Review

Arrhythmia Monitoring for Risk Stratification in Hypertrophic Cardiomyopathy

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ABSTRACT

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy, presenting significant clinical heterogeneity. Arrhythmia risk stratification and detection are critical components in the evaluation and management of all cases of HCM. The 2020 American Heart Association/American College of Cardiology HCM guidelines provide new recommendations for periodic 24-48-hour ambulatory electrocardiogram monitoring to screen for atrial and ventricular arrhythmias. A strategy of more frequent or prolonged monitoring would lead to earlier arrhythmia recognition and the potential for iteration of the HCM guidelines. Detection of AF is of critical importance in successful mitigation of the thromboembolic risk with anticoagulation. Likewise, identification of nonsustained ventricular tachycardia (NSVT) remains an important component of SCD risk stratification. The aim of this article is to review current as well as investigative or potential future strategies in arrhythmia detection in patients with HCM and how that may inform treatment strategies and future guidelines.

Arrhythmia Detection

The primary objectives of arrhythmia monitoring in HCM are the detection of AF and ventricular arrhythmias so that appropriate treatment, including anticoagulation and ICD implantation, may be considered. The 2020 American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend ambulatory electrocardiogram (AECG) monitoring at initial evaluation and periodically, every 1 to 2 years.1 Extended 24-hour ECG monitoring or event recording is recommended for patients with palpitations or light-headedness until symptom-rhythm correlation is established. More frequent and prolonged periods of monitoring lead to a higher detection rate of AF and NSVT in patients with HCM across all risk groups.8,9 However, how this monitoring should be incorporated into the evaluation of patients with HCM is not well established.
appropriate treatment. However, whether such a strategy in patients with HCM results in improved outcomes is not yet established. The available evidence, knowledge gaps, and potential merits of such an approach are reviewed. Cardiac implantable electronic devices provide an opportunity for early arrhythmia detection, with the potential to enable early management strategies in order to improve outcomes.

In recent decades, an increasing number of cardiac implantable electronic devices (CIEDs), which encompass permanent pacemakers, ICDs, and implantable loop recorders (ILRs), have been used in patients with cardiovascular disease. CIEDs are capable of recording spontaneous episodes of arrhythmias using programmable detection criteria, enabling an estimate of asymptomatic arrhythmia burden in some patient populations. For example, studies have established a threshold for the prevalence of subclinical AF (SCAF) that is high in individuals with these devices. The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) evaluated 2580 patients aged over 65 years who had hypertension without a history of AF. These patients all had either a pacemaker or a defibrillator. Within the first 3 months following implantation, subclinical atrial tachyarrhythmias were detected in 10.1% of patients and were associated with an increased risk of ischemic stroke or systemic embolism. In the non-HCM population, an SCAF duration of > 6 minutes increases the risk of stroke 2.5-fold, which highlights the importance of prolonged monitoring. However, large variability is present in AF detection algorithms, and sensitivity and specificity across different CIEDs, which may impact their utility in AF detection. Controversy also surrounds the question of whether the components of CIED-detected AF (ie, duration, burden, and CHA2DS2-VASc components of CIED-detected AF) are effective predictors of stroke. Stroke risk is lower in patients with device-detected AF, compared to those with clinical AF with identical stroke risk scores.

Cardiac monitoring for SCD risk stratification

Risk stratification for SCD in HCM remains a challenge for clinicians. In both AHA/ACC and European Society of Cardiology (ESC) guidelines, secondary prevention with ICDs is recommended in patients with previous cardiac arrest or hemodynamically significant ventricular tachycardia/ventricular fibrillation (VT/VF) and reasonable life expectancy. Appropriate ICD interventions are 10%-17% per year in this population, a level significantly higher compared with that for patients implanted for primary prevention, per retrospective registry data. 

The low event rates of SCD in HCM present a challenge for primary prevention ICDs. Primary prevention using the European guidelines is based on the calculation of SCD risk within the next 5 years. Routine assessment of risk factors should be performed using echocardiogram and 48-hour AECG. Variables in the risk calculator include patient age, family history of SCD, personal history of unexplained syncope, left ventricular (LV) outflow gradient, maximum LV wall thickness, left atrial diameter, and NSVT (Fig. 1). In general, for patients with a 5-year SCD risk less than 4%, ICD implantation is not recommended. Consideration of ICDs should be given to patients with a 5-year SCD risk ≥ 4%.

AHA/ACC guidelines recommend a similar evaluation but add a recommendation for cardiac magnetic resonance imaging to assess for additional risk factors in patients at low or moderate risk. According to the 2020 AHA/ACC guidelines, consideration should be given to patients with HCM with the following risk factors: family history of SCD, maximum LV wall thickness ≥ 30 mm, personal history of unexplained syncope, ejection fraction ≤ 50%, and presence of an apical aneurysm. NSVT and extensive late gadolinium enhancement (LGE) ≥ 15% of LV mass are also established risk factors used in SCD risk stratification. The details of LGE as a risk factor have been extensively reviewed in the literature. NSVT used in risk stratification is based on episodes identified on 24- to 48-hour AECG. Neither European nor American risk calculators provide firm recommendations on the detection of NSVT on prolonged monitoring. The use of implantable devices to detect NSVT and AF results in an abundance of data, which currently have little import for change in clinical management. AHA/ACC guidelines suggest that repeated, longer, or faster runs of NSVT should prompt clinicians to consider primary prevention ICDs.

Continuous rhythm monitoring over several years is made possible using implantable devices. These include ILRs, which can help clinicians identify concerning features of ventricular arrhythmias through single-lead electrograms. Patients with HCM and suspicion for arrhythmias but without previously unidentified NSVT or AF may benefit from prolonged monitoring using ILRs. Prior studies in patients with other cardiomyopathies have demonstrated the utility of ILRs in the detection of clinically relevant arrhythmias. However, data supporting changes in clinical management based on arrhythmias detected using this method are sparse. Despite this lack of data, offering extended monitoring to patients with low ESC risk scores seems reasonable if they have uncounted risk factors, such as moderate-to-extensive ventricular scarring or apical aneurysms. Other patients who also may benefit include those with moderate SCD risk in which identification of NSVT would put them into the high—SCD risk group. Given recent data correlating faster and longer NSVT episodes with appropriate ICD therapy, patients
with previously detected slow or short NSVT runs also may benefit from extended rhythm monitoring. Although current guidelines do not recommend the use of ILRs, a suggested framework for the use of loop recorders for risk stratification is proposed in Figure 2.

No prospective, randomized controlled trials have evaluated the performance of ICDs in HCM, despite their widespread adoption. Mortality rates in HCM were as high as 4%-5% per year prior to the advent of ICD therapy in referral cohorts.\textsuperscript{29-31} The decision to proceed with ICD therapy must be balanced with the risk of inappropriate shocks and other adverse events. A cohort of 217 consecutive patients with HCM followed for over 10 years found that 64% of patients had ICD discharges occurring \textgreater{} 5 years after implantation, whereas 54% of patients experienced inappropriate shocks \textless{} 5 years after implantation.\textsuperscript{32} A meta-analysis of 27 observational studies encompassing 2190 patients with HCM across 16 international patient cohorts found appropriate—ICD intervention rates of 3.3% per year, and low cardiac mortality rates of 0.6% following ICD therapy.\textsuperscript{33} Inappropriate ICD intervention in this meta-analysis was 4.8% per year. An updated meta-analysis in 2017 covering 3797 patients found marginally higher appropriate—ICD intervention rates of 4.8% per year and inappropriate-shock rates of 4.9% per year.\textsuperscript{34} A noteworthy point is that not all ICD discharge events are equivalent to SCD. The decision for primary prevention therapy is further complicated by the relatively young age at which many patients with HCM must first consider implantation. Subcutaneous ICDs are an emerging technology that may have benefits for primary and secondary prevention of SCD in younger patient populations.\textsuperscript{35} A single-centre series of subcutaneous ICDs in HCM patients showed that the devices are effective at identifying and terminating induced VF at implantation.\textsuperscript{36}

**Figure 1.** Pathophysiology of hypertrophic cardiomyopathy, and risk factors currently used for risk stratification. LV, left ventricle; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MRI, magnetic resonance imaging; SCD, sudden cardiac death; VT, ventricular tachycardia. Reproduced from Geske et al.\textsuperscript{21} with permission from Elsevier.

**Figure 2.** Suggested framework for use of implantable loop recorders (ILRs) for risk stratification of sudden cardiac death (SCD). *Additional risk factors include, but are not limited to, late gadolinium enhancement, apical aneurysms, previous nonsustained ventricular tachycardia episodes with no high-risk features, and genetic variants of concern. ESC, European Society of Cardiology; ICD, implantable cardioverter defibrillator; SDM, shared decision-making.
AF in HCM

AF is a common sequela in HCM and is associated with impaired quality of life and increased risk of stroke. Prolonged AECG monitoring can be considered for adult patients with HCM who do not have risk factors for AF but are eligible for anticoagulation therapy, in order to screen for asymptomatic paroxysmal AF at initial evaluation and periodic follow-up every 1 to 2 years. Extended AECG monitoring can be considered for adult patients with HCM who do not have risk factors for AF but are eligible for anticoagulation therapy, in order to screen for asymptomatic paroxysmal AF at initial evaluation and periodic follow-up every 1 to 2 years.

Traditional device monitoring for AF in HCM

The prevalence of AF in HCM is 4-to-6-fold higher than it is in the similarly aged general population. Based on 24-48-hour AECG monitoring, the overall incidence of AF is 3.1% per 100 patients per year, with a lifetime prevalence of 22.5%. A case-control study of 104 patients with HCM showed the presence of AF in approximately 5% of patients at the time of HCM diagnosis. An additional 10% of patients developed the arrhythmia during the 5-year follow-up period. Another study found that AF developed in 22% of patients with HCM (n = 480) over 9 years of follow-up. In these studies, paroxysmal AF was the most common subtype identified, with 42% of patients with HCM eventually developing chronic persistent or permanent AF.

Implantable device monitoring for AF in HCM

In a small, high-risk population of 44 patients with HCM with ICDs or pacemakers, the prevalence of AF increased from 32% to 68%, with 16 patients developing de novo AF during extended monitoring. Another retrospective study in a separate cohort of 132 patients with HCM with ICDs or pacemakers found an annualized incidence of device-detected AF of 7.0%. Device-detected AF, defined as symptom-free episodes of rapid atrial rates lasting more than 30 seconds, led to changes in clinical management for most patients in these 2 studies. These contemporary studies also suggest that SCAF is more prevalent than previously thought; however, these studies represented highly selected populations, and the true prevalence of AF in the overall HCM population remains unknown. Table 1 shows AF prevalence and incidence across several studies, as detected by AECG, compared with prolonged rhythm-monitoring devices.

Current guidelines recommend lifelong therapy with a direct oral anticoagulant as the first-line therapy in all patients with HCM and AF, regardless of CHA2DS2-VASc score. Individuals with HCM and SCAF detected by internal or external cardiac devices and lasting > 24 hours should receive anticoagulant therapy. The role of anticoagulation is less clear in patients with device-detected SCAF with an episode duration of > 5 minutes but < 24 hours. In these cases, duration of the AF episodes, total AF burden, underlying risk factors, and bleeding risk should all be taken into consideration. Prolonged ambulatory monitoring with an ILR or wearable devices could be a consideration for patients with HCM with a high pretest probability for AF and consequent thromboembolic risk. Consumer-level external cardiac monitoring devices, such as smartwatches and pocket ECG monitoring devices, as they become more accessible, may soon play a larger role in AF detection. These devices would allow for earlier detection of AF and prompt initiation of appropriate treatment strategies to reduce the risk of stroke and heart failure. Of note, a recent study of 302 consecutive Canadian patients found AF to be a significant predictor of ventricular tachyarrhythmias leading to ICD therapy in patients with HCM.

NSVT in HCM

NSVT is a common arrhythmia used to estimate sudden-death risk and determine suitability for ICD therapy in both the ESC5 and AHA/ACC4 guidelines. Most studies define NSVT as ≥ 5 consecutive beats at ≥ 120 beats per minute (bpm) and lasting < 30 seconds. However, this definition uses a low threshold for NSVT and does not appear to confer the same degree of risk in an older vs a younger HCM patient. The presence of NSVT is a class IIb recommendation in adults but a class IIa recommendation in children in the 2020 ACC/AHA guidelines. Longer, faster, and more-frequent episodes of NSVT are felt to confer increased risk also. However, a noteworthy point is that earlier investigations into

| Study            | Patients, n | Prolonged monitoring device (n) | Detected AF prevalence, % | Detected AF incidence, % per year |
|------------------|-------------|--------------------------------|---------------------------|-----------------------------------|
| Guttmann et al.  | 7381        | 24-48-h Holter                  | 23                        | 3                                 |
| Olivotto et al.  | 480         | Office ECG                      | 22                        | 2                                 |
| Wilke et al.     | 44          | ICD (38), PM (5), or ILR (1)    | 33                        | 53 (over 595-d median follow-up)  |
| van Velzen et al.| 132         | ICD (116) or PM (16)            | —                         | 7                                 |
| Magnusson and Morner | 30           | ILR                             | 30                        | —                                 |

ICD, implantable cardiac device; ILR, implantable loop recorder; PM, pacemaker.
these variables based on 24- and 48-hour AECG monitoring suggested that they have little prognostic value.\textsuperscript{56,57} The updated guidelines acknowledge that more NSVT episodes are detected on prolonged monitoring, but they maintain the prior 2011 guideline recommendations of AECG monitoring every 1 to 2 years.\textsuperscript{58} Several studies have evaluated the frequency of NSVT in intermittent ambulatory monitoring of patients with HCM. In large, unselected, and non-tertiary patient populations, the frequency of the arrhythmia is estimated to be between 20% and 30% on 24- and 48-hour AECG monitoring,\textsuperscript{56,57,59} compared with less than 4% in the general population.\textsuperscript{60} In both HCM and general populations, the prevalence of NSVT increases with age.\textsuperscript{57,60} Given the high prevalence of NSVT, in combination with the low rate of SCD in patients with HCM, NSVT has been criticized for having poor positive predictive value.\textsuperscript{56} In a study assessing the impact of arrhythmias in 178 patients with HCM, NSVT detected on 24-hour ambulatory monitoring had negative and positive predictive values for SCD of 95% and 9%, respectively.\textsuperscript{56}

**NSVT as a risk factor for SCD**

Several studies evaluating NSVT detected by 24- and 48-hour AECG have determined that it is not a significant independent risk factor for SCD.\textsuperscript{61-64} Both the population of patients included and the statistical power generated may have an impact on the utility of risk markers under study. For example, one study that was unable to find NSVT to be a significant risk marker for SCD included a predominantly low-risk HCM population.\textsuperscript{64} Patients included in this study were either asymptomatic or mildly symptomatic with heart failure symptoms (New York Heart Association class I or II), had no history of syncope, and were not taking any cardioactive medications. In contrast, another study found that NSVT was a significant risk factor when patients had concurrent left ventricular outflow tract obstruction.\textsuperscript{62} In patients with severe outflow tract obstruction (≥ 90 mm Hg), NSVT carried a relative risk of 3.84 for SCD on multivariate analysis. With newer studies and more-refined patient populations, NSVT has been independently associated with an increased risk of SCD in young patients with HCM,\textsuperscript{57} and in those with exercise-induced NSVT.\textsuperscript{65} In 174 patients aged < 30 years, NSVT was associated with an odds ratio for sudden death of 4.35. Fifteen patients died suddenly in this age group, including 6 of 26 with NSVT. Exercise-induced NSVT is a rare finding, but it has also been identified as an independent marker for increased risk of SCD.\textsuperscript{65} A total of 24 of 1380 patients with HCM experienced exercise-induced NSVT during Bruce or modified-Bruce protocols. Exercise-NSVT alone was associated with a 2.82-fold increased risk of SCD or resuscitated ventricular arrhythmia. Both of these studies that identified NSVT as an independent marker of SCD are limited by low event rates, and both studies were conducted at a single tertiary care centre. A study from 1981 found that SCD or cardiac arrest occurred in 4 of 17 patients with NSVT, compared with 2 of 66 patients without recorded NSVT on 24-hour ambulatory monitoring.\textsuperscript{66} However, this study predated much of our current understanding about risk factors in HCM.

The prevalence of NSVT is likely underestimated due to the brevity of ambulatory monitoring resulting in missed...
episodes. Table 2 shows NSVT rates detected by 24- to 48-hour Holter monitoring, compared to those detected by prolonged rhythm-monitoring devices, with comparison between detection rates and SCD risk populations. NSVT detection on ILR is lower in several studies, as the rate and interval (number of beats) required for automatic detection are higher, compared with those for Holter monitoring. Contemporary extended monitoring studies evaluating arrhythmias detected in patients with an ICD suggest that the prevalence of NSVT in this high-risk population is upward of 80%. High-risk patients with HCM likely suffer from a higher burden of ventricular arrhythmias, as the risk of sudden death increases along with increased wall thickness. Given the high prevalence of NSVT on prolonged monitoring, its characteristics have been investigated more thoroughly, including rate, length, and frequency. One study of 160 patients using ICD data concluded that NSVT was independently associated with ICD-treated ventricular arrhythmias. In particular, NSVT rates greater than 200 bpm, those with more-than-7-beat runs, and repetitive runs (defined as > 1 run over ≥ 6 months of monitoring) were more predictive of ICD-treated ventricular arrhythmias. ICD treatment in this study included anti-tachycardia pacing for VT in 10 patients, and shocks for VT/VF in 14 patients. The average VT zone in the study was 202 ± 13 bpm, and the average VF zone was 233 ± 13 bpm. On ICD interrogation, the mean number of beats was 14 at a mean rate of 222 bpm, compared with 11 beats at a mean rate of 152 bpm on AECG monitoring.

Another observational study found evidence that longer duration and faster NSVT episodes are predictive of appropriate ICD intervention for VT/VF, although no cutoff was proposed. In this study, 41 of 51 total patients had Holter- and/or ICD-recorded NSVT. Of these patients, 31 had NSVT recorded on their ICD across a median of 32 months. Ten patients with previously recorded Holter NSVT did not have any episodes of ICD-recorded NSVT (29%); by comparison, 7 of 17 patients (41%) with no prior Holter-NSVT then had at least one episode of ICD-detected NSVT. A large proportion of patients in this study had NSVT episodes detected by Holter monitoring prior to ICD implantation (67%). All patients enrolled in this study had either one major risk factor for SCD and advanced HCM phenotype, or multiple major risk factors. Authors in this study derived an equation to predict NSVT severity (heart rate x length in beats/100 ≥ 28), with a hazard ratio of 5.45 for ICD intervention.

Another contemporary study involving 60 patients with prophylactic ICD therapy found that rapid NSVT (> 150 bpm lasting 4-16 beats) detected by ICD carried a hazard ratio of 6.2 (P = 0.01) for device-treated ventricular arrhythmias. Of patients who went on to have ventricular arrhythmias in this study, 7 of 9 also had ICD-detected rapid NSVT. The following aspects are consistent across all these studies that evaluated NSVT detected on prolonged monitoring via ICD: the identification of patients without prior NSVT on AECG; the identification of faster and longer runs of NSVT; and the finding that ICD-detected NSVT is significantly associated with ventricular arrhythmias leading to antitachycardia pacing and/or shock treatment by ICD. As a caveat, many of these earlier studies used antitachycardia pacing and shock treatment by ICD as a surrogate for SCD. The Primary Prevention Parameters Evaluation (PREPARE), Role of Long Detection

Figure 3. (A, B) nonsustained ventricular tachycardia electrogram episodes. (C) Atrial flutter (AF) electrogram, detected by the Confirm Rx Implantable Cardiac Monitor (Abbott, Chicago) in 3 different hypertrophic cardiomyopathy patients being monitored for risk stratification. Numbers denote milliseconds between beats. T, tachycardia; VS, ventricular sensing; Act, recording activation.
Window Programming in Patients With Left Ventricular Dysfunction, Non-Ischemic Etiology in Primary Prevention Treated With a Biventricular ICD (RELEVANT), and Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy (MADIT-RIT) studies suggest that high-rate therapy (ie, faster heart rate detection and longer delays to therapy) reduces the rate of inappropriate therapy, as VT episodes likely will resolve without intervention.69-71

Traditional device monitoring for NSVT in HCM

One retrospective study comparing the diagnostic yield of 14-day Holter monitoring to traditional 24-48-hour monitoring found that 75% of patients with HCM had NSVT detected during 14-day monitoring.9 Only 17% of the 77 patients enrolled in this study had NSVT detected in the first 24 hours, and 34% did in the first 48 hours. Patients who exhibited NSVT episodes in the first 48 hours were more likely to have future episodes of NSVT, with a median number of 5 runs throughout the 14 days. These same patients had longer and faster runs of NSVT. Longer and faster runs were frequently detected beyond the initial 48 hours of monitoring. Only 9% of patients with runs > 10 beats were identified in the first 48 hours, compared with 37.7% of patients in whom these longer runs occurred. Most patients recruited to this study had one or more major risk factors for SCD, and many patients also had moderate or severe LGE on cardiac magnetic resonance imaging. Most patients underwent 14-day Holter testing for the purpose of risk stratification, and thus this study population was created with considerable referral bias. No patient outcome data were assessed in this study; therefore, whether the presence of NSVT on 14-day ambulatory monitoring has any prognostic implications is unclear. However, this monitoring may provide additional risk stratification if faster and longer episodes are detected. A study of 60 patients with primary prevention ICD found that Holter-detection alone was not a significant predictor of ICD-treated ventricular arrhythmia events.28

Implantable device monitoring for NSVT in HCM

ILRs present a viable option for continuous rhythm monitoring in patients with HCM who do not meet criteria for a primary prevention ICD. ILRs are currently recommended for evaluating patients at high risk of developing ventricular arrhythmias, such as those with recurrent unexplained syncope or recurrent palpitations without a diagnosis.72 A meta-analysis comprising 4381 patients undergoing ILR insertion for undetermined syncope revealed a diagnosis in 43.9% of patients. Important to note is that the rate of ventricular arrhythmias diagnosed in the study was 2.7%, despite the exclusion in most studies of patients suspected of having VT/VF.73

Two studies have evaluated the use of ILRs in patients with HCM after alcohol septal ablation (ASA). This procedure can theoretically induce ventricular arrhythmias through induction of myocardial scarring. One study in 44 low-risk patients post-ASA found sustained VT/VF in 3 patients within 30 days of ASA, including 2 cases of procedural VF.74 Another study evaluating all arrhythmias (supraventricular tachycardia, AF, NSVT, VT, complete heart block) in 56 patients found that the first occurrence of any arrhythmia was 71% at 18 months of follow-up, and 43% at 3 months of ASA.75 NSVT and VT were detected in 5 patients (9%). A study published in 2020 that evaluated ILRs in a low-risk HCM population detected NSVT in 7 of 30 patients (23%), with new detection in 5 patients with previously undetected NSVT on Holter monitoring.8 No episodes of VT/VF were detected in this study. Figure 3 shows NSVT and atrial flutter electrograms recorded by the same type of ILR used in this study. A similar recent study in the Netherlands included 50 low- or intermediate-risk patients with HCM.76 Half of the patients received an ILR. Continuous monitoring detected de novo AF only in the ILR group, and one patient from each of the 2 groups received a primary prevention ICD. This study demonstrates the utility of extended continuous monitoring resulting in actionable events, although studies have yet to demonstrate a change in patient outcomes.

Conclusion

Arrhythmia risk stratification and detection in HCM are critical components of disease evaluation and management. Patients with HCM are at an increased risk of developing arrhythmias, including AF and NSVT, which are associated with increased morbidity and mortality. Current HCM guidelines recommend monitoring for these arrhythmias on an annual basis, using AECG for those without an ICD. Early detection of arrhythmias in HCM prompts initiation of appropriate medical and device therapies, thereby preventing fatal sequelae of the disease. SCAF is better detected with CIEDs, as demonstrated by studies showing increased incidence of AF on prolonged monitoring, compared with traditional 24- to 48-hour ambulatory monitoring. A similar pattern appears with NSVT on prolonged monitoring. Emerging studies suggest that faster and longer NSVT episodes are more predictive of SCD. However, data supporting a change in management based on NSVT episodes detected on ILR or other prolonged monitoring methods remain limited. Overall, a general clinical trend and mounting evidence support longer and more-intensive outpatient electrocardiographic monitoring in patients with HCM who do not have implantable devices. However, a need remains to demonstrate that this expensive and resource-intensive strategy can translate into improved patient outcomes.

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