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STATE-OF-THE-ART REVIEW

Atrial Fibrillation in Hypertrophic Cardiomyopathy

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ABSTRACT

Atrial fibrillation (AF) is common among patients with hypertrophic cardiomyopathy (HCM) with a prevalence greater than 25%. AF in HCM is associated with a high risk of stroke and can be a marker of more advanced cardiomyopathy. Although, it frequently results in cardiac hemodynamic changes which are poorly tolerated, it can be subclinical. Thus, prompt diagnosis and adequate management of AF are essential to minimizing AF-related adverse outcomes in HCM. All HCM patients should be screened for AF regularly, and those with high-risk features should be screened more frequently preferably with extended ambulatory monitoring. Once AF is detected, oral anticoagulation should be initiated. Both general and HCM-specific modifiable risk factors should be addressed and assessment for cardiomyopathy progression should be performed. Although no randomized controlled studies have compared rate versus rhythm control in HCM, early rhythm control could be considered to prevent further LA remodeling. (JACC Adv. 2024;3:101210)

Hypertrophic cardiomyopathy (HCM) is the most common monogenetic cardiomyopathy and causes a multitude of disease-related morbidities and symptoms. Cardiac arrhythmias are common in HCM, and while sustained ventricular arrhythmias are the most concerning, supraventricular arrhythmias and among those, particularly atrial fibrillation (AF) are far more common, occurring in approximately 25% of the HCM patients and are 4-6-fold more prevalent than in age-matched patients without HCM.[1-4] Several aspects of AF are problematic in HCM: 1) the stroke risk associated with AF in HCM surpasses that of AF in patients without HCM; 2) AF is a risk marker of more advanced cardiomyopathy and can indicate an adverse disease trajectory;[1,5] 3) AF-related changes in cardiac hemodynamics are poorly tolerated and frequently cause worsening heart failure symptoms due to loss of synchronized atrial contraction, decreased passive diastolic filling time, and worsening left ventricular outflow obstruction (LVOTO); and 4) AF can acutely cause tachycardia-mediated systolic heart failure, especially in the setting of cardiac myosin inhibitors.[6] Therefore, screening, prompt recognition, and adequate treatment of AF are key to minimizing AF-related complications in HCM. In this review, we will discuss briefly the pathomechanisms of AF in HCM, approaches to screening for risk factors

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ABBREVIATIONS AND ACRONYMS

AAD = anti-arrhythmic drug

AF = atrial fibrillation

DOAC = direct oral anticoagulants

ECG = electrocardiogram

HCM = hypertrophic cardiomyopathy

ICM = insertable cardiac monitor

LA = left atrium

LVOTO = left ventricular outflow tract obstruction

OAC = oral anticoagulation

OSA = obstructive sleep apnea

PAF = paroxysmal AF

PV = pulmonary vein

PVI = pulmonary vein isolation

SCAF = subclinical AF

SCD = sudden cardiac death

for the development of AF, and best-practice recommendations for medical and device-based therapies of AF in HCM patients.

DEFINITION OF AF IN HCM

AF can be classified as subclinical AF(SCAF) in asymptomatic patients or *clinical* in those who seek medical attention for symptoms caused by AF.[7] This distinction becomes important due to an increasing number of HCM patients recognized to have SCAF as detected by internal and external cardiac devices and arrhythmia monitors.[8,9]

The further classification of AF that focuses on duration and length of clinical episodes in HCM patients follows the standard definitions in non-HCM patients, including categories of paroxysmal, persistent, long-standing persistent, and permanent AF.[10] More specific to HCM patients, an additional category of postoperative AF (after surgical myectomy) can be considered.

BRIEF SUMMARY OF UNDERLYING PATHOMECHANISMS IN HCM

There is overlap of the putative mechanisms of AF among patients with and without HCM, such as cardiac changes associated with older age. The cardiac substrate for AF can be categorized in structural and electrical changes (ie, remodeling) of the left atrium (LA), which usually is the site of the origin and perpetuation of AF.[11,12] Electrocardiographic markers for AF which may indicate those structural and electrical abnormalities include P-wave duration and P-wave dispersion.[13] Activation of the sympathetic nervous system (especially in the setting of concomitant obstructive sleep apnea [OSA]),[14] as well as inflammatory pathways, may also be involved in the generation of AF.[14] Evidence for an HCM-related atrial myopathy with decreased atrial systolic function and excessive fibrosis has also been documented and may further contribute to the development of AF and the excess risk of associated thromboembolic stroke noted in HCM (**Figure 1**).[12,15-17]

RISK FACTORS FOR AF IN HCM

Age is by far the most potent nonmodifiable risk factor for AF in the general population and is also an important risk factor in HCM patients.[2] More limited data exist on the role of modifiable risk factors for AF

HIGHLIGHTS

- AF is common in HCM with a prevalence above 25%.
- AF in HCM carries high-risk of stroke and can be a marker of advanced cardiomyopathy.
- Prompt diagnosis and adequate management are essential to minimizing AF-related adverse outcomes.
- Early rhythm control could be considered to prevent further LA remodeling.

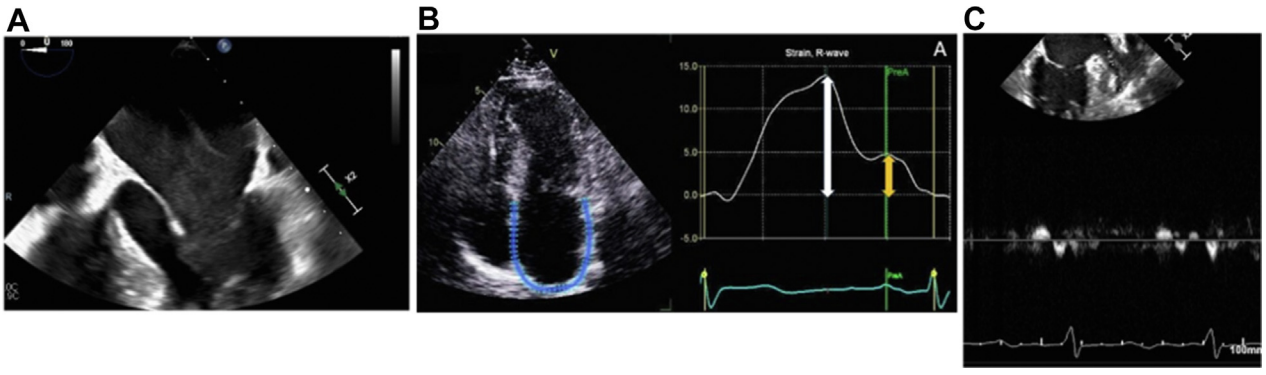
specific to HCM: some reports suggest correlations between traditional modifiable risk factors and AF,[3,18] while others have not found these correlations and surmise that AF in HCM is driven primarily by the cardiomyopathy itself, making it potentially a non-modifiable risk factor.[19] An overview of the existing studies is presented in **Table 1** and supports at least some associations between modifiable risk factors and AF in HCM, albeit limited by their retrospective nature and sample size. Recognition of risk factors and concomitant disease present a complementary treatment approach for AF in the general and HCM patient population (**Table 2**), both from a primary as well as a secondary prevention perspective (**Figure 2**).

Lifestyle factors such as tobacco and alcohol use are associated with increased rates of AF in non-HCM cohorts,[36] though few studies have investigated these relationships in HCM. Limited data suggest that HCM patients less commonly use tobacco and alcohol than the general population (**Table 1**),[31] which may indicate that these factors are not principal AF risk factors in HCM, although minor contributions may still be at play.

Increased physical exercise appears to be associated with a decreased AF risk in the general population;[36] however, one (underpowered) study did not find an association between physical activity and AF prevalence.[32] As guidelines recommendations are evolving regarding exercise for HCM patients, it will become more evident from clinical observations and trials whether exercise protects or increases the risk for AF.

Although hypertension and diabetes mellitus are important AF risk factors in the general population, no clear data exist on their association with AF among HCM patients.[3,5,19]

FIGURE 1 Anatomical Changes in HCM Contributing to AF Development



(A) Dilated left atrium with spontaneous echo contrast. (B) A marked reduction in all left atrium strain components in the 4-chamber view is seen. The reservoir strain is 14% (white double arrow) and contractile strain is -5% (yellow double arrow). (C) Atrial myopathy with low left atrium appendage emptying velocities.

Given that atherosclerotic disease is typically a comorbidity (rather than a driver) of HCM, it may represent an under-recognized modifiable AF risk factor in HCM. Two large retrospective studies suggest a correlation between atherosclerotic disease and AF in HCM,[3,5] with one study estimating a hazard ratio of 1.41.[3] Prevention and treatment of atherosclerotic disease according to recognized guidelines is

TABLE 1 Prevalence of Modifiable Risk Factors in HCM

Group	Modifiable Risk Factor for AF	Prevalence in HCM Patients (Each Cell Is 1 Paper)				Prevalence in HCM (range)	Prevalence in the General Population
Metabolic	Obesity	Preobese 39% Obesity 31.7% (Fumagalli, 2019[18])	Preobese 38% Obesity 37% (Olivotto, 2013[20])	Obesity 43% (Sridharan, 2022[19])		Preobesity 38%-39% Obesity 31.7%-43%	42.4% (Hales, 2020[21])
	Diabetes mellitus	9.3% (Fumagalli, 2019[18])	Septal thickness 13-14 mm 13% ≥15 mm 0% (Lopes, 2021[22])	6% (Guttmann, 2017[3])	11% (Sridharan, 2022[19])	6%-13%	9.8% (Benjamin, 2019[23])
	Hyperlipidemia	39% (Sridharan, 2022[19])	Septal thickness 13-14 mm 31.7% ≥15 mm 26.5% (Lopes, 2021[22])	28% (Sorajja, 2003[24])		31%.7-39%	11.7% (Benjamin, 2019[23])
Sleep	OSA	Nocturnal Hypoxia 71% (Eleid, 2009[25])	Sleep disordered breathing 33% (Konecny, 2010[26])	40% (Pedrosa, 2010[27])	44% (Prinz, 2011[28])	32%-71%	14.5% (Peppard, 2013[29])
Cardiovascular	Hypertension	38.9% (Fumagalli, 2019[18])	46% (Cannan, 1995[30])	28% (Guttmann, 2017[3])	27% (Sridharan, 2022[19])	27%-46%	46% (Benjamin, 2019[23])
	Atherosclerotic disease	2% (Guttmann, 2017[3])	CAD 8% (Sridharan, 2022[19])	CAD severe 26% mild 27% (Sorajja, 2003[24])	17% Siontis et al.[5]	2%-17%	
Lifestyle	Smoking	Previous 48.5% current 6.1% (Lopes, 2021[22])	Current or prior 42% (Sorajja, 2003[24])	Current 20% (Reineck, 2013[31])			15.5% current (Benjamin, 2019[23])
	Physical exercise	Vigorous recreational activities 23% (Reineck, 2013[31])					Leisure-time aerobic and muscle-strengthening 22.5% (Benjamin, 2019[23])
	C2 consumption	Regular alcohol intake 45.5% (Lopes, 2021[22])	1.7 drinks/day (Reineck, 2013[31])				

AF = atrial fibrillation; CAD = coronary artery disease; HCM = hypertrophic cardiomyopathy; OSA = obstructive sleep apnea.

TABLE 2 Role of Modifiable Risk Factors for AF in HCM Patient Population

First Author, Year	Description	AF as Dependent or Independent Variable	Obesity	T2DM	Hyperlipidemia	OSA	Hypertension	Vascular Disease	Smoking	Physical Exercise	C2 Consumption
Sridharan, 2022[19]	n = 2,269 retrospective	Dependent	Yes, in univariate OR: 1.7	No	No		No	No	No		No
Dejgaard, 2018[32]	n = 187 small retrospective	Independent								No	
Saberi, 2017[33]	n = 136 RCT moderate intensity exercise	Independent								No	
Fumagalli, 2019[18]	n = 3,282 international retrospective cohort	Independent	Yes Preobesity, HR: 1.067 (95% CI: 0.846-1.345) Obesity, HR: 1.416 (95% CI: 1.115-1.798)								
Guttmann, 2017[3]	n = 4,907 international retrospective cohort	Dependent		Yes, in univariate			Yes HR: 1.17	Yes HR: 1.41			
Konecny, 2010[26]	n = 91 prospective evaluation of OSA	Dependent				Yes					
Olivotto, 2013[20]	n = 275 retrospective patients for Obesity. NB: small AF n = 30	Independent	No								
Pedrosa, 2010[27]	n = 80 prospective OSA evaluation	Dependent				Yes HR: 1.07					
Prinz, 2011[28]	n = 113 prospective OSA evaluation. NB: small AF n = 10	Independent				No					
Siontis, 2014[5]	n = 3,673 retrospective study	Dependent					No	Yes			
Wasserstrum, 2019[34]	n = 937 retrospective study	Independent		Yes							
Zhang, 2022[35]	n = 712 HCM patients undergoing septal myectomy	Dependent	Yes								

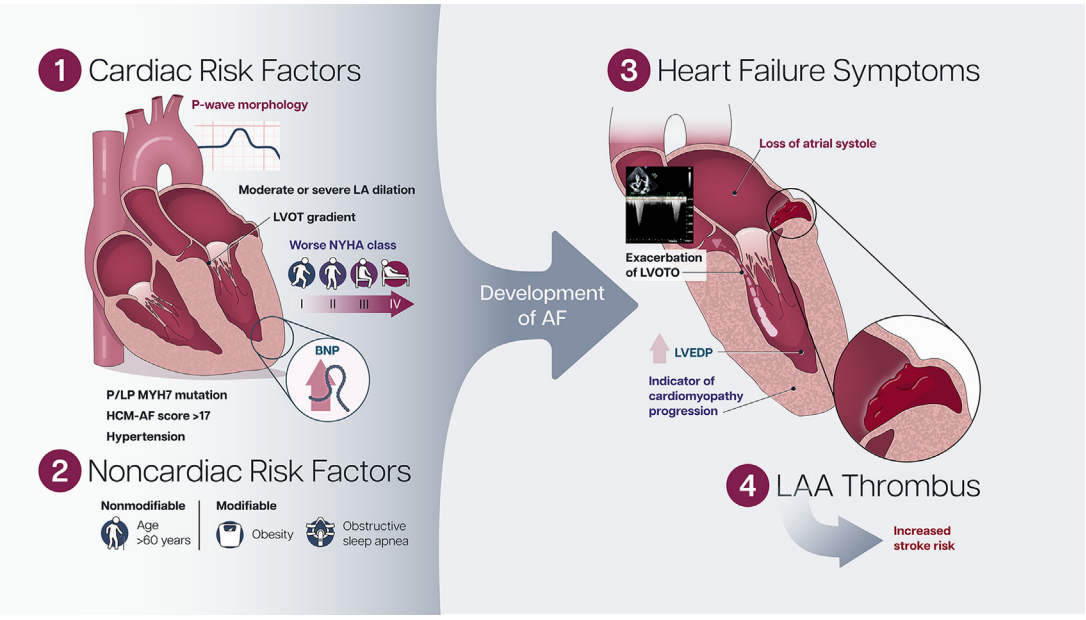
AF = atrial fibrillation; OSA = obstructive sleep apnea; RCT = randomized control trial; T2DM = type 2 diabetes mellitus.

recommended regardless of whether HCM is present or not.

Obesity is a risk factor for developing HCM and has been shown to affect disease severity.[37] Mechanistically, there is likely an overlap between obesity and sleep apnea. As in the general population, obesity is also a risk factor for developing AF among those with HCM.[18,19] In univariate analysis, the AF risk increases by 40% to 70% in obese patients, based on two large retrospective studies.[18,19] In a study investigating the risk of AF after septal myectomy, obesity was associated with an odds ratio of 2.8.[35] Weight loss reduces AF frequency and symptom burden and can even convert persistent to paroxysmal AF.[36]

OSA is associated with AF in general.[36] OSA is more common among HCM patients (32%-71%) than in the general population (3%-49%) and may be associated with AF in HCM,[38] albeit with some conflicting data.[26] This association may be confounded by an interaction between OSA and LA size and diastolic dysfunction.[26,27] Autonomic instability mediated by OSA may facilitate AF development in the pulmonary vein ostia, which are densely innervated by adrenergic and

FIGURE 2 Cardiac and Noncardiac Factors Driving AF Development and its Consequences



AF = atrial fibrillation; BNP = brain natriuretic peptide; HCM = hypertrophic cardiomyopathy; LA = left atrium; LAA = left atrium appendage; LVOTO = left ventricular outflow tract obstruction; LVEDP = left ventricular end-diastolic pressure; P/LP = pathogenic/likely pathogenic.

vagal neurons.[39] While the benefits of continuous positive pressure treatment in OSA are well-established in the general population, with some association with a reduction in AF burden[40] (but not consistently)[36] in HCM, this treatment effect is not well studied.[41]

Beyond risk factors for AF identified in the general population, the contribution of LVOTO in HCM patients may be relevant. Sun et al. identified several risk factors associated with chronic LVOTO, including LA enlargement, which predicted AF incidence following septal myectomy.[42]

In addition, the assessment of biomarkers is useful to determine AF risk, specifically brain natriuretic peptide, and less so troponin levels are associated with incident AF.[5,13]

In summary, modifiable risk factors for AF specific to HCM have not been well characterized. However, treating obesity, OSA, and LVOTO appear to hold the greatest potential for AF prevention and management. Additionally, atherosclerotic disease may be an underappreciated modifiable risk factor. Given the high prevalence of AF in HCM and given that treating the comorbidities listed above has intrinsic merits, identification and treatment of these comorbidities should be incorporated into routine clinical HCM care pathways. However, further studies focusing on the impact of risk factor modification specific to HCM patients are needed.

AF AS RISK FACTOR FOR PREMATURE MORTALITY AND SUDDEN CARDIAC DEATH

AF in HCM is associated with increased risk of heart failure and stroke as well as overall mortality in multiple studies.[2,5,43] Olivotto et al. found AF to be an independent risk factor for cardiovascular death where the annual HCM-related mortality was 3% in HCM patients with AF, compared with 1% among those in sinus rhythm, driven by excess stroke and heart failure-related mortality. The risk was significantly higher in the presence of LVOTO and in patients who developed AF at a young age (<50 years).[2] Consistent with these findings, a retrospective study of over 3,500 patients found AF to be an independent predictor for all-cause mortality.[5] There are contradicting reports whether development of AF is associated with an increased risk of sudden cardiac death

(SCD). In the aforementioned studies, AF was not associated with SCD.[2,5] Conversely, two meta-analyses found AF to be associated with increased risk for SCD.[44,45] In contrast to older studies, a recent report showed a more favorable clinical course with current management where AF was not associated with heart failure morbidity, SCD, or thromboembolism.[46] Moreover, with anti-arrhythmic drugs (AADs) and/or catheter or surgical ablation, only 26% of patients with paroxysmal AF (PAF) developed permanent AF, where sinus restoration was abandoned.[47] These observations suggest that with contemporary management, AF has a favorable course and outcomes.

FREQUENCY AND TOOLS FOR ATRIAL FIBRILLATION SCREENING

There are no consistent and clear recommendations regarding the type and frequency of screening for AF in HCM patients. The current guidelines recommend extended ambulatory monitoring for HCM patients who have additional risk factors for AF, such as LA dilatation, advanced age, and NYHA functional class III-IV symptoms, and who are eligible for oral anticoagulation (OAC), as part of the initial evaluation and annually (Class I recommendation).[7] The guidelines note that ambulatory monitoring may be considered also for patients without risk factors for AF beyond the diagnosis of HCM alone who are eligible for OAC (Class IIb recommendation). The 2014 European Society of Cardiology guidelines recommend 48-hour ambulatory electrocardiogram (ECG) monitoring every 6 to 12 months to detect AF in patients who are in sinus rhythm and have a LA diameter of 45 mm or more (**Central Illustration**).[47]

The HCM-AF score is a novel predictive tool for the detection of HCM patients at risk for developing AF at 2 and 5 years, who will benefit from increased ambulatory monitoring. It was developed from a cohort of 1900 HCM patients and was externally validated in a cohort of 387 HCM patients. It includes four parameters: LA dimensions, current age, age at diagnosis, and heart failure symptoms. The HCM-AF score stratifies risk as low (<1.0%/y; score ≤17), intermediate (1.0%-2.0%/y; score 18-21), and high (>2.0%/y; score ≥22). The score has a higher yield for AF prediction than LA dimensions alone. The authors suggest that patients with low-risk scores are less likely to benefit from frequent monitoring for AF and should be reassured, whereas patients with high-risk scores require close ambulatory monitoring for the development of AF.[48]

A survey among international HCM experts found that most experts (87%) perform routine screening for AF, with the majority (61%) conducting it on an annual basis.[49] A 24-to-48-hour Holter monitor was the preferred first-line tool (91%), followed by prolonged Holter monitoring. Consumer wearable devices were the third most-used screening tool (56%); but 91% of experts would not rely on these to start OAC and pursue further Holter or event monitor screening if a patient reports AF on these devices. LA dilatation was an important factor when considering screening for AF by most experts (78%). Additional factors that prompted increased frequency of screening included severe mitral regurgitation (61%), NYHA functional class III-IV (43%), and dynamic LVOTO (19%).

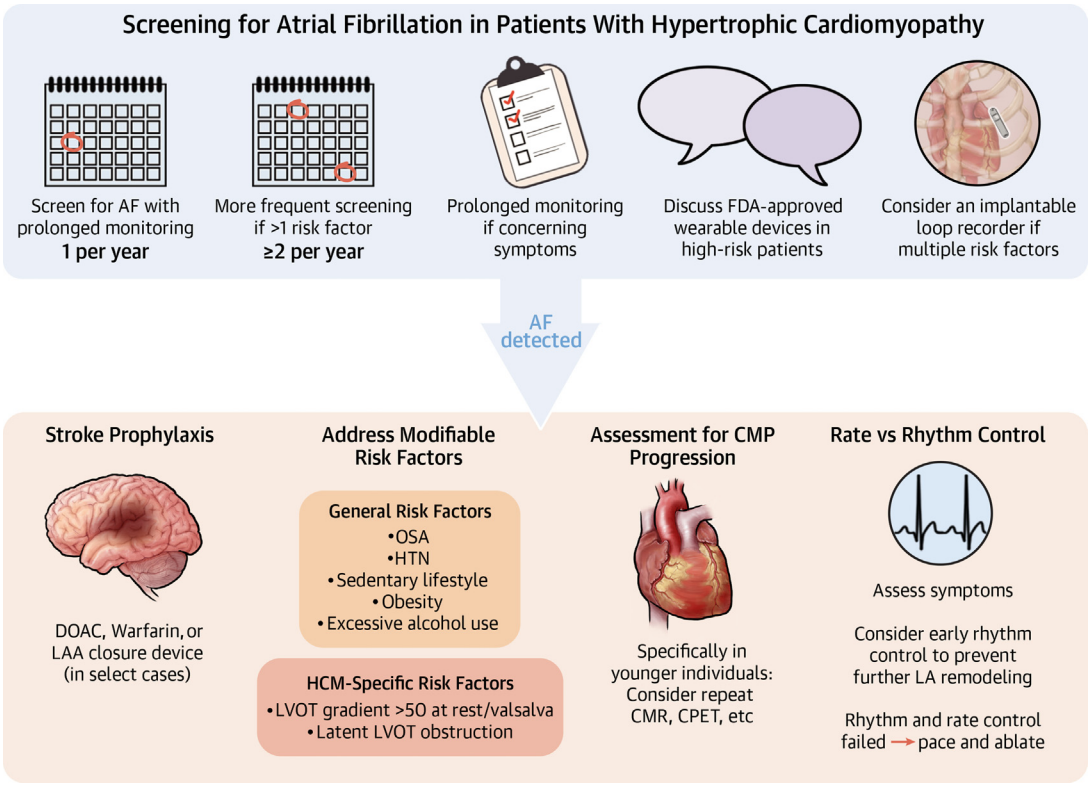
Whether extended ECG monitoring is more sensitive than the standard 24 to 48-hour Holter monitoring was examined in two small studies. Weissler-Snir et al. found newly diagnosed AF in 4 of 77 patients using 14-day ambulatory arrhythmia monitoring, none of which occurred during the first 48 hours of monitoring.[50] The TEMPO-HCM study compared the yield of a 24-hour vs 30-day ambulatory arrhythmia monitoring in 100 HCM patients with a clinical indication for AF screening or for risk stratification for SCD. The 30-day monitoring detected 3 more cases of newly diagnosed AF than 24-hour monitoring. The difference was not statistically significant, likely due to the small sample size. However, the study suggests that extended ECG monitoring may have a role for AF screening in HCM.

Data regarding the yield of an insertable cardiac monitor (ICM) for AF detection in HCM are scarce. A prospective observational study of 30 unselected HCM patients detected AF using ICM in 7 patients (5 asymptomatic) without a prior diagnosis of AF during an 18-month follow-up period.[51] An additional study of 25 HCM patients who received an ICM for either recurrent near-syncope, palpitations, myocardial fibrosis by cardiovascular magnetic resonance, or HCM Risk-SCD score ≥4 to <6% found newly diagnosed AF in 3 patients during a 30-month follow-up period. Only 1 of the 3 patients developed symptoms. No AF was diagnosed in the control group, who received conventional follow-up (ie, Holter monitoring every 6-24 months based on treating physician's discretion).[52]

MANAGEMENT OF AF IN HCM

RHYTHM VS RATE CONTROL. There have been no randomized trials comparing rhythm vs rate control for AF in HCM. Moreover, most randomized trials

CENTRAL ILLUSTRATION **Approach to AF Screening and Management in HCM Patients**



Weissler-Snir A, et al. JACC Adv. 2024;3(9):101210.

AF = atrial fibrillation; CMR = cardiovascular magnetic resonance; CPET = cardiopulmonary exercise testing; DOAC = direct oral anticoagulants; FDA = Food and Drug Administration; HTN = hypertension; LA = left atrium; LVOTO = left ventricular outflow tract; OSA = obstructive sleep apnea.

comparing rhythm to rate control in the general population excluded HCM patients. Several registries included small numbers of HCM patients and found better outcomes for rhythm control; however, none performed a sub-analysis within the HCM subpopulation.[53,54] As patients with AF and HCM tend to be quite symptomatic, particularly in the presence of rapid ventricular rates and LVOTO, a rhythm control strategy may be preferred. However, as AF can be a marker of advanced disease—especially in young people—progression of cardiomyopathy should be assessed (eg, repeat cardiovascular magnetic resonance, cardiopulmonary exercise test, right heart catheterization) and addressed prior to pursuing rhythm control. Furthermore, in the presence of high LVOT gradients, pursuing rhythm control is unlikely to be successful without treating the obstruction. If LVOTO is not present at rest, provocative maneuvers—or a stress echocardiogram to assess for latent obstruction—should be performed. Beta-blockers or nondihydropyridine calcium channel blockers such as verapamil and diltiazem are the preferred agents for rate control therapy with the avoidance of nondihydropyridine calcium channel blockers in patients with signs and symptoms of heart failure, cardiogenic shock, pre-excitation, and very high LVOT gradients.[55] Rate control therapy should also be considered for those who are intolerant to AADs. Lastly, data on the efficacy of digoxin for rate control of AF in HCM are lacking, although there is a theoretical concern that digoxin can exacerbate LVOTO due to its positive inotropic effect. However, in the absence of LVOTO, it may be a reasonable option (**Central Illustration**).

RHYTHM CONTROL: ANTI-ARRHYTHMIC DRUGS

Data on the use of various AADs in HCM are limited to small retrospective and observational studies. Amiodarone has the longest experience and until recently was considered the drug of choice for rhythm control in HCM. However, as many HCM patients with AF are relatively young, amiodarone should be avoided if possible due to its many potential long-term side effects and toxicities. Alternatives to amiodarone include the other class III agents sotalol and dofetilide and the relatively weak class Ia agent disopyramide. Several small retrospective studies have shown that both sotalol and dofetilide are safe in HCM and have moderate efficacy. A recent retrospective analysis of 98 HCM patients with AF compared the safety profile, efficacy, and side effects of sotalol (n = 45), amiodarone (n = 47), dofetilide (n = 20), and disopyramide (n = 18).[56] No sudden deaths occurred with any agent. Overall, the use of AADs was relatively safe, with 4.6% of the total cohort experiencing serious side effects or safety events. The probability of remaining on a single AAD was 62% at 1 year and 42% at 3 years. Amiodarone demonstrated the lowest rate of discontinuation for inefficacy (8.5%), but the highest rate of discontinuation for side effects (19.1%). Documented inefficacy resulting in cessation occurred in 12 patients (8.7%) on sotalol, 5 patients (22%) on disopyramide, and 6 patients (15.8%) on dofetilide. Another single-center observational study of 72 HCM patients treated with dofetilide [31] and sotalol for either AF [57] or ventricular arrhythmia [18] found similar moderate efficacy for sotalol and dofetilide with 40 to 45% recurrence rate at 1 year.[58] No patients developed sustained torsade de pointes. Moreover, QTc prolongation was infrequent and precluded dofetilide loading in only 10% of the patients and resulted in postloading sotalol discontinuation in 6%. In a retrospective study of 1,404 patients with AF treated with dofetilide, of whom 25 had HCM, dofetilide was well tolerated in HCM with 11/25 (52%) of the patients remaining on it after a median follow-up of 396 days.[59]

Disopyramide, a class Ia AAD, may be particularly beneficial in patients with symptomatic LVOTO and AF given its negative inotropic effects and proven efficacy in reducing LVOTO,[60] although it should be combined with a beta-blocker or nondihydropyridine calcium channel blocker as it can potentially be proarrhythmic due to enhanced AV nodal conduction in the setting of rapid ventricular response during AF episodes. Adler et al. demonstrated in 168 patients that outpatient initiation of disopyramide was safe, with no cardiac events in the first 3 months of therapy at both the starting dose (300 mg daily) and subsequent uptitration (600 mg daily). Its excellent safety profile despite QT prolongation may be explained by its multichannel inhibitory effects and membrane stabilizing actions, which may be protective against ventricular as well as atrial arrhythmias.[61] Yet, although in vitro studies show that disopyramide has promising antiarrhythmic properties, its clinical efficacy in the management of AF in HCM is not well established.

RHYTHM CONTROL: CATHETER ABLATION

There are no prospective randomized controlled studies comparing catheter ablation to AADs in HCM. Acknowledging that the HCM population is underrepresented in clinical trials, the 2018 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement suggests that it is reasonable to use similar indications for AF ablation in selected HCM patients as in patients without HCM (Class IIa recommendation).[57] All studies examining the short- and long-term success rate of catheter ablation in HCM are relatively small, yet they consistently show that the success rate of catheter ablation in HCM patients is substantially lower than in patients without HCM.[62-64] The success rates are higher for patients with PAF than persistent AF, with most patients requiring more than one ablation and concurrent AADs. A recent meta-analysis of 25 studies with data on a total of 1817 HCM patients found a 1-year success rate following a single procedure of 61%.[65] The success rate declined to only 34.7% at 4 years and 27.5% at 7 years. However, the success rates increased substantially following multiple ablations, with arrhythmia-free rates of 71.1%, 48.9%, and 46.8% at 1, 4, and 6 years, respectively. Similar to patients without HCM, the success rate was higher in those with PAF vs persistent AF, with a 12-month success rate of 63.7% in PAF compared to 46.1% in persistent AF after 1 procedure and 79.2% in PAF and 67.2% in persistent AF after multiple ablations. Notably, many patients were on concurrent AADs and the success rate at latest follow-up in patients without AADs was only 33.4%. Another meta-analysis found that HCM patients underwent ablation relatively late after the initial diagnosis of AF, with a median time from initial diagnosis to ablation of 5.9 years.[62] Recent trials in non-HCM patients lend support to early catheter ablation for paroxysmal AF.[66-68] Although it is unclear whether their results can be extrapolated to HCM patients, it can be postulated

that early catheter ablation for HCM patients with PAF may decrease the atrial electrophysiological and structural remodeling, resulting in a decreased risk of progression to persistent AF.[68] It is plausible that a significant delay in performing catheter ablation after onset of AF in HCM patients may contribute to the worse ablation success rates noted in HCM patients as compared with the general population. Hence, considering the advances in catheter ablation with shorter procedure time and same-day discharge on the one hand and the moderate success of AADs in maintaining sinus rhythm and the relatively young age of HCM patients with AF on the other hand, catheter ablation can be considered first-line strategy in selected HCM patients with PAF. With respect to persistent AF, a catheter ablation can also be considered as first-line strategy in selected patients with the expectation that several procedures and AADs may be needed for long-term sinus rhythm maintenance. A recent study by Haq et al. showed that genotype-positive patients undergoing AF ablation (n = 12) had more low-amplitude LA signals suggestive of fibrosis, than genotype-negative patients (n = 15), albeit with a greater number of procedures (1.67 ± 0.65 vs 1.20 ± 0.41, $P = 0.03$), they had similar 12-month freedom from AF (75% vs 73%, $P = 0.92$). It is noteworthy that a greater proportion of patients in the genotype-positive cohort had persistent AF (66.6% vs 50%, $P = 0.09$). Notably, all patients in the gene-positive cohort and 93% of the genotype-negative patients were on AADs post-ablation.[69]

PULMONARY VEIN ISOLATION ONLY VS SUBSTRATE MODIFICATION

As HCM patients may have non-pulmonary vein (PV) triggers for AF, an important question is whether there is any additional benefit to performing substrate modification and extensive ablation beyond PV isolation (PVI) during the first ablation. Some studies suggest that ablation beyond PVI may not be associated with improved efficacy outcomes in HCM,[70] whereas others suggest that PVI and posterior wall isolation alone may be insufficient to maintain long-term freedom from recurrent arrhythmia despite achieving permanent isolation and that non-PV triggers may represent the dominant etiology for arrhythmia recurrence in HCM patients, with subsequent improvement in arrhythmia-free survival after targeted ablation of non-PV triggers.[71] Zahid et al.[72] observed that HCM patients and PAF have reduced atrial conduction velocity despite having normal bipolar voltage amplitude, suggesting that this might contribute to arrhythmia persistence after catheter ablation in HCM patients with PAF. Their observations also question the utility of the "conventional" methods to assess the atrial tissue (eg, voltage mapping) in deciding whether to perform further substrate modification in addition to PVI in HCM patients.

RADIOFREQUENCY AND CRYOBALLOON CATHETER ABLATION

In the general population, cryoballoon catheter ablation has emerged as an effective alternative to radiofrequency ablation, with similar efficacy reported in several studies.[73-76] This general theme does appear to be applicable to HCM patients. In an observational multicenter study of 137 HCM patients, cryoballoon ablation demonstrated similar efficacy and complication rates compared to radiofrequency ablation for both PAF and persistent AF.[70] However, cryoballoon catheter is designed for PVI only, with emerging data that it can also be used safely for posterior wall isolation. Thus, many electrophysiologists prefer using radiofrequency over cryoballoon catheter ablation for HCM patients.

PULSED-FIELD ABLATION. Pulsed-field ablation has been shown to have similar outcomes to thermal ablation but with fewer complications due to its tissue selectivity.[77] It is currently approved only for PVI. However, there are data from nonrandomized trials demonstrating its safety and efficiency for posterior wall as well as mitral isthmus and cavotricuspid isthmus isolation (with the use of intravenous nitrates).[78] Thus, it will likely to be approved for ablation of non-PV triggers and substrate modification. Notably, no data are available on PFA in HCM patients. Yet, there is no reason to postulate that the safety profile of pulsed-field ablation will be lower in HCM patients.

SAFETY OF CATHETER ABLATION

Two meta-analyses found similar complication rates of catheter ablation procedures in patients with and without HCM.[62,63] In contrast, an observational multicenter study of 135 patients with 225 ablations reported a higher rate of major complications, with cardiac tamponade rates 4 times higher than the general population in the participating center.[70] However, there was a significant reduction in the rate of complications over time. Notably, there was no significant difference in the overall complication rate between RF and cryoballoon ablation. The authors postulated possible explanations for the increase in complications, including a greater anatomical challenge with trans-septal punctures and decreased hemodynamic tolerance with a small increase in pericardial fluid due

to worse diastolic function in HCM patients. The real-world safety of catheter ablation for AF in HCM was assessed in a large-scale study investigating the nationwide trends of 1,563 catheter ablation cases (47% female) during two time periods of 2003 to 2008 ("early years") and 2009 to 2015 ("later years").[79] The authors found that at least 1 complication occurred in 16.1% of the cases, with an all-cause in-hospital mortality of 1%. However, similar to the abovementioned study, there was a decrease in complication rates from the "early years" to "later years" (20.9% vs 14%).[79] The lower complication rates in the "later years" is likely due to improved operator experience, techniques, and equipment in more recent years.[79]

RHYTHM CONTROL: SURGICAL ABLATION DURING SEPTAL MYECTOMY

Studies on surgical ablation for HCM patients are limited and have been mostly done on patients with drug-refractory AF undergoing concomitant septal myectomy. Most studies show lower rates of AF recurrence with surgical ablation than catheter ablation, with 70% to 85% and 50% to 70% freedom from AF at 1 and 3 years, respectively.[46,80,81] As surgical ablation is not typically done as a stand-alone procedure and is usually performed at the time of septal myectomy, the results can be confounded by the relief of LVOTO. It is difficult to determine whether the better outcomes are due to increased efficacy of surgical ablation alone or the favorable effects that septal myectomy has on reducing the LVOT gradient, with subsequent reduction in mitral regurgitation and LA size and remodeling. A recent meta-analysis of over 600 patients (68% with PAF) found surgical AF ablation during septal myectomy to be safe and effective, with overall survival and freedom from recurrent AF at 7 years of 90.5% and 63.2%, respectively.[82] Thus, the current guidelines recommend consideration of concomitant surgical AF ablation at the time of septal myectomy for patients with AF (class IIa recommendation).[7] Whether patients with nonobstructive HCM might benefit from a stand-alone surgical AF ablation or the hybrid procedure of surgical and endocardial ablation has not been studied.

PACE AND ABLATE

A substantial subset of patients who have failed medical therapy and/or ablation for AF are highly symptomatic due to rapid ventricular response and/or the irregular rhythm. For this group of patients, a pacemaker implantation and AV node ablation (ie, pace-and-ablate strategy) might offer an effective therapy option. Butcher et al[83] have recently reported their experience with this approach in 42 patients, of whom 18 (43%) had undergone previous catheter ablation. Cardiac resynchronization therapy devices were implanted in 24 patients (57%). Most patients (83%) experienced improvement in symptoms, including those who underwent the procedure to regularize the rhythm. Left ventricular systolic function remained stable regardless of the type of device implanted. It is also noteworthy that the growing use of physiologic pacing (eg, left bundle branch area pacing, His-bundle pacing), which significantly reduces the risk for pacemaker-mediated cardiomyopathy, makes the option of pace-and-ablate even more attractive for this group of patients. However, more data are needed to confirm the feasibility and safety of conduction system pacing in HCM.

CARDIAC MYOSIN INHIBITORS. Cardiac myosin inhibitors (eg mavacamten, aficamten) are a novel class of agents which decreases the cardiac hypercontractility by reducing the actin-myosin interactions in the cardiomyocytes. The effects of these agents on the incidence and severity of AF in HCM are currently uncertain. As these agents alleviate LVOTO and improve diastolic dysfunction, they are expected to favorably affect the frequency of new-onset or recurrent AF. However, in randomized clinical trials, AF represented an adverse event in 2%-4% of the patients randomized to mavacamten.[84,85] In a "real world" cohort of 67 patients with oHCM from the Mayo clinic, the incidence of newly recognized AF after mavacamten initiation was 11%.[86] In a large, randomized double-blinded trial of aficametn in patients with symptomatic oHCM, there was no observed increase in the incidence or recurrence of AF within the aficamten arm.[87] Thus, further studies are needed to understand the effects of cardiac myosin inhibitors on AF in HCM.

STROKE PROPHYLAXIS

The risk of systemic embolization associated with AF is high in HCM patients. A meta-analysis that included 33 studies and 7,381 patients revealed an overall prevalence of thromboembolism in HCM patients and AF of 27.1% and an incidence of 3.75 per 100 patients.[4] The stroke risk cannot be predicted by CHA_2DS_2-VASc score[88,89]—a significant number of strokes are observed in HCM patients with a score of 0.

No randomized controlled trials have compared direct oral anticoagulants (DOACs) with warfarin; however, observational data demonstrate that DOACs are at least as effective as warfarin in reducing the risk of stroke in this population, with the added benefits of increased patient satisfaction and reduction of major bleeding complications and death.[90-92]

The numbers of HCM patients included in the trials of LA appendage occlusion devices are very limited, thus the role of these devices in thromboembolic risk reduction in HCM patients is largely unknown. One pilot study of 36 HCM patients and AF who underwent LA appendage closure procedure showed the safety and feasibility of this approach in primary and secondary stroke prevention, with no thromboembolic events or deaths during a mean follow-up time of 28.4 months and 97.2% of patients remaining free of anticoagulation during that time.[93] Conversely, an analysis of the National Readmissions Database of patients undergoing LA appendage closure between 2016 to 2019 showed that HCM was independently associated with increased odds of in-hospital mortality (OR: 5.44) and peripheral vascular complications (OR: 4.18).[94] Additionally, a recent analysis of HCM patients with AF from 2015 to 2024, using the TriNetX Global Research Network, found that HCM patients treated with LA appendage occlusion devices had higher rates of ischemic stroke (13% vs 8%, HR 1.9, $P = 0.006$) and systemic embolism (14% vs 9%, HR 1.8, $P = 0.006$), but no difference in mortality compared to matched HCM patients on OAC.[95]

Anticoagulation is recommended for all HCM patients and clinical (symptomatic) AF.[55] While the relationship of SCAF to stroke has not been investigated in a specific HCM population, in a meta-analysis of seven studies and 15,353 patients, SCAF was associated with a 2.4-fold increased risk of stroke, with an absolute annual rate of 1.89 per 100 person-years in the general population.[96,97] The definitions of episodes that predicted stroke varied significantly between studies, reported as episodes as short as 5 and 6 minutes[97] or episodes >5.5 hours within the past 30 days.[98]

However, subsequent studies show that most events occurred in patients with >24 hours of SCAF.[99] Another recent study showed that short AF episodes (<20 seconds) were not associated with clinical events.[100] These data suggest that the risk of events is dependent on AF burden (duration and frequency). Similar risk stratification is unavailable in HCM; however, these data can likely be extrapolated to HCM patients. If a very short duration of SCAF is detected by device or monitor, patients should have ongoing monitoring as increasing burden is likely to occur over time.

CONCLUSIONS

AF is common and poses a significant clinical dilemma for HCM patients as a major cause for stroke, trigger for heart failure symptoms, and indicator of progressive cardiomyopathy with an increased mortality risk. Modifiable and nonmodifiable risk factors for AF in HCM are obesity, OSA, and LVOTO, and age as well as myocardial fibrosis, respectively. These risk factors should be addressed to avoid the development of AF, and patients with a higher AF risk profile require more frequent arrhythmia surveillance. We recommend yearly AF screening in most patients who are eligible for OAC. Once detected, stroke prophylaxis—preferably with a DOAC—should be initiated in patients without contraindication to such therapy. With the increased use of wearable devices that can detect subclinical (ie, asymptomatic) AF, the AF burden may be a consideration before starting anticoagulation; however, short of more definitive data, we recommend erring on the side of treatment rather than ignoring brief AF episodes. Data on the efficacy and safety of LA appendage occluder devices are very limited but they seem to be a reasonable alternative for patients with high bleeding risk. Similarly, whether rhythm control is superior to rate control in patients with AF is not well studied. However, especially in symptomatic PAF, the former may be preferable. Reduction of risk factors for recurrent AF should be addressed. Both AADs and catheter ablation are reasonable approaches to rhythm control, although weighing effectiveness and side effects of AADs and a possibly higher ablation-related complication rate in HCM patients compared to their counterparts without HCM must be considered. Surgical Cox-Maze in conjunction with septal myectomy lowers the risk for recurrent AF and thus is recommended in current HCM guidelines.

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