HAT₂ CH₂ Score Performance Predicting Neurologic Events After Cardiac Implantable Electronic Device

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Abstract

The HAT₂CH₂ score has been evaluated for predicting new-onset atrial fibrillation in several clinical conditions, but never for adverse neurologic events. We aimed to evaluate the effectiveness of HAT₂CH₂ score in predicting neurologic events in patients with cardiac implantable electronic device (CIED), comparing with atrial high-rate episodes (AHRE). This case-control study enrolled 314 consecutive patients aged 18 years or older with CIED implantation between January 2015 and April 2021. Patient data were analyzed retrospectively. The primary endpoint was subsequent neurologic events (NE) after implantation. AHRE was defined as > 175 bpm (Medtronic®) lasting ≥ 30 seconds. Variables associated with independent risk of NE were identified using multivariate Cox regression analysis with time-dependent covariates. Patients' median age was 73 years and 61.8% of them were male. During follow-up (median 32 months), 18 NE occurred (incidence rate 2.15/100 patient-years, 95% CI 1.32-4.30). Multiple Cox regression analysis showed that the HAT₂CH₂ score (HR 2.972, 95% CI 2.143-4.123, $p < 0.001$) was an independent predictor for NE. Optimal HAT₂CH₂ score cutoff value was 3 with highest Youden index (AUC, 0.923; 95% CI, 0.881–0.966; $p < 0.001$). Significant increase was observed in NE occurrence rates using the HAT₂CH₂ score ($p < 0.001$). The HAT₂CH₂ score and episodes of AHRE lasting ≥ 1 minute are independent risk factors for NE in patients with CIED.

Introduction

The HAT₂CH₂ score, which comprises hypertension <1 point>, age >75 years <1 point>, stroke or transient ischemic attack <2 points>, chronic obstructive pulmonary disease [COPD] <1 point>, and heart failure <2 points>, was first developed in 2010 to identify patients likely to progress to sustained forms of atrial fibrillation (AF) in the near future ¹. Since then, numerous studies have been conducted to examine the prediction of AF in several clinical conditions, including post ablation for atrial flutter ², cancer patients ³, after coronary bypass surgery ⁴, patients receiving electric cardioversion ⁵, and emergency-department patients ⁶. Recently, the C₂HEST score ⁷ and mCHEST score ⁸ were also evaluated for predicting new AF, which revealed acceptable discriminating power. However, the predictive performance of the HAT₂CH₂ score, C₂HEST score and mCHEST score for new-onset atrial fibrillation and neurologic events (NE) in patients with cardiac implantable electronic device (CIED) was rarely evaluated.

The latest European Society of Cardiology (ESC) guidelines regarding non-valvular AF ⁹ state that AHRE > 5-6 minutes and > 180 bpm detected by CIED increase the risk for NE and clearly recommend that AHRE should be closely monitored and treated. The CHA₂DS₂-VASc score is also recommended for risk stratification of NE ¹⁰. However, the utility of CHA₂DS₂-VASc in non-valvular AF patients is debated and controversial, primarily because it is a vascular scoring system, which does not incorporate AF-related parameters ¹⁰. Meta-analysis showed that the discriminative power of the CHA₂DS₂-VASc score was only modest in predicting NE, and results were similar in the presence or absence of non-valvular AF ¹⁰. Also, the performance of several scoring systems (CHA₂DS₂-VASc score, HAT₂CH₂ score, C₂HEST score and

mCHEST score) and the optimal cutoff for AHRE duration to predict subsequent NE in patients with CIED have not been well studied previously. Therefore, more accurate NE prediction models are still needed for the non-valvular AF population and patients with CIED.

The present study aimed to investigate the performance of the HAT₂CH₂ score in predicting NE compared to AHRE in minutes and other scoring systems (CHA₂DS₂-VASc score, C₂HES₂ score and mCHEST score) in patients with CIED and without a history of AF.

Methods

Consecutive patients aged 18 years or older who underwent CIED implantation (Medtronic®: 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 included. All patient data were retrieved from hospital records and were analyzed retrospectively.

Ethical considerations

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 for data to be recorded for later publication in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Patient and Public Involvement statement

Patients and the public did not involve in the design, or conduct, or reporting, or dissemination plans of the research.

Data collection and definitions ¹¹

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-hour plasma glucose concentration ≥ 200 mg/dL from a 75-g oral glucose tolerance test, or taking antidiabetic medication. 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 was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/ min / 1.73 m² for at least 3 months. The primary endpoint was the occurrence of NE after the date of CIED implantation, including stroke or TIA diagnosed

by experienced neurologists. For each outcome, only the first event of that outcome in a specific subject was included. For the composite outcome, only the first event in a given patient was included.

AHRE were extracted from the devices via telemetry performed 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. AHRE was defined as heart rate >175 bpm and at least 30 seconds of atrial tachyarrhythmia recorded by the devices on any day during the study period.

Statistical analysis¹¹

Categorical variables are presented as percentages and continuous variables as means and standard deviations (mean $\pm$ SD) for normally distributed values or medians and interquartile interval (IQI) 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-test was used to analyze continuous variables. Survival was estimated by the Kaplan–Meier method, and differences in survival were evaluated with the log-rank test. Multivariate Cox regression analysis was used to identify variables associated with NE occurrence, reported as hazard ratios (HR) with 95% confidence intervals (CI). If the p value for any factor in univariable analysis was < 0.05, the parameter was entered into multivariable analysis. Because CHA₂DS₂-VASc scores, HASBLED scores, and HAT₂CH₂ scores overlapped many factors in univariate analysis, they were used as independent factors in multivariate Cox regression analysis. The receiver-operating characteristic (ROC) area under the curve (AUC) for AHRE and the HAT₂CH₂ score and the associated 95% confidence intervals (CI) were evaluated for associations with future NE after CIED implantation. The optimal cutoff values with the highest Youden index were chosen based on the results of ROC curve analysis and used to evaluate the associated values of AHRE in minutes and HAT₂CH₂ score for determining NE. For all comparisons, p < 0.05 was considered statistically significant. All data were analyzed using SPSS statistical package version 23.0 (SPSS Inc. Chicago, IL, USA).

Results

Between January 1, 2014 and April, 2021, a total of 453 consecutive patients receiving Medtronic CIED transplantation at National Cheng Kung University Hospital were recruited initially. Patients with previous AF (n=139) were excluded. The final analysis included data of 314 patients, of whom 18 had experienced NE.

The median follow-up period was 32 months after implantation of CIEDs. Table 1 shows patients' baseline demographic and clinical characteristics based on the occurrence of NE or not. Patients' median age was 73 years and 61.8% of patients were men. Types of CIEDs included dual chamber pacemaker (220, 70.1%),

dual chamber ICD (66, 21.0%), CRTP (23, 7.3%) and CRTD (5, 1.6%). The most common indication for CIED implantation was sick sinus syndrome (44.9%), followed by atrioventricular block (25.2%) and ventricular tachyarrhythmia (29.9%) (Table 1). Overall atrial pacing median percentages (25.0%) and ventricular pacing median percentages (1.9%) were noted. High percentages of hypertension (80.6%), hyperlipidemia (76.8%), and diabetes (45.2%) suggest relatively high risk of NE for the entire study cohort. Components of NE, incidence rates, and 95% CI are reported in Table 2. Overall, the total number of NE was 18 (incidence rate (IR) 2.15/100 patient-years, 95% CI 1.32-4.30) (Table 2).

Table 1
Baseline Characteristics of the Overall Study Group and with/without neurologic events

Variables	All Patients (n=314)	Neurologic events		Univariate P value
		Yes (N=18)	No (N=296)	
Age (years)	73 (62-81)	75 (68-83)	72 (61-81)	0.153
Gender				0.212
Male	194(61.8%)	14(77.8%)	180(60.8%)	
Female	120(38.2%)	4(22.2%)	116(39.2%)	
BMI ^a (kg/m ²)	24.6(22.5-26.3)	23.9(22.6-25.9)	24.6(22.4-26.3)	0.616
Device type				0.318
Dual chamber PM ^b	220(70.1%)	16(88.9%)	204(68.9%)	
Dual chamber ICD ^c	66(21.0%)	1(5.6%)	65(22.0%)	
CRT ^d	23(7.3%)	1(5.6%)	22(7.4%)	
CRTD ^e	5(1.6%)	0(0.0%)	5(1.7%)	
Primary Indication				0.178
Sinus node dysfunction	141(44.9%)	13(72.2%)	128(43.2%)	
Atrioventricular block	79(25.2%)	3(16.7%)	76(25.7%)	
Heart failure/VT ^f /VF ^g	94(29.9%)	2(11.2%)	92(9.1%)	
Atrial pacing (%)	25.0 (5.8-71.4)	18.5(1.2-87.9)	25.2(6.1-70.6)	0.922
Ventricular pacing (%)	1.9 (0.2-98.3)	14.4(0.2-75.1)	1.6(0.2-98.4)	0.522
Hypertension	253(80.6%)	17(94.4%)	236(79.7%)	0.215
Diabetes mellitus	142(45.2%)	14(77.8%)	128(43.2%)	0.006
Hyperlipidemia	241(76.8%)	18(100.0%)	223(75.3%)	0.010
Chronic obstructive pulmonary disease	14 (4.5%)	1(5.6%)	13(4.4%)	0.570
Prior stroke	19(6.1%)	6(33.3%)	13(4.4%)	<0.001
Prior myocardial infarction	57(18.2%)	5(27.8%)	52(17.6%)	0.275
Heart failure				0.462

Variables	All Patients (n=314)	Neurologic events		Univariate P value
		Yes (N=18)	No (N=296)	
Preserved LVEF ^h	44(14.0%)	2(11.1%)	42(14.2%)	
Reduced LVEF ^h	68(21.7%)	6(33.3%)	62(20.9%)	
None	202(64.3%)	10(55.6%)	192(64.9%)	
Chronic kidney disease	108(34.4%)	9(50.0%)	99(33.4%)	0.151
Chronic liver disease	15(4.8%)	1(5.6%)	14(4.7%)	0.596
Thyroid disease	22 (7.0%)	1(5.6%)	21(7.1%)	0.950
Hemoglobin (mg/dL)	12.0(11.0-13.0)	11.6(10.0-12.2)	12.0(11.0-13.0)	0.184
Platelet	206 (175-229)	201(156-244)	206(181-225)	0.738
Echo parameters				
LVEF ^h (%)	66 (53.8-73.0)	60.0 (44.3-72.0)	66.0 (54.0-73.0)	0.242
Mitral E/e'	11.0 (8.0-13.6)	11.0 (9.7-14.3)	11.0 (8.0-13.4)	0.614
LA ⁱ diameter (cm)	3.8 (3.2-4.1)	3.8 (3.5-4.4)	3.8 (3.2-4.1)	0.529
RV ^j systolic function (s', m/s)	12.0 (11.0-13.6)	12.0 (10.8-14.0)	12.0 (11.0-14.0)	0.849
Drug prescribed at baseline				
Antiplatelets	121(38.5%)	12(66.7%)	109(36.8%)	0.012
Anticoagulants	30(9.6%)	1(5.6%)	29(9.8%)	1.000
Beta blockers	122(38.9%)	6(33.3%)	116(39.2%)	0.621
Ivabradine	25(8.0%)	3(16.7%)	22(7.4%)	0.164
Amiodarone	58(18.5%)	2(11.1%)	56(18.9%)	0.543
Dronedarone	4(1.3%)	2(11.1%)	2(0.7%)	0.017
Flecainide	1(0.3%)	0(0.0%)	1(0.3%)	1.000
Propafenone	13(4.1%)	0(0.0%)	13(4.4%)	1.000
Digoxin	5(1.6%)	0(0.0%)	5(1.7%)	1.000
non-DHP CCBs ^k	12(3.8%)	0(0.0%)	12(4.1%)	1.000

Variables	All Patients (n=314)	Neurologic events		Univariate P value
		Yes (N=18)	No (N=296)	
RAAS ^l inhibitors	141(45.0%)	7(38.9%)	134(45.4%)	0.589
Diuretics	47(15.0%)	4(22.2%)	43(14.5%)	0.325
Statins	121(38.5%)	6(33.3%)	115(38.9%)	0.640
Metformin	50(15.9%)	3(16.7%)	47(15.9%)	1.000
SGLT2 ^m inhibitors	13(4.1%)	0(0.0%)	13(4.4%)	1.000
Follow-up duration (months)	32 (16-52)	23.5 (11.8-44.5)	34.0 (16.0-52.0)	0.069
CHA ₂ DS ₂ -VASc score ⁿ	3 (2-4)	4 (3-5)	3 (2-4)	0.005
HAS-BLED score ^o	2 (1-3)	3 (2-3)	2 (1-3)	0.002
C ₂ HES ^t score ^p	3 (1-3)	3 (1-4)	3 (1-3)	0.114
mC ₂ HES ^t score ^q	3 (2-3)	3(2-4)	3(1-3)	0.099
HAT ₂ CH ₂ score ^r	2 (1-3)	4 (3-5)	2 (1-3)	<0.001
AHRE ^s Duration (minutes)	0.9(0.0-30.0)	45.0(3.5-12893.7)	0.6(0.0-14.1)	<0.001

Variables	All Patients	Neurologic events		Univariate
	(n=314)	Yes	No	P value
		(N=18)	(N=296)	

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 $p < 0.05$. ^aBMI, body mass index; ^bPM, pacemaker; ^cICD, implantable cardioverter defibrillator; ^dCRTP, cardiac resynchronization therapy pacemaker; ^eCRTD, cardiac resynchronization therapy defibrillator; ^fVT, ventricular tachycardia; ^gVF, ventricular fibrillation; ^hLVEF, left ventricular ejection fraction; ⁱLA, left atrium; ^jRV, right ventricle; ^knon-DHP CCBs, non-dihydropyridine calcium channel blockers; ^lRAAS, renin-angiotensin-aldosterone system; ^mSGLT2, sodium glucose co-transporters 2; ⁿCHA₂DS₂-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; ^oHASBLED score, Range from 0 to 9. Point score is calculated as 1 point each for hypertension, abnormal kidney function, abnormal liver function, prior stroke, prior bleeding or bleeding predisposition, labile international normalized ratio (INR), older than 65 years, medication usage predisposing to bleeding, and alcohol use; ^pC₂HES₂ score, Range from 0 to 8. C₂: 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); ^qmC₂HES₂ score, Range from 0 to 8. C₂: 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); ^rHAT₂CH₂ 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; ^sAHRE, atrial high-rate episodes.

Table 2
Types and incidences of neurologic events

Types of neurologic events	Number	Incidence rate (100 patient-years)	95% CI ^a
Transient ischemic attack	11	1.31	0.81-2.63
Ischemic stroke	7	0.84	0.51-1.67
Total events	18	2.15	1.32-4.30
^a CI, confidence intervals			

Univariate analysis and multivariate Cox regression analysis to identify independent predictors of NE

Univariate analysis revealed that diabetes mellitus, hyperlipidemia, AHRE in minutes, CHA₂DS₂-VASc score, HAS-BLED score, and HAT₂CH₂ score were significantly associated with NE occurrence (Table 1).

Multivariate Cox regression analysis using model 1-3 (including CHA₂DS₂-VASc score, HASBLED score,

and HAT₂CH₂ score as confounders) showed that only HAT₂CH₂ score (HR 2.972, 95% CI 2.142 – 4.123, $p < 0.001$) was independently associated with NE (Table 3).

Table 3
Multivariate Cox regression analysis of neurologic events

Variables	Model 1			Model 2			Model 3		
	HR	95%CI	p	HR	95%CI	p	HR	95%CI	p
Diabetes mellitus (yes)				3.672	0.946-14.257	0.060	1.722	0.458-6.484	0.422
Hyperlipidemia (yes)	1.732	0.000-5.219	0.964	1.439	0.000-2.227	0.965	1.773	0.000-3.232	0.965
AHRE Duration (mins)	1.000	1.000-1.000	<0.001	1.000	1.000-1.000	<0.001	1.000	1.000-1.000	0.001
CHA ₂ DS ₂ -VASc score	1.468	1.000-2.158	0.050						
HAS-BLED score				1.327	0.813-2.166	0.258			
HAT ₂ CH ₂ score							2.972	2.142-4.123	<0.001

ROC-AUC determination of AHRE and HAT₂CH₂ score cutoff values as predictive factors for future NE and survival analysis

The optimal AHRE cutoff value predictive of future NE was 1 minute with the highest Youden index (sensitivity, 94.4%; specificity, 56.1%; AUC, 0.761; 95% CI, 0.664–0.857; $p < 0.001$) (Fig. 1). The optimal HAT₂CH₂ score cutoff value predictive of future NE was 3 with the highest Youden index (sensitivity, 100.0%; specificity, 73.0%; AUC, 0.923; 95% CI, 0.881–0.966; $p < 0.001$) (Fig. 1). Kaplan-Meier curves depict the different accumulative survival rates free from NE for HAT₂CH₂ score groups from 0-7. The survival curve shows that patients with HAT₂CH₂ scores of 4-7 had higher risk for NE development compared with those with HAT₂CH₂ scores of 0-3 (log-rank test, $P < 0.001$) (Fig. 2). The NE occurrence percentage increased significantly with HAT₂CH₂ scores from 0-2 (0%), 3 (9.8%), 4 (17.1%), 5 (37.5%), to 6-7 (100%) ($p < 0.001$) (Fig. 3). Included patients could be further classified as very low risk with HAT₂CH₂ scores of 0-2, low risk with HAT₂CH₂ scores of 3, medium risk with HAT₂CH₂ scores of 4, high risk with HAT₂CH₂ scores of 5, and very high risk with HAT₂CH₂ scores of 6-7.

Discussion

The main finding of the present study is that the HAT₂CH₂ score and AHRE are significantly and independently associated with NE in a Taiwanese population with CIED and no history of AF. The optimal

cutoff value of the HAT₂CH₂ score for subsequent NE was 3 and AHRE was 1 minute. These results suggest that comprehensive assessment of the HAT₂CH₂ score and AHRE in patients with CIEDs is essential to support early, aggressive therapy to prevent NE.

The leading scoring systems for predicting subsequent NE after CIED implantation include the CHA₂DS₂-VASc score, HAT₂CH₂ score, C₂HES₂T score and mCHEST score, often used in conjunction with the optimal cutoff for AHRE duration. Of these, the CHA₂DS₂-VASc score is a well-known and guideline-recommended measure⁹ for NE risk prediction. However, recent studies^{10,12} have reported that the CHA₂DS₂-VASc score has insufficient discriminative power for NE prediction. The meta-analysis of Siddiqi et al¹⁰ reviewed and analyzed 9 studies of patients (n = 453747) with non-valvular AF and 10 studies of patients (n = 138262) without non-valvular AF and found only a modest discriminative power using C-statistics. Similarly, Hu et al¹² used the Taiwan Health Insurance Research Database to select and evaluate a large group of patients with venous thromboembolism (n= 56996), finding that the area under the curve of ROC of CHA₂DS₂-VASc score for predicting NE was 0.66, which was also modest. In the present study, the area under the curve of ROC curve was 0.92, indicating a highly discriminative measure. To the best of our knowledge, the present study is the first to reveal that the HAT₂CH₂ score is superior to the CHA₂DS₂-VASc score, C₂HES₂T score and mCHEST score in the reliable prediction of NE in patients with CIED. Further, results of the present study support our proposed risk stratification system for NE as follows: HAT₂CH₂ scores of 0-2 indicate very low risk, HAT₂CH₂ scores of 3 indicate low risk, HAT₂CH₂ scores of 4 indicate medium risk, HAT₂CH₂ scores of 5 indicate high risk, and HAT₂CH₂ scores of 6-7 indicate very high risk. In future study, an external validation population is needed to ensure HAT₂CH₂ score accuracy in predicting NE in patients with CIED.

Results of the present study also demonstrated that the HAT₂CH₂ score (AUC of ROC 0.65) independently predicts new onset AF in this study population (data not shown). The HAT₂CH₂ score includes COPD as one point, rather than diabetes or vascular disease as one point in the CHA₂DS₂-VASc score, which highlights the varied impact of different diseases in NE in patients with CIED based on our study results. COPD-related systemic inflammation and oxidative stress may promote platelet hyperactivity and cerebral vascular dysfunction¹³, and COPD increases the risk of NE, independent of other shared risk factors of cardiovascular disease¹⁴. Smoking has been recognized as a major causative factor for COPD¹⁵ and also a leading cause of NE¹⁶. Additional prospective studies are required to elucidate the possible mechanisms underlying COPD-related NE risk, and then to identify effective preventive interventions.

Different cutoff values of AHRE have been proposed previously. One Japanese study even demonstrated that AHRE lasting $\geq$ 30 seconds was associated with increased risk of stroke¹⁷. That study enrolled 348 patients who received CIED from Medtronic (atrial rate > 175 beats/minutes), Abbott (atrial rate > 190 beats/minutes), and Biotronik (atrial rate > 200 beats/minutes). Atrial sensitivity was programmed to 0.5 mV with bipolar sensing. Another study¹⁸ enrolled 355 patients who received dual chamber pacemakers from Medtronic (atrial rate > 175 beats/minutes) and Biotronik (atrial rate > 200 beats/minutes) and atrial

sensitivity was programmed to 0.3 mV with Medtronic bipolar sensing and 0.2 mV with Biotronic bipolar sensing. That study also revealed that AHRE ≥ 2 minutes increased risk of NE. In the present study, all 314 patients included had been implanted with Medtronic CIED to prevent the different default settings for AHRE detection from affecting multivariate analysis; we concluded that the optimal AHRE cutoff was 1 minute for subsequent NE after CIED implantation. Even though the latest guidelines⁹ recommend that AHRE > 5-6 minutes and > 180 bpm detected by CIED increase the risk for NE, we still suggest that physicians should confirm the default setting of AHRE after patients have undergone CIED implantation.

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. As a result, causality cannot be inferred between AHRE and NE, and the presence of confounding factors cannot be denied. Also, the results may not be generalizable to other populations or locations. Second, this study did not investigate heart rhythms at the time of NE onset, which may not give a complete picture of individual patient conditions. Third, in this retrospective analysis of patient data, we could not confirm that patients had started anticoagulants due to CIED-detected AHRE, although these patients were not excluded because no significant differences were found between anticoagulants use and presence (1, 5.6%) or absence (29, 9.8%) of NE ($p = 1.000$), as shown in Table 1. Prospective multicenter studies with larger samples are required to confirm results of the present study.

Conclusions

The HAT₂CH₂ score and episodes of AHRE lasting ≥ 1 minute are independent risk factors for NE in patients with CIED during mid-term follow-up. When AHRE ≥ 1 minute is detected in patients with CIED, long-term monitoring is advisable to detect clinical AF as well as performing comprehensive assessment of NE risk using the HAT₂CH₂ score. Results of the present study suggest that early detection of AHRE ≥ 1 minute and calculation of the HAT₂CH₂ score in patients with CIED may be warranted to support early, aggressive therapy to prevent NE.

Abbreviations

AF, atrial fibrillation; AHRE, atrial high-rate episodes; AMI, acute myocardial infarction; CIED, cardiac implantable electronic device; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; NE, neurologic events; TIA, transient ischemic attacks

Declarations

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

Conflict-of-interest/financial disclosure: The authors declare no conflicts of interest.

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Disclosures:

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Consent to participate: All patients provided signed informed consent at the time of CIED implantation for their data to be recorded for later publication.

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Availability of data and material: Not applicable

Authors' 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.

References

1. de Vos, C. B. *et al.* Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. *J. Am. Coll. Cardiol*, **55** (8), 725–731 (2021).
2. Chen, K. *et al.* HATCH score in the prediction of new-onset atrial fibrillation after catheter ablation of typical atrial flutter. *Heart. Rhythm*, **12** (7), 1483–1489 (2015).
3. Hu, W. S. & Lin, C. L. Comparison of CHA₂DS₂-VASc, CHADS₂ 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 (2017).
4. Emren, V. *et al.* Usefulness of HATCH score as a predictor of atrial fibrillation after coronary artery bypass graft. *Kardiol. Pol*, **74** (8), 749–753 (2016).
5. Emren, S. V. *et al.* The role of HATCH score in predicting the success rate of sinus rhythm following electrical cardioversion of atrial fibrillation. *Kardiol. Pol*, **74** (9), 978–984 (2016).
6. Barrett, T. W., Self, W. H., Wasserman, B. S., McNaughton, C. D. & Darbar, D. Evaluating the HATCH score for predicting progression to sustained atrial fibrillation in ED patients with new atrial fibrillation. *Am. J. Emerg. Med*, **31** (5), 792–797 (2013).
7. Li, Y. G. *et al.* A Simple Clinical Risk Score (C2HEST) 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** (3), 510–518 (2019).

8. Li, Y. G. *et al.* Refining age stratum of the C2HEST score for predicting incident atrial fibrillation in a hospital-based Chinese population. *Eur. J. Intern. Med*, **90**, 37–42 (2021).
9. Hindricks, G. *et al.* 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. *Eur. Heart. J.* **42** (5), 373–498 (2021).)
10. Siddiqi, T. J. *et al.*. **Utility of the CHA2DS2-VASc score for predicting ischaemic stroke in patients with or without atrial fibrillation: a systematic review and meta-analysis.***Eur. J. Prev. Cardiol.*zwab018(2021).
11. Lu, W. D. & Chen, J. Y. Atrial highrate episodes and risk of major adverse cardiovascular events in patients with dual chamber permanent pacemakers: a retrospective study. *Sci. Rep*, **11** (1), 5753 (2021).)
12. Hu, W. S. & Lin, C. L. The predictive role of CHA2DS2-VASc score between venous thromboembolism and ischemic stroke: a large-scale cohort study. *J. Hypertens.* **36** (3), 628–633 (2018).)
13. Austin, V., Crack, P. J., Bozinovski, S., Miller, A. A. & Vlahos, R. COPD and stroke: are systemic inflammation and oxidative stress the missing links? *Clin. Sci. (Lond)*. **130** (13), 1039–1050 (2016).)
14. Kim, Y. R. *et al.* Stroke risk among patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis., **(Sao Paulo)**. **73**, e177 ((2018).)
15. Mannino, D. M. & Buist, A. S. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet*, **370** (9589), 765–773 (2007).
16. Shah, R. S. & Cole, J. W. Smoking and stroke: the more you smoke the more you stroke. *Expert. Rev. Cardiovasc. Ther*, **8** (7), 917–932 (2010).
17. Nakano, M. *et al.* Impact of atrial high-rate episodes on the risk of future stroke. *J. Cardiol*, **74** (2), 144–149 (2019).
18. Lu, W. D. & Chen, J. Y. The optimal cutoff of atrial high-rate episodes for neurological events in patients with dual chamber permanent pacemakers. *Clin. Cardiol*, **44** (6), 871–879 (2021).

Figures

Diagonal segments are produced by ties.

Figure 1

Receiver-operating characteristic curve analysis of AHRE and HAT2CH2 score for neurologic events
 Receiver-operating characteristic curve analysis of atrial high-rate episodes (minutes) and HAT2CH2 score in patients with CIED with subsequent neurologic events. Atrial high-rate episodes (minutes): optimal cutoff value with the highest Youden index, 1 minute; sensitivity, 94.4%; specificity, 56.1%; AUC, 0.761; 95% CI, 0.664–0.857; $p < 0.001$. HAT2CH2 score: optimal cutoff value with the highest Youden index, 3; sensitivity, 100.0%; specificity, 73.0%; AUC, 0.923; 95% CI, 0.881–0.966; $p < 0.001$. (CIED, cardiac implantable electronic device; CI, confidence interval; AUC, area under curve)

Figure 2

Event-free survival after cardiac implantable electronic devices implantation stratified by HAT2CH2 score. Kaplan-Meier curves depict the accumulative survival rates free from neurologic events regarding HAT2CH2 score (0-7, log-rank $p < 0.001$).

Figure 3

Neurologic event rate and HAT2CH2 score Neurologic events rate significantly increased with the HATCH score.