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Simple predictors for new onset atrial fibrillation

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ABSTRACT

Background: Predicting atrial fibrillation is a tremendous challenge. Only few studies have included 24 h-Holter monitoring characteristics to predict new onset AF (NOAF).
Objectives: Our aim is to define simple predictors for NOAF.
Methods: The study population included 468 patients undergoing Holter for any cause. After excluding 169 patients for history of AF prior to or during the Holter monitoring period, 299 patients were assessed for incidence of NOAF.
Results: Age at inclusion was 62.5 ± 18 years (53.5% male). After a median follow up of 39.1 [IQI 36.6–40] months, the incidence of NOAF was 10.4%. With univariate analysis, age, hypertension, diabetes, renal impairment, heart failure/cardiomyopathy, left ventricle ejection fraction ≤50%, left atrium diameter ≥40 mm, CHA_2DS_2 VASc ≥4, premature atrial complexes (PAC) ≥0.2%, and PR interval were associated with NOAF. With multivariate analysis, age (HR 1075; p = 0.001 per year), presence of heart failure/cardiomyopathy (HR 6,16; p < 0.001), PAC ≥ 0.2% (HR 3,32; p = 0.003) and PR interval (HR 1.011; p = 0.006 per millisecond) were independent predictors for NOAF. Those predictors were used to create a risk calculator for NOAF, which was validated in an independent cohort of 200 consecutive patients with similar baseline characteristics. This new tool resulted in good discrimination capacity calculated by the C index for NOAF prediction: Area under curve (AUC) (95% CI) 0.794 (0.714–0.875) at 2 years and 0.794 (0.713–0.875) at 3 years.
Conclusions: Simple clinical, ECG and Holter monitoring parameters are able to predict NOAF in a broad population and may help guide more rigorous monitoring for atrial fibrillation.

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice. Its prevalence in the developed world is approximately 1.5–2% [1], and increases with age. AF is associated with a higher risk of stroke, heart failure and mortality. However, AF may be asymptomatic, and the diagnosis is often made after an adverse event has already occurred. For these reasons, AF is considered a tremendous medical challenge associated with elevated economic and social costs. Early identification of populations at higher risk for new-onset AF (NOAF) can possibly help to prevent a number of AF related complications.

Risk factors already known to be associated with NOAF include age, hypertension, diabetes mellitus, obesity, ischemic heart disease, valvular heart disease, heart failure/cardiomyopathy (HF/CM), atrioventricular conduction impairment, chronic obstructive pulmonary disease and obstructive sleep apnea [2–8]. Several of these risk factors have been used to develop risk scores for AF prediction [9–11]. However, only few studies have used 24-hour Holter monitoring (HM) [12–16], and its role in a broader, more general population remains to be established.

The aim of our study was to define and validate clinical, ECG and HM predictors of NOAF in a broad population of patients undergoing a 24-hour HM for a number of different indications.

2. Methods

2.1. Original cohort

We retrospectively studied a cohort of consecutive patients referred from Primary Care Physicians or the Cardiology Department for HM to investigate symptoms, ECG abnormalities or structural heart disease, between March 2011 and October 2011. The only exclusion criteria were a prior history of AF or the documentation of AF during the index HM. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

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Clinical characteristics were collected in all patients. Similar to the description used by the CHA_2DS_2 VASC score, we recorded "heart failure" and "cardiomyopathy" in the same variable for practical purposes [17]. Heart failure was considered in the presence of 2 major Framingham criteria or 1 major criterion in conjunction with 2 minor criteria. Cardiomyopathy comprised any structural heart disease and/or at least moderate left ventricle systolic disfunction, including patients with ischemic and at least moderate valvular heart disease. Channelopaties were not included in this condition.

The majority of patients had a recent transthoracic echocardiogram. If available, we recorded the left atrium diameter (LAD) measured in the parasternal axis, and the left ventricle ejection fraction (LVEF) estimated by Simpson's.

2.2. Holter monitoring and ECG characteristics

ECG parameters were obtained from the baseline ECG in all patients. Twenty-four-hour Holter recordings were performed with the use of 3-channel SpaceLabs tape recorders (DMS 300–7 Holter recorder, Beijing, China). All HM were reviewed by an electrophysiologist using the ECG Holter Analyzer (CardioScan Premiere 12 Holter system, Beijing, China). The total number of premature atrial complexes (PAC), the percentage of PAC (obtained by dividing the total number of PAC by the total number of beats during the 24-hour period), the total number of episodes of non-sustained supraventricular tachycardia (NSSVT) and the maximum number of beats (MNB) in tachycardia were assessed in all patients. We defined Atrial Burden as the product of NSSVT by the MNB of the longest NSSVT.

2.3. Follow up

All patients were followed in the Cardiology Outpatient Clinics or by their Primary Care Physician, and all events and reports were registered in a common electronic medical record, which included the occurrence of NOAF, adverse events and death. Occurrence of NOAF was defined as the documentation of an AF episode lasting at least 30 s, recorded by ECG, repeated HM, pacemaker, or internal loop recorder.

2.4. Validation cohort

The clinical predictors for AF were used to create a risk calculator for NOAF. In order to validate our model, we retrospectively studied a second independent cohort of consecutive patients undergoing HM for any cause between November 2011 and March 2012, without previous history of AF or AF during the index Holter recording. This cohort was evaluated for the same clinical, ECG and HM parameters as described in the original cohort.

2.5. Statistical analyses

Continuous quantitative variables are described as mean ± standard deviation (SD) if they had a Gaussian distribution, or as median and interquartilic interval (IQI) if the distribution was not normal, while categorical variables are described as frequencies and percentages. Cox-regression models were used to establish predictors associated with the development of NOAF in univariate and multivariate analyses. In the multivariate analysis, we used a stepwise backward elimination (including initial variables with P values less than 0.1 in univariate analysis). The hazard ratio (HR) was expressed with a confidence interval at 95% (95% CI). The predicted probability of NOAF at 2 and 3 years for an individual patient was calculated using the AF predictors obtained in the multivariate analysis, combined in an equation, in accordance to their HR.

We validated the calculator on the new validation cohort, using Hosmer–Lemeshow test for survival data. The discrimination capacity was calculated by the C-index and the corresponding generalization of Somers' Dxy rank correlation for a censored response variable. All the analyses were carried out using SPSS 18.0 software package (SPSS Inc., Chicago, Illinois).

3. Results

3.1. Original cohort

From an initial population of 468 consecutive patients undergoing 24 h Holter monitoring, 169 were excluded because of a history of prior AF or because of the presence of at least one sustained run (>30 s) of AF during the index HM. The resulting study cohort included 299 patients. The indication for HM was for symptoms in 65% of patients, predominantly for palpitations (50%) or syncope (40%). In 29%, the Holter was used to assess for arrhythmic disorders or conduction disturbances in patients with abnormal ECG at baseline, and in 6%, to evaluate for ventricular arrhythmias in patients with structural heart disease. Original cohort baseline characteristics are shown in Table 1.

Table 1
Baseline characteristics of the original cohort.

Population characteristics	N = 299
Clinical characteristics	
Male; n (%)	160 (53.5%)
Age; mean, SD (years)	62.5, 17.9
Hypertension; n (%)	156 (52.3%)
Diabetes mellitus; n (%)	52 (17.4%)
Ischemic heart disease; n (%)	45 (15.1%)
Valvular heart disease; n (%)	8 (2.6%)
HF/CM; n (%)	27 (8%)
Creatinine clearance <60 ml/min; n (%)	37 (12.6%)
Cerebrovascular accident; n (%)	21 (7%)
CHA_2DS_2 VASc score; n (%)	39 (14.2%)
0	76 (27.8%)
1	95 (34.7%)
2–3	63 (23%)
≥4	
Atrioventricular node blockers; n (%)	72 (24.5%)
Antiarrhythmic drugs; n (%)	11 (3.7%)
Echocardiographic parameters	
Left atrium diameter; mean, SD (mm)	36.7, 6.4
LVEF; mean, SD (%)	62.3, 9.9
ECG and Holter findings	
Percentage of PAC; median [IQI]	0.05 [0.05–0.24]
NNSVT; median [IQI]	0 [0–2]
MNB; median [IQI]	0 [0–5]
Atrial burden (NSSVT × MNB); median [IQI]	0 [0–10]
PR interval; mean, SD	175, 42.5

HF/CM: heart failure/cardiomyopathy; LVEF: left ventricle ejection fraction. MNB: maximum number of beats; NNSVT: number of non sustained supraventricular tachycardia; PAC: premature atrial complexes.

3.2. Follow-up and predictors of new-onset AF

All patients had repeated ECGs during the follow-up, with a mean of 6.72 (SD 3.51) ECGs per patient. In addition, 13% of patients had at least one repeated HM, and in 7%, a pacemaker or an internal loop recorder was implanted. Of the 299 patients, 31 (10.4%) developed AF during a median follow-up of 39.12 months [IQI 36.6–40].

Clinical predictors associated with the development of NOAF in univariate analysis are shown in Table 2. Multivariate analysis identified age (HR 1.09 per year; 95% CI 1.05–1.14; $p < 0.001$), history of HF/CM (HR 5.4; 95% CI 2.3–12.4; $p < 0.001$), percentage of PAC ≥0.2% (HR 2.7; 95% CI 1.2–5.8; $p = 0.01$) and increasing PR interval (HR 1.011; 95% CI 1.0–1.02; $p = 0.006$ per millisecond) as independent predictors for NOAF (Table 3).

We used these 4 independent predictors to create a calculator to predict NOAF at mid-term (2 years and 3 years), with each of the 4

Table 2
Univariate analysis: variables associated with NOAF.

Variables	HR (95% CI)	P
Male	1.7 (0.8–3.47)	0.144
Age	1.09 (1.0–1.1)	<0.001
Hypertension	4.71 (1.8–12.32)	0.002
Diabetes	2.78 (1.32–5.85)	0.007
Creatinine clearance < 60 ml/min	3.29 (1.5–7.2)	0.003
Ischaemic heart disease	2.16 (0.96–4.87)	0.06
Valvular heart disease	2.7 (0.65–11.44)	0.17
HF/CM	4.36 (1.95–9.75)	<0.001
LVEF ≥ 50%	0.33 (0.13–0.84)	0.02
Left atrium diameter ≥ 40 mm	2.85 (1.2–6.37)	0.01
Stroke	0.93 (0.2–3.91)	0.92
CHA_2DS_2 VASc ≥ 4	7.11 (3.16–15.99)	<0.001
PAC ≥ 0.2%	3.64 (1.78–7.4)	<0.001
Atrial burden ≥ 15	2.85 (1.39–5.84)	0.004
PR interval	1.08 (1.05–1.11)	<0.001

HF/CM: heart failure/cardiomyopathy; LVEF: left ventricle ejection fraction; PAC: premature atrial complexes.