Journal of Cardiology 73 (2019) 65–72

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Simple risk model and score for predicting of incident atrial fibrillation in Japanese

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ARTICLE INFO

Article history:
Received 9 April 2018
Received in revised form 22 May 2018
Accepted 28 June 2018
Available online 29 July 2018

Keywords:
Atrial fibrillation
Epidemiology
Risk factors
Risk prediction
Risk score

ABSTRACT

Background: Investigating regarding a predicted risk score of incident atrial fibrillation (AF) for an Asian general population has not been enough. Whether addition of electrocardiogram (ECG) variables to risk factors improves prediction of incident AF is unclear in a context that ECGs are extensively used at medical check-ups and outpatient clinics in Japan.
Methods: Participants undergoing periodic health check-ups during 2008–2014 followed-up by December 2015 including 96,841 (65.1% male) aged 40–79 years were pooled to derive prediction models and risk scores for incident AF. Multivariable Cox regression identified clinical risk factors associated with incident AF in 7 years among 65,984 eligible participants including 349 AF cases.
Results: A 7-year prediction model ("Simple-model") including the variables of age, waist circumference, diastolic blood pressure, alcohol consumption, heart rate, and cardiac murmur, had good discrimination (C-statistic, 0.77), requiring no blood sampling. Addition model of the ECGs variables ("Added-model") including left ventricular hypertrophy, atrial enlargement, atrial premature contraction, and ventricular premature contraction, improved significantly the overall model discrimination (C-statistic, 0.78; categorical net reclassification improvement, 0.063; 95%CI, 0.031–0.099). The risk scores derived from the two models respectively showed an approximation of the observed and predicted probability for each score. Participants with score $\leq$4 or $\geq$9 points had, respectively, $\leq$1% and $\geq$5% predicted probability of incident AF in 7 years. The receiver-operating characteristics curve for the risk score of the added-model was significantly higher than the simple-model (0.769 vs 0.753, $p < 0.001$). Atrial enlargement on ECG and the highest age group were the highest risk points of the significant predictors.
Conclusions: We developed 7-year risk scores for incident AF using usually available clinical factors including ECGs in primary care. These risk scores could identify individuals with high risk of incident AF at health check-up and outpatient clinics.

Introduction

Atrial fibrillation (AF) is one of the major causes of stroke and heart failure [1,2]. The global burden of elevated prevalence of AF with aging [3] has greatly affected healthcare costs [4]. The increased public health significance of AF encourages efforts to identify individuals with high risk of developing AF and its complications [5].

Over the past few years, several risk scores for the prediction of AF in the predominantly white general population [6–9] including the Framingham Heart Study (FHS) have been developed and validated. But, the utility of these risk scores to predict risk of incident AF in non-whites, especially Asians, is uncertain. This is particularly relevant given the lower risk of AF among Asians compared to whites [10]. A risk score for incident AF in an urban Japanese population [11] published recently was somewhat complicated and derived from a small sample size.

Another limitation is that electrocardiogram (ECG) findings have not been sufficiently leveraged among several predictors for incident AF adopted in the previous risk scores [6–9]. ECG is widely available, and some of its abnormal findings reflect electrical and structural changes of the heart, and could be associated with incident AF also for general Japanese people [12]. In Japan, ECG has been mandated as a medical examination item by the Industrial Safety and Health Act [13] and widely implemented in the occupational health check-up.

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https://doi.org/10.1016/j.jjcc.2018.06.005
0914-5087/

Incorporating ECG findings in the predictors for incident AF could make possible that the prediction of AF in general Japanese people will be further improved. Further, risk stratification utilizing ECG may be useful in health examinations and routine outpatient clinical checks in Japan to identify individuals with high risk of developing AF. Therefore, we aimed to develop a risk score to predict incident AF based on risk factors including ECG findings that can be available in the health check-ups using a large Japanese population database.

Methods

Study population

This retrospective cohort study was based on the periodic complete medical check-ups ("Ningen Dock") at Seirei Center for Health Promotion and Preventive Medicine in Hamamatsu City, Shizuoka, Japan. Details of the study design and procedures have been previously reported [14]. In brief, a total of 96,841 participants aged 40–79 years, who underwent check-ups to identify non-communicable disease and its risk factors from April 2008 to March 2014, were included, and the data from the first check-up were used as a baseline. The participants with any abnormalities by the check-ups were introduced to neighboring clinics and the results were confirmed by medical certificates or telephone survey. For this study, those who had AF or atrial flutter at the baseline and in past ECGs, clinical history of AF, and no subsequent check-up were excluded. Consequently, 69,593 participants who had received at least one check-up after the next year of the baseline from April 2009 to December 2015 remained. Further, those people who had any missing data regarding anthropometric measures ($n = 493$), critical values from specimens ($n = 130$) [15], or possible influential conditions on incident AF [e.g. artificial dialysis and/or end-stage renal failure ($n = 58$), medical history of collagen-related diseases ($n = 539$), cancer ($n = 2562$), heart surgery ($n = 213$), and pacemaker implantation ($n = 54$)] at baseline were excluded. Informed consent was obtained from all participants for epidemiological studies. The study was approved by the Ethics Review Committee of the Seirei Center.

Study variables

The medical check-ups conducted followed the standardized protocol of Japan Society of Ningen Dock [16]. Body weight (kg) and height (m) were measured with an electronic scale (TBF-210® Tanita) to the first decimal place. Body mass index (BMI) was calculated as weight divided by height squared. Waist circumference (WC) (cm) was measured in a standing position at the umbilical level to the nearest 0.1 cm and classified into normal-WC or abdominal-obesity ($<$ or $\geq$85 cm for male and $<$or $\geq$90 cm for female) [17]. After at least 1 min of seated rest, blood pressure (BP) was recorded as the lower of two consecutive measurements taken more than 2 min apart. The presence of a clinically significant cardiac murmur was identified during the physical examination by trained clinicians using a stethoscope.

Routine blood tests of the check-ups include serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), non-HDL (calculated by subtracting the HDL from the TC), fasting glucose, glycosylated hemoglobin (HbA1c), white blood cell count, hemoglobin, and C-reactive protein. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease equation [18].

A resting 12-lead ECG was used to define the presence of prolonged PR interval (PR $\geq$ 220 ms), left ventricular hypertrophy (LVH; Sokolow-Lyon voltage was $\geq$45 mm), atrial enlargement (AE; p wave amplitude $>$2.5 mm in II and/or terminal p negativity in V1 duration $\geq$0.04 s, depth $\geq$1 mm), atrial premature contraction, and ventricular premature contraction. All ECG findings at check-ups were confirmed visually by experienced cardiologists using the software FCP-7431® (Fukuda Denshi, Tokyo, Japan) [19] for computer coding. In case of disagreement of judgment, that of an experienced cardiologist was priority.

Information on the history of heart disease (including coronary heart disease, chronic heart failure, myocardial disease, and valvular disease), stroke (including cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage), current medications (for hypertension, diabetes, and dyslipidemia), and habitual behaviors [smoking status: never or ever (former and current), alcohol intake: alcohol intake gram per day, physical activity: inactive or active ($<$ or $\geq$1 h of walking and/or equivalent physical activity per day)] was collected using standardized self-reported questionnaires and confirmed by physicians and nurses.

Definition of incident AF and the endpoint of follow-up

Diagnoses of AF until December 31, 2015 were identified both from 12-lead ECGs performed and self-report when the participants received check-ups. All ECGs performed were analyzed and confirmed by experienced cardiologists using the software FCP-7431® [19] for computer coding. The date of incident AF was defined as whichever came earlier of the first presentation of AF/atrial flutter on an ECG or the self-reported information on physician diagnosed AF during the follow-up period.

The endpoint of the follow-up period for each participant was defined based on one of the following options that occurred first: (i) the year of the first AF event confirmed by ECG or interview at the check-ups, (ii) year of the last check-up, or (iii) December 2015 (censored).

Statistical analysis

We assessed potential risk predictors for incident AF during 7 years using Cox proportional hazards regression model, which accounts for the discrepancy in follow-up time. Candidate predictors for our model were selected based on previous prospective findings for AF [6,7,11,20–26], including age, sex, physical measurements, blood pressure, fasting plasma glucose, treatment for hypertension, diabetes mellitus and dyslipidemia, eGFR, blood cholesterol, triglycerides, smoking, alcohol drinking, physical exercise, heart rate, ECG findings, history of heart disease and stroke. First, age and sex-adjusted univariate associations of incident AF with the above candidate predictors were evaluated using Cox proportional hazards models. All significant ($p < 0.10$) predictors from the univariate models were included in a multivariate Cox model and a backwards stepwise elimination was used to identify significant ($p < 0.05$) predictors in our multivariate model. Interaction tests between predictors identified in the model and log of follow-up time confirmed the proportional hazards assumption was met. Model-based individual 7-year risk of incident AF was calculated.

Once the final Cox model was determined, the model discrimination was estimated using the *C*-statistic [27] and calibration assessed by agreement between predicted and observed 7-year probability in deciles of predicted probability (modified Hosmer–Lemeshow statistic for survival analysis [28]; p-value of $<$0.01 required to reject the hypothesis that a model was well calibrated). We ran a validation of the model discrimination using bootstrapping with 1000 replications with replacement [29].

Furthermore, we followed the method used by the FHS [30] to assign risk points in any category of the significant predictors in the multivariate model and predicted the 7-year probability of developing AF by the risk point total (i.e. risk score). For the risk points, we considered the following categorical variables based on

clinical criteria: age [in five-year increments, 40 to <45 years (reference)], gender [male, female (reference)], abdominal-obesity [no (reference), yes], alcohol drinking status [never (reference), 1 to <40, 40 to <60, ≥60 g/day] [31], diastolic blood pressure [<90 (reference), ≥90 mmHg], cardiac murmur [no (reference), yes], heart rate [≤50, >50 (reference) beats per minute], and ECG findings [no (reference), yes]. The risk scores for all participants in the data set were calculated by the risk points total for each of them.

To facilitate the use of the risk score in clinical settings with limited access to ECG, we first developed a prediction model that did not require information of ECG (labeled "simple-model"). We then developed an extended model adding ECG variables (labeled "added-model"). The ECG variables were retained in the models if they were significantly ($p < 0.05$) associated with incident AF after multivariable adjustment. We calculated the predicted probability of the added-model and compared it to the simple-model with the increment in the *C*-statistic, calibration in deciles of predicted probability, integrated discrimination index (IDI) as a continuous outcome across the range of risk, and the categorical net reclassification improvement (NRI) using the following risk categories of <1.0%, 1.0–5%, >5%. Bootstrap resampling was used to conduct a validation of *C*-statistic of the added-model and 95% confidence intervals for reclassification statistic. The risk points and risk score for the added-model were calculated if there was improvement in the discrimination. The discrimination of risk score derived from added-model was compared with that of the simple-model, using the area under the receiver-operating characteristics curve (AROC) [32].

Means and standard deviation and frequency distribution of relevant covariates were calculated. All analyses were performed in R version 3.4.2 [33].

Results

Baseline characteristics

A total of 65,984 participants, of which 42,942 (65.1%) were male, were eligible for this study. Over a mean follow-up of 5.5 (SD 1.6) years, 299 males and 50 females developed AF. The incidence rate was 1.57 per 1000 person-years in males and 0.53 in females. The baseline characteristics of the participants with and without incident AF are presented in Table 1. There was no difference in

Table 1
Baseline characteristics of study participants and hazard ratio for 7 year risk of incident atrial fibrillation.

Covariate	No AF (n = 65,635)	AF (n = 349)	P^{**}	Hazard ratio (95% CI)*	p
Age (year)	52.4 (8.8)	58.6 (8.2)	<0.001	1.08 (1.07–1.10)	<0.001
Male (%)	42,942 (65.4)	299 (85.4)	<0.001	2.92 (2.17–3.93)	<0.001
Height (cm)	164.7 (8.6)	167.1 (8.3)	<0.001	1.54 (1.31–1.81)	<0.001
Weight (kg)	62.3 (11.6)	66.3 (11.7)	<0.001	1.51 (1.34–1.71)	<0.001
Body mass index (kg/m^2)	22.8 (3.2)	23.6 (3.3)	<0.001	1.29 (1.15–1.43)	<0.001
Waist circumference (cm)	82.7 (8.8)	85.6 (9)	<0.001	1.31 (1.17–1.46)	<0.001
Abdominal obesity (%)	21,649 (33)	180 (51.4)	<0.001	1.70 (1.37–2.12)	<0.001
Systolic BP (mmHg)	116.9 (15.4)	123.3 (15.6)	<0.001	1.19 (1.07–1.32)	0.001
Diastolic BP (mmHg)	71.7 (10.8)	75 (10.3)	<0.001	1.22 (1.10–1.36)	<0.001
Pulse pressure (mmHg)	45.3 (9.9)	48.3 (10.5)	<0.001	1.05 (0.95–1.17)	0.315
Fasting glucose (mg/dL)	100 (17.8)	103.8 (18)	<0.001	1.04 (0.95–1.14)	0.416
HbA1c (%)	5.7 (0.6)	5.8 (0.7)	0.048	0.98 (0.88–1.09)	0.733
Uric acid (mg/dL)	5.5 (1.4)	5.9 (1.3)	<0.001	1.13 (1.00–1.28)	0.050
Triglycerides (mg/dL)	114.6 (78.6)	122.5 (77.5)	0.062	1.03 (0.93–1.14)	0.584
HDL (mg/dL)	63.7 (17.6)	60.2 (16.6)	<0.001	0.96 (0.85–1.07)	0.443
LDL (mg/dL)	128.8 (30.7)	129.7 (28.8)	0.564	0.99 (0.89–1.11)	0.887
non-HDL (mg/dL)	141.6 (34.1)	143.6 (32.1)	0.271	1.01 (0.90–1.13)	0.271
WBC ($\times 10^3/\mu$L)	5.52 (1.55)	5.56 (1.39)	0.581	1.00 (0.90–1.12)	0.990
Hemoglobin (g/dL)	14.3 (1.5)	14.7 (1.2)	<0.001	1.11 (0.96–1.29)	0.159
CRP (mg/dL)	0.11 (0.29)	0.12 (0.26)	0.808	0.97 (0.86–1.09)	0.586
eGFR (mL/min/1.73 m^2)	77.6 (13.6)	72.3 (13.1)	<0.001	0.85 (0.76–0.96)	0.007
Drug use (%)					
Antihypertensive agent	8595 (13.1)	89 (25.4)	<0.001	1.40 (1.09–1.79)	0.009
Hypoglycemic agent	2001 (3.0)	14 (4.0)	0.381	0.91 (0.53–1.56)	0.742
Antidyslipidemia agent	4983 (7.6)	33 (9.4)	0.233	0.98 (0.68–1.41)	0.914
Alcohol consumption (g/day)	16.4 (21.5)	25.5 (25.5)	<0.001	1.27 (1.15–1.40)	<0.001
Ever smokers (%)	33,983 (51.8)	242 (69.1)	<0.001	1.40 (1.08–1.82)	0.011
Physical activity (%)	20,957 (31.9)	135(38.7)	0.009	1.02 (0.82–1.27)	0.868
Heart rate (beats per minute)	62.89 (9.13)	60.73 (9.18)	<0.001	0.98 (0.97–0.99)	<0.001
Electrocardiogram findings (%)					
APC	540 (0.8)	21 (6)	<0.001	5.09 (3.26–7.95)	<0.001
LVH	1753 (2.7)	27 (7.7)	<0.001	2.07 (1.39–3.06)	<0.001
AE	74 (0.1)	5 (1.4)	<0.001	11.8 (4.88–28.6)	<0.001
Prolonged PR interval	1014 (1.5)	14 (4.0)	<0.001	1.77 (1.04–3.03)	0.036
VPC	604 (0.9)	10 (2.9)	<0.001	2.44 (1.30–4.59)	0.005
Cardiac murmur (%)	380 (0.6)	6 (1.7)	0.015	2.50 (1.11–5.61)	0.026
History of heart disease (%)	461 (0.7)	6 (1.7)	0.032	1.73 (0.82–3.67)	0.151
History of stroke (%)	637 (1)	8 (2.3)	0.026	1.40 (0.69–2.83)	0.350

AE, atrial enlargement; AF, atrial fibrillation; APC, atrial premature contraction; BP, blood pressure; CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; PR interval prolonged, PR interval on an electrocardiogram ≥220 ms; VPC, ventricular premature contraction; WBC, white blood cell.
Covariates correspond to mean (SD) or *N* (%).
* Hazard ratios and 95% CI are expressed per 1 SD increase for continuous variables and the condition present in dichotomous calculated using a Cox proportional hazards model adjusted for age and sex.
** Unpaired *t*-test was used for continuous variables and Chi-square test was used for categorical variables: comparison between those who developed AF and those who did not.

Table 2
Multivariable Cox proportional hazards models assessed by discrimination and risk points of each covariate for 7-year risk of atrial fibrillation.

			Simple model			Added model
C-statistic (SE)			0.77 (0.02)			0.78 (0.02)
Model calibration [χ2 (P-value)]*			13.9 (0.13)			9.74 (0.37)
IDI (95% CI)						0.006 (0.002–0.017)
Continuous NRI (95% CI)						0.108 (0.006–0.153)
Model covariates	β (SE)	HR (95% CI)	Point	β (SE)	HR (95% CI)	Point
Age (years)						
40 to <45		1.00 (reference)	0		1.00 (reference)	0
45 to <50	0.197 (0.293)	1.22 (0.69–2.16)	0	0.170 (0.293)	1.19 (0.67–2.1)	0
50 to <55	1.119 (0.246)	3.06 (1.89–4.96)	2	1.109 (0.246)	3.03 (1.87–4.91)	2
55 to <60	1.233 (0.247)	3.43 (2.12–5.57)	2	1.188 (0.247)	3.28 (2.02–5.32)	2
60 to <65	1.885 (0.240)	6.59 (4.12–10.5)	3	1.816 (0.240)	6.15 (3.84–9.85)	3
65 to <70	1.997 (0.259)	7.37 (4.44–12.2)	4	1.891 (0.260)	6.63 (3.98–11.0)	4
70 to <75	2.632 (0.276)	13.9 (8.1–23.9)	5	2.484 (0.278)	12.0 (6.95–20.7)	5
75 to <80	2.227 (0.461)	9.27 (3.75–22.9)	5	2.126 (0.462)	8.38 (3.39–20.7)	5
Gender						
Female		1.00 (reference)	0		1.00 (reference)	0
Male	0.687 (0.170)	1.99 (1.43–2.77)	2	0.635 (0.170)	1.89 (1.35–2.63)	2
Waist circumference (cm)						
<85/90 (male/female)		1.00 (reference)	0		1.00 (reference)	0
≥85/90 (male/female)	0.508 (0.112)	1.66 (1.33–2.07)	1	0.550 (0.112)	1.73 (1.39–2.16)	1
Diastolic BP (mmHg)						
<90		1.00 (reference)	0		1.00 (reference)	0
≥90	0.477 (0.171)	1.61 (1.15–2.25)	1	0.443 (0.172)	1.56 (1.11–2.18)	1
Alcohol drinking status(g/day)						
Never		1.00 (reference)	0		1.00 (reference)	0
0< to <40	0.081 (0.134)	1.08 (0.83–1.41)	0	0.081 (0.134)	1.08 (0.83–1.41)	0
40 to <60	0.350 (0.164)	1.42 (1.03–1.96)	1	0.354 (0.164)	1.42 (1.03–1.97)	1
≥60	1.043 (0.231)	2.84 (1.81–4.46)	2	1.063 (0.231)	2.9 (1.84–4.56)	2
Heart rate (beats per minute)						
>50		1.00 (reference)	0		1.00 (reference)	0
≤50	0.674 (0.165)	1.96 (1.42-2.71)	1	0.688 (0.165)	1.99 (1.44–2.75)	1
Cardiac murmur (yes)	0.934 (0.413)	2.54 (1.13-5.72)	2			
Electrocardiogram (yes)						
APC				1.736 (0.229)	5.68 (3.62–8.89)	3
LVH				0.623 (0.204)	1.86 (1.25–2.78)	1
AE				2.576 (0.458)	13.1 (5.36–32.2)	5
VPC				0.863 (0.325)	2.37 (1.25–4.48)	2

AE, atrial enlargement; APC, atrial premature contraction; BP, blood pressure; CI, confidence interval; HR, hazard ratio; IDI, integrated discrimination improvement; LVH, left ventricular hypertrophy; NRI, net reclassification improvement.
* p-value of <0.01 required to reject the hypothesis that a model was well calibrated.

baseline characteristics between the follow-up and no follow-up groups (details not shown).

Derivation of the predictive model

Risk factors that were associated with incident AF ($p < 0.1$) in the Cox model adjusted for age and sex (Table 1) were eligible for inclusion in the multivariable Cox model. The final prediction model included age, sex, WC, diastolic BP, alcohol consumption, heart rate, and cardiac murmur after a backwards stepwise elimination ($p < 0.05$) (Table 2, "simple-model").

The simple-model had *C*-statistic of 0.77 (SD 0.02) and calibration of χ^2 13.9 ($p = 0.13$), indicating good discrimination, with the mean of the 1000 bootstrap validated *C*-statistic at 0.77 (SD 0.01) and calibration of χ^2 20.5 ($p = 0.015$). Each predicted probability per decile estimated from the simple-model was approximate to the observed counterpart (Fig. 1A).

To determine the "added-model", significant ($p < 0.10$) predictors from the age- and sex-adjusted models with the addition of the ECG variables were entered into multivariate Cox model to identify significant ($p < 0.05$) predictors using backwards stepwise elimination (Table 2 "added-model"). In the added-model, cardiac murmur was not significant and ECG variables except for "prolonged PR interval" remained significant. Especially after adjustment for AE of the ECG variables, the association between incident AF and cardiac murmur was not significant. The added-model had *C*-statistic of 0.78 (SD 0.02) and calibration of χ^2 9.74 ($p = 0.37$) with similar estimates of observed and predicted probability (Fig. 1B). The validation of the added-model, based on 1000 bootstrap samples, revealed *C*-statistic at 0.79 (SD 0.01) and calibration of χ^2 19.4 ($p = 0.022$). The added-model with incorporation of ECG variables significantly improved the *C*-statistic compared with the simple-model ($p < 0.001$), IDI showed a positive shift of improvement [0.006 (0.002–0.017)], the continuous NRI [0.108 (0.006–0.153)] (Table 2), and the NRI [0.063 (0.031–0.099)] (Table 3).

Risk points for each category of predictors and risk score

Table 2 lists significant predictors and risk points for each category of them in the simple- and added-models. The 7-year predicted probability of incident AF by total risk score is presented in Fig. 2. The participants scoring ≤1 or ≥10 were compiled respectively into one group because of the small sample sizes. In both models, individuals scoring ≤4 points had a 7-year predicted probability of incident AF of <1%, while scoring ≥9 points had that of >5%. The 7-year predicted probability for each risk score was similar to the observed probability in both models. The AROC for the risk score of the added-model was significantly higher than that of the simple-model (0.769 vs 0.753, $p < 0.001$).

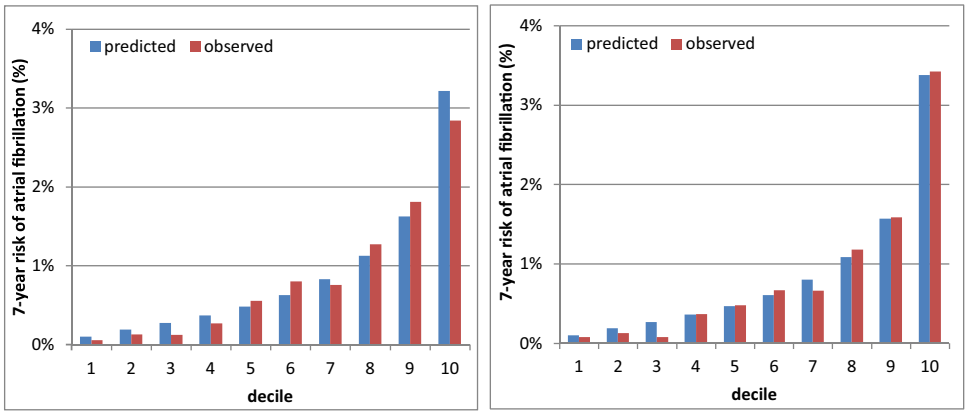

Fig. 1. Observed and predicted atrial fibrillation (AF) probability by decile of predicted AF risk. The *x*-axis refers to deciles of predicted AF risk derived from simple (A) and added (B) multivariable cox regression model respectively. Each bar in the graph represents the average observed and predicted AF risk in each decile group. A: Simple model. B: Added model.

Table 3
Reclassification among individuals who develop and who did not develop atrial fibrillation (AF) during a 7 year follow-up with "added model" including electrocardiogram findings.

A	Participants who developed AF			
	Added model			
Simple model	<1.0%	1.0–5.0%	>5.0%	total
<1.0%	96 (27.5)	13 (3.7)	1 (0.3)	110 (31.5)
1.0–5.0%	2 (0.6)	199 (57)	20 (5.7)	221 (63.3)
>5.0%	0 (0)	4 (1.1)	14 (4)	18 (5.2)
total	98 (28.1)	216 (61.9)	35 (10)	349 (100)

B	Participants who did not developed AF			
	Added model			
Simple model	<1.0%	1.0–5.0%	>5.0%	total
<1.0%	45182 (68.8)	784 (1.2)	31 (0.05)	45997 (70.1)
1.0–5.0%	512 (0.8)	18178 (27.7)	417 (0.6)	19107 (29.1)
>5.0%	0 (0)	119 (0.2)	412 (0.6)	531 (0.8)
total	45694 (69.6)	19081 (29.1)	860 (1.3)	65635 (100)

Net reclassification improvement (NRI), 0.063; 95% CI, 0.031–0.099.
Data are number of participants (%). Green cells correspond to desirable reclassification, while red cells correspond to undesirable reclassification.

Discussion

We developed two 7-year prediction models and risk scores (the simple- and added-model) for incident AF using a large Japanese population undergoing periodic health check-ups. The simple-model showed good discrimination and did not need blood samples, therefore, it was easier to use than previous published models [6,7,11]. Furthermore, the added-model with the addition of ECG findings as predictor variables significantly improved the *C*-statistic and reclassification statistic compared with the simple-model, meaning increased ability to predict incident AF. These prediction models for incident AF in 7 years could be useful in health check-ups and outpatient clinics to identify individuals with high risk of developing AF in a general Japanese population.

AF risk scores based on general populations have been reported by previous studies [6–9]. The risk-score elements common to these studies were age, sex, obesity, BP, and cardiac murmur, which were also included in the present study for Japanese, suggesting that these elements may be common to various ethnic groups. Unlike the previous studies, use of antihypertensive medication and history of heart disease were not significantly associated with AF, resulting from the low morbidity of hypertension and coronary heart disease in the present study. We found that low heart rate (≤50 beats/min) was associated with incident AF. The cut-off threshold of heart rate to detect the increased risk of incident AF by moving 1 beat/min was examined (details not shown). As a result, heart rate ≤50 beats/min group showed significantly the highest hazard ratio of incident AF compared to heart rate >50 beats/min group in the simple- and added-model. A recent study showed that cardiac autonomic dysfunction denoted by low resting short-term heart rate variability was associated with higher AF incidence, indicating that a low heart rate could be associated with incident AF [34]. One Norwegian study supported that the risk of drug-treated lone AF increases with declining resting heart rate in both sexes [35].

In the previous studies, several ECG findings have been shown to be associated with incident AF, and have been used as predictors [6,7], but their use was limited. In the present study, when the added-model was derived by incorporating ECG variables into the simple-model, it significantly increased ability to predict incident AF. In particular, it was worth mentioning that AE on ECG showed particularly the highest risk point (i.e. the most important element) among predictors in the present study. The previous study explained that the ECG's criteria for left AE (i.e. the duration of the negative phase of P wave in lead V1 ≥ 0.04 s) had high sensitivity 83% and specificity 80% determined by echocardiography [36]. This corresponds with the fact that the expansion of the atrium is closely related to the onset and persistence of AF [37]. ECG-diagnosed premature complexes (atrial premature contraction, and ventricular premature contraction) [12,38] and LVH [39], which had higher risk points, have both been shown to elevate the risk of incident AF. The above facts encourage active use of ECG at medical check-ups for prevention of incident AF.

Another remarkable finding was that in the present study cardiac murmur of a significant predictor in the simple-model was invalidated by special adjustment for AE of ECG variables, although cardiac murmur was a common risk-score component in the previous studies for the prediction of AF [6,7,9,11]. This suggests that AE on ECG could be equal or more useful than cardiac murmur for identifying individuals likely to develop AF. This finding might result from the fact that AE on ECG reflects closely atrial load due to heart disorders causing AF [40] and that the reliable identification of a cardiac murmur by non-cardiologists is variable while ECG is objective and reproducible. Further, the added-model with the ECG

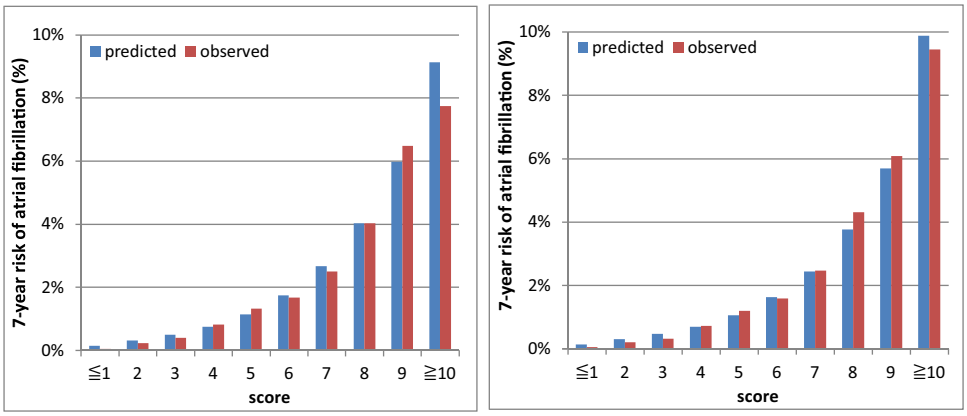

Fig. 2. Observed and predicted atrial fibrillation (AF) probability for each risk score. The x-axis refers to risk score of predicting AF risk derived from simple (A) and added (B) model respectively. Each bar in the graph represents the average observed and predicted AF risk in each score. A: Risk score from simple model. B: Risk score from added model.

variables was also valuable for reclassification of incident AF risk for individuals and suggested that the AF risk stratification utilizing ECG could be useful. Routine use of ECG at health check-ups should be justifiable for primary prevention screening to predict risk of AF in the general Japanese population.

Obesity and overweight by BMI are associated with incident AF in previous studies [41]. In the present study, each anthropometric factor was associated with increased risk of incident AF after adjustment for age and sex (Table 1), but only WC was significantly associated with incident AF after stepwise multivariable adjustment. Our previous study [14] showed that the criteria of abdominal-obesity measured by WC for the Japanese (male $\geq$85 cm, female $\geq$90 cm) [17] could be more suitable than that of overweight (BMI $\geq$ 25 kg/m^2) for the identification of incident AF. Abdominal-obesity defined by WC represents central body fat distribution and visceral fat mass and exhibits a distinct effect on inflammation and modulates the inflammatory network [42], promoting both onset and persistence of AF [43,44]. The present study is the first to incorporate abdominal obesity into the prediction model of incident AF. WC would be applicable to predict the risk of AF in comparatively low BMI individuals such as Asians that tend to have a higher percentage of body fat than Caucasians with the same BMI [45].

A further advantage of the present models we developed was to use only simple tests that are usually available in primary care settings and not to require blood samples. Nevertheless, the *C*-statistics of the present models were similar to those of the previous studies [6–9,11]. Although some models that combine various variables other than ECG were compared with each other, there was no model significantly improving discrimination and calibration than the added-model.

Strengths and limitations

Our study also several limitations. Firstly, there might be a possibility that some of the participants who were classified as not having developed AF had asymptomatic and paroxysmal AF, leading to an underestimation of incident AF. However, we identified incident AF by the use of not only ECG and self-report at the check-ups, but also the medical certificates from clinics and hospitals where participants underwent precision examination. The incidence rates by sex and by 10-year age groups in the present study closely resemble those in a previous Japanese population-based study [14,46]. Second, ECG findings were analyzed by the software. We could not verify other companies' software. However, ECG findings were confirmed by specialists, and the criteria of ECG findings used are widely used in a general health examination and in routine outpatient clinics. Third, we could not conduct a validation of our risk models and scores using other cohorts. Instead, we ran the validation of the *C*-statistic and calibration using bootstrap method with 1000 replications, providing more stable estimates with lower bias compared to other methods (e.g. split-sample validation) [29]. Fourth, the present study used the anthropometry and habitual behaviors at baseline and was unable to control for their changes during follow-up. Fifth, detailed information of medicines for participants' comorbidity was not available for the database. But, we confirmed whether they were taking medicines at each check-up. Lower heart rate was closely related to incident AF in the present study. This might be affected by a rhythm control medication. The participants especially with cardiac disease and hypertension are more likely to take this medicine, but Cox analyses were adjusted for the history of these comorbidities. Finally, our results might be affected by uncontrolled or residual confounding, such as valvar disease or hyperthyroidism related to enlarged atria. Our dataset was not good enough to exclude accurately the participants with these comorbidities. For that reason, we reanalyzed with the exception of participants treated for heart disease (including valvar disease) or hyperthyroidism at baseline. As a result, the model calibration was improved (Supplementary Table S1).

However, this study was conducted using a large population with standardized health check-up protocols to clarify the models predicting for incident AF including ECG findings for the first time in Japan. Although the present research is a retrospective cohort study, a previous study showed that the data obtained in a retrospective epidemiological study using large Japanese healthcare database akin to our health check-up database were comparable with results obtained in prospective cohort studies conducted in Japan [47]. Development of the risk scoring system benefited from the population-based nature of the cohort, readily accessible clinical risk factors, rigorous adjudication of AF events, and the combination of established risk factors to improve the accuracy of prediction.

In conclusion, we have developed 7-year prediction models and risk scores for incident AF that could be appropriate for the general Japanese population using large data registry with a standardized format. Furthermore, the added-model with the addition of ECG findings significantly improved the statistic discrimination compared with the simple-model. These models do not require blood

sampling and extra diagnostic tests beyond what is usually available in primary care settings, so that they have clinical usability and versatility to identify individuals likely to develop AF. Moreover, the feasibleness of replacing cardiac murmur with ECG among the models we developed expanded evidence on the role of risk factors in AF prevention strategies.

Funding

This study received no grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosures

The authors declare that there is no conflict of interest.

Acknowledgments

The authors are deeply grateful to all participants and Mr Yusuke Takamori at Seirei Center for Health Promotion and Preventive Medicine for his assembling the database.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jjcc.2018.06.005.

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