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Evaluation of a clinical score for predicting atrial fibrillation in cryptogenic stroke patients with insertable cardiac monitors: results from the CRYSTAL AF study

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Abstract

Background: The HAVOC score was previously developed to predict the risk of atrial fibrillation (AF) after cryptogenic stroke (CS) or transient ischemic attack (TIA). The purpose of this study was to apply the HAVOC score to patients who received insertable cardiac monitors (ICMs) in the CRYSTAL AF study.

Methods: All patients from the CRYSTAL AF study who received an ICM were included. HAVOC score (one point each for peripheral vascular disease and obesity with body mass index >30, two points each for hypertension, age \geq 75, valvular heart disease, and coronary artery disease, 4 points for congestive heart failure) was computed for all patients. The primary endpoint was AF detection by 12 months of ICM monitoring.

Results: A total of 214 patients who received ICM were included. AF was detected in 40 patients while the remaining 174 patients were AF negative. The HAVOC score was significantly higher among patients with AF [median 3.0 with interquartile range (IQR) 2–4] than those without AF [median 2.0 (IQR 0–3)], $p = 0.01$. AF increased significantly across the three HAVOC score groups: 11% in Group A (score 0–1), 18% in Group B (score 2–3), and 32% in Group C (score \geq 4) with $p = 0.02$.

Conclusions: The HAVOC score was shown in this post hoc analysis of CRYSTAL AF to successfully stratify AF risk post CS or TIA. The 11% AF rate in the lowest HAVOC score group highlights the significance of nontraditional contributors to AF and ischemic stroke.

Keywords: atrial fibrillation, cryptogenic stroke, insertable cardiac monitor, risk stratification, transient ischemic attack

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Introduction

Cryptogenic stroke (CS), defined as stroke of unknown etiology after exhaustive workup, makes up approximately one-third of all ischemic strokes.^{1,2} Up to 30% of CS is due to occult paroxysmal atrial fibrillation (AF), with a majority of these patients being over 65 years of age.^{3–5} Diagnosing AF after CS or transient ischemic attack (TIA) is important, as long-term oral anti-coagulation is very effective at preventing recurrent stroke in patients with AF,⁶ but has not been

proven superior to antiplatelet therapy in stroke patients without AF or other cardiac sources of embolism.⁷ As AF is often paroxysmal and asymptomatic, it can remain undiagnosed in many stroke patients despite standard of care ambulatory electrocardiographic monitoring.^{8,9} The CRYptogenic STroke And underLying Atrial Fibrillation Study (CRYSTAL AF),³ an international randomized controlled trial, reported the use of insertable cardiac monitors (ICMs) for long-term monitoring in post-CS patients. In CRYSTAL AF, 441 patients

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with CS were randomized to either standard monitoring or at least 12 months of monitoring with ICM. By 12 months, the AF detection rate in the ICM arm was 12.4% compared with only 2.0% in the standard monitoring arm. Results from the CRYSTAL AF³ and EMBRACE (which used 30-day event monitor) studies⁴ underscore the importance of prolonged monitoring for the detection of AF and reclassification of ischemic stroke subtype. A cost-effective analysis¹⁰ of ICMs demonstrated that compared with the standard of care, monitoring CS patients with an ICM was associated with greater reduction in recurrent stroke events and increased quality-adjusted life years, yet the benefit was modest (7.37 *versus* 7.22 years), and there was an overall higher cost associated with ICMs than standard of care. Treating neurologists and cardiologists are often left to their own judgment as to whom to refer for ICM post CS or TIA. To meet this clinical need to identify a subset of the CS/TIA population who could benefit most from prolonged rhythm monitoring, the HAVOC score¹¹ [abbreviation for seven common clinical variables: Hypertension, Age ≥ 75 years, Valvular heart disease, Vascular disease, Obesity with body mass index >30 , Congestive heart failure, and Coronary artery disease (CAD)] was constructed from a retrospective cohort of 9,589 patients ≥ 40 years old with CS/TIA based on data from the Stanford Translational Research Integrated Database Environment (STRIDE). The HAVOC score was able to successfully stratify patients into low-, intermediate-, and high-risk groups for AF detection post CS/TIA with an overall *c*-statistic of 0.77.

The aim of this study was to assess whether the HAVOC risk score could predict AF among CS/TIA patients in the CRYSTAL AF study who were continuously monitored by an ICM.

Methods

The CRYSTAL AF trial design has been described in detail elsewhere.^{3,12} The study protocol was approved by all relevant institutional review boards or ethics committees, and all patients provided written informed consent before randomization. The trial is registered under CRYSTAL AF (ClinicalTrials.gov identifier: NCT00924638).

In brief, the study included patients 40 years of age or older, with a CS or TIA (index event) within 90 days of study enrollment. The index

event was considered cryptogenic after 12-lead electrocardiogram (ECG), 24-hour ECG monitoring (Holter or telemetry), transesophageal echocardiography (TEE), screening for thrombophilic states (in patients younger than 55 years of age), and detailed vascular imaging were performed and no other etiology was found. Patients were excluded if they had known AF or atrial flutter, a permanent indication or contraindication for anticoagulation at enrollment, or an indication for implantation of a permanent pacemaker, implantable cardioverter defibrillator, or cardiac resynchronization therapy devices. The presence of patent foramen ovale (PFO) with or without atrial septal aneurysm was not an exclusion criterion *per se*, unless considered an indication for permanent anticoagulation at enrollment by the treating physicians. The primary endpoint was time to first detection of AF by 6 months, and the key secondary endpoint was time to first detection of AF by 12 months. AF was defined as an episode ≥ 30 s in duration of an irregular rhythm without discernible P waves. All first episodes of AF were adjudicated by an independent committee.

For this post hoc analysis of the CRYSTAL AF data, all patients who received ICMs from both arms of the trial were included. Age, sex, race, body mass index (BMI), type and severity of index event (TIA or ischemic stroke), CHADS₂ score, and presence of diabetes, hypertension, valvular disease, history of congestive heart failure were collected. The HAVOC score,¹¹ ranging between 0 and 14 points, incorporates commonly encountered clinical variables including hypertension (2 points), age (≥ 75 years, 2 points), valvular heart disease (2 points), peripheral vascular disease (1 point), obesity (BMI >30 , 1 point), congestive heart failure (4 points), and CAD (2 points), and was computed for all patients who received an ICM in the CRYSTAL AF study. Of note, vascular disease status was not collected at baseline for all CRYSTAL AF patients. As it carries only one point in HAVOC and has a strong correlation with CAD, patients with CAD were assigned one point for presumed vascular disease as well. The primary endpoint was AF detection by 12 months of study enrollment, which was the minimum follow-up duration specified by the trial protocol.

Data were presented as mean \pm standard deviation, median (interquartile range, IQR), or *n* (%). Independent *t* tests or Wilcoxon rank sum

(for nonparametric variables) were used to evaluate continuous variables, and chi-squared test or Fisher's exact test were used for categorical variables. The Cox proportional hazards model was used to assess the associations between AF detection and each component of the HAVOC score. Hazard ratio (HR) and 95% confidence intervals (CIs) were determined for each variable individually. Kaplan–Meier analysis of the HAVOC subgroups was performed. All analyses were done with SAS software version 9.4 (SAS Institute, Cary, NC, USA). *p* values less than 0.05 were considered statistically significant.

Results

In CRYSTAL AF, 447 patients were enrolled and 441 were randomized to the ICM arm ($n = 221$) or to the control arm ($n = 220$). As shown in Figure 1, 208 patients in the ICM arm and 6 patients in the control arm received an ICM. A total of 214 patients were therefore included in our analysis.

Table 1 describes the demographic and clinical information of this cohort of patients who received ICMs in the CRYSTAL AF study. AF patients were significantly older with higher CHADS₂ score than those without AF, whereas sex, race, BMI, index event characteristics were not significantly different between the AF positive *versus* AF negative patients.

The median HAVOC score was significantly higher among patients with AF ($n = 40$) than those without AF ($n = 174$): 3.0 (IQR 2–4) *versus* 2.0 (IQR 0–3) with $p = 0.01$.

The original HAVOC score (ranging from 0 to 14) stratified CS/TIA patients into low (score 0–4), medium (score 5–9), and high (score 10–14) categories with AF risk of 2.5%, 11.8%, and 24.9%, respectively.¹¹ The median HAVOC score for the current cohort of 214 patients from CRYSTAL AF, however, was 2 [IQR 1–3] with 89% of scores ≤ 4 . Given the clustering at the lower end of the score range, the cohort was split into the following three groups: Group A (score 0–1, $n = 66$), which was further subdivided into Group A₀ with score of 0 ($n = 51$) and Group A₁ with score of 1 ($n = 15$, all for obesity with BMI > 30), Group B (score 2–3, $n = 104$), and Group C (score ≥ 4 , $n = 44$). The distribution of

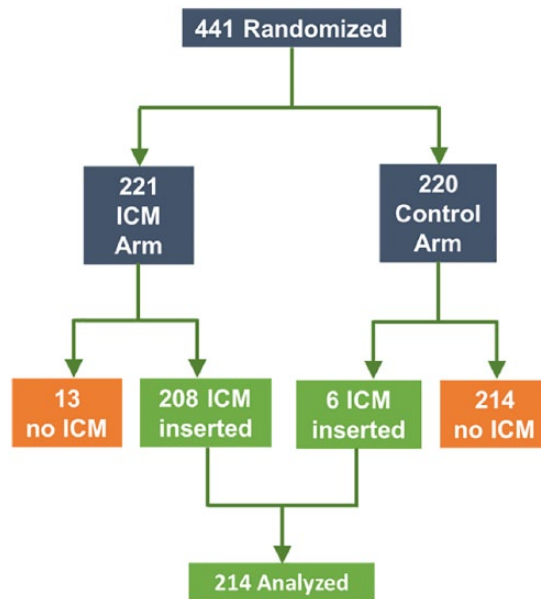


Figure 1. Study flowchart of patients who received insertable cardiac monitors (ICMs) in the CRYSTAL AF study.

each individual HAVOC risk score component by group is outlined in Table 2.

The proportion of patients with newly diagnosed AF after 12 months of ICM monitoring increased significantly across the HAVOC score groups (Figure 2): 11% in Group A, 18% in Group B, and 32% in Group C ($p = 0.02$). Within Group A₀, five patients were found to have AF (5/51, 9.8%). Two of the 15 patients in Group A₁ were also confirmed to have AF (2/15, 13.3%).

Predictive values of individual HAVOC score components for AF detection in CRYSTAL AF are listed in Table 3. Age was the only individual component that reached statistical significance (<0.05).

Given the overlapping nature of the HAVOC and CHADS₂ systems, we also compared the AF detection rate between these two scores. It is noted that the lower HAVOC categories have a similar rate of AF detection at 12 months (28.9% with HAVOC score ≤ 3) as the lower CHADS₂ categories (28% with CHADS₂ ≤ 3) (Table 4).

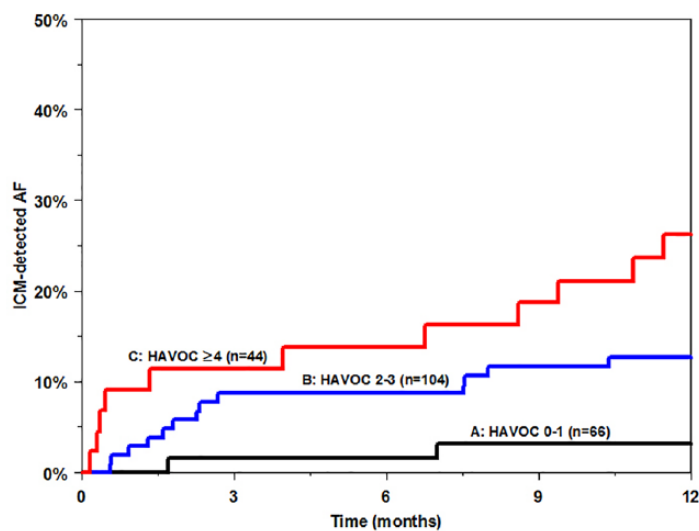
Using low risk defined as ≤ 3 for both scores, the test performance of HAVOC and CHADS₂ was compared (Table 5). Although numerically similar,

Table 1. Demographic and clinical information.

	All patients (n = 214)	Patients with AF (n = 40)	Patients without AF (n = 174)	p value
Age (years)	61.4 (11.2)	67.8 (9.3)	59.9 (11.1)	<0.001
Male gender	141 (66%)	28 (70%)	113 (65%)	0.54
Race				0.32
White	187 (87%)	33 (83%)	154 (89%)	
Other	12 (6%)	2 (5%)	10 (6%)	
N/A	15 (7%)	5 (13%)	10 (6%)	
BMI	28.3 (5.6)	28.4 (4.1)	28.3 (5.9)	0.87
Index event				0.45
Stroke	194 (91%)	35 (88%)	159 (91%)	
TIA	20 (9%)	5 (13%)	15 (9%)	
Modified Rankin				0.57
0	72 (34%)	15 (38%)	57 (33%)	
1	76 (36%)	13 (33%)	63 (36%)	
2	30 (14%)	7 (18%)	23 (13%)	
3	15 (7%)	4 (10%)	11 (6%)	
4	18 (8%)	1 (3%)	17 (10%)	
5	2 (1%)	0 (0%)	2 (1%)	
NIH Stroke Scale	1.6 (2.8)	1.4 (1.5)	1.6 (3.0)	0.47
CHADS ₂ score (mean)	3.0 (0.9)	3.4 (0.9)	2.9 (0.8)	0.003
2	65 (30.4%)	7 (18%)	58 (33%)	
3	93 (43.5%)	16 (40%)	77 (44%)	
4	45 (21.0%)	12 (30%)	33 (19%)	
5	10 (4.7%)	5 (13%)	5 (3%)	
6	1 (0.5%)	0 (0%)	1 (1%)	
Heart failure	7 (3%)	1 (3%)	6 (3%)	0.76
Hypertension	141 (66%)	30 (75%)	111 (64%)	0.18
Diabetes	34 (16%)	11 (28%)	23 (13%)	0.03
PR interval (ms)	169 (33)	184 (29)	166 (33)	0.001
PFO	49 (23%)	12 (30%)	37 (21%)	0.24
Values are n (%) or mean ± SD. AF, atrial fibrillation; BMI, body mass index; NIH, National Institutes of Health; PFO, patent foramen ovale; TIA, transient ischemic attack.				

Table 2. HAVOC risk score components by group.

HAVOC score	Hypertension	Age	Valvular heart disease	Vascular disease (peripheral)	Obesity	Congestive heart failure	Coronary artery disease
Group A (0–1) N = 66	0 (0%)	0 (0%)	0 (0%)	0 (0%)	15 (22.7%)	0 (0%)	0 (0%)
Group B (2–3) N = 104	98 (94.2%)	6 (5.8%)	0 (0%)	1 (1.0%)	47 (45.2%)	0 (0%)	0 (0%)
Group C (≥ 4) N = 44	43 (97.7%)	29 (65.9%)	6 (13.6%)	14 (31.8%)	11 (25.0%)	7 (15.9%)	14 (31.8%)
Overall N = 214	141 (65.9%)	35 (16.4%)	6 (2.8%)	15 (7.0%)	73 (34.1%)	7 (3.3%)	14 (6.5%)

**Figure 2.** Time-to-event analysis of insertable cardiac monitor (ICM)-detected atrial fibrillation (AF) based on HAVOC scores.

the numbers were too small (40 with positive AF out of 214 in the CRYSTAL AF cohort as compared with 482 positive AF out of 9,589 patients in the original HAVOC validation cohort¹¹) for a statistically meaningful comparison (Table 5).

Discussion

There is a compelling association between AF and ischemic stroke, resulting in substantial morbidity, mortality, reduction in quality of life, and burden on cost of care.^{13,14} Identifying a subgroup of patient with CS [also known as embolic stroke

of unknown source (ESUS), which is a highly heterogeneous group of patients¹⁵] at high risk for AF has become a priority in both the neurology and cardiology communities. However, AF is often paroxysmal and asymptomatic and is likely to go undetected with traditional monitoring methods, thus leaving many CS/TIA patients unprotected by oral anticoagulant therapy owing to the lack of a firm diagnosis of AF. Furthermore, empiric anticoagulation in patients with CS has not been shown to be efficacious for secondary stroke prevention in the WARSS,¹⁶ NAVIGATE ESUS,¹⁷ and the RE-SPECT ESUS trials.¹⁸ The

Table 3. Predictive value of individual HAVOC score components for atrial fibrillation detection in CRYSTAL AF.

Predictor	HR (95% CI)	p value
Hypertension	1.49 (0.71–3.16)	0.293
Age	3.00 (1.50–6.00)	0.002
Valvular heart disease	1.28 (0.29–5.62)	0.748
Vascular disease (peripheral)	N/A*	N/A*
Obesity	0.87 (0.43–1.76)	0.701
Congestive heart failure	0.32 (0.04–2.71)	0.297
Coronary artery disease	1.25 (0.36–4.37)	0.722

*Not included in the model owing to the high degree of correlation with coronary artery disease. CI, confidence interval; HR, hazard ratio.

Table 4. Comparison of the HAVOC and CHADS₂ categories in the CRYSTAL AF cohort.

	Number of patients	Number of patients with atrial fibrillation
HAVOC 0–1	66	7 (10.6%)
HAVOC 2–3	104	19 (18.3%)
HAVOC > 3	44	14 (31.8%)
CHADS ₂ = 2	65	7 (10.8%)
CHADS ₂ = 3	93	16 (17.2%)
CHADS ₂ > 3	56	17 (30.4%)

Table 5. Test performance of the HAVOC and CHADS₂ scores in the CRYSTAL AF cohort for AF prediction.

	HAVOC	CHADS ₂
Sensitivity	35.0%	42.5%
Specificity	82.8%	77.6%
PPV	31.8%	30.4%
NPV	84.7%	85.4%
Accuracy	73.8%	71.0%

Note: low risk was defined as ≤ 3 for both scores, high risk > 3 . NPV, negative predictive value; PPV, positive predictive value.

CRYSTAL AF study has presented convincing data in support of using ICMs to extend

monitoring duration in the CS population at high risk for recurrent events. The safety profile of the ICMs has also been shown to be favorable with very low incidence of adverse events in both trial data and real-world registries.¹⁹ Increasing spending pressure on healthcare systems, however, mandates judicious patient selection prior to applying new technologies to particular patient groups. Therefore, there is an urgent need to identify predictors of AF to stratify CS/TIA patients at high and low risk of AF, and to aid in deciding in whom ICM utilization would be most clinically beneficial as well as economically reasonable.

The retrospectively derived and internally validated HAVOC score appears well positioned to meet this purpose. The strengths of the HAVOC score, as compared with other risk-stratification schemes,^{20–26} are many, most notably the large

sample size used for its derivation, stringent model construction as well as easy clinical applicability. The CHADS₂ and CHA₂DS₂-VASc scores, both used in stratifying stroke risk in patients with documented AF, have also been studied to predict post-stroke AF occurrences, though with conflicting results.^{27,28} Indeed, when analyses were run using the CHADS₂ score, due to the overlapping nature between CHADS₂ and HAVOC (HAVOC shares three out of the five features of CHADS₂), it is not surprising that they perform similarly in this small cohort of 214 patients. Head-to-head comparison in the HAVOC validation study shows that HAVOC is statistically superior to CHA₂DS₂-VASc in the low-risk category in terms of test specificity and overall accuracy.¹¹ Furthermore, the HAVOC score introduces two risk factors that are not part of CHADS₂ but are well known to be intricately linked to AF, namely, obesity and nonrheumatic, nonprosthetic valvular heart disease. Use of CHADS₂ and CHA₂DS₂-VASc for the purpose of predicting AF in a post-CS population may be problematic as both give heavy weighting to prior stroke, which all CS patients have by definition. In addition, stroke is generally thought of as a consequence of AF, not a cause, and therefore may not be beneficial in predicting occult AF. The median HAVOC score was significantly higher among patients with AF as compared with those without AF. The HAVOC score was also able to stratify three groups of patients (Group A, B, and C) with increasing AF detection rates by 12 months of monitoring. Among the patients in the highest-risk group, Group C (HAVOC score ≥ 4), 32% were found to have AF. This rate more than doubled what was seen in the ICM arm of CRYSTAL AF (12.4%) at 12 months, thus supporting the use of the HAVOC score to further enrich the diagnostic yield of ICM in select groups of CS/TIA patients.

Of the individual components of the HAVOC score, age unsurprisingly emerged as the strongest factor associated with AF, consistent with previous reports.^{20–23,25,26} Obesity, unlike the other risk factors that rose steadily across the three subgroups, was distributed nonlinearly, with the highest percentage of obesity (45.2% of the 104 patients) in the mid-tier patients in Group B, *versus* 22.7% in Group A (low risk) and 25.0% in Group C (high risk). This observation may be simply due to sampling error given the relatively small size of this cohort (214 patients.) It is also

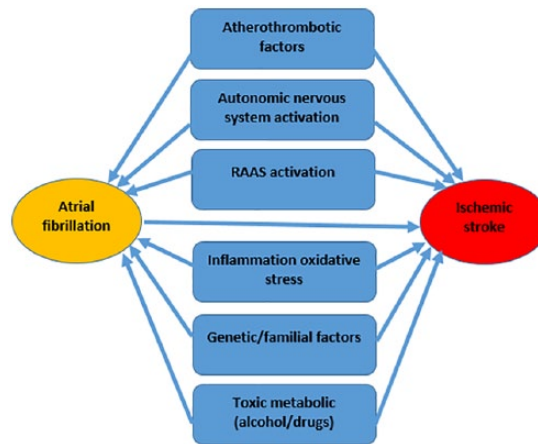


Figure 3. Schematic diagram depicting relationships between atrial fibrillation, ischemic stroke, and their contributing factors.

plausible that BMI lacks the discriminatory power to differentiate between body fat and lean mass and, hence, is not a faithful representative of obesity severity. Alternatively, the well-recognized yet poorly-understood phenomenon of the obesity paradox^{29,30} may also be at play here in that patients with the most atherosclerosis risk factors (Group C) paradoxically had a lower rate of obesity. This hypothesis warrants further elucidation.

Arguably the most intriguing finding from our analysis, however, resides within the lowest-risk group, Group A (Group A₀ and Group A₁). Five of the 51 patients (9.8%) in Group A₀ (with HAVOC score of 0) and 2/15 (13.3%) in Group A₁ (with HAVOC score of 1, all from obesity with BMI > 30) were AF positive. This finding therefore does not support the use of HAVOC score to exclude patients at the lower end of risk spectrum for consideration of ICMs. Most importantly, though, it highlights the concept that there may be non-traditional AF risk factors that do not fit into the conventional atherosclerosis-centric paradigm³¹: familial aggregation, ethnic differences, genetics,³² excess physical activity/endurance training,^{33,34} insomnia and frequent night-time awaking,³⁵ alcoholism and substance abuse,^{36,37} to name just a few. In addition, psychological factors such as anxiety, depression, and certain personality traits have been suggested to influence AF onset, progression, severity, and outcomes, but their role is far from clear.³⁸ As depicted schematically in Figure 3, all these factors may lead to ischemic stroke/

TIA directly³⁹ or indirectly via AF. As long as the AF prediction schemes, HAVOC score included, cover only part of the AF pathogenesis spectrum, model performance will remain in the moderate range and there will be a sizeable portion of cases that elude classification. It has been hypothesized that persons with characteristics that are known to confer risk for cardiovascular disease will experience the most intense monitoring, which could result in overestimation of the AF risk associated with these characteristics.⁴⁰ Our findings highlight the opposite side of this ‘detection bias’ in that patients with few or none of the traditional risk factors may be excluded from intense rhythm monitoring owing to perceived low risk. Future studies are needed to investigate these emerging AF risk factors (particularly the potentially modifiable yet largely overlooked neuro-hormonal factors), for the purpose of not only secondary prevention of ischemic stroke, but to combat the rising epidemic of AF in the nonstroke population in general.

Another notable finding is the relatively low overall HAVOC score in the CRYSTAL AF cohort, with 89% of patients having scores ≤ 4 . The relatively low-risk profile of CRYSTAL AF patients may partially explain the lower AF detection rate than reported previously.^{4,5,41,42} One potential application of the HAVOC score, therefore, may be the assessment of patient risk profiles between different studies, which may help put AF detection rates from different studies into appropriate context. It may also be considered for patient selection/categorization in prospective studies.

Study limitations

Our study has several weaknesses. First, this was a retrospective analysis of the CRYSTAL AF trial with the attendant limitations inherent with *post hoc* analyses. Second, the analysis was restricted to the first 12 months of follow up owing to incompleteness of device data at later time points for some patients. Valvular heart disease was a checkbox entry on the baseline case report form and was provided at the discretion of the enrolling physician, without formal definition. Not all risk factors for AF, including peripheral vascular disease, heavy alcohol use, exercise, sleep apnea, psychiatric condition, illicit drug use, or biological markers such as thyroid function or brain natriuretic peptide, could be analyzed because

they were either not collected systematically or not retrievable in a standardized fashion in CRYSTAL AF. Future prospective studies including these nontraditional features may further enhance AF risk stratification in the post CS/TIA population.

Conclusions

The HAVOC score was shown to successfully stratify AF detection in ICM recipients from the CRYSTAL AF cohort. Whereas our findings suggest that patients with moderate and high HAVOC scores might benefit most from long-term continuous monitoring with ICMs, CS/TIA patients with low HAVOC scores cannot afford to be overlooked, as emerging, non-atherosclerosis-based risk factors for AF pathogenesis warrant further scrutiny.

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Conflict of interest statement

PDZ and JLK are employees and shareholders of Medtronic, Inc. RSP reports speaker fees from Medtronic and Biotronik. SXZ, CK, and MHC report no relationships relevant to the contents of this paper to disclose.

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