Received: 6 April 2022 | Revised: 10 May 2022 | Accepted: 16 May 2022

DOI: 10.1111/anec.12978

ORIGINAL ARTICLE

WILEY

The performance of five models compared with atrial high rate episodes predicts new atrial fibrillation after cardiac implantable electronic devices implantation

Ju-Yi Chen MD, PhD | **Tse-Wei Chen MD** | **Wei-Da Lu MD**

Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Correspondence
Ju-Yi Chen, Division of Cardiology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, 138 Sheng-Li Road, Tainan 704, Taiwan.
Email: pili927@yahoo.com

Funding information
The authors would like to thank the Ministry of Science and Technology of the Republic of China, Taiwan, for financially supporting this research under contract MOST 110-2218-E-006-017 and MOST 110-2218-E-006-015. Obtained funding: J-YC

Abstract

Aims: Several predicting models have been evaluated for new-onset atrial fibrillation (AF) in several clinical conditions, but never in patients with cardiac implantable electronic devices (CIED). We aimed to evaluate the five predicting models compared with atrial high rate episodes (AHRE) to predict new AF in patients with CIED.

Methods and Results: We retrospective enrolled 470 consecutive patients with CIED and without a history of AF. The five predicting models, including CHA_2DS_2-VASc score, C_2HEST score, mCHEST score, HAT_2CH_2 score, and HAVOC score were used. The primary endpoint was new AF documented by 12-lead electrocardiography (ECG) or 30-s ECG strip. Multivariable Cox regression analysis was used to determine variables associated with independent factors of new AF. Patients' median age was 76 years and 58.7% were male. During follow-up (median 29 months), 34 new AF occurred (incidence rate 2.99/100 patient-years, 95% CI 1.67–6.20). Multivariable Cox regression analysis showed AHRE ≥6 min and 24 h, and HAT_2CH_2 score were independent predictors for new AF. Optimal AHRE cutoff value was 9.3 min with highest Youden index (AUC, 0.806; 95% CI, 0.722–0.889; $p < .001$). The AF occurrence rate of AHRE ≥9.3 min was 7 times AHRE <9.3 min ($p < .001$).

Conclusions: We compared 5 predicting models for new AF in patients with CIED and without a history of AF. AHRE ≥6 min and 24 h, and HAT_2CH_2 score were independent predictors for AF.

KEYWORDS
atrial fibrillation, cardiac implantable electronic device, predicting models

1 | INTRODUCTION

Atrial fibrillation (AF) is a leading arrhythmia worldwide and the major risk of systemic thromboembolic events (Hindricks et al., 2021; January et al., 2019). Several predicting models, including CHA_2DS_2-VASc score (Hu & Lin, 2018; Zuo et al., 2013), C_2HEST score (Li, Bisson, et al., 2019; Li, Pastori, et al., 2019; Lip et al., 2020), mCHEST score (Li, Bai, et al., 2021), HAT_2CH_2 score (Emren et al., 2016; Hu & Lin, 2017), and HAVOC score (Ntaios et al., 2020; Zhao et al., 2019) have been elucidated for predicting new AF in different populations and all revealed acceptable discriminating power. A prospective study enrolled 528 symptomatic arrhythmic patients and showed a CHA_2DS_2-VASc

score with a C statistic 0.63 and an optimal cutoff at 2 for new-onset AF (Zuo et al., 2013). Hu et al. used Longitudinal Health Insurance Database of Taiwan to demonstrate CHA_2DS_2-VASc score with the area under the curve of the receiver operating characteristic 0.67 for new-onset AF in patients with type II diabetes mellitus and hyperosmolar hyperglycaemic state (Hu & Lin, 2018). C_2HEST score was used to predict new AF in a Danish Healthy Population (Lip et al., 2020), post-stroke patients from France, (Li, Bisson, et al., 2019) and Chinese and Korean subjects (Li, Pastori, et al., 2019). The mCHEST score was refined in a hospital-based Chinese population and showed better predictive performance than other predicting models for incident AF (Li, Bai, et al., 2021). HAT_2CH_2 score has a slightly but significantly better predictive performance than CHA_2DS_2-VASc score for new AF in cancer patients (Hu & Lin, 2017), and can be used to predict the development of AF in patients after coronary artery bypass surgery (Emren et al., 2016). HAVOC score was also a newly developed score for predicting new AF in cryptogenic stroke patients with insertable cardiac monitors (Zhao et al., 2019). Overall, these five practical predicting models have not been well evaluated in patients with cardiac implantable electronic devices (CIED).

The latest guidelines regarding non-valvular AF (Hindricks et al., 2021; January et al., 2019) state that AHRE >5–6 min and >180 bpm detected by CIED increase the risk for new AF and clearly recommended AHRE should be closely monitored and treated. Sustained AHRE ≥24 h could be viewed as new AF and should be considered anticoagulant therapy in patients with CIED if a CHA2DS2-VASc score of ≥2 for men and ≥3 for women (Hindricks et al., 2021; January et al., 2019). Therefore, sustained AHRE ≥24 h could be hypothesized as a surrogate marker for new AF in patients with CIED (Li, Pastori, et al., 2021). The AHRE >5–6 min would increase the risk of stroke and clinical new AF in patients with CIED without prior AF which has been documented in a recent systemic review article (Doundoulakis, Gavriilaki, et al., 2021). Therefore, the optimal cutoff value for AHRE is still a debated issue and more pieces of evidence should be elucidated.

Hence, the present study aimed to investigate the performance of five commonly used predicting models for new AF and comparing to AHRE ≥6 min and AHRE ≥24 h in patients with CIED and without a history of AF. The novelty of this study is that there are no previous studies compared with predicting models and AHRE for new AF prediction.

2 | METHODS

2.1 | Study participants

Consecutive patients aged 18 years or older who underwent CIED implantation (Medtronic® and Biotronik®: dual-chamber pacemaker, dual-chamber implantable cardioverter defibrillator, cardiac resynchronization therapy-pacing, and cardiac resynchronization therapy defibrillator) in the Cardiology Department of National Cheng Kung University Hospital from January 2015 to April 2021 were retrospectively included.

2.2 | Ethical considerations

The procedures followed were in accordance with the "Declaration of Helsinki" and the ethical standards of the responsible committee on human experimentation (institutional or regional). The protocol for this cohort study was reviewed and approved by the ethics committee of National Cheng Kung University Hospital and was conducted according to guidelines of the International Conference on Harmonization for Good Clinical Practice (B-ER-108-278). All included patients provided signed informed consent at the time of their implantation procedures.

2.3 | Data collection and definitions

Patients' medical history and data of co-morbidities and echocardiographic parameters were collected from chart records for retrospective evaluation. Diabetes mellitus was defined by the presence of symptoms and casual plasma glucose concentration ≥200 mg/dl, fasting plasma glucose concentration ≥126 mg/dl, 2-h plasma glucose concentration ≥200 mg/dl from a 75-g oral glucose tolerance test, or taking medication for diabetes mellitus. Hypertension was defined as in-office systolic blood pressure values ≥140 mmHg and/or diastolic blood pressure values ≥90 mmHg or taking antihypertensive medication. Dyslipidemia was defined as low-density lipoprotein ≥140 mg/dl, high-density lipoprotein <40 mg/dl, triglycerides ≥150 mg/dl, or taking medication for dyslipidemia. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2 for at least 3 months. Coronary artery disease (CAD) was defined as patients with a history of acute coronary syndrome or >50% stenosis of coronary angiography. Peripheral artery disease was defined as patients with a history of a value of ankle-brachial index below 0.9 at rest or percutaneous transluminal angioplasty. Valvular heart disease was defined as patients with moderate or severe valvular stenosis or regurgitation using formal echocardiographic reports. Heart failure was diagnosed as preserved or reduced left ventricular ejection fraction by formal echocardiography reports and patients' clinical symptoms. The primary endpoint for this study was the occurrence of new-onset AF after the date of CIED implantation, diagnosed by experienced cardiologists based on 12-lead electrocardiography (ECG) or one-channel ECG strip ≥30 seconds or 24-h Holter recordings. In every office visit for pacemaker interrogation, one 12-lead ECG will be done. If AHRE ≥6 min was detected, more new AF detection by 24-h Holter or 12-lead ECG would be arranged. The follow-up duration will be similar in all patients.

AHRE were extracted from the devices via telemetry at each office visit (3–6 months). AHRE electrograms were reviewed by at least one experienced electrophysiologist, who carefully considered the possibility that AHRE included lead noise or artifacts, far-field R-waves, paroxysmal supraventricular tachycardia, and visually confirmed AF in the detected AHRE. Atrial sensitivity was programmed to 0.3 mV with bipolar sensing of Medtronic devices and 0.2 mV with

bipolar sensing of Biotronik devices. AHRE was defined as heart rate >175 bpm (Medtronic) or >200 bpm (Biotronik) and at least 30 s of atrial tachyarrhythmia recorded by the devices on any day during the study period. To evaluate the cutoff threshold for new AF, AHRE was categorized by duration: ≥6 min, and ≥24 h. If patients had multiple AHREs, the longest AHRE duration was used for analysis. If a patient's longest AHRE duration was 10 h, the result was counted as AHRE ≥6 min but not ≥24 h.

2.4 | Statistical analysis

Categorical variables are presented as percentages and continuous variables as means and standard deviations for normally distributed values or medians and interquartile interval for non-normally distributed values. The normal distribution for continuous variables was assessed using the Kolmogorov–Smirnov method. Pearson's chi-square test or Fisher's exact test was used to determine differences in baseline characteristics for categorical variables, and a two-sample student's t-test or Mann–Whitney U-tests was used to analyze continuous variables. Multivariable Cox regression analysis was used to identify variables associated with new-onset AF, reported as hazard ratios (HR) with 95% confidence intervals (CI). If the *p*-value in the univariable analysis was <.05, the parameter was entered into the multivariable analysis. The receiver-operating characteristic (ROC) area under the curve (AUC) of the AHRE in minutes and the associated 95% confidence intervals (CI) were evaluated for association with new-onset AF after CIED implantation. The optimal cutoff values with the highest Youden index were chosen based on the results of the ROC curve analysis and used to evaluate the associated values of the AHRE duration for determining new-onset AF. For all comparisons, $p < .05$ was considered statistically significant. All data were analyzed using SPSS statistical package version 23.0 (SPSS Inc.).

3 | RESULTS

3.1 | Patient characteristics

Between January 1, 2014 and April 30, 2021, a total of 644 consecutive patients receiving CIED transplantation at National Cheng Kung University Hospital were recruited initially. Patients with previous AF ($n = 174$) were excluded. The final analysis included data of 470 patients, of which 34 had experienced new AF. Table 1 shows the all variables in the 5 models.

The median follow-up period was 29 months after implantation of CIED and similar between the two groups (Table 2). Table 2 shows patients' baseline demographic and clinical characteristics based on whether new AF occurrence or not. Patients' median age was 76 years and 58.7% of patients were men. Types of CIED included dual-chamber pacemaker (376, 80.0%), dual-chamber ICD (66, 14.0%), CRTP (23, 4.9%), and CRTD (5, 1.1%). Medtronic was 66.8% and Biotronik was 33.2%. AHRE ≥6 minutes detected in Medtronic devices was 32.8% (103/314) and 14.7% (23/156) in Biotronik devices. The most common indication for CIED implantation was sick sinus syndrome (52.8%), followed by atrioventricular block (27.2%) and ventricular tachyarrhythmia (20.0%) (Table 2). Overall atrial pacing median percentages (34.0%) and ventricular pacing median percentages (4.2%) were noted. High percentages of hypertension (82.6%), hyperlipidemia (77.9%), diabetes (47.9%), CKD (37.2%), heart failure (30.2%), and CAD (25.5%) suggest a relatively high risk of AF for the entire study cohort. More

TABLE 1 The list of variables used in the five predicting models

	CHA_2DS_2-Vasc score		C_2HEST score		mC_2HEST score		HAT_2CH_2 score		HAVOC score	
Variable	**9**		**8**		**8**		**7**		**14**	
History of heart failure	✓	1					✓	2	✓	4
Hypertension	✓	1	✓	1	✓	1	✓	1	✓	2
Diabetes mellitus	✓	1								
Age 65–74 years	✓	1			✓	1				
Age ≥ 75 years	✓	2	✓	2	✓	2	✓	1	✓	2
Prior stroke, transient ischemic attack	✓	2					✓	2		
Vascular diseases	✓	1								
Female gender	✓	1								
Valvular heart disease									✓	2
Peripheral vascular disease									✓	1
Obesity (body mass index >30)									✓	1
Chronic obstructive pulmonary disease			✓	1	✓	1	✓	1		
Coronary artery disease			✓	1	✓	1			✓	2
Systolic heart failure			✓	2	✓	2				
Thyroid disease (hyperthyroidism)			✓	1	✓	1				

TABLE 2 Baseline characteristics of the overall study group and with/without new atrial fibrillation

Variables	All patients (n = 470)	New atrial fibrillation		Univariate p value
		Yes (N = 34)	No (N = 436)	
Age (years)	76 (65–83)	77 (68–83)	75 (65–83)	.284
Gender				
Male	276 (58.7%)	27 (79.4%)	249 (57.1%)	.011
Female	194 (41.3%)	7 (20.6%)	187 (42.9%)	
Body mass index (kg/m^2)	24.8 (22.6–26.1)	24.8 (23.1–26.5)	24.8 (22.6–26.1)	.617
Device brand				
Medtronic	314 (66.8%)	28 (82.4%)	286 (65.6%)	.057
Biotronik	156 (33.2%)	6 (17.6%)	150 (34.4%)	
Device type				
Dual chamber pacemaker	376 (80.0%)	33 (97.1%)	343 (78.7%)	.067
Dual chamber implantable cardioverter defibrillator	66 (14.0%)	0 (0.0%)	66 (15.1%)	
Cardiac resynchronization therapy	23 (4.9%)	1 (2.9%)	22 (5.0%)	
Cardiac resynchronization therapy defibrillator	5 (1.1%)	0 (0.0%)	5 (1.1%)	
Primary indication				
Sinus node dysfunction	248 (52.8%)	21 (61.7%)	227 (52.1%)	.001
Atrioventricular block	128 (27.2%)	12 (35.3%)	116 (26.6%)	
Heart failure/ventricular tachycardia/ventricular fibrillation	94 (20.0%)	1 (2.9%)	93 (21.3%)	
Atrial pacing (%)	34.0 (8.7–75.7)	34.9 (8.5–64.6)	34.0 (8.6–76.3)	.877
Ventricular pacing (%)	4.2 (0.2–96.8)	13.2 (0.8–43.3)	3.0 (0.2–97.3)	.340
Hypertension	388 (82.6%)	32 (94.1%)	356 (81.7%)	.096
Diabetes mellitus	225 (47.9%)	21 (61.8%)	204 (46.8%)	.092
Hyperlipidemia	366 (77.9%)	33 (97.1%)	333 (76.4%)	.002
Peripheral artery disease	6 (1.3%)	1 (2.9%)	5 (1.1%)	.364
Coronary artery disease	120 (25.5%)	9 (26.5%)	111 (25.5%)	.896
Valvular heart disease	57 (12.1%)	3 (8.8%)	54 (12.4%)	.785
Chronic obstructive pulmonary disease	23 (4.9%)	3 (8.8%)	20 (4.6%)	.227
Prior stroke	25 (5.3%)	1 (2.9%)	24 (5.5%)	1.000
Prior myocardial infarction	91 (19.4%)	9 (26.5%)	82 (18.8%)	.276
Heart failure				
Preserved left ventricular ejection fraction	52 (11.1%)	6 (17.6%)	46 (10.6%)	.204
Reduced left ventricular ejection fraction	90 (19.1%)	8 (23.5%)	82 (18.8%)	.500
Chronic kidney disease	175 (37.2%)	19 (55.9%)	156 (35.8%)	.020
Chronic liver disease	26 (5.5%)	1 (2.9%)	25 (5.7%)	.711
Thyroid disease	22 (7.0%)	1 (5.6%)	21 (7.1%)	.950
Hemoglobin (mg/dL)	12.0 (10.8–13.0)	12.0 (11.0–13.6)	12.0 (10.7–13.0)	.953
Platelet	203 (175–221)	204 (175–222)	203 (175–221)	.793
Echo parameters				
Left ventricular ejection fraction (%)	67.0 (56.0–74.0)	64.5 (52.3–71.5)	68.0 (56.0–74.0)	.216
Mitral E/e'	11.0 (8.7–14.0)	11.9 (9.7–15.3)	11.0 (8.6–14.0)	.259
Left atrial diameter (cm)	3.8 (3.2–4.1)	4.0 (3.5–4.4)	3.7 (3.2–4.1)	.028
Right ventricular systolic function (s', m/s)	12.0 (11.0–14.0)	12.0 (11.0–14.0)	12.0 (11.0–14.0)	.284

TABLE 2 (Continued)

Variables	All patients (n = 470)	New atrial fibrillation		Univariate p value
		Yes (N = 34)	No (N = 436)	
Drug prescribed at baseline				
Antiplatelets	179 (38.1%)	10 (29.4%)	169 (38.8%)	.280
Anticoagulants	42 (8.9%)	17 (50.0%)	25 (5.7%)	<.001
Beta blockers	164 (34.9%)	17 (50.0%)	147 (33.7%)	.055
Amiodarone	76 (16.2%)	15 (44.1%)	61 (14.0%)	<.001
Propafenone	15 (3.2%)	3 (8.8%)	12 (2.8%)	.086
Flecainide	1 (0.2%)	0 (0.0%)	1 (0.2%)	1.000
Dronedarone	5 (1.1%)	2 (5.9%)	3 (0.7%)	.044
Ivabradine	26 (5.5%)	2 (5.9%)	24 (5.5%)	1.000
Digoxin	7 (1.5%)	0 (0.0%)	7 (1.6%)	1.000
Non-dihydropyridine calcium channel blockers	16 (3.4%)	1 (2.9%)	15 (3.4%)	1.000
Diuretics	78 (16.6%)	9 (26.5%)	69 (15.8%)	.108
Renin-angiotensin-aldosterone system inhibitors	205 (43.7%)	16 (47.1%)	189 (43.4%)	.683
Statins	181 (38.5%)	12 (35.3%)	169 (38.8%)	.689
Metformin	79 (16.8%)	8 (23.5%)	71 (16.3%)	.277
Sodium glucose co-transporters 2 inhibitors	15 (3.2%)	1 (2.9%)	14 (3.2%)	1.000
Follow-up duration (months)	29.0 (14.0–52.0)	26.0 (12.0–47.0)	29.0 (14.0–52.0)	.503
CHA_2DS_2-VASc score	3 (2–4)	4 (3–4)	3 (2–4)	.297
C_2HEST score	3 (1–3)	3 (3–4)	3 (1–3)	.026
mC_2HEST score	3 (2–4)	3 (3–4)	3 (2–4)	.034
HAVOC score	4 (2–6)	6 (4–8)	4 (2–6)	.025
HAT_2CH_2 score	2 (1–3)	3 (2–4)	2 (1–3)	.001
AHRE ≥6mins	126 (26.8%)	24 (70.6%)	102 (23.4%)	<.001
AHRE ≥24 h	39 (8.3%)	14 (41.2%)	25 (5.7%)	<.001

Note: Data are presented as medians (interquartile interval) or n (%). Non-parametric continuous variables, as assessed using the Kolmogorov–Smirnov method, were analyzed using the Mann–Whitney U test. Statistical significance is set at $p < 0.05$. AHRE, atrial high-rate episodes; CHA_2DS_2-Vasc score, range from 0 to 9. History of heart failure, hypertension, diabetes, vascular disease, age 65–74 years, and female sex each is calculated as 1 point; 75 years or older and prior stroke, TIA, or thromboembolism each is calculated as 2 points; C_2HEST score, range from 0 to 8. C_2: CAD/COPD (1 point each); H: hypertension (1 point); E: elderly (age ≥ 75 years, 2 points); S: systolic HF (2 points); and T: thyroid disease (hyperthyroidism, 1 point); HAT_2CH_2 score, range from 0 to 7. Hypertension, 1 point; age >75 years, 1 point; stroke or transient ischemic attack, 2 points; chronic obstructive pulmonary disease, 1 point; heart failure, 2 points; HAVOC score, H: hypertension (2 points); A: age (age ≥ 75 years, 2 points); V: valvular heart disease (2 points), peripheral vascular disease (1 point); O: obesity (1 point); C: congestive heart failure (4 points) and coronary artery disease (2 points); mC_2HEST score, Range from 0 to 8. C_2: CAD/COPD (1 point each); H: hypertension (1 point); E: elderly (age 65–74 years, 1 point; age ≥75 years, 2 points); S: systolic HF (2 points); and T: thyroid disease (hyperthyroidism, 1 point).

patients used antiplatelet therapy because of more patients with CAD and prior stroke. Overall, the total number of new AF was 34 (incidence rate 2.99/100 patient-years, 95% CI 1.67–6.20).

3.2 | Univariable analysis and multivariable logistic regression analysis to identify independent predictors of new AF

Univariable analysis revealed that male gender, sick sinus syndrome, hyperlipidemia, chronic kidney disease, left atrial diameter, AHRE ≥6 min, AHRE ≥24 h, C_2HEST score, mCHEST score, HAVOC score, and HAT_2CH_2 score were significantly associated with new AF occurrence (Table 2). Multivariable Cox regression analysis showed that only AHRE ≥6 min (Model B-1 ~ B-4 in Table 3) and AHRE ≥24 h (Model A-1 to A-4 in Table 3) were independently associated with new AF. Only the HAT_2CH_2 score was independently associated with new AF.

3.3 | ROC–AUC determination of the AHRE cutoff values as a predictive factor for future AF

The optimal AHRE cutoff value predictive of future AF was determined to be 9.3 minutes with the highest Youden index (sensitivity,

TABLE 3 Multivariable cox regression analysis for new atrial fibrillation

	Model A1			Model A2			Model A3			Model A4		
Variables	**HR**	**95%CI**	***p***	**HR**	**95%CI**	***p***	**HR**	**95%CI**	***p***	**HR**	**95%CI**	***p***
Male gender	2.140	0.896–5.110	.087	2.144	0.893–5.145	.088	2.126	0.902–5.015	.085	1.902	0.800–4.521	.145
Sick sinus syndrome (yes)	0.843	0.101–7.073	.875	0.853	0.100–7.257	.884	0.977	0.114–8.364	.983	1.177	0.138–10.057	.882
Hyperlipidemia (yes)	3.579	0.445–28.812	.231	3.570	0.440–28.972	.234	3.204	0.392–26.164	.277	2.664	0.325–21.858	.362
Chronic kidney disease (yes)	1.079	0.471–2.474	.857	1.092	0.474–2.511	.837	1.001	0.434–2.307	.998	0.882	0.398–1.955	.757
Left atrial diameter (cm)	1.386	0.778–2.468	.268	1.388	0.780–2.470	.265	1.343	0.747–2.415	.324	1.281	0.701–2.342	.421
AHRE ≥24 hrs	5.141	2.386–11.075	<.001	5.181	2.410–11.138	<.001	4.899	2.243–10.704	<.001	4.942	2.273–10.746	<.001
C_2HEST score	1.076	0.831–1.393	.578									
mC_2HEST score				1.069	0.807–1.416	.642						
HAVOC score							1.084	0.932–1.261	.295			
HAT_2CH_2 score										1.473	1.113–1.949	.007
	Model B1			**Model B2**			**Model B3**			**Model B4**		
Variables	**HR**	**95%CI**	***p***	**HR**	**95%CI**	***p***	**HR**	**95%CI**	***p***	**HR**	**95%CI**	***p***
Male gender	1.716	0.720–4.085	.223	1.702	0.712–4.071	.232	1.787	0.757–4.219	.185	1.700	0.719–4.020	.227
Sick sinus syndrome (yes)	1.079	0.125–9.293	.945	1.121	0.129–9.763	.917	1.175	0.136–10.160	.883	1.387	0.156–12.305	.769
Hyperlipidemia (yes)	2.568	0.312–21.122	.380	2.508	0.304–20.719	.393	2.371	0.286–19.621	.423	2.226	0.263–18.831	.463
Chronic kidney disease (yes)	1.240	0.542–2.836	.611	1.258	0.546–2.897	.590	1.254	0.562–2.801	.581	1.168	0.547–2.495	.688
Left atrial diameter (cm)	1.327	0.746–2.360	.335	1.333	0.751–2.368	.326	1.313	0.737–2.338	.355	1.268	0.699–2.299	.435
AHRE ≥6 mins	3.983	1.843–8.611	<.001	3.988	1.845–8.620	<.001	3.697	1.696–8.060	.001	3.576	1.651–7.747	.001
C_2HEST score	1.157	0.907–1.477	.239									
mC_2HEST score				1.157	0.884–1.514	.288						
HAVOC score							1.097	0.951–1.266	.202			
HAT_2CH_2 score										1.436	1.096–1.880	.009

Note: AHRE, atrial high-rate episodes; CHA_2DS_2-Vasc score, range from 0 to 9. History of heart failure, hypertension, diabetes, vascular disease, age 65–74 years, and female sex each is calculated as 1 point; 75 years or older and prior stroke, TIA, or thromboembolism each is calculated as 2 points; C_2HEST score, range from 0 to 8. C_2: CAD/COPD (1 point each); H: hypertension (1 point); E: elderly (age ≥ 75 years, 2 points); S: systolic HF (2 points); and T: thyroid disease (hyperthyroidism, 1 point); HAT_2CH_2 score, range from 0 to 7. Hypertension, 1 point; age >75 years, 1 point; stroke or transient ischemic attack, 2 points; chronic obstructive pulmonary disease, 1 point; heart failure, 2 points; HAVOC score, H: hypertension (2 points); A: age (age ≥75 years, 2 points); V: valvular heart disease (2 points), peripheral vascular disease (1 point); O: obesity (1 point); C: congestive heart failure (4 points) and coronary artery disease (2 points); mC_2HEST score, range from 0 to 8. C_2: CAD/COPD (1 point each); H: hypertension (1 point); E: elderly (age 65–74 years, 1 point; age ≥75 years, 2 points); S: systolic HF (2 points); and T: thyroid disease (hyperthyroidism, 1 point).

70.6%; specificity, 78.2%; AUC, 0.806; 95% CI, 0.722–0.889; $p < .001$) (Figure 1). The AF occurrence rate significantly increased (around 7 times) if patients with AHRE ≥9.3 minutes than AHRE <9.3 minutes (Figure 2).

4 | DISCUSSION

4.1 | Major finding

The main finding of this study is that five predicting models (CHA_2DS_2-VASc score, C_2HEST score, mCHEST score, HAT_2CH_2 score, and HAVOC score) for new AF, compared to AHRE ≥6 min or ≥24 h in a Taiwanese population with CIED and no history of AF, only HAT_2CH_2 score was the independent predictor. The optimal cutoff value of AHRE for subsequent AF was 9.3 min. These results suggest that if patients with CIED, closely monitoring AHRE occurrence and assessing the HAT_2CH_2 score is important.

4.2 | Are 5 predicting models independently predicting new AF in patients with CIED and without a history of AF?

The present study was conducted because of the performance of several predicting models (CHA_2DS_2-VASc score, C_2HEST score, mCHEST score, HAT_2CH_2 score, and HAVOC score) to predict new AF in patients with CIED and without a history of AF had not been well studied before. All variables and predicting models are listed in Table 1. Only hypertension and age ≥75 years are commonly used variables in all 5 systems. Among them, the CHA_2DS_2-VASc score is the most well-known and guideline-recommendation (Hindricks et al., 2021; January et al., 2019) one for risk-predicting systemic thromboembolic events in patients with non-valvular AF. Also regarding the HAT_2CH_2 score, C_2HEST score, mCHEST score, and HAVOC score, no study has been conducted for new AF prediction in patients with CIED and without a history of AF. To the best of our knowledge, the current study is the first one to reveal that AHRE ≥6 min or ≥24 h is better than these 5 predicting models, except for the HAT_2CH_2 score, to predict new AF in patients with CIED and without a history of AF and the area under the curve of ROC curve is adequate, 0.806. We did not compare other more complicated AF-prediction models, such as BASIC-AF score (Samaras et al., 2021) and CHARGE-AF score (Alonso et al., 2013). BASIC-AF score (Samaras et al., 2021) includes biomarkers (N-terminal pro-B-type natriuretic peptide and high-sensitivity troponin-T), echocardiographic parameter (left atrial volume index), and electrographic parameter (intraventricular conduction delay). High-cost biomarkers and skill-dependent echocardiographic parameters would limit the clinical use. CHARGE-AF score (Alonso et al., 2013) comprises big-measurement-change of systolic and diastolic blood pressure and for the only white race. Also, complicated calculation formula limits its clinical use.

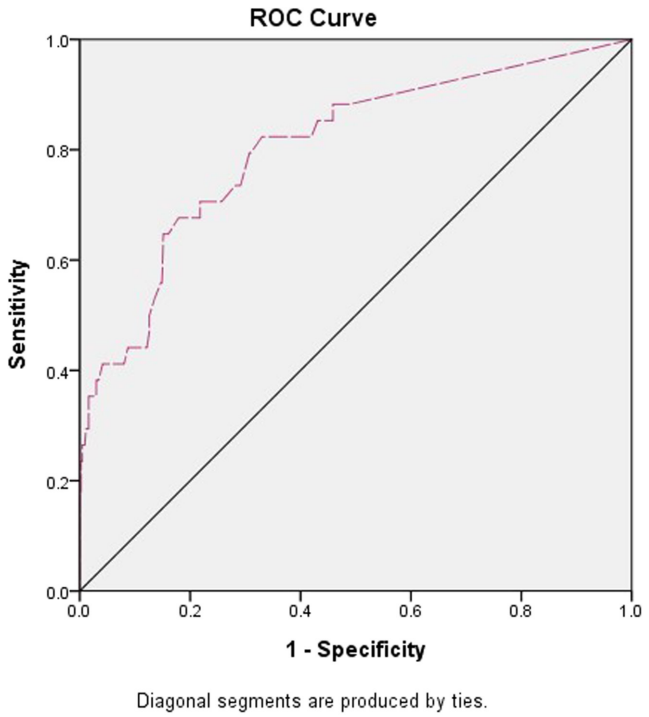

FIGURE 1 Receiver-operating characteristic curve analysis of the AHRE in patients with CIED with new atrial fibrillation. AHRE in minutes: Optimal cutoff value with the highest Youden index, 9.3 minutes; sensitivity, 70.6%; specificity, 78.2%; AUC, 0.806; 95% CI, 0.722–0.889; $p < .001$

Originally, the HAT_2CH_2 score has been validated to predict the development of post-operative AF (Emren et al., 2016). As shown in Table 1, the HAT_2CH_2 score includes chronic obstructive pulmonary disease (COPD) as one point (not included in the CHA_2DS_2-VASc score and HAVOC score), which highlights the varied impact of different diseases in new AF occurrence in patients with CIED based on our study results. COPD-related hypoxemia/hypercapnia, systemic inflammation and accelerated aging may promote increased sympathetic nerve activity, pulmonary vascular constriction, and structural modeling process, which all leads to increased automaticity and action potential shorting, and local conduction disturbances, therefore, increasing the risk of clinical AF (Simons et al., 2021). Additional prospective studies are required to elucidate the possible mechanisms underlying COPD-related AF risk, and then to identify effective preventive interventions.

4.3 | Why AHRE is a more powerful prediction surrogate for new AF?

Sustained AHRE ≥24 h detected by CIED has a similar risk of systemic thromboembolic events as clinical AF (Li, Pastori, et al., 2021), although AF could be only diagnosed by 12-lead electrocardiography or a 30-second electrocardiographic strip (Hindricks et al., 2021; January et al., 2019). Even, current guidelines recommend if patients with AHRE ≥6 minutes, more aggressive anti-thrombotic therapy

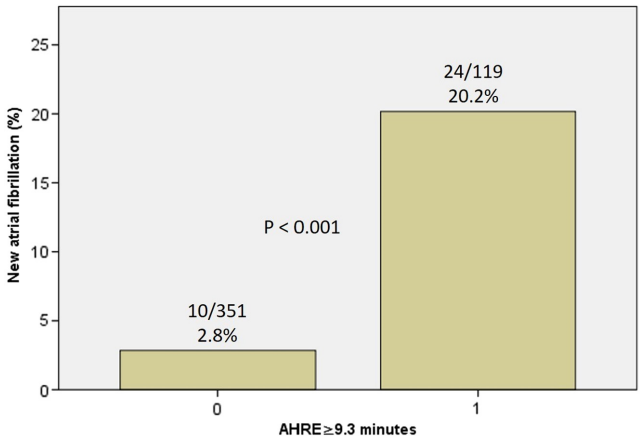

FIGURE 2 The occurrence rate of atrial fibrillation and AHRE ≥9.3 minutes or not. The occurrence rate of atrial fibrillation in patients with AHRE ≥9.3 minutes was 7 times without AHRE ≥9.3 minutes

should be considered (Hindricks et al., 2021; January et al., 2019). AHRE is closer to clinical AF than these 5 prediction models, which suggests that in patients with CIED, more closely monitoring of AHRE duration is needed. We also showed patients with AHRE ≥9.3 min have 7-time for new AF than patients with AHRE <9.3 min. Accurate reading of the signals of the atrial channel for AHRE recorded by CIED, excluding artifacts and atrial-oversensing, should be integrated into routine patient care in patients with CIED to early predict new AF.

In a recent review article (Doundoulakis, Gavriilaki, et al., 2021), eight retrospective or prospective studies including 4322 patients with CIED and without a documented AF history have been used in this meta-analysis. AHREs were defined as the atrial rate >170–225 beats per minute and duration >5–6 min (Doundoulakis, Gavriilaki, et al., 2021). The prevalence rate of AHREs was 10.1%–50.0% and the overall incidence ratio of AHRE cases per 100 person-years was 2.64–40.47. The key message (Doundoulakis, Gavriilaki, et al., 2021) was that patients with AHREs were 4.45 times more likely to develop clinical AF in the follow-up periods (mean duration: 1.6–6.6 years). They also concluded that the cutoff value for AHREs may be longer than 5–6 min, which was comparable with our data of 9.3 min. Based on this meta-analysis and our study, in patients with CIED without a history of AF, early detection of AHREs could be an acceptable predictor for new-onset AF.

The next step for these patients with AHREs ≥9.3 min, we suggested more AF detection using different tools should be arranged in daily practice and the current guidelines also recommended reassessing clinical AF regularly (Hindricks et al., 2021; January et al., 2019). Furthermore, AHREs have been viewed as a marker of atrial cardiomyopathy recently (Doundoulakis, Tsiachris, et al., 2021; Vitolo et al., 2022). Atrial cardiomyopathy could be a thromboembolic source even in patients without documented AF. According to the current guidelines, anticoagulants might be considered in patients with AHREs ≥1 h if CHA_2DS_2-VASc score ≥2 in male and ≥3 in female (Hindricks et al., 2021; January et al., 2019). Ongoing two trials (Kirchhof et al., 2017; Lopes et al., 2017) will give us the answer to deal with this situation. Based on our findings, more short-cutoff of AHREs 9.3-minute may promote primary physicians to early detection of AF and more stroke prevention algorithm will be used.

5 | LIMITATIONS

The present study has several limitations. First, this was a single-center, retrospective, observational study with a relatively small number of patients with CIED in a hospital setting, and all patients were Taiwanese. The results may not be generalizable to other populations. Prospective multicenter studies with larger samples are required to confirm the results of this study. Second, we did not compare all published prediction models and complicated predicting models, which may overemphasize the AHRE. Third, the different default settings of generators for AHRE detection may reduce the accuracy. However, we believe that the duration ≥6 min or 24 h could be ensured enough to exclude the possibility. Fourth, 50% of patients with new AF received anticoagulants at baseline in our study indicated probably that physicians used the AHRE ≥5–6 min or ≥24 h as new-onset AF. If high risks of systemic thromboembolic events (CHA_2DS_2-VASc score ≥1 in male or CHA_2DS_2-VASc score ≥2 in female), they will prescribe anticoagulants. Finally, few ICD/CRT patients preclude comment on the heart failure population.

6 | CONCLUSIONS

New AF is common in patients after CIED implantation and without a history of AF. The AHRE and HAT_2CH_2 scores are independent predictors for new AF in this population during mid-term follow-up. Our results suggest that closely monitoring AHRE occurrence and duration during the interrogation of CIED and assessing the HAT_2CH_2 score should be warranted.

AUTHOR CONTRIBUTIONS

Conception and design: J-YC; data acquisition: T-WC, W-DL; data analysis and interpretation: J-YC; statistical analysis: J-YC; drafting and finalizing the article: J-YC; critical revision of the article for important intellectual content: J-YC.

ACKNOWLEDGMENTS

The authors would like to thank Convergence CT for assistance with English editing of the manuscript.

CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Ju-Yi Chen, MD, PhD.

ETHICAL APPROVAL

IRB information: Approved by the Institutional Review Board of National Cheng Kung University Hospital (B-ER-108-278).

CONSENT TO PUBLICATION

Not applicable.

ORCID

Ju-Yi Chen https://orcid.org/0000-0003-2760-9978

REFERENCES

Alonso, A., Krijthe, B. P., Aspelund, T., Stepas, K. A., Pencina, M. J., Moser, C. B., Sinner, M. F., Sotoodehnia, N., Fontes, J. D., Janssens, A. C. J. W., Kronmal, R. A., Magnani, J. W., Witteman, J. C., Chamberlain, A. M., Lubitz, S. A., Schnabel, R. B., Agarwal, S. K., McManus, D. D., Ellinor, P. T., … Benjamin, E. J. (2013). Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: The CHARGE-AF consortium. *Journal of the American Heart Association*, *2*, e000102.

Doundoulakis, I., Gavriilaki, M., Tsiachris, D., Arsenos, P., Antoniou, C. K., Dimou, S., Soulaidopoulos, S., Farmakis, I., Akrivos, E., Stoiloudis, P., Notas, K., Kimiskidis, V. K., Giannakoulas, G., Paraskevaidis, S., Gatzoulis, K. A., & Tsioufis, K. (2021). Atrial high-rate episodes in patients with devices without a history of atrial fibrillation: A systematic review and meta-analysis. *Cardiovascular Drugs and Therapy*. https://doi.org/10.1007/s10557-021-07209-8

Doundoulakis, I., Tsiachris, D., Gatzoulis, K. A., Stefanadis, C., & Tsioufis, K. (2021). Atrial high rate episodes as a marker of atrial cardiomyopathy: In the quest of the holy grail. *European Journal of Internal Medicine*, *93*, 115–116.

Emren, V., Aldemir, M., Duygu, H., Kocabaş, U., Tecer, E., Cerit, L., & Erdil, N. (2016). Usefulness of HATCH score as a predictor of atrial fibrillation after coronary artery bypass graft. *Kardiologia Polska*, *74*, 749–753.

Hindricks, G., Potpara, T., Dagres, N., Arbelo, E., Bax, J. J., Blomström-Lundqvist, C., Boriani, G., Castella, M., Dan, G. A., Dilaveris, P. E., Fauchier, L., Filippatos, G., Kalman, J. M., la Meir, M., Lane, D. A., Lebeau, J. P., Lettino, M., Lip, G. Y. H., Pinto, F. J., … ESC Scientific Document Group. (2021). 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European heart rhythm association (EHRA) of the ESC. *European Heart Journal*, *42*, 373–498.

Hu, W. S., & Lin, C. L. (2017). Comparison of CHA_2DS_2-VASc, $CHADS_2$ and HATCH scores for the prediction of new-onset atrial fibrillation in cancer patients: A nationwide cohort study of 760,339 study participants with competing risk analysis. *Atherosclerosis*, *266*, 205–211.

Hu, W. S., & Lin, C. L. (2018). Role of CHA_2DS_2-VASc score in predicting new-onset atrial fibrillation in patients with type 2 diabetes mellitus with and without hyperosmolar hyperglycaemic state: Real-world data from a nationwide cohort. *BMJ Open*, *8*, e020065.

January, C. T., Wann, L. S., Calkins, H., Chen, L. Y., Cigarroa, J. E., Cleveland, J. C., Jr., Ellinor, P. T., Ezekowitz, M. D., Field, M. E., Furie, K. L., Heidenreich, P. A., Murray, K. T., Shea, J. B., Tracy, C. M., & Yancy, C. W. (2019). 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the Management of Patients with Atrial Fibrillation: A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. *Circulation*, *140*, e125–e151.

Kirchhof, P., Blank, B. F., Calvert, M., Camm, A. J., Chlouverakis, G., Diener, H. C., Goette, A., Huening, A., Lip, G. Y. H., Simantirakis, E., & Vardas, P. (2017). Probing oral anticoagulation in patients with atrial high rate episodes: Rationale and design of the non-vitamin K antagonist oral anticoagulants in patients with Atiral high rate episodes (NOAH-AFNET 6) trial. *American Heart Journal*, *190*, 12–18.

Li YG, Bai J, Zhou G, Li J, Wei Y, Sun L, Zu L, Liu S Refining age stratum of the C_2HEST score for predicting incident atrial fibrillation in a hospital-based Chinese population. *European Journal of Internal Medicine* 2021; *S0953-6205*(21)00137–0, 42.

Li, Y. G., Bisson, A., Bodin, A., Herbert, J., Grammatico-Guillon, L., Joung, B., Wang, Y. T., Lip, G. Y. H., & Fauchier, L. (2019). C_2 HEST score and prediction of incident atrial fibrillation in Poststroke patients: A French Nationwide study. *Journal of the American Heart Association*, *8*, e012546.

Li, Y. G., Pastori, D., Farcomeni, A., Yang, P. S., Jang, E., Joung, B., Wang, Y. T., Guo, Y. T., & Lip, G. Y. H. (2019). A simple clinical risk score (C_2HEST) for predicting incident atrial fibrillation in Asian subjects: Derivation in 471,446 Chinese subjects, with internal validation and external application in 451,199 Korean subjects. *Chest*, *155*, 510–518.

Li, Y. G., Pastori, D., Miyazawa, K., Shahid, F., & Lip, G. Y. H. (2021). Identifying at-risk patients for sustained atrial high-rate episodes using the C_2 HEST score: The West Birmingham atrial fibrillation project. *Journal of the American Heart Association*, *10*, e017519.

Lip, G. Y. H., Skjøth, F., Nielsen, P. B., & Larsen, T. B. (2020). Evaluation of the C_2 HEST risk score as a possible opportunistic screening tool for incident atrial fibrillation in a healthy population (from a Nationwide Danish cohort study). *The American Journal of Cardiology*, *125*, 48–54.

Lopes, R. D., Alings, M., Connolly, S. J., Beresh, H., Granger, C. B., Mazuecos, J. B., Boriani, G., Nielsen, J. C., Conen, D., Hohnloser, S. H., Mairesse, G. H., Mabo, P., Camm, A. J., & Healey, J. S. (2017). Rationale and design of the Apixaban for the reduction of Thromboembolism in patients with device-detected sub-clinical atrial fibrillation (ARTESiA) trial. *American Heart Journal*, *189*, 137–145.

Ntaios, G., Perlepe, K., Lambrou, D., Sirimarco, G., Strambo, D., Eskandari, A., Karagkiozi, E., Vemmou, A., Koroboki, E., Manios, E., Makaritsis, K., Vemmos, K., & Michel, P. (2020). External performance of the HAVOC score for the prediction of new incident atrial fibrillation. *Stroke*, *51*, 457–461.

Samaras, A., Kartas, A., Akrivos, E., Fotos, G., Dividis, G., Vasdeki, D., Vrana, E., Rampidis, G., Karvounis, H., Giannakoulas, G., & Tzikas, A. (2021). A novel prognostic tool to predict mortality in patients with atrial fibrillation: The BASIC-AF risk score. *Hellenic Journal of Cardiology*, *62*(5), 339–348.

Simons, S. O., Elliott, A., Sastry, M., Hendriks, J. M., Arzt, M., Rienstra, M., Kalman, J. M., Heidbuchel, H., Nattel, S., Wesseling, G., Schotten, U., van Gelder, I. C., Franssen, F. M. E., Sanders, P., Crijns, H. J. G. M., & Linz, D. (2021). Chronic obstructive pulmonary disease and atrial fibrillation: An interdisciplinary perspective. *European Heart Journal*, *42*, 532–540.

Vitolo, M., Imberti, J. F., Proietti, M., Lip, G. Y. H., & Boriani, G. (2022). Atrial high rate episodes as a marker of atrial cardiomyopathy: In the quest of the holy grail. Author's reply. *European Journal of Internal Medicine*, *98*, 115–116.

Zhao, S. X., Ziegler, P. D., Crawford, M. H., Kwong, C., Koehler, J. L., & Passman, R. S. (2019). Evaluation of a clinical score for predicting atrial fibrillation in cryptogenic stroke patients with insertable

cardiac monitors: Results from the CRYSTAL AF study. *Therapeutic Advances in Neurological Disorders*, *12*, 1756286419842698.

Zuo, M. L., Liu, S., Chan, K. H., Lau, K. K., Chong, B. H., Lam, K. F., Chan, Y. H., Lau, Y. F., Lip, G. Y. H., Lau, C. P., Tse, H. F., & Siu, C. W. (2013). The CHADS2 and CHA 2DS 2-VASc scores predict new occurrence of atrial fibrillation and ischemic stroke. *Journal of Interventional Cardiac Electrophysiology*, *37*, 47–54.

How to cite this article: Chen, J-Y, Chen, T-W, & Lu, W-D (2022). The performance of five models compared with atrial high rate episodes predicts new atrial fibrillation after cardiac implantable electronic devices implantation. *Annals of Noninvasive Electrocardiology*, *27*, e12978. https://doi.org/10.1111/anec.12978