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EPIDEMIOLOGY AND CLINICAL CHARACTERISTICS OF ATRIAL FIBRILLATION IN PATIENTS WITH INHERITED HEART DISEASES

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Article type: Original- Clinical

NO CONFLICTS OF INTEREST

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jce.14346.

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ABSTRACT

Background: The prevalence and clinical course of atrial fibrillation (AF) in hypertrophic cardiomyopathy (HCM) is well described, though less so for other inherited cardiomyopathies (familial dilated cardiomyopathy [DCM], arrhythmogenic right ventricular cardiomyopathy [ARVC], left ventricular non-compaction [LVNC]); and inherited arrhythmia syndromes (long QT syndrome [LQTS], Brugada syndrome [BrS] or catecholaminergic polymorphic ventricular tachycardia [CPVT]). We examined frequency, clinical characteristics and AF-related management and outcomes amongst this patient population.

Methods: We retrospectively studied consecutive probands with inherited cardiomyopathy (n=962) and inherited arrhythmia syndromes (n=195) evaluated between 2002-2018.

Results: AF was observed in 5-31% of patients, with the highest frequency in HCM. Age of AF onset was 45.8 ± 21.9 years in the inherited arrhythmia syndromes compared to 53.3 ± 15.3 years in the inherited cardiomyopathies, with 4 CPVT patients developing AF at median age of 20 years. Overall, 11% of patients with AF had a transient ischemic attack or stroke of which a total of 80% were anticoagulated; with 48% of events occurring at a CHA_2DS_2-VASc <2. Amongst sarcomere-positive HCM, AF was independently associated with

age (OR 1.05, 95% CI 1.02-1.08, *p*=0.0014), left atrial (LA) area (OR 1.11, 95% CI 1.05-1.17, *p*=0.0005) and *MYH7* variants (OR 2.55, 95% CI 1.16-5.61, *p*=0.020).

Conclusion: Up to one third of inherited heart disease patients will develop AF. While common general population risk factors are key in patients with HCM, genotype is independently associated with AF. Amongst inherited arrhythmia syndromes, AF is less common, though often occurs below the age of 50 years.

Keywords: atrial fibrillation, inherited cardiomyopathy, inherited arrhythmia syndrome, sarcomere genes

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia affecting 1-4% of the general population,[1-3] and is responsible for substantial morbidity and mortality due to the increased risk of heart failure and stroke.[4] AF is generally classified according to episode duration, mode of termination and goals of management, describing various stages of AF from paroxysmal AF to persistent or permanent AF.[5] AF is associated with older age, however the incidence of AF in the young is increasing,[6] likely due to physical inactivity, obesity and other cardiovascular risk factors and comorbidities.[7] Increased risk of AF to first-degree relatives points to both polygenic and environmental causes but in rare cases, AF may present as a familial disorder with an autosomal dominant inheritance pattern.[8-10]

AF is common in hypertrophic cardiomyopathy (HCM), complicating the clinical course of disease in approximately 25% of patients, and in some cases may be the presenting feature.[11-13] There is marked clinical heterogeneity in HCM, and although variable penetrance and expressivity are hallmarks of the disease, recognition of sarcomere-positive and non-familial forms of disease as distinct sub-groups may further explain the observed spectrum of disease.[14, 15] There is also emerging data to suggest that a patient's underlying genetics may play an important role in AF development.[14, 16] We report the frequency of AF in patients with inherited cardiomyopathies and inherited arrhythmia syndromes, including factors associated with AF in those with sarcomere-positive HCM. Further, we examine the clinical characteristics and AF-related management and outcomes amongst this patient population.

METHODS

Study design and participants

This retrospective cohort study consisted of consecutive unrelated patients referred to the Hypertrophic Cardiomyopathy and Genetic Heart Disease Clinics at the Royal Prince Alfred Hospital, Sydney Australia between 2002 and 2018. All adult and pediatric patients with a clinical diagnosis of either an inherited cardiomyopathy (HCM, DCM, ARVC, LVNC) or inherited arrhythmia syndrome (LQTS, BrS or CPVT) were included. Eligibility criteria comprised probands who were the first affected family member to seek medical advice for their inherited heart disease in our clinic. Probands were excluded if AF data were not available, or if the first presentation was a sudden cardiac

death. A secondary analysis was also performed in HCM, including sarcomere-positive probands (pathogenic/likely pathogenic variant or variant of unknown significance where there was a positive family history of disease) and non-familial HCM probands (no family history of disease and no variant identified in a key sarcomere gene).[15] Those where the HCM sub-type was unknown were excluded from this analysis (Figure 1). The study was approved by the local human research ethics committee.

Clinical and demographic data

Clinical data were obtained from patient medical records and the Australian Genetic Heart Disease Registry.[17] Information collected included basic demographics; clinical history; outcomes; genetics; cardiac investigations; AF history (type, age of onset, presentation, hospitalisations); AF medications (aspirin, warfarin or new oral anticoagulants [NOACs]); AF interventions (cardioversion, AF ablation) and AF outcomes (transient ischemic attack [TIA] and stroke). Presence of comorbidities and medication use were adjudicated based on mention in the consulting physician report. CHA_2DS_2-VASc was calculated (one point for congestive heart failure, hypertension, age 65–74 years, diabetes mellitus, vascular disease and female gender; two points for age ≥ 75 years and previous stroke/TIA) to assess risk of stroke in patients with AF.

Clinical diagnosis of inherited heart disease and AF

Clinical diagnoses were made according to relevant disease guidelines.[18-22] AF was diagnosed if documented on electrocardiography (ECG), ambulatory

ECG or intracardiac electrogram from their implantable cardioverter defibrillator or permanent pacemaker. If a patient had an ICD, this is recorded in Table 1. In accordance with the 2012 American Heart Association AF guidelines,[23] paroxysmal AF was defined as AF which terminates spontaneously or with intervention within 7 days of onset and persistent AF was continuous AF that is sustained for >7 days. Echocardiographic characteristics were captured from the most recent transthoracic echocardiography report available. LA area was measured using planimetry of the right and left atrium in the apical four chamber view. All measurements were made by an experienced operator.

HCM genetic testing

Variants were identified by genetic testing performed either commercially or on a research basis. Variant classification was performed according to the *MYH7* modified American College of Medical Genetics and Genomics and Association of Molecular Pathologists (ACMG/AMP) criteria.[24] Rare variants with a minor allele frequency of ≤0.004% in the Exome Aggregation Consortium (ExAC) dataset; http://exac.broadinstitute.org/) in established HCM genes (*MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL2, MYL3, ACTC1*) were considered. Probands with causative variants in HCM phenocopies (*PRKAG2, LAMP2, GLA*) and atypical HCM phenotypes (*ACTN2, PLN, CACNA1C)* were excluded from further analysis.[25, 26]

Statistical Analysis

Statistical analysis was performed using Prism version 8.0 (GraphPad Software Inc., La Jolla, CA) and SAS Studio (SAS Institute Inc., Cary, NC). Descriptive analysis was performed to determine the frequency of AF for each inherited heart disease sub-group. The inherited cardiomyopathy and inherited arrhythmia syndrome patients were then compared. Categorical variables were given as a number and a percentage and were compared using χ^2 test. Continuous variables are expressed as mean ± SD and were compared using unpaired *t* test. Kaplan-Meier survival analysis with log-rank comparison was used to compare age of AF onset between sarcomere-positive and non-familial HCM. Univariable and multivariable logistic regression analyses were performed amongst sarcomere-positive HCM patients to determine independent factors associated with AF. This was performed using a backward stepwise approach, including variables with $p<0.1$ on univariable analysis and not clinically similar to another included variable, then removing non-significant variables. Finally, descriptive analysis of clinical attributes was carried out for patients with AF to describe the AF-related management and outcomes.

RESULTS

Patient characteristics

A total of 1283 unrelated probands were seen in the time period. After excluding those where AF status was missing (n=63), or first presentation was due to sudden cardiac death (n=63) there were 1157 probands, including 844

with HCM (n=271 sarcomere-positive HCM patients and n=254 non-familial HCM), 48 with DCM, 21 with ARVC, 49 with LVNC, 80 with LQTS, 96 with BrS and 19 with CPVT. The median follow-up time from diagnosis with an inherited heart disease was 6.4 (IQR 2.3-12.8). The mean age was 52.0 ± 17.2 years, 719 (62%) were male, mean age of inherited heart disease diagnosis was 43.3 ± 17.2 and mean maximum LA area was 25.6 ± 7.4cm2 (Table 1).

Frequency of AF in patients with inherited heart diseases

The frequency of AF across patient groups is shown in Figure 2. Overall, AF was most common in patients with HCM (n=257/844, 31%). The frequency of AF amongst patients with other inherited cardiomyopathies was: LVNC (n=9/49, 18%), DCM (n=8/48, 17%) and ARVC (n=3/21, 14%). Amongst patients with inherited arrhythmia syndromes AF was overall less frequent compared to the cardiomyopathies, however it was most commonly seen in those with CPVT (n=4/19, 21%), followed by BrS (n=8/96, 8%) and LQTS (n=4/80, 5%).

The key clinical differences between inherited cardiomyopathy and inherited arrhythmia syndromes are shown in Table 1. In comparison to patients with a cardiomyopathy, those with an arrhythmia syndrome were more likely to be younger ($p<0.0001$) and be younger at diagnosis of their inherited heart disease ($p=0.014$). Cardiomyopathy patients were overall more likely to have AF ($p<0.0001$), have a higher BMI ($p=0.015$), hypertension ($p<0.0001$), sleep apnoea ($p=0.033$), heart failure ($p=0.001$), coronary artery disease (CAD) ($p=0.024$) and more likely to be on betablockers at time of study inclusion

(P<0.0001). Further, patients with cardiomyopathies had a greater LA area (p<0.0001) than those with arrhythmia syndromes.

Clinical characteristics associated with AF in patients with sarcomere-positive HCM

There were 271 patients with sarcomere-positive HCM, of which 79 (29%) had AF, and 254 non-familial HCM patients, of which 82 (32%) had AF. Those with AF in the sarcomere-positive group had a mean age of 49.5 ± 16.2 and 155 (57%) were male, while those with AF and non-familial HCM had a mean age of 60.3 ± 15.6 and 184 (72%) were male. Kaplan-Meier survival analysis with log rank comparison showed AF onset occurs at a younger age in individuals with sarcomere-positive HCM compared to non-familial HCM (log rank p=0.007), with approximately 50% of AF having developed by the age of 50 years in the sarcomere-positive group (Figure 3). Of the 79 sarcomere-positive HCM patients with AF, 42 (53%) were males and mean age was 56.4 ± 14.9 years (Table 2). After adjusting for potential confounders of AF, age (OR 1.05; 95% CI 1.02-1.08; *p*=0.0014), LA area (OR 1.11; 95% CI 1.05-1.17; *p*=0.0005) and variants in the *MYH7* gene (OR 2.55; 95% CI 1.16-5.61; *p*=0.020) were independently associated with AF in sarcomere-positive HCM (Table 3).

AF-related management and outcomes

AF-related characteristics of patients with inherited cardiomyopathies are shown in Table 4. There were 257 HCM patients, 8 DCM patients, 3 ARVC patients and 9 LVNC patients identified with AF (total n=277). The mean or

median age at AF onset for each disease sub-group was as follows: ARVC 54.0 (IQR 26-64), HCM (53.8 ± 14.9 years), LVNC 47.0 (IQR 31-59) and DCM 43.5 (IQR 37.5-52.5), with an overall mean age of 53.3 ± 15.3 years (Table 4). Of cardiomyopathy patients with AF, 170 (67%) had paroxysmal AF and the remaining 85 (33%) were reported to have persistent AF. There were 143 (71%) who were symptomatic at AF onset. The mean CHA_2DS_2-VASc was 1.7 ± 1.4, with 49 (23%) scoring 0, 52 (24%) scoring 1 and 113 (53%) scoring ≥ 2. There were 119 (46%) patients on warfarin, 73 (28%) on a NOAC, 37 (14%) taking aspirin only and 30 (12%) were not anticoagulated (Table 4). There were 29/261 (11%) AF patients who had either a TIA or a stroke. There were 101 (50%) patients with AF-related hospitalisation, with 99 (41%) undergoing cardioversion and 35 (14%) an AF ablation.

AF-related characteristics of patients with inherited arrhythmia syndromes are shown in Table 4. AF was less common than in cardiomyopathies, only identified in 4 LQTS, 8 BrS and 4 CPVT patients (total n=16). The mean or median age of AF onset for each disease sub-group was as follows: LQTS 56.0 (IQR 45.0-66.5), BrS 52.0 (IQR 41-64) and for CPVT 20.0 (IQR 12-39) with an overall mean age of 45.8 ± 21.9 years (Table 4). Amongst AF patients with inherited arrhythmia syndromes, 15 (94%) patients had paroxysmal AF, while 1 (6%) had persistent AF. Ten (63%) patients were symptomatic at AF onset. Only 1 (6%) patient had a transient ischemic attack (TIA) or stroke. The mean CHA_2DS_2-VASc score for this group was 1.4 ± 1.5, with 6 (38%) scoring 0, 3 (19%) scoring 1 and 7 (44%) scoring ≥ 2. There were 4 (25%) patients taking warfarin, 2 (13%) a NOAC, 8 (50%) were taking aspirin only and 2 (13%) were not anticoagulated (Table 4). The 1 patient who had a

cerebrovascular event, had a CHA_2DS_2-VASc ≥ 2, was aged 70 years, was taking aspirin and had BrS. There were 6 (38%) patients with AF-related hospitalisations, with 5 (31%) undergoing cardioversion and 3 (19%) an AF ablation. A significant difference was observed in AF type between the two groups. Cardiomyopathy patients were more likely to have persistent AF, while arrhythmia syndrome patients were more likely to have paroxysmal AF (p=0.02).

DISCUSSION

The prevalence and clinical course of AF in patients with HCM has been previously described, but there are limited data available for other inherited cardiomyopathies and inherited arrhythmia syndromes likely as a result of the low number of patients in these sub-groups.[12, 27] We report the frequency, clinical characteristics and AF-related management and outcomes in patients with AF and inherited heart diseases. We show that AF occurs in 5-31% of patients, with the greatest frequency amongst those with HCM. Patients with CPVT also had a high risk of AF (21%) though due to the rarity of disease the sample size is small. While overall AF was relatively less common amongst patients with inherited arrhythmia syndromes, the mean age of AF onset was 46 years, with 4 CPVT patients developing AF at ages 5, 19, 21 and 57 years. Overall, 9% had a TIA or stroke and 26% of patients had a CHA_2DS_2-VASc < 2 with 80% anticoagulated. AF occurs at a younger age in those with sarcomere-positive HCM compared to non-familial HCM. Age, LA area and variants in the *MYH7* gene are significantly and independently associated with AF in sarcomere-positive HCM. Thus, patients with inherited heart disease

have an increased risk of developing AF and sub-typing HCM may in future allow for personalised management of AF.

In this study, the frequency of AF was up to 5 times that of the general population.[1-3] AF was most commonly observed in patients with HCM, and frequency was comparable to previously published studies, ranging from 20-30%.[11-13, 28] While the number of patients with AF in our study was modest, particularly amongst the inherited arrhythmia syndrome patient groups, descriptive analyses are able to offer some unique insights. In terms of outcomes, 38%-50% had at least one AF-related hospitalisation, and 6-10% suffered a cerebrovascular event. Our data are consistent with recent studies in HCM and in keeping with international guidelines, which do not support the use of CHA_2DS_2-VASc to predict stroke risk[13, 18, 29, 30] with 26% of events occurring at a CHA_2DS_2-VASc < 2. Further, the higher frequency of AF in patients with cardiomyopathies or inherited arrhythmia syndromes should be consider when implanting ICD devices and form part of the discussion in patients when considering potential risks of inappropriate shocks.

In the general population, development of AF is relatively uncommon amongst young people, with most studies demonstrating an increase in prevalence from the 6th decade of life.[31-33] In our patient groups, the mean age at onset of AF for inherited cardiomyopathies was 53 years, while for inherited arrhythmia syndromes it was 46 years. This suggests that patients with an underlying inherited heart disease are predisposed to develop AF at a younger age than that of the general population. This was especially the case for CPVT in which AF onset was found to occur at a mean of 26 years of age. While this result

should be viewed with caution due to the small number of CPVT patients identified with AF in our cohort (n=4), we suggest this young age of onset may be related to a common underlying mechanism of disease. Variants in the major genes associated with CPVT, cardiac ryanodine calcium release channel *(RYR2*) and cardiac calsequestrin (*CASQ2*)[27] result in abnormal calcium handling and these pathological changes may lead to rapid triggers of AF. In contrast, the development of AF in HCM is likely due to changes in atrial architecture and the development of an atriopathy as a result of diastolic dysfunction, myocardial ischemia and autonomic dysregulation.[12, 29] This hypothesis, differentiating structural versus electrical mechanisms, is supported by our data which show clear association between increased LA area and AF in the inherited cardiomyopathies, but not in the inherited arrhythmia syndromes. This may also explain the difference we observed in AF type between the two groups, with inherited cardiomyopathy patients more likely to have persistent AF, while patients with inherited arrhythmia syndromes were more likely to have paroxysmal AF.

Ho et al [14] recently reported insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe), a large multi-center comprehensive HCM cohort, and demonstrated that sarcomeric HCM is associated with significantly earlier onset of AF compared to disease not caused by sarcomere variants. Our results support this finding, with AF occurring at a significantly younger age in those with variants in sarcomere-related genes. Patients with identified sarcomere gene variants are therefore at an increased risk of developing AF earlier in life. Further, it has been demonstrated that variation in the *MYH7* gene is associated with incident AF, independent of

established risk factors of AF in the general population, age and LA size.[16] Our results likewise show AF is independently associated with age, LA area and *MYH7* variants compared to *MYBPC3*. While age and LA area are both predictors of AF in the general population, the presence of an underlying cardiomyopathy especially with an identified sarcomere gene variant in *MYH7* may tip the scales towards AF onset earlier than those without underlying inherited disease. Genotype may in future guide prevention and management of AF in HCM patients.

Our study has several limitations. First this was a retrospective study with a relatively low sample size for all diseases except HCM. We suggest that larger prospective studies of AF in inherited heart disease are necessary to ascertain the true impact of this arrhythmia. Missing clinical data were dealt with by case-wise drop out of variables in the HCM regression model. There is the possibility of under detection of asymptomatic AF episodes, which may lead to bias in the results, and potential over-detection in those with an ICD. We did not collect any data on cardioversion success rates or AF ablation outcomes and therefore this could not be assessed. While the majority of patients who experienced a TIA or stroke were anticoagulated, it is unknown whether their events occurred in follow-up or if they were the index event leading to the diagnosis of AF. Therefore, it is possible that some of these patients were not anticoagulated prior to their cerebrovascular event. Finally, there is growing evidence of the impact of lifestyle factors on AF development, which should be investigated in patients with inherited heart diseases in future studies.

CONCLUSION

Patients with inherited heart disease have an increased risk of developing AF compared to the general population. They are predisposed to develop AF earlier in life, and amongst the arrhythmia syndromes the mean AF onset was below 50 years of age. Sub-typing HCM may in future allow personalised patient management and therefore understanding how disruption of the sarcomere leads to earlier AF should be the focus of future research.

ACKNOWLEDGEMENTS

CS is the recipient of a National Health and Medical Research Council (NHMRC) Practitioner Fellowship (#1154992). JCI is the recipient of a Cardiac Society of Australia and New Zealand Research (CSANZ) Scholarship. JI is the recipient of an NHMRC Career Development Fellowship (#1162929). This work is funded in part by a Cardiac Society of Australia and New Zealand Boehringer Ingelheim Innovation Award.

DISCLOSURES

JI receives research grant support from MyoKardia, Inc.

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FIGURE LEGENDS

FIGURE 1. Flow diagram of study participants.

Abbreviations: AF, atrial fibrillation; SCD, sudden cardiac death; HCM, hypertrophic cardiomyopathy; DCM, familial dilated cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; LVNC, left ventricular non-compaction; LQTS, long QT syndrome; BrS; Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia.

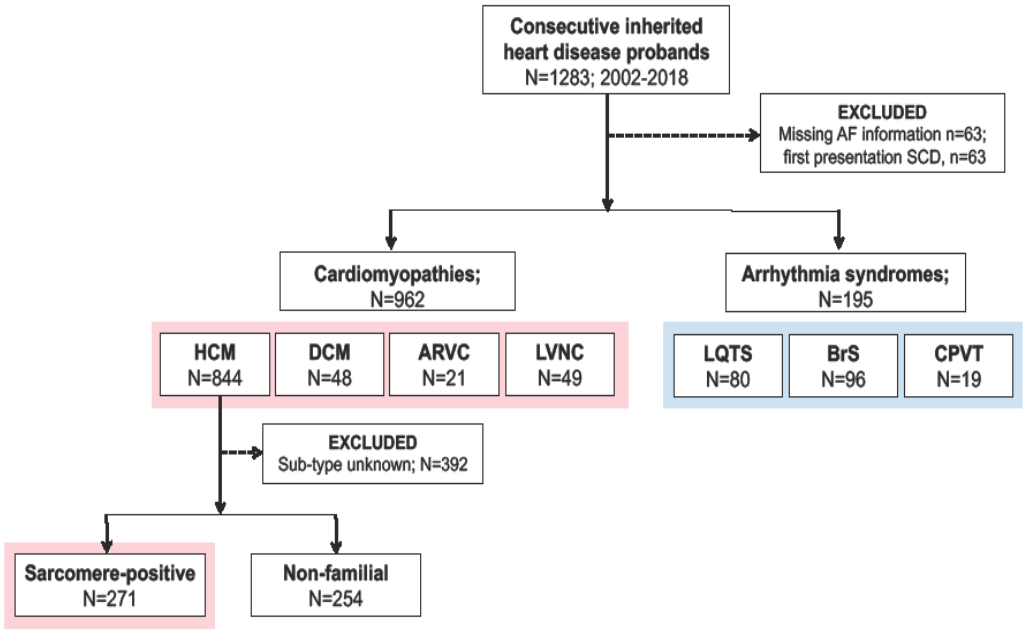


FIGURE 2. Frequency of AF in inherited cardiomyopathies and inherited arrhythmia syndrome patients.

Abbreviations: AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy; DCM, familial dilated cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; LVNC, left ventricular non-compaction; LQTS, long QT syndrome; BrS; Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia.

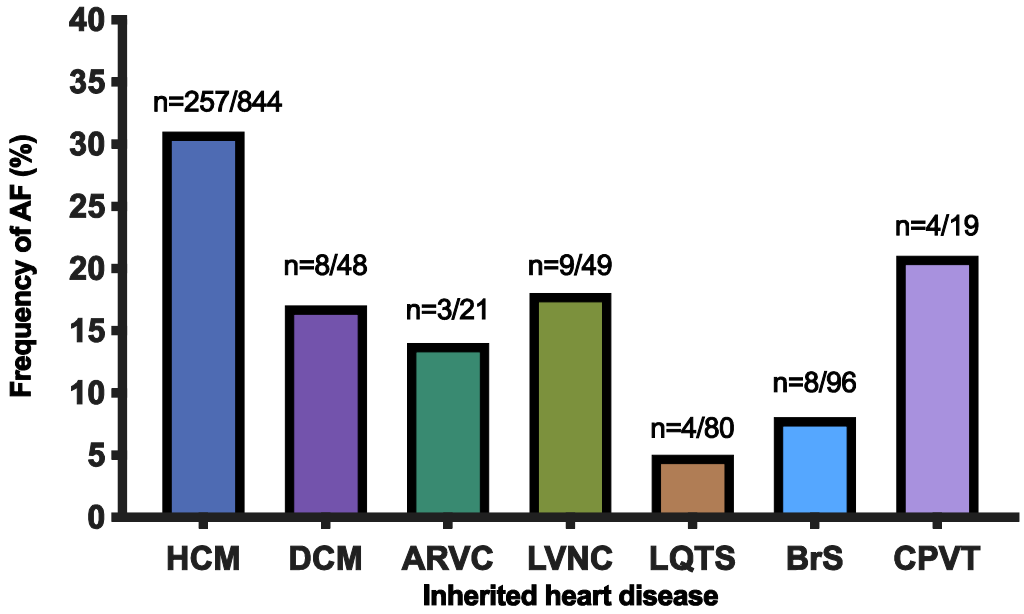
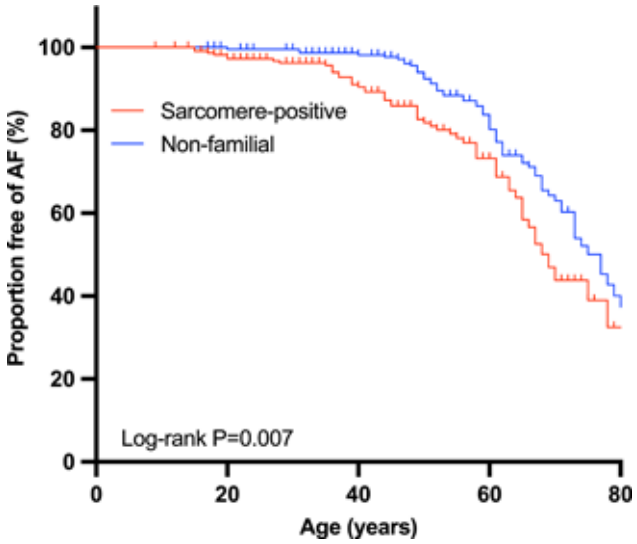


FIGURE 3. Kaplan-Meier survival plot showing that AF onset occurs at a younger age in those with sarcomere-positive HCM compared to non-familial HCM.



Abbreviations: AF, atrial fibrillation.

TABLE 1: Characteristics of inherited cardiomyopathies and inherited arrhythmia syndromes.

	Total cohort	Inherited Cardiomyopathy	Inherited Arrhythmia Syndrome	p-value
N	1157 (100)	962 (83.1)	195 (16.9)	
Age, years	52.0 ± 17.2	53.8 ± 16.9	43.0 ± 15.8	<0.001
Male sex	719 (62.1)	606 (63.0)	113 (58.0)	0.185
Follow-up time, years median (range)	6.4 (2.3-12.8)	7.5 (2.70-14.1)	3.0 (1.3-5.8)	<0.001
Symptomatic presentation	597 (57.7)	507 (57.4)	90 (59.2)	0.680
Age of IHD diagnosis, years	43.3 ± 17.2	43.8 ± 17.2	39.9 ± 16.3	0.014
Atrial fibrillation	293	277 (28.8)	16 (8.2)	<0.001
BMI, kg/m^2	28.0 ± 5.7	28.1 ± 5.7	25.9 ± 5.9	0.015
Hypertension	318 (29.1)	291 (31.7)	27 (15.4)	<0.001
Diabetes	93 (10.1)	83 (10.8)	10 (6.7)	0.123
Sleep apnoea	70 (7.7)	65 (8.6)	5 (3.4)	0.033
Heart failure (EF<50%)	66 (6.3)	65 (7.3)	1 (0.6)	0.001
CAD	65 (7.1)	61 (7.9)	4 (2.7)	0.024
Stroke/TIA	44 (4.6)	37 (4.6)	7 (4.7)	0.959
ICD	392 (35.9)	327 (35.4)	65 (38.2)	0.483
PPM	170 (15.9)	151 (16.6)	19 (12.0)	0.137
Betablockers	596 (56.8)	523 (59.6)	73 (42.2)	<0.001
Anti-arrhythmics	73 (7.0)	60 (6.9)	13 (7.5)	0.759
LA area, cm^2	25.6 ± 7.4	26.0 ± 7.4	19.8 ± 4.8	<0.001

Data shown as n (%) or mean ± SD.

Abbreviations: IHD, inherited heart disease; EF, ejection fraction; CAD, coronary artery disease; TIA, transient ischemic attack;

ICD, implantable cardioverter defibrillator; PPM, permanent pacemaker; LA area, left atrial area.

TABLE 2: Characteristics of sarcomere-positive HCM patients with and without atrial fibrillation (AF).

Characteristic		Total cohort	AF +	AF -	p-value
N		271	79	192	
Age (years)		49.5 ± 16.2	56.4 ± 14.9	46.5 ± 16.1	<.0001
Males		155 (57.2)	42 (53.2)	113 (58.9)	0.390
Age of diagnosis (years)		36.6 ± 16.5	38.6 ± 18.3	35.4 ± 15.7	0.151
Symptomatic presentation		138 (52.1)	45 (60.8)	93 (48.7)	0.076
Sarcomere gene	*MYBPC3*	150 (64.7)	36 (54.6)	114 (68.7)	0.085
	MYH7	82 (35.3)	30 (45.5)	52 (31.3)	
Non-sustained VT		73 (28.3)	26 (35.6)	47 (25.4)	0.101
LVOTO ever		87 (32.6)	33 (44.0)	54 (28.1)	0.013
Heart Failure		25 (9.5)	16 (21.9)	9 (4.8)	<.0001
SCD event		34 (12.9)	13 (17.8)	21 (11.0)	0.139
History of syncope		72 (29.6)	24 (34.3)	48 (27.8)	0.312
BMI (kg/m2)		27.4 ± 5.9	27.8 ± 6.1	27.2 ± 5.9	0.450
Hypertension		56 (20.8)	24 (30.8)	32 (16.8)	0.010
Diabetes		24 (9.9)	11 (15.1)	13 (7.7)	0.078
Sleep apnoea		12 (5.0)	7 (9.7)	5 (3.0)	0.028
Coronary artery disease		12 (5.0)	5 (6.9)	6 (4.1)	0.373
Stroke/TIA		17 (6.8)	10 (13.7)	6 (3.5)	0.003
ICD		150 (56.0)	49 (64.5)	101 (52.6)	0.078
PPM		57 (21.4)	22 (29.3)	35 (29.3)	0.047
Beta-blockers		154 (60.0)	60 (81.1)	94 (51.4)	<0.0001
Anti-arrhythmics		21 (8.2)	14 (18.9)	7 (3.9)	<0.0001
Echocardiography					
Maximum wall thickness (mm)		20.5 ± 5.8	20.1 ± 5.4	20.7 ± 5.9	0.441

Posterior wall thickness (mm)		10.6 ± 2.7	11.3 ± 2.8	10.4 ± 2.6	0.012
Septal morphology	Asymmetric	245 (94.2)	67 (91.8)	178 (95.2)	0.003
	Apical	7 (2.7)	0 (0)	7 (3.7)	
	Concentric	8 (3.1)	6 (8.2)	2 (1.1)	
Maximum gradient (mmHg)		21.7 ± 27.9	26.0 ± 30.3	20.8 ± 27.4	0.223
LVEDD (mm)		43.8 ± 7.8	44.1 ± 8.1	43.6 ± 7.5	0.636
LVESD (mm)		27.6 ± 7.9	28.3 ± 8.5	27.3 ± 7.6	0.337
LA area (cm^2)		26.9 ± 7.3	30.5 ± 8.1	25.4 ± 6.4	<0.0001

Data shown as n (%) or mean ± SD.

Abbreviations: AF, atrial fibrillation; LVOTO, left ventricular outflow tract obstruction; SCD, sudden cardiac death; BMI, body mass index; TIA, transient ischemic attack; ICD, implantable cardioverter defibrillator; PPM, permanent pacemaker; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LA, left atrial.

TABLE 3: Unadjusted and adjusted factors associated with atrial fibrillation (AF) in sarcomere-positive hypertrophic cardiomyopathy (HCM).

	Univariable analyses			**Multivariable analyses** N=57		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age (years)	1.04	1.02-1.06	<.0001	1.05	1.02-1.08	0.0014
Male sex	0.79	0.47-1.34	0.390	0.71	0.33-1.53	0.378
MYH7 variant	1.83	1.02-3.28	0.044	2.55	1.16-5.61	0.020
NSVT	1.62	0.91-2.91	0.103			
LVOTO ever	2.01	1.15-3.49	0.014	1.93	0.85-4.35	0.115
Heart Failure (EF <50%)	5.61	2.35-13.39	0.0001			

Diabetes	2.13	0.91-5.01	0.083			
Sleep apnoea	3.51	1.08-11.46	0.038			
Coronary artery disease	1.70	0.52-5.55	0.378			
History of syncope	1.36	0.75-2.46	0.313			
Hypertension	2.21	1.20-4.08	0.0112	1.47	0.58-3.75	0.417
BMI (kg/m2)	1.02	0.97-1.07	0.449			
Maximum wall thickness (mm)	0.98	0.94-1.03	0.440			
Posterior wall thickness (mm)	1.13	1.03-1.25	0.014	0.99	0.84-1.15	0.867
LVEDD (mm)	1.01	0.97-1.04	0.635			
LVESD (mm)	1.02	0.98-1.05	0.337			
LA area (cm^2)	1.10	1.06-1.15	<0.0001	1.11	1.05-1.17	0.0005

Abbreviations: CI, confidence interval; OR, odds ratio; NSVT, non-sustained ventricular tachycardia; LVOTO; BMI, body mass index; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LA, left atrial.

C-statistic for the area under the curve (AUC) for this model was 0.79, and R square was 0.21 Intercept -6.03.

TABLE 4: Atrial fibrillation (AF) related characteristics of patients with inherited cardiomyopathies and inherited arrhythmia syndromes.

		Inherited Cardiomyopathies	**Inherited Arrhythmias**
	N	277*	16
Age of AF onset, years		53.4 ± 15.3	45.8 ± 21.9
AF Type +	Paroxysmal	170 (66.7)	15 (93.8)

	Persistent	85 (33.3)	1 (6.3)
Symptomatic at diagnosis		143 (70.8)	10 (62.5)
	Stroke/TIA	29 (11.1)	1 (7.1)
AF related hospitalisation		101 (50.4)	6 (37.5)
	AF ablation	35 (14.2)	3 (18.8)
	Cardioversion	99 (41.4)	5 (31.3)
CHA_2DS_2-VASc score		1.7 ± 1.4	1.4 ± 1.5
CHA_2DS_2-VASc score=0		49 (22.9)	6 (37.5)
CHA_2DS_2-VASc score= 1		52 (24.3)	3 (18.8)
CHA_2DS_2-VASc score ≥ 2		113 (52.8)	7 (43.8)
Medical therapy	Warfarin	119 (46.0)	4 (25.0)
	NOAC	73 (28.2)	2 (12.5)
	Aspirin	37 (14.3)	9 (56.3)
	None	30 (11.6)	1 (6.3)

Data shown as n (%) or mean ± SD.

*Percentage does not add up to 100% due to missing data.

+There was a significant difference between number of patients with paroxysmal AF vs persistent AF between the groups (p=0.02).

Abbreviations: AF, atrial fibrillation; TIA, transient ischemic attack; NOAC, new oral anticoagulant.