stein KM, et al. Newly detected atrial fibrillation following dual chamber pacemaker implantation. *J Cardiovasc Electrophysiol.* 2006;17(12):1323-1328. doi:10.1111/j.1540-8167.2006.00648.x
14. Sade LE, Atar I, Ozin B, Yuce D, Muderrisoglu H. Determinants of new-onset atrial fibrillation in patients receiving CRT: mechanistic insights from speckle tracking imaging. *JACC Cardiovasc Imaging.* 2016;9(2):99-111. doi:10.1016/j.jcmg.2015.05.011
15. Caulfield S, Menezes G, Marignol L, Poole C. Nomograms are key decision-making tools in prostate cancer radiation therapy. *Urol Oncol.* 2018;36(6):283-292. doi:10.1016/j.urolonc.2018.03.017
16. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. *Lancet Oncol.* 2015;16(4):e173-e180. doi:10.1016/S1470-2045(14)71116-7
17. Grimes DA. The nomogram epidemic: resurgence of a medical relic. *Ann Intern Med.* 2008;149(4):273-275. doi:10.7326/0003-4819-149-4-200808190-00010
18. Chun FK, Karakiewicz PI, Briganti A, et al. A critical appraisal of logistic regression-based nomograms, artificial neural networks, classification and regression-tree models, look-up tables and risk-group stratification models for prostate cancer. *BJU Int.* 2007;99(4):794-800. doi:10.1111/j.1464-410X.2006.06694.x
19. Gandaglia G, Ploussard G, Valerio M, et al. A novel nomogram to identify candidates for extended pelvic lymph node dissection among patients with clinically localized prostate cancer diagnosed with magnetic resonance imaging-targeted and systematic biopsies. *Eur Urol.* 2019;75(3):506-514. doi:10.1016/j.eururo.2018.10.012

20. Jehi L, Yardi R, Chagin K, et al. Development and validation of nomograms to provide individualised predictions of seizure outcomes after epilepsy surgery: a retrospective analysis. *Lancet Neurol.* 2015;14(3):283-290. doi:10.1016/S1474-4422(14)70325-4
21. Hartaigh BÓ, Gransar H, Callister T, et al. Development and validation of a simple-to-use nomogram for predicting 5-, 10-, and 15-year survival in asymptomatic adults undergoing coronary artery calcium scoring. *JACC Cardiovasc Imaging.* 2018;11(3):450-458. doi:10.1016/j.jcmg.2017.03.018
22. Aboyans V, Ricco JB, Bartelink MEL, et al; ESC Scientific Document Group. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Endorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J.* 2018;39(9):763-816. doi:10.1093/eurheartj/ehx095
23. Gorenek BC, Bax J, Boriani G, et al. Device-detected subclinical atrial tachyarrhythmias: definition, implications and management-an European Heart Rhythm Association (EHRA) consensus document, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). *Europace.* 2017;19(9):1556-1578. doi:10.1093/europace/eux163
24. Hess PL, Healey JS, Granger CB, et al. The role of cardiovascular implantable electronic devices in the detection and treatment of subclinical atrial fibrillation: a review. *JAMA Cardiol.* 2017;2(3):324-331. doi:10.1001/jamacardio.2016.5167
25. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med.* 2012;366(2):120-129. doi:10.1056/NEJMoa1105575
26. Noseworthy PA, Kaufman ES, Chen LY, et al. Subclinical and device-detected atrial fibrillation: pondering the knowledge gap: a scientific statement from the American Heart Association. *Circulation.* 2019;140(25):e944-e963. doi:10.1161/CIR.0000000000000740
27. Kim BS, Chun KJ, Hwang JK, et al. Predictors and long-term clinical outcomes of newly developed atrial fibrillation in patients with cardiac implantable electronic devices. *Medicine (Baltimore).* 2016;95(28):e4181. doi:10.1097/MD.0000000000004181
28. Goto S, Bhatt DL, Rother J, et al. Prevalence, clinical profile, and cardiovascular outcomes of atrial fibrillation patients with atherothrombosis. *Am Heart J.* 2008;156(5):855-863, 863.e2. doi:10.1016/j.ahj.2008.06.029
29. Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. *Am J Cardiol.* 2009;104(11):1534-1539. doi:10.1016/j.amjcard.2009.07.022
30. Winkel TA, Hoeks SE, Schouten O, et al. Prognosis of atrial fibrillation in patients with symptomatic peripheral arterial disease: data from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Eur J Vasc Endovasc Surg.* 2010;40(1):9-16. doi:10.1016/j.ejvs.2010.03.003
31. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur J Cardiothorac Surg.* 2016;50(5):e1-e88. doi:10.1093/ejcts/ezw313
32. Perez MV, Wang PJ, Larson JC, et al. Risk factors for atrial fibrillation and their population burden in postmenopausal women: the Women's Health Initiative Observational Study. *Heart.* 2013;99(16):1173-1178. doi:10.1136/heartjnl-2013-303798
33. O'Neal WT, Efird JT, Nazarian S, Alonso A, Heckbert SR, Soliman EZ. Peripheral arterial disease and risk of atrial fibrillation and stroke: the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc.* 2014;3(6):e001270. doi:10.1161/JAHA.114.001270
34. Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol.* 1994;74(3):236-241. doi:10.1016/0002-9149(94)90363-8
35. Griffin WF, Salahuddin T, O'Neal WT, Soliman EZ. Peripheral arterial disease is associated with an increased risk of atrial fibrillation in the elderly. *Europace.* 2016;18(6):794-798. doi:10.1093/europace/euv369
36. Bekwelem W, Norby FL, Agarwal SK, et al. Association of peripheral artery disease with incident atrial fibrillation: the ARIC (Atherosclerosis Risk in Communities) Study. *J Am Heart Assoc.* 2018;7(8):e007452. doi:10.1161/JAHA.117.007452
37. da Silva RM. Influence of inflammation and atherosclerosis in atrial fibrillation. *Curr Atheroscler Rep.* 2017;19(1):2. doi:10.1007/s11883-017-0639-0
38. Fuster V, Moreno PR, Fayad ZA, Corti R, Badimon JJ. Atherothrombosis and high-risk plaque: part I: evolving concepts. *J Am Coll Cardiol.* 2005;46(6):937-954. doi:10.1016/j.jacc.2005.03.074
39. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet.* 2009;373(9658):155-166. doi:10.1016/S0140-6736(09)60040-4
40. Sweeney MO, Hellkamp AS. Heart failure during cardiac pacing. *Circulation.* 2006;113(17):2082-2088. doi:10.1161/CIRCULATIONAHA.105.608356
41. Sweeney MO, Bank AJ, Nsah E, et al. Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease. *N Engl J Med.* 2007;357(10):1000-1008. doi:10.1056/NEJMoa071880
42. Stojnić BB, Stojanov PL, Angelkov L, Pavlovic SU, Radjen GS, Velimirovic DB. Evaluation of asynchronous left ventricular relaxation by Doppler echocardiography during ventricular pacing with AV synchrony (VDD): comparison with atrial pacing (AAI). *Pacing Clin Electrophysiol.* 1996;19(6):940-944. doi:10.1111/j.1540-8159.1996.tb03390.x
43. Lee MA, Dae MW, Langberg JJ, et al. Effects of long-term right ventricular apical pacing on left ventricular perfusion, innervation, function and histology. *J Am Coll Cardiol.* 1994;24(1):225-232. doi:10.1016/0735-1097(94)90567-3
44. Wijffels MC, Kirchhof CJ, Dorland R, Power J, Allessie MA. Electrical remodeling due to atrial fibrillation in chronically instrumented conscious goats: roles of neurohumoral changes, ischemia, atrial stretch, and high rate of electrical activation. *Circulation.* 1997;96(10):3710-3720. doi:10.1161/01.cir.96.10.3710
45. Gülker H. A summary of the acute effects of falipamil in man. *Eur Heart J.* 1987;8 suppl L:141-146. doi:10.1093/eurheartj/8.suppl_l.141
46. Gramley F, Lorenzen J, Knackstedt C, et al. Age-related atrial fibrosis. *Age (Dordr).* 2009;31(1):27-38. doi:10.1007/s11357-008-9077-9
47. Heijman J, Algalarrondo V, Voigt N, et al. The value of basic research insights into atrial fibrillation mechanisms as a guide

to therapeutic innovation: a critical analysis. *Cardiovasc Res.* 2016;109(4):467-479. doi:10.1093/cvr/cvv275
48. Kovacic JC, Moreno P, Hachinski V, Nabel EG, Fuster V. Cellular senescence, vascular disease, and aging: part 1 of a 2-part review. *Circulation.* 2011;123(15):1650-1660. doi:10.1161/CIRCULATIONAHA.110.007021
49. Kaufman ES, Israel CW, Nair GM, et al. Positive predictive value of device-detected atrial high-rate episodes at different rates and durations: an analysis from ASSERT. *Heart Rhythm.* 2012;9(8):1241-1246. doi:10.1016/j.hrthm.2012.03.017
50. Shi Y, Ducharme A, Li D, Gaspo R, Nattel S, Tardif JC. Remodeling of atrial dimensions and emptying function in canine models of atrial fibrillation. *Cardiovasc Res.* 2001;52(2):217-225. doi:10.1016/s0008-6363(01)00377-7
51. De Jong AM, Maass AH, Oberdorf-Maass SU, Van Veldhuisen DJ, Van Gilst WH, Van Gelder IC. Mechanisms of atrial structural changes caused by stretch occurring before and during early atrial fibrillation. *Cardiovasc Res.* 2011;89(4):754-765. doi:10.1093/cvr/cvq357
52. Royston P, Altman DG. External validation of a Cox prognostic model: principles and methods. *BMC Med Res Methodol.* 2013;13:33. doi:10.1186/1471-2288-13-33