Management of Atrial Fibrillation in Hypertrophic Cardiomyopathy

Ciorsti MacIntyre, MD; Neal K. Lakdawala, MD

Case Presentation: A 38-year-old man with hypertrophic cardiomyopathy (HCM) was referred for management of intermittent palpitations and exertional dyspnea with routine activities despite escalated β-blocker therapy. His initial examination was notable for a regular pulse at 72 bpm and harsh systolic murmur that increased with the Valsalva maneuver. A 12-lead electrocardiography revealed sinus rhythm with increased QRS voltage, repolarization abnormalities, and a QTc of 430 milliseconds. Echocardiography was notable for severe asymmetrical hypertrophy (septal thickness, 22 mm), normal systolic function, severe outflow tract obstruction (70 mmHg), and left atrial (LA) enlargement. A 24-hour Holter monitor detected 6 minutes of rapid atrial fibrillation (AF) that coincided with his palpitations. Therapy was recommended with warfarin to prevent stroke and with disopyramide to minimize outflow tract obstruction and frequency of AF.

Introduction

HCM, which affects 0.2% of the population, is an important cause of heart failure and is the leading cause of nonviolent sudden death in the young. Traditionally defined as left ventricular hypertrophy that develops in the absence of abnormal hemodynamics, it is caused by dominant mutations in sarcomere genes. Prevention of sudden death and management of left ventricular outflow tract obstruction (LVOTO) have been the primary focus of HCM clinical research and management since its original descriptions. However, AF is more prevalent than either sudden death or medically refractory obstruction and is the most common sustained arrhythmia in HCM. The combination of HCM and AF is associated with a markedly increased risk of stroke, overall mortality, and heart failure. This Clinician Update focuses on the epidemiology, pathophysiology, and clinical management of AF in patients with HCM.

AF Prevalence and Detection

AF represents the most common sustained arrhythmia in both the general and HCM populations. In the general population, AF prevalence increases progressively with age and occurs predominantly in patients >60 years of age. Beyond age, established risk factors for developing AF include male sex, hypertension, and obesity. The recognition of a hereditary component has led to the discovery of predisposing genetic variants for AF. AF in patients with HCM appears to be 4- to 6-fold more common than in the general population, with a reported prevalence between 18% and 28% (Table 1).

In light of the high prevalence of AF in HCM, the American Heart Association, American College of Cardiology, and European Society of Cardiology have included recommendations for AF screening in their contemporary practice guidelines (Table 2). The European Society of Cardiology guidelines advise that 48-hour ambulatory ECG monitoring should be performed (Class IIA recommendation) every 6 to 12 months in patients with LA anterior-posterior diameter ≥45 mm. The 2011 American College of Cardiology/American Heart Association guidelines advise that 24-hour ambulatory ECG monitoring might be considered (Class IIB) in adults with HCM to assess for asymptomatic AF.

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(Circulation. 2016;133:1901-1905. DOI: 10.1161/CIRCULATIONAHA.115.015085.)

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Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.115.015085
American Heart Association guidelines do not make a recommendation for repeat testing. The yield of ambulatory ECG monitoring for detection of AF in previously asymptomatic patients is largely unknown. In a retrospective analysis, 24-hour Holter detected AF in 9% of HCM patients, in whom advancing age, severe heart failure symptoms, and LA enlargement were more common than in patients in sinus rhythm. However, ambulatory ECG was performed in only ≈60% of the HCM patients in this cohort, likely biasing prevalence estimates.

**LA Remodeling and AF in HCM**

Increased LA size and LA volume are associated with the presence of AF. In pooled cross-sectional data, the average LA diameter of patients in sinus rhythm was 38 mm compared with 45 mm in patients with AF. However, it is not clear whether LA enlargement develops antecedent to the development of AF rather than as a secondary phenomenon. The cause of LA enlargement in HCM is likely multifactorial. Diastolic dysfunction, a fundamental

### Table 1. Key Natural History Studies of AF in HCM

<table>
<thead>
<tr>
<th>Study</th>
<th>AF Prevalence, %</th>
<th>Age at HCM Diagnosis, y*</th>
<th>LVOTO, All/AF, %</th>
<th>Warfarin, All/AF, %</th>
<th>Stroke or Embolic Event, All/AF, %</th>
<th>NYHA III–IV, All/AF, %</th>
<th>Mortality Risk Associated With AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olivetto et al1 (n=480)</td>
<td>22</td>
<td>45 (20)</td>
<td>.../32</td>
<td>.../69</td>
<td>.../7</td>
<td>.../15</td>
<td>3.7†</td>
</tr>
<tr>
<td>Kubo et al1 (n=261)</td>
<td>28</td>
<td>57 (15)</td>
<td>15/11</td>
<td>...</td>
<td>7/20</td>
<td>7/23</td>
<td>...</td>
</tr>
<tr>
<td>Maron et al1 (n=900)</td>
<td>21</td>
<td>46 (20)</td>
<td>24/...</td>
<td>.../43</td>
<td>6/23</td>
<td>8/...</td>
<td>...</td>
</tr>
<tr>
<td>Siontis et al1 (n=3673)</td>
<td>18</td>
<td>...</td>
<td>36/31</td>
<td>9/41</td>
<td>5/10</td>
<td>40/46</td>
<td>1.5‡</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; HCM, hypertrophic cardiomyopathy; LVOTO, left ventricular outflow tract obstruction; and NYHA, New York Heart Association.

*Standard deviation is included when provided in original citation.
†Multivariate-corrected odds ratio for HCM-related mortality associated with AF.
‡Multivariate-corrected hazard ratio for total mortality associated with AF.

### Table 2. Key Questions Regarding the Management of AF in Adult* Patients With HCM

<table>
<thead>
<tr>
<th>Question</th>
<th>AHA/ACC 2011 Guidelines</th>
<th>ESC 2014 Guidelines</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should patients be screened for asymptomatic AF?</td>
<td>24-h Holter might be considered (Class IIb)</td>
<td>48-h Holter should be performed (Class IIa) every 6–12 mo if LA ≥45 mm</td>
<td>Risk stratification studies are needed to improve the efficiency of screening for AF</td>
</tr>
<tr>
<td>How should patients with palpitations be evaluated?</td>
<td>24-h Holter monitor should be performed (Class I)</td>
<td>48-h Holter monitor should be performed (Class I)</td>
<td>Examination of stored electrograms can enable detection of AF when a dual-chamber pacer or defibrillator is present</td>
</tr>
<tr>
<td>Which patients with HCM and AF should receive anticoagulation?</td>
<td>All patients (Class I)</td>
<td>All patients (Class I)</td>
<td>Use of CHA2DS2-VASc, or similar risk stratification tools is not recommended for HCM patients to guide anticoagulation decision making</td>
</tr>
<tr>
<td>What anticoagulant should be started for patients with AF and HCM?</td>
<td>Warfarin to target INR 2.0–3.0 (Class I)</td>
<td>VKA to target INR 2.0–3.0 (Class I)</td>
<td>An oral direct thrombin or factor Xa inhibitor should be used if VKA cannot be used or is rejected by the patient</td>
</tr>
<tr>
<td>What are the preferred antiarrhythmic medications for AF in HCM?</td>
<td>Amiodarone (Class Ila) or disopyramide combined with a β-blocker, verapamil, or diltiazem (Class Ila)</td>
<td>Amiodarone (Class Ila)</td>
<td>Avoid other antiarrhythmics, especially in patients without an ICD, because of the risk of proarrhythmia</td>
</tr>
<tr>
<td>What is the role for percutaneous or surgical ablation for AF in HCM?</td>
<td>Catheter ablation should be considered (Class Ila) in patients without severe LA enlargement who have medically refractory symptomatic AF</td>
<td>Catheter ablation can be beneficial (Class Ila) in patients with medically refractory symptomatic AF</td>
<td>The success rate of AF ablation is significantly lower than that seen in the general population</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; AHA/ACC, American College of Cardiology/American Heart Association; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; ILR, implantable loop recorder; INR, international normalized ratio; LA, left atrium; LAA, left atrial appendage; LVOTO, left ventricular outflow tract obstruction; and VKA, vitamin K antagonist.

*Limited data exist for pediatric HCM.
feature of the disease,\(^1\) leads to elevated left ventricular filling pressures and, in turn, LA remodeling and dilation.\(^12\) Additional factors may include primary sarcomeric atrial myopathy, LVOTO, and mitral regurgitation, as well as background AF risk related to unrelated genetic or acquired risk factors (e.g., hypertension).

### Cardiac Biomarkers in AF and HCM

Highly sensitive cardiac troponin T (cTnT) has previously been shown to predict adverse outcomes in HCM.\(^13,14\) However, limited data exist on the utility of this or other cardiac biomarkers in the assessment of AF in the HCM population. A single cross-sectional study found that cTnT levels were an independent predictor of the presence and total burden of AF. The mechanism underlying cTnT elevation in this population is unclear. It has been proposed that cTnT may be released in the setting of cardiac remodeling, atrial myocyte death, and fibrosis.\(^15\) Further research is required before routine evaluation of cTnT or other biomarkers in AF surveillance or management can be advised.

### Clinical Outcomes Associated With AF in HCM

Stroke and systemic embolic events are known complications of HCM. Ischemic strokes are 8 times more frequent in HCM patients with AF (21%) compared with those in sinus rhythm (2.6%).\(^2\) The prevalence of stroke is independent of whether AF is paroxysmal or chronic (22% versus 27%) and the number of paroxysms (1 versus 2, 23% versus 18%).\(^2\) In a report of 900 consecutively enrolled patients with HCM, 45 patients had a stroke (n=44), of whom 11 (25%) had severe permanent neurological impairment such as aphasia and 10 (20%) died.\(^6\)

AF is an independent predictor of all-cause mortality in HCM.\(^2,7\) The presence of AF confers a 4-fold increase in the risk of HCM-related death compared with sinus rhythm, including a higher rate of both death resulting from stroke and heart failure. Patients with HCM who develop AF before 50 years of age are at especially high risk for early death.

### Anticoagulation and AF

Systemic anticoagulation with warfarin reduces the risk of ischemic stroke in patients with AF who do not have HCM.\(^16\) Although less studied in HCM and not completely protective against systemic embolization, warfarin has been associated with a lower risk of stroke and is more efficacious than antiplatelet agents in HCM.\(^2,6,17\) There are no data on the use of target specific oral anticoagulants in stroke risk reduction in the HCM population.

The CHA\(_2\)DS\(_2\)-VAsc score is commonly used for stroke risk stratification.\(^16\) This score, however, is not validated in the HCM population. Indeed, retrospective subgroup analysis of 4821 HCM patients followed up at 7 centers revealed that the CHA\(_2\)DS\(_2\)-VAsc score did not provide effective risk stratification for thromboembolism.\(^17\) Accordingly, current consensus guidelines advise that all patients with HCM and AF receive anticoagulation with warfarin.\(^3,9\) Given the high risk of recurrent AF and stroke, systemic anticoagulation with warfarin should be considered even with only 1 episode.\(^3,9\)

### Rate Versus Rhythm Control for AF

The relative benefit of rhythm versus rate control in the management of AF in HCM is uncertain. However, patients with HCM may develop highly symptomatic AF, particularly in the presence of rapid ventricular rates and LVOTO, and will benefit from the restoration of normal sinus rhythm. Amiodarone is generally the most effective drug to

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**Figure.** Pathological left atrial electromechanical remodeling underlies relatively low success rates with catheter ablation of atrial fibrillation (AF) in hypertrophic cardiomyopathy (HCM). Electroanatomic bipolar voltage map in the anterior-posterior and posterior-anterior views of (A) a patient with paroxysmal AF and a structurally normal heart and (B) a patient with persistent AF and HCM. Low voltage (<0.4mV) suggesting scar is shown in red. Healthy tissue is shown in pink. Note the increased scar burden in the patient with HCM and persistent AF. Corresponding apical 4-chamber echocardiographic images reveal normal left atrial (LA) volume index (LAVI; 29.4 mL/m\(^2\)) in the patient with paroxysmal AF (C) and severe LA dilation (LAVI=65.7 mL/m\(^2\)) in the patient with HCM and persistent AF (D).
reduce the recurrence of AF. However, side effects can be problematic with long-term therapy. Antiarrhythmic alternatives include disopyramide in combination with a rate-controlling agent, especially in the presence of LVOTO. Disopyramide, a class I antiarrhythmic with negative inotropic effects, has been studied specifically for relief of symptomatic LVOTO. A retrospective analysis of 118 disopyramide-treated patients drawn from a multicenter cohort of 491 HCM patients did not identify disopyramide to be associated with increased risk of ventricular arrhythmia or sudden death. However, disopyramide monotherapy, without β-blockers, diltiazem, or verapamil, is potentially harmful because of the enhancement of atrioventricular conduction and consequently increased ventricular rates during AF. Disopyramide should be initiated in an acute care setting with concomitant rate-control therapy and continuous telemetry to allow the detection of QT prolongation and arrhythmia. Disopyramide should be discontinued or the dose reduced if the QTc interval exceeds 480 milliseconds during up titration, and the concurrent use of other QT-prolonging medications should be avoided.

Radiofrequency ablation for symptomatic AF can be considered for HCM patients without a satisfactory response to medical therapy. Restoration of sinus rhythm and suppression of AF recurrence can be achieved in approximately two thirds of HCM patients over 2 years. The success rate is lower than with lone AF (Figure), likely related to the advanced atrial remodeling in HCM patients. Repeat procedures are required in approximately half of patients undergoing ablation, with LA size and AF duration predictive of AF recurrence. There are limited data on isolated surgical management of AF in HCM. One option is the Maze procedure with exclusion of the LA appendage in patients with AF undergoing surgical myectomy.

Summary
The most common arrhythmia in HCM is AF, affecting 1 in 5 patients, in whom it is associated with markedly increased risk of stroke. Once AF is present, patients should be treated with anticoagulation, regardless of stroke risk scores, which have not been validated in HCM. A subset of patients develop limiting symptoms with AF and benefit from rhythm control, which can be undertaken with amiodarone, disopyramide, or catheter ablation. Further study of patients with HCM is needed to improve the detection of AF and to minimize associated complications.

Disclosures
None.

References


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*Circulation*. 2016;133:1901-1905
doi: 10.1161/CIRCULATIONAHA.115.015085
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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