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Incidence of stroke in patients with hypertrophic cardiomyopathy in stable sinus rhythm during long-term monitoring

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ABSTRACT

Introduction: Patients with hypertrophic cardiomyopathy (HCM) are at increased risk of stroke, but the incidence and factors associated with cardioembolic events in HCM patients without atrial fibrillation (AF) remain unresolved. We determined the incidence of stroke in patients in sinus rhythm (SR) monitored with a cardiac implantable electronic device (CIED).

Methods: All consecutive patients diagnosed with HCM and referred to CIED implantation with >16 years at diagnosis and ≥ 1 year follow-up post CIED implantation were retrospectively reviewed. Severe LA dilatation was defined as ≥48 mm. Patients were stratified by rhythm as: *Pre-existing AF* (AF present prior to CIED); De novo *AF* (AF present after CIED implantation); *SR*: no episodes of AF.

Results: Of 1651 patients, 185 (11.2%) implanted with a CIED were included (57% men, age: 54 ± 17 years). Baseline, *pre-existing AF* was present in 73 (39%) patients. Ischemic stroke was reported in 19 (10.3%, 1.78%/year) patients and was similar across the three groups (2.3%/year vs 1.1%/year vs 0.6%/year in patients in *SR* vs *pre-existing AF* vs de novo *AF*, respectively, $p = 0.235$).

In *SR* patients, a LAD≥48 mm posed the greatest risk of stroke (Hazard Ratio: 10.03,95% Confidence-Interval 2.79–16.01). At Cox multivariable analysis, after adjustment for oral anticoagulation, LA was independently associated with stroke while rhythm was not.

Conclusions: in HCM patients with CIED long-term monitoring and no prior history of AF, stroke rates were similar in those with de novo AF or stable SR. Severe LA dilatation was a powerful risk factor, irrespective of AF.

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List of abbreviations

AF	Atrial Fibrillation
CIED	Cardiac Implantable Electronic Device
HCM	Hypertrophic Cardiomyopathy
HR	Hazard Ratio
ICD	Implantable Cardioverter Defibrillator
IQR	Interquartile range
LAD	Left Atrial Dilatation
LVOT	Left Ventricular Outflow Tract
PM	Pacemaker
SAM	Systolic Anterior Motion
SR	Sinus Rhythm

1. Introduction

Patients with hypertrophic cardiomyopathy (HCM) are at increased risk of atrial fibrillation (AF) and ischemic stroke, especially at advanced stages of the disease [1,2]. Both AF and stroke are associated with a high burden of morbidity and disability, impaired quality of life, loss of productivity and adverse outcome [3,4]. Thromboembolic risk stratification in HCM is challenging as common risk scores like the CHA_2DS_2-VASc score have limited predictive power and high estimated false negative rates [5]. Moreover, despite a clear correlation of cardioembolic stroke with AF, limited data suggest the possibility of stroke occurring in patients in sinus rhythm, due to the hemodynamic consequences of severe left ventricular dysfunction associated with the disease. To date, however, the prevalence, predictors, and clinical impact of cardioembolic events in HCM patients without AF remain unresolved, due to the limited monitoring time reported in most studies and therefore due to the possibility of events occurring in the context of silent AF.

The possibility of cardio-embolic events in patients with sinus rhythm raises obvious implications regarding primary prophylaxis with oral anticoagulation beyond the canonical indications, as suggested in other settings (such as cardiac amyloidosis) and deserves consideration in a disease largely affecting young individuals with limited competing risks.

The only definite means of assessing this challenging issue is to observe patients on long term monitoring with implantable devices (pacemakers [PM], implantable cardioverter defibrillators [ICD] and loop recorders). Therefore, in the present study, we determined the incidence of stroke in patients in sinus rhythm monitored with a cardiac implantable electronic device (CIED) in a large Referral Center with >40 years of experience in HCM management. Since left atrial (LA) remodeling represents the obvious predisposing factor to cardio-embolic complications, and may reach massive proportions in HCM patients, particular care was taken in assessing risk of stroke with anatomical evidence of LA disease.

2. Methods

2.1. Patient selection

Clinical and instrumental data of patients with HCM implanted with CIEDs (either pacemakers [PM] or implantable cardioverter defibrillator [ICD]) from 2002 to 2019 were retrospectively reviewed. Patients were referred for ICD implantation either in primary prevention, if risk factors for sudden cardiac death were present (e.g. young age at diagnosis, increased septal thickness, left atrial diameter, obstructive physiology, family history of sudden cardiac death, unexplained syncope etc.) or in secondary prevention (cardiac arrest or equivalent) [6,7]. PM was implanted according to international pacing guidelines [8].

Inclusion criteria were diagnosis of HCM (defined by the presence of an increased asymmetric left ventricular wall thickness ≥ 15 mm in the absence of abnormal loading conditions [7,9]), age at diagnosis >16 years, presence of dual chamber devices, follow up ≥1 year and CIED interrogation performed regularly every 6 months (or less if clinically necessary) by senior EP physician at our institution and information regarding cerebrovascular events. Patients with subcutaneous ICD, critical carotid arteries stenoses, hemorrhagic strokes or neurologic impairment due to nonvascular causes (e.g., brain tumor) and HCM phenocopies (such as Anderson-Fabry disease or other storage or infiltrative conditions) were excluded from the analysis. The study was approved by the Careggi University Hospital Ethics Committee for Human Research (*Comitato Etico Area Vasta Centro*, Florence, Italy).

2.2. Follow up strategy

All patients were evaluated following a protocol standardized at our center, including baseline 12 lead ECG, and comprehensive two-dimensional (2D) and Doppler echocardiography. Peak instantaneous left ventricular outflow tract (LVOT) gradient, due to mitral valve systolic anterior motion (SAM) and mitral septal contact, was assessed with continuous Doppler under standard conditions. Exercise echocardiography was routinely performed since 2003. CIED interrogation was performed by the Electrophysiology Clinic at our center and reviewed by a senior electrophysiologist (PP, GR, LC) every 6 months or earlier if deemed clinically necessary. Each follow up visit was scheduled at 12 months or earlier if deemed clinically necessary. All medical documentation would be reviewed prior to scheduled appointments.

2.3. Type of stroke

Stroke was defined as transient or permanent neurologic impairment and disability due to vascular causes, including episodes lasting <24 h which were regarded as transient ischemic attacks (TIA) [10]. Upon medical visit, patients were interviewed and questioned about admissions to Emergency Room services and/or to medical wards. When possible, records and imaging were acquired and verified. For patients being admitted to at our institution (Careggi University Hospital), records for medical admissions were routinely reviewed through electronic charts from 2015. Given the retrospective nature of this study, as well as the well-recognized difficulties in establishing the etiology of ischemic stroke subtypes, no attempt was made to distinguish cardioembolic stroke from other ischemic subtypes in the present study [1].

2.4. Definition of atrial fibrillation

Pre-implantation AF was diagnosed according to guidelines with rhythm documentation with a surface electrocardiogram (ECG) > 30s. In patients with atrial high-rate episodes (AHRE) or subclinical AF detected by CIED, complete cardiovascular evaluation with ECG recording and closer follow up visits were performed. Only AHRE /subclinical AF lasting >5 min later adjudicated to be AF by senior electrophysiology specialists were included (derived from the observations of the ASSERT trial [11], REVEAL AF [12] and current European Society of Cardiology Guidelines [13]).

2.5. Echocardiography

Echocardiographic studies were performed with commercially available instruments. Left ventricular (LV) wall thickness, left atrial size and other echocardiographic dimensions were measured as previously described: in particular, given the prognostic importance of the anteroposterior LA diameter for patients with HCM [6,14] and its widespread availability in medical records, this was chosen as reference to assess LA remodeling for each patient [15].

2.6. Endpoint

The primary endpoint was the incidence of stroke/TIA at follow up after CIED implantation.

2.7. Statistical analysis

Continuous variables, reported as mean ± standard deviation (SD) or as median and interquartile range (IQR; for non-normal distributions), were compared between groups ("without stroke" vs "with stroke") with Student's *t*-test or non-parametric tests, as appropriate. Categorical variables, reported as percentages, were compared between groups with chi-squared test (or a Fisher's exact test when any expected cell count was <5).

In order to explore the role of left atrial diameter (LAD), patients were also stratified by LAD in two groups (<48 vs ≥48 mm) [16].

Based on CIED interrogation, patients were stratified by rhythm status and classified as follows:

- *Pre-existing AF*: Patients diagnosed with AF prior to CIED implantation;
- De novo *AF*: Senior EP adjudicated AF episodes after comprehensive evaluation of CIED interrogation, surface ECG and clinical evaluation;
- *Sinus rhythm* (SR): Senior EP adjudication of sinus rhythm.

For the present analysis, follow-up started at CIED implantation. Survival analysis was carried according to the Kaplan–Meier method to determine stroke-free survival and incidence rate of stroke was compared with standardized median CHA_2DS_2-VASc risk score [17].

Cox multivariable regression analysis adjusted for overlap effects, with stepwise backward deletion or redundant variables, was used to study candidate predictors potentially associated with stroke with a $p < 0.10$ at univariable analysis. A final two-sided *p*-value <0.05 was considered as statistically significant. Given the potential bias induced by sample power, de novo *AF* and *pre-existing AF* were combined for multivariable analysis. All analyses were performed using IBM SPSS Statistics for Macintosh, Version 27.0 (Armonk, NY: IBM Corp., USA) and GraphPad Prism v. 9.0.1.

3. Results

3.1. Incidence of stroke and AF at long-term monitoring

Of 1651 patients followed at our Unit, a total of 236 (14.6%) had been implanted with a CIED: 51 patients did not meet the inclusion criteria and were excluded. Overall, 185 (11.2%) were included in the study (57% men, mean age at implantation 54 ± 17 years, Table 1 and Fig. 1). At baseline, 73 (39%) patients had pre-existing AF.

A total of 19 (10.3%) patients experienced an ischemic stroke after CIED implantation, with annual rate of 1.78%/year. In particular:

−10 strokes occurred among 90 patients with CIED confirmed *sinus rhythm* (overall incidence: 11.1%, 2.3%/year): only 1/10 patient was anticoagulated because of recent heart surgery),

−8 strokes occurred among 73 patients with *pre-existing AF* (overall incidence: 9.7%, 1.2%/year): 4/8 patients were anticoagulated – one 24-year-old female patient with end-stage HCM had voluntarily suspended rivaroxaban 4 months prior, and.

−1 stroke occurred among 22 patients with de novo *AF* (overall incidence: 4.5%, 0.6%/year, no patients on anticoagulation therapy - stroke was the primary manifestation of AF).

Incidence was similar across the three rhythm groups (overall $p = 0.235$).

Long-term, after 5 [2–9] years from CIED implantation, de novo AF was detected in 24 (13%) individuals (sub-clinical $N = 10/24$), resulting in an average annual incidence rate of 4.1%/year: in 2 cases AF was detected 3 and 6 months after ischemic stroke. The remaining patients remained in stable sinus rhythm (Fig. 1).

Table 1
Baseline clinical characteristics of patients without and with stroke.

	No stroke *N* = 166	Stroke *N* = 19	p
Demographic features			
Age at implant	53 ± 17	54 ± 16	0.342
Gender (women), N (%)	75 (45.2)	7 (36.8)	0.560
NYHA III/IV, N (%)	43 (25.9)	3 (15.8)	0.411
Genetic Test*, N (%)	119 (71.7)	10 (52.6)	
1 P/LP variant, N (%)	62 (52.1)	4 (40.0)	0.680
>1 P/LP variant, N (%)	14 (11.8)	1 (10.0)	
Follow up duration after CIED Implantation, median [IQR]	5 [2–10]	5 [2–9]	0.688
Rhythm category at stroke			
Sinus Rhythm, N (%)	80 (48.1)	10 (52.6)	
AF prior to CIED implantation, N (%)	65 (39.2)	8 (42.1)	0.764
AF after CIED implantation, N (%)	21 (12.6)	1 (5.3)	
CHA_2DS_2-VASc, median [IQR]	2 [0–3]	2 [1–3]	0.741
CHA_2DS_2-VASc≥2	74 (44.5)	9 (47.3)	0.814
Heart Failure, N (%)	38 (22.9)	2 (10.5)	0.215
Hypertension, N (%)	51 (30.7)	6 (31.6)	0.939
Diabetes Mellitus, N (%)	31 (18.7)	1 (5.3)	0.143
Vascular disease**, N (%)	25 (15.1)	4 (21.1)	0.496
PM, N (%)	66 (39.8)	9 (47.4)	0.595
ICD, N (%)	122 (73.5)	16 (84.2)	0.347
Echocardiographic parameters			
Left atrial diameter (mm)	47 ± 8	53 ± 7	0.007
Left atrial diameter ≥ 48 mm, N (%)	84 (50.6)	17 (89.5)	0.019
IVS thickness	21 ± 6	19 ± 5	0.163
LVEDD (mm)	46 ± 7	49 ± 8	0.266
EF (%)	60 ± 10	57 ± 13	0.214
EF ≤ 50%, N (%)	23 (13.9)	4 (21.1)	0.401
HOCM, N (%)	26 (15.7)	1 (5.3)	0.224
Apical HCM, N (%)	19 (11.4)	3 (15.8)	0.580

AF: atrial fibrillation. CIED: cardiac implantable electronic device [PM: pacemaker. ICD: Implantable Cardioverter Defibrillator]. EF: ejection fraction. HOCM: hypertrophic obstructive cardiomyopathy. IQR: Interquartile range. IVS: interventricular septal. LVEDD: left ventricular end diastolic diameter. NYHA: New York Heart Association functional class.

* Available in 129 patients.

** Prior myocardial infarction, peripheral artery disease, or aortic plaque.

3.2. Characteristics of patients with and without stroke

Baseline characteristics of participants who did or did not report stroke, are presented in Table 1. Overall, the two study groups were similar: no differences were noted in terms of age at implantation, gender distribution, heart failure symptoms or CHA_2DS_2-VASc (mean CHA_2DS_2-VASc 1.7 ± 1.4 vs 1.8 ± 1.2, $p = 0.741$ in patient without vs with stroke, respectively). Furthermore, genetic testing was available for 129 (69.7%) patients. Of these, 66 (51.1%) had 1 pathogenic/likely pathogenic [P/LP] variant in a sarcomeric gene and 15 (11.6%) had >1 P/LP variant, with no differences among patients with or without stroke (Table 1, $p = 0.680$).

At echocardiographic evaluation, patients with stroke had larger left atria (53 ± 7 vs 47 ± 8, $p < 0.007$), with a higher prevalence of severe left atrial dilatation (≥48 mm: 90% vs 51%, $p = 0.019$). Severe LAD dilatation (LAD≥48 mm) was present in 101/185 patients and was more prevalent in patients with *pre-existing AF* ($N = 57$ [78%]) vs. de novo *AF* ($N = 10$ [42%]) vs. *sinus rhythm* ($N = 34$ [38%]) at last follow-up, $p < 0.0001$.

No other differences in terms of ejection fraction, obstructive physiology or apical phenotype were noted.

3.3. Factors associated with stroke

In patients with *Pre-existing AF* or de novo *AF*, only patients with LAD≥48 mm experienced stroke ($N_{\text{Pre-existing AF}} = 8/57$, $N_{\text{de novo AF}} = 1/10$, Fig. 1).

Among patients with stable *sinus rhythm*, those with LAD≥48 mm were at highest risk of stroke ($N = 8/34$ [23.5%] vs $N = 2/56$ [3.6%] in

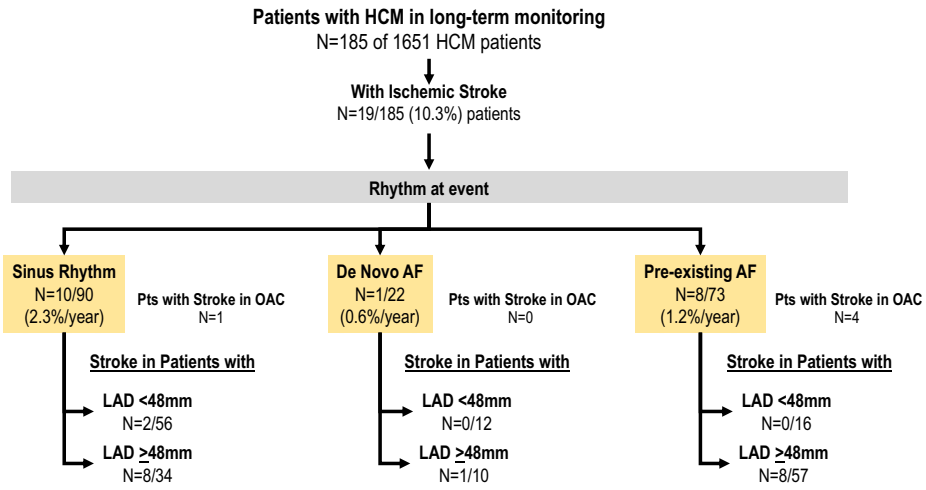

Fig. 1. Study population. Number of ischemic stroke episodes and final rhythm (sinus rhythm, de novo atrial fibrillation (de novo AF) and pre-existing AF. AF: atrial fibrillation. HCM: Hypertrophic Cardiomyopathy.

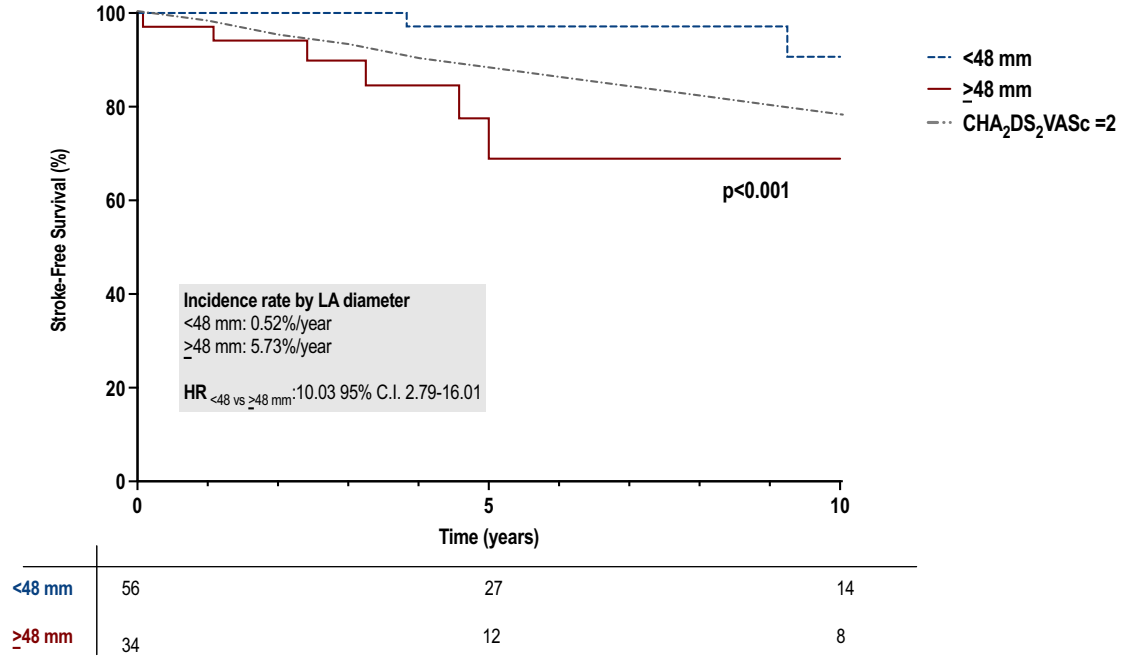

Fig. 2. Stroke-free survival analysis in patients with HCM in sinus rhythm by left atrial diameter (<48 vs ≥48 mm). HR: Hazard Ratio, LA: Left atrium.

Table 2
Factors associated with stroke at Cox multivariable regression analysis.

Variables	HR	95% Confidence Intervals	p
CHA_2DS_2-VASc (per Δ unit)	1.194	0.896–1.592	0.163
Use of Oral Anticoagulants (yes vs no)	0.126	0.040–0.364	0.008
Left atrial diameter (per Δ mm)	1.120	1.056–1.188	<0.001

HR: Hazard Ratio. Variables excluded at univariable analysis: hypertrophic obstructive cardiomyopathy, left ventricular ejection fraction and atrial fibrillation.

patients with baseline LAD ≥48 vs <48 mm, respectively) with an Odds $Ratio_{LAD\geq 48\ vs<48mm}$ 8.31 [95% C.I.: 1.74–27.01]; $p = 0.005$).

At Kaplan Meier survival analysis, patients with stable *sinus rhythm*, incidence rate of stroke was highest in those with dilated atria (5.73%/year vs. 0.52%/year, $p = 0.001$, for LAD≥48 vs <48 mm, respectively - Fig. 2). Hazard ratio (HR, calculated with the log-rank method) for stroke in patients in *sinus rhythm* with LAD≥48 mm was 10.03 (95% Confidence Interval (C.I.): 2.79–16.01).

At Cox multivariable regression analysis (Table 2), after adjustment for CHA_2DS_2-VASc score, oral anticoagulation, left atrial diameter (HR per mm increase: 1.108, 95% C.I. 1.046–1.173, $p < 0.001$) was associated with risk of stroke at follow up. Obstructive physiology, rhythm category and ejection fraction were excluded at univariable analysis.

4. Discussion

In HCM patients in long-term monitoring with CIED, stroke occurred with similar rates in patients with pre-existing AF (who were anticoagulated), and de novo AF or stable sinus rhythm (who were not). CHA_2DS_2-VASc was low on average and considerably underestimated risk; while no association with genotype was recorded (likely due to the sample size) [18], severe degrees of LA remodeling and dilatation consistently predicted risk of stroke in the three patient subsets. Overall,

incidence of stroke was >10% at follow up, considerably higher than previously reported in a series of 900 patients diagnosed with HCM (6% over a 7 year follow up period) [1]: our population was highly selected (referred to either PM or ICD), with a potentially higher prevalence of advanced disease stage and chamber remodeling, and atrial remodeling. Elevated filling pressures, potential atrial standstill and severely enlarged atria may be responsible for the almost doubled risk of stroke. The present data suggests that left atrial disease, reflected by severe anatomical remodeling, is both a necessary and sufficient cardioembolic prerequisite even in the absence of documented atrial standstill due to AF. Specifically, a cut-off of 48 mm in LA diameter, a known predictor of adverse outcome in HCM, represented a clinically simple and useful threshold to define cardio-embolic risk [16,19]. Among patients with stable sinus rhythm, risk was >10-fold higher in patients with LAD ≥48 mm compared to those <48 mm, and 2 to 4 times higher than previously reported in unselected HCM cohorts [1,19–21]. Notably, however, risk was not zero even below this threshold. Of particular note is the fact that patients with pre-existing AF at the time of CIED implantation did not appear at higher cardioembolic risk, and rather showed a trend towards risk reduction, compared with the other two subgroups, despite longer duration of disease and greater LA size. This finding indirectly but strongly supports the efficacy of anticoagulation in HCM patients with known AF [22]. Indeed, oral anticoagulation independent of CHA_2DS_2-VASc is now an established principle in the management of HCM [13]. However, our findings have additional, novel implications for potential broadening of primary prophylaxis of cardio-embolic events in this disease. In the presence of severe LA disease characterized by marked dilatation (exceeding 48 mm) and dysfunction [23] consideration for oral anticoagulation should be given even in presence of stable sinus rhythm. A similar concept is emerging also in other diseases such as amyloidosis, and is consistent with recent literature suggesting that AF is only an additional risk factor for cardio-embolism and no longer its sine-qua-non [24–29]. While we cannot advocate systematic implementation of prophylaxis in all such patients, given the as yet unknown risk/benefit ratio in large HCM populations, our experience suggests that waiting for AF to manifest may expose patients to risk even in when rhythm is constantly monitored by CIED, allowing timely recognition of the arrhythmia. Indeed, because HCM hearts seem to develop AF only when LA is severely dilated, AF is often a late marker of atrial disease. Future studies are needed to ascertain whether a more refined risk stratification involving individual propensity for thrombus formation (obesity [30], older age, moderate or severe mitral regurgitation and thrombophilia [31]) combined with evaluation of LA function (e.g. by global longitudinal strain [32]) may help improve prognostic accuracy and appropriateness in prophylaxis.

While cardioembolic complications may occur in patients in stable sinus rhythm, early identification of AF remains an important goal in HCM management, due to the risk of an acceleration of LA remodeling and hemodynamic decompensation. In our cohort, incidence of de novo AF was 4.1% per year. Compared to historical data from our cohort in patients without CIED (2% per year), long-term monitoring had a diagnostic yield almost 2-fold higher. Data from large registries on cryptogenic stroke have shown that diagnosis of AF may be challenging in real world practice and that patients without documented AF may have episodes of short paroxysmal arrhythmias which may be detected only after systemic embolic events [33,34]. Detection of silent AF, even of short duration can be as much as 7%/year in selected populations and is an element that makes anticoagulation absolutely indicated [35,36]. Therefore, CIED should be routinely checked for AF and use of ILR should be considered in high-risk patients without a device. Of note, a score to predict de novo AF was recently validated in a large HCM cohort [37].

We acknowledge several limitations of this study. This is a retrospective study and therefore its results should be interpreted in this context. By study design all patients had a CIED: such patients generally have more severe clinical features than those without a device. Therefore, these data cannot be considered representative of the overall HCM spectrum. Furthermore, detailed information on the type of oral anticoagulant (OAC) prescribed and the exact timing of the shift from Vitamin K antagonist to direct OAC was not always available. Hence, no possible interaction could be excluded.

Furthermore, while LA diameter can be considered a good proxy for LA function, we did not directly assess LA volume or function, which has been previously associated with hospitalization and outcome [23,38,39]: recently, an LA volume > 34 ml/m2 and a cut-off of left peak longitudinal strain of 15% were identified as potential tools to identify clusters of patients with HCM at higher risk of hospitalizations (both acute and programmed) [39] or AF and stroke [40]. Severe LAD and strain could be used as proxy of an advanced left atrial disease; this issue, however, requires also larger dedicated studies.

5. Conclusion

In HCM patients with CIED long-term monitoring and no prior history of AF, stroke occurred with similar rates in those with de novo AF or stable sinus rhythm. CHA_2DS_2-VASc was low and considerably underestimated risk, whereas severe LA dilatation was a powerful predictor of stroke, irrespective of rhythm category. These findings suggest the need for consideration of oral anticoagulation of a broader spectrum of HCM patients at high cardioembolic risk.

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Declaration of Competing Interest

None to disclose. The authors report no relationships that could be construed as a conflict of interest. All authors had access to the data and a role in writing the manuscript.

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