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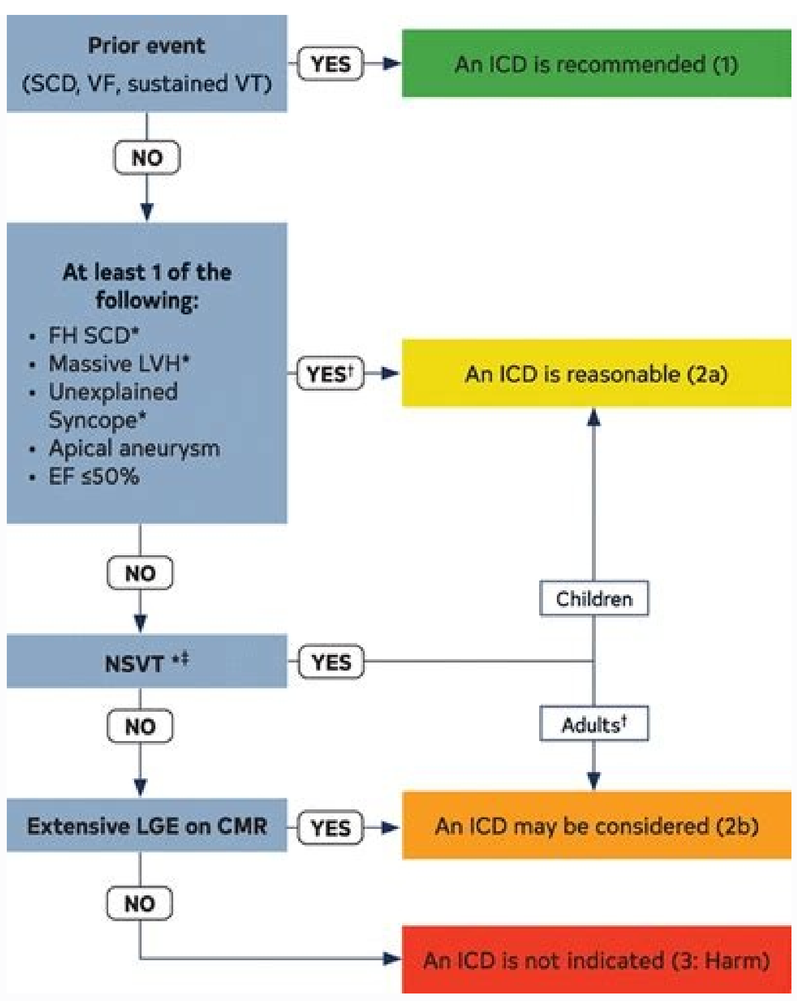

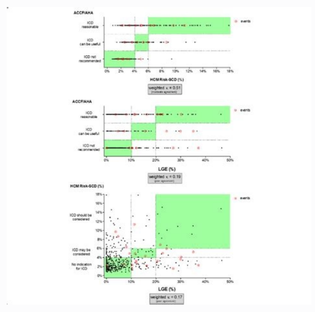

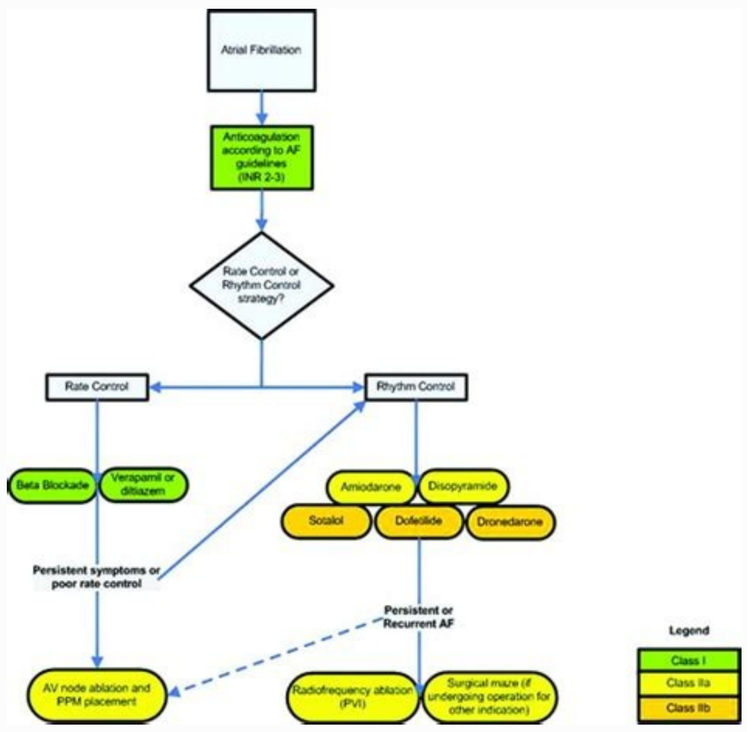

Recommendations for Management of Patients With Nonobstructive HCM With Preserved EF
Referenced studies that support the recommendations are summarized in Online Data Supplement 10.

COR	LOE	Recommendations
1	C-LD	1. In patients with nonobstructive HCM with preserved EF and symptoms of exertional angina or dyspnea, beta blockers or non-dihydropyridine calcium channel blockers are recommended.[209,238-246]
2a	C-EO	2. In patients with nonobstructive HCM with preserved EF, it is reasonable to add oral diuretics when exertional dyspnea persists despite the use of beta blockers or non-dihydropyridine calcium channel blockers.
2b	C-LD	3. In patients with nonobstructive HCM with preserved EF, the usefulness of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the treatment of symptoms (angina and dyspnea) is not well established.[247]
2b	C-LD	4. In highly selected patients with apical HCM with severe dyspnea or angina (NYHA class III or class IV) despite maximal medical therapy, and with preserved EF and small LV cavity size (LV end-diastolic volume <50 mL/m^2 and LV stroke volume <30 mL/m^2), apical myectomy by experienced surgeons at comprehensive centers may be considered to reduce symptoms.[248]
2b	C-EO	5. In asymptomatic patients with non-obstructive HCM, the benefit of beta blockers or calcium channel blockers is not well established.

Recommendations for Angiography and Invasive Hemodynamic Assessment
Referenced studies that support the recommendations are summarized in Online Data Supplement 9.

COR	LOE	Recommendations
1	B-NR	1. For patients with HCM who are candidates for SRT and for whom there is uncertainty regarding the presence or severity of LVOTO on noninvasive imaging studies, invasive hemodynamic assessment with cardiac catheterization is recommended.[45,107-109]
1	B-NR	2. In patients with HCM with symptoms or evidence of myocardial ischemia, coronary angiography (CT or invasive) is recommended.[110]
1	B-NR	3. In patients with HCM who are at risk of coronary atherosclerosis, coronary angiography (CT or invasive) is recommended before surgical myectomy.[111]

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Reviewer Relationships With Industry and Other Entities (Comprehensive) e628Shared decision-making, a dialogue between patients and their care team that includes full disclosure of all testing and treatment options, discussion of the risks and benefits of those options and, importantly, engagement of the patient to express their own goals, is particularly relevant in the management of conditions such as hypertrophic cardiomyopathy (HCM).Although the primary cardiology team can initiate evaluation, treatment, and longitudinal care, referral to multidisciplinary HCM centers with graduated levels of expertise can be important to optimizing care for patients with HCM. Challenging treatment decisions—where reasonable alternatives exist, where the strength of recommendation is weak (eg, any Class 2b decision) or is particularly nuanced, and for invasive procedures that are specific to patients with HCM—represent crucial opportunities to refer patients to these HCM centers.Counseling patients with HCM regarding the potential for genetic transmission of HCM is one of the cornerstones of care. Screening first-degree family members of patients with HCM, using either genetic testing or an imaging/electrocardiographic surveillance protocol, can begin at any age and can be influenced by specifics of the patient/family history and family preference. As screening recommendations for family members hinge on the pathogenicity of any detected variants, the reported pathogenicity should be reconfirmed every 2 to 3 years.Optimal care for patients with HCM requires cardiac imaging to confirm the diagnosis, characterize the pathophysiology for the individual, and identify risk markers that may inform decisions regarding interventions for left ventricular outflow tract obstruction and sudden cardiac death (SCD) prevention. Echocardiography continues to be the foundational imaging modality for patients with HCM. Cardiovascular magnetic resonance imaging will also be helpful in many patients, especially those in whom there is diagnostic uncertainty, poor echocardiographic imaging windows, or where uncertainty persists regarding decisions around implantable cardioverter-defibrillator (ICD) placement.Assessment of an individual patient’s risk for SCD continues to evolve as new markers emerge (eg, apical aneurysm, decreased left ventricular systolic function, and extensive gadolinium enhancement). In addition to a full accounting of an individual’s risk markers, communication with patients regarding not just the presence of risk markers but also the magnitude of their individualized risk is key. This enables the informed patient to fully participate in the decision-making regarding ICD placement, which incorporates their own level of risk tolerance and treatment goals.The risk factors for SCD in children with HCM carry different weights than those observed in adult patients; they vary with age and must account for different body sizes. Coupled with the complexity of placing ICDs in young patients with anticipated growth and a higher risk of device complications, the threshold for ICD implantation in children often differs from adults. These differences are best addressed at primary or comprehensive HCM centers with expertise in children with HCM.Septal reduction therapies (surgical septal myectomy and alcohol septal ablation), when performed by experienced HCM teams at dedicated centers, continue to improve in safety and efficacy such that earlier intervention may be possible in select patients with drug-refractory or severe outflow tract obstruction causing signs of cardiac decompensation. Given the data on the significantly improved outcomes at comprehensive HCM centers, these decisions represent an optimal referral opportunity.Patients with HCM and persistent or paroxysmal atrial fibrillation have a sufficiently increased risk of stroke such that oral anticoagulation with direct oral anticoagulants (or alternatively warfarin) should be considered the default treatment option independent of the CHA2DS2VASc score. As rapid atrial fibrillation is often poorly tolerated in patients with HCM, maintenance of sinus rhythm and rate control are key pursuits in successful treatment.Heart failure symptoms in patients with HCM, in the absence of left ventricular outflow tract obstruction, should be treated similarly to other patients with heart failure symptoms, including consideration of advanced treatment options (eg, cardiac resynchronization therapy, left ventricular assist device, transplantation). In patients with HCM, an ejection fraction 2.5 may be appropriate to identify early HCM in asymptomatic children with no family history, whereas for children with a definitive family history or a positive genetic test, a threshold of z >2 may suffice for early diagnosis. The emergence of the HCM phenotype in younger family members who carry a pathogenic sarcomere variant without previously evident LVH at initial screening (ie, genotype-positive/previously phenotype-negative) is well recognized and underscores the principle that normal or mildly increased LV wall thicknesses will be encountered in individuals with genetically affected status, as the disease manifests. In the absence of increased wall thickness, such individuals should be considered at risk for subsequent development of, but not yet having, clinically evident HCM.Nearly any pattern and distribution of LV wall thickening can be observed in HCM, with the basal anterior septum in continuity with the anterior free wall the most common location for LVH. In a subset of patients, hypertrophy can be limited and focal, confined to only 1 or 2 LV segments with normal LV mass. Although common in HCM, neither systolic anterior motion (SAM) of the mitral valve nor hyperdynamic LV function is required for a clinical diagnosis. A number of other morphologic abnormalities are also not diagnostic of HCM but can be part of the phenotypic expression of the disease, including hypertrophied and apically displaced papillary muscles, myocardial crypts, anomalous insertion of the papillary muscle directly in the anterior leaflet of the mitral valve (in the absence of chordae tendinae), elongated mitral valve leaflets, myocardial bridging, and right ventricular (RV) hypertrophy.2.4. EtiologyIn the early 1990s, the DNA sequencing of HCM pedigrees led to the discovery that damaging variants in genes coding for sarcomere proteins segregated (or were co-inherited) with LVH identified by echocardiographic assessment, abnormal ECGs, and physical findings. HCM thereby became regarded as a monogenic cardiac disease, helping to consolidate a clinically heterogeneous disease into a single entity based on genetic substrate.1Currently, variants in 1 of 8 or more genes encoding proteins of the cardiac sarcomere (or sarcomere-related structures) have been implicated in causing LVH, the sine qua non of HCM. Among patients with HCM, ~30% to 60% have an identifiable pathogenic or likely pathogenic genetic variant. A substantial proportion of patients with HCM are currently without any evidence of a genetic etiology to their disease, including a subgroup (up to 40% of patients in 1 study) who also have no other affected family members (ie, “non-familial” HCM).2 These observations suggest that other novel pathophysiologic mechanisms may be responsible or contribute to phenotypic expression in these affected patients with HCM.Among patients with HCM and a pathogenic sarcomeric gene variant, the 2 most common genes are beta myosin heavy chain 7 (MYH7) and myosin-binding protein C3 (MYBPC3), identified in 70% of variant-positive patients, while other genes (TNNI3, TNNT2, TPM1, MYL2, MYL3, ACTC1) each account for a small proportion of patients (1% to 5%). Within these genes, >1500 variants have been recognized, the majority of which are “private” (unique to the individual family). Each offspring of an affected family member has a 50% chance of inheriting the variant.3 Although the likelihood of developing clinical HCM is high in family members with a pathogenic variant, the age at which disease expression occurs in a given individual is variable.The precise mechanisms by which sarcomere variants result in the clinical phenotype have not been fully elucidated. Mutant sarcomere genes trigger myocardial changes, leading to hypertrophy and fibrosis, which ultimately results in a small, stiff ventricle with impaired systolic and diastolic performance despite a preserved LVEF. Similarly, abnormal sarcomeric proteins may not be solely responsible for all of the clinical characteristics observed in patients with HCM. Diverse disease features including abnormal intramural coronary arteries responsible for small vessel ischemia, elongated mitral valve leaflets, and congenital anomalies of the sub-mitral valve apparatus, which are widely recognized components of the HCM phenotype, appear to have no known direct association with sarcomere variants.2.5. Natural History/Clinical CourseAlthough HCM can be compatible with normal life expectancy without limiting symptoms or the need for major treatments in most patients, other patients can experience significant consequences that are attributable to the disease. To this point, there is increasing recognition of patients with HCM identified clinically at advanced ages of >60 years with little to no disability. Yet, a multicenter registry report has suggested that the lifelong risk of adverse events (eg, mortality, HF, stroke, ventricular arrhythmia, AF) caused by HCM may be greater among patients with pathogenic sarcomeric gene variants or those diagnosed early in life.1 The large number and diversity of the HCM-associated variants does not allow the specific genotype to be used to inform the anticipated outcomes in individual patients.Among referral-based cohorts of patients with HCM, 30% to 40% will experience adverse events, including: 1) sudden death events; 2) progressive limiting symptoms because of LVOTO or diastolic dysfunction; 3) HF symptoms associated with systolic dysfunction; and 4) AF with risk of thromboembolic stroke. Nevertheless, studies reporting relatively long-term HCM patient outcomes have demonstrated that for patients at risk for, or who develop one of these, disease-related complications, the application of contemporary cardiovascular therapies and interventions has lowered HCM mortality rates to 90%>90%Rest and provoked LVOT gradient 90%>90%A comprehensive HCM center comprises a similar organizational structure as a primary HCM center but has demonstrated graduated levels of expertise and resources specific for HCM that include additional competencies (Table 3). Referral to a comprehensive HCM center should

specifically be considered for those patients with HCM who are candidates for any procedure specific to, or which requires specialized expertise to perform in, HCM, including particularly complex invasive SRTs,3,8,9 catheter ablation for ventricular and complex atrial tachyarrhythmias,10,11 and advanced HF therapies, including transplant.12,13 In addition, referral to a comprehensive HCM center can aid in complex disease-related management decisions including, but not limited to, particularly challenging primary prevention ICD decision-making as well as counseling patients with HCM on the potential risks associated with participating in competitive sports.4Recommendation-Specific Supportive TextWhen performed in centers with limited experience and low procedural volume, invasive SRTs for relief of LVOTO are associated with increased mortality and morbidity, as well as mitral valve replacement.1–3,15,16 Strong consideration should therefore be given to referral of patients with obstructive HCM who are candidates for invasive SRTs to established high-volume primary or comprehensive HCM centers, which can perform these procedures with optimal safety and benefit outcomes.Given the unique needs of HCM in clinical cardiovascular practice, as well as the specialized training and interpretation associated with many of the procedures and testing that are now routinely applied to this complex genetic heart disease, challenging management decision-making can arise for which it would be reasonable to offer patients referral to or consultation with an HCM center.4–136. Diagnosis, Initial Evaluation, and Follow-up6.1. Clinical DiagnosisSynopsisClinical evaluation for HCM may be triggered by the identification of a family history of HCM, symptoms including a cardiac event, a heart murmur during physical examination, during echocardiography performed for other indications, or an abnormal 12-lead ECG. A proper clinical evaluation should start with a comprehensive cardiac history, a family history including 3 generations, and a comprehensive physical examination (including maneuvers such as Valsalva, squat-to-stand, passive leg raising, or walking). This should be followed by an ECG and cardiac imaging to identify LVH when clinical findings are suggestive.Recommendation-Specific Supportive Text1. Many patients with HCM are asymptomatic and identified incidentally or as a result of screening. Clinical history includes a detailed cardiac history and family history (3 generations) to identify relatives with HCM or with unexpected/sudden death. Assessment of overall fitness and functional capacity, with emphasis on training regimen and symptoms in response to exertion—chest pain, dyspnea, palpitations, and syncope. Associated syndromic or systemic/extracardiac symptoms or organ involvement are also documented (eg, ataxia, hearing, visual, or cognitive impairment, failure to thrive, neurodevelopmental abnormalities). Alternative etiologies to be considered include physiologic remodeling of the athlete, long-standing systemic hypertension, renal disease, or infiltrative diseases (amyloid cardiomyopathy). In neonates, a history of maternal gestational diabetes is sought, and in infants 7 to 8 years of age, because young children are often unable to cooperate with exercise testing.Intra-operative TEE is a standard part of surgical myectomy and adjunctive repairs for patients with HCM. TEE can assess mitral valve abnormalities and MR and extent of septal hypertrophy, as well as provide assessment of residual SAM of the mitral valve and LVOTO, and occurrence of a ventricular septal defect or new aortic insufficiency.27–30TTE or TEE imaging helps guide alcohol septal ablation, particularly in localizing the appropriate left anterior descending septal perforator by intracoronary contrast injection as well as monitoring of LVOT gradient reduction during the procedure. The use of transthoracic guidance with ultrasound-enhancing agents has resulted in greater procedural success, decreased intervention time, smaller infarct size, and lower heart block rates.6,31–35 In cases where transthoracic image quality is suboptimal, intraprocedural TEE with ultrasound- enhancing agents can be used to guide septal ablation therapy.6,35Following SRT, efficacy of therapy, particularly evidence of septal thinning and LVOT gradient decrease, should be assessed. Residual SAM of the mitral valve and MR, aortic insufficiency, LV systolic and diastolic function, and ventricular septal defect should also be assessed. Although these results are usually apparent immediately after surgical septal myectomy, changes in LVOTO and formation of a myocardial septal scar may evolve over time (typically complete in 3 months but in some patients may persist for a year) after septal ablation.36,38,39,48,49When a diagnosis of HCM is made in a proband, echocardiographic screening of first-degree relatives is offered to identify affected relatives. In 2 large pediatric studies, yield on echocardiographic screening for clinical HCM in first-degree relatives was 10% to 15% throughout childhood and adolescence with similar disease rates of penetrance across age range.39,43,50 The median age at HCM onset was 8.9 (4.7 to 13.4) years, with earlier onset in males, those with family history of SCD, and pathogenic variants in MYH7/MYBPC3.39 Likewise, the median time from HCM onset to a major cardiac event, including death, SCD, or cardiac intervention (myectomy, ICD), was 1.5 years.39,49–51 Taken together, these data support family screening initiated in childhood and repeated on a periodic basis as outlined in Table 6 in children and adults. It is also important to note that changes in LV systolic strain and diastolic function can precede definitive hypertrophy.52–54 Family members with these abnormalities likely warrant closer follow-up.The ongoing screening of genotype-positive, phenotype-negative family members of all ages is important. Previous small studies reported onset of clinical HCM in adolescence or young adulthood for most genotype-positive cases.2,55 However, recent large studies suggest that clinical HCM can develop in younger family members, with 5% to 10% being phenotype-positive at first screening and another 3% to 5% before 18 years of age. Phenotype conversion can occur in young adults and therefore continued screening into adulthood is warranted, although frequency of screening can be lowered because disease penetrance is lower in individuals who are >18 years of age.41–44,56 Although there is an absence of systematic evidence, most physicians continue clinical screening until midlife (age 50s) because disease can manifest in adults albeit at a lower frequency.TEE can be particularly useful if there is uncertainty regarding mitral valve structural abnormalities, mechanism of MR, or suspicion of alternate causes of outflow obstruction (discrete subaortic stenosis, valvular stenosis) on TTE or suspected or by other clinical parameters.30In patients with HCM, LVH can be localized to any segment of the LV wall, and care should be taken to completely image all LV wall segments. In cases where the LV apex is suboptimally visualized, use of ultrasound-enhancing agent or CMR imaging can aid in detection of apical hypertrophy, aneurysm, and thrombus.45,57,58In patients who are asymptomatic, understanding whether they have LVOTO at rest or provocation is important in understanding the potential pathophysiology. Even in asymptomatic patients, knowing that they have provocable obstruction can influence health advice (eg, regarding hydration) or choice of therapies for concomitant conditions (eg, diuretics or vasodilators for patients with hypertension).21,23–26Table 6. Screening With Electrocardiography and 2D Echocardiography in Asymptomatic Family Members*Age of First-Degree RelativeInitiation of ScreeningRepeat ECG, EchoPediatric Children and adolescents from genotype-positive families, and families with early onset diseaseAt the time HCM is diagnosed in another family memberEvery 1-2 y All other children and adolescentsAt any time after HCM is diagnosed in a family member but no later than pubertyEvery 2-3 yAdultsAt the time HCM is diagnosed in another family memberEvery 3-5 y6.3. Cardiovascular Magnetic Resonance ImagingFigure 1. Recommended evaluation and testing for HCM. Colors correspond to the Class of Recommendation in Table 2. *The interval may be extended, particularly in adult patients who remain stable after multiple evaluations. CMR indicates cardiovascular magnetic resonance; CPET, cardiopulmonary exercise test; ECG, electrocardiography/electrocardiogram; HCM, hypertrophic cardiomyopathy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVOTO, left ventricular outflow tract obstruction; P/LP, pathogenic or likely pathogenic variant; SCD, sudden cardiac death; and VUS, variant of unknown significance.SynopsisCMR imaging provides high spatial resolution and fully tomographic imaging of the heart, as well as assessment of myocardial fibrosis after injection of contrast with LGE.1,2 These attributes of CMR imaging are well-suited for characterizing the diverse phenotypic expressions of HCM, providing diagnosis, risk prediction, and preprocedural planning for septal reduction.1,7 For these reasons, CMR imaging is an important complementary imaging technique in the evaluation of patients with HCM.CMR imaging has the distinct advantage, by virtue of producing images with sharp contrast between the blood pool and myocardium, to provide highly accurate LV wall thickness measurements, robust quantification of LV and RV chamber size, LV mass, systolic function, and can identify areas of LVH not well visualized by echocardiography.1–7 CMR imaging has also expanded our appreciation for the diversity in morphologic abnormalities, including LV apical aneurysms as well as structural abnormalities of the mitral valve and subvalvular apparatus that contribute to LVOTO, findings which may impact management strategies.7–9,16–19 Additionally, extensive LGE (ie, myocardial fibrosis) represents a noninvasive marker for increased risk for potentially life-threatening ventricular tachyarrhythmias and HF progression with systolic dysfunction.11–14 It is recognized that CMR imaging may not be feasible in certain patients because of availability, cost, contraindications attributable to pacemakers or ICDs, severe renal insufficiency, and patient factors (pediatric age and a requirement for general anesthesia, or sedation, claustrophobia, or body habitus).Recommendation-Specific Supportive TextFor patients in whom HCM is suspected based on cardiac symptoms, an abnormal 12-lead ECG, or family history of inherited heart disease, and in whom echocardiographic examination is nondiagnostic or inconclusive, CMR imaging is an important adjunctive test to clarify diagnosis.1–7 In such clinical situations, CMR imaging can identify focal areas of LVH, particularly when hypertrophy is confined to certain regions of the LV wall, including the anterolateral wall, posterior septum, and apex. This increased sensitivity in detecting LVH by CMR imaging is attributable to high spatial resolution and the fact that CMR imaging is not encumbered by poor acoustic windows caused by pulmonary or thoracic parenchyma.4–6Important differences in the pattern and location of LVH, cavity dimensions, and the pattern and distribution of LGE can aid in the differentiation of HCM from other cardiovascular diseases associated with LVH, including other inherited cardiomyopathies (eg, lysosomal or glycogen storage diseases), infiltrative cardiomyopathies (eg, amyloid), or conditions with secondary hypertrophy attributable to pressure overload (eg, hypertension or athletic conditioning).7In some patients with HCM, maximal LV wall thickness measurements can be underestimated (or overestimated) with echocardiography compared with CMR imaging.1–7 This observation can have direct management implications for SCD risk assessment, because LV wall thickness is one of the major risk markers for SCD.4–6,10 In addition, apical aneurysms may not always be detected by echocardiography.8,9 Extensive LGE, often occupying multiple LV segments, is associated with increased risk for future potentially life-threatening ventricular arrhythmias, independent of location or pattern within the LV wall11–13 Some studies have promoted a threshold for extensive LGE of ≥15% of the LV mass as representing a significant (2-fold) increase in SCD risk.12 However, there is no consensus on the optimal quantification technique(s) that can yield varying results. The absence of (or minimal) LGE is associated with lower risk for SCD.12,13,21 LGE can serve as an arbitrator to aid in decision-making when the decision on whether to pursue ICD placement remains ambiguous after standard risk stratification.12Patients with HCM and systolic dysfunction (EF 35 years of age, and also that longer and faster NSVT is associated with greater incidence of ICD-treated arrhythmias.14 There is also evidence that longer periods of monitoring will diagnose more episodes of NSVT15; however, NSVT as a risk factor for SCD has historically been based on a 24- to 48-hour monitor. The optimal time frame of monitoring is not yet established and, thus, at this time, it is reasonable to perform serial ambulatory electrocardiographic monitoring every 1 to 2 years in patients who do not have ICDs.In the presence of symptoms, ambulatory electrocardiographic monitoring should be continued until a patient has symptoms while wearing the monitor. In some patients with infrequent symptoms, portable event monitors or implantable monitors may be warranted.7ECGs are considered to be a standard part of the initial screening of relatives of patients with HCM.AF is associated with adverse outcomes (including stroke) in patients with HCM. Although several studies show that asymptomatic AF is present is up to 50% of patients,8–12 it is unclear that asymptomatic episodes, especially if short in duration, contribute to adverse outcomes. Predictors of AF include left atrial dilatation, advanced age, and NYHA class III to class IV HF. Thus, patients with these characteristics should be assessed more frequently and possibly including extended ambulatory electrocardiographic screening.AF is associated with adverse outcomes (including stroke) in patients with HCM. Although several studies show that asymptomatic AF is present is up to 50% of patients,8–12 it is unclear that asymptomatic episodes, especially if short in duration, contribute to adverse outcomes. Predictors of AF include left atrial dilatation, advanced age, and NYHA class III to class IV HF. Thus, patients with these characteristics should be assessed more frequently and possibly including extended ambulatory electrocardiographic screening.6.6. Angiography and Invasive Hemodynamic AssessmentSynopsisOver the past 60 years, the hemodynamic profile and assessment of patients with obstructive HCM has been well established. Echocardiography remains the gold standard for the reliable, noninvasive assessment of dynamic outflow tract obstruction in HCM. For this reason, there is no compelling rationale to consider invasive hemodynamic evaluation in the routine assessment of patients with obstructive HCM or routine coronary angiography in the general population who has HCM. Invasive hemodynamic assessment should be undertaken only when the diagnostic information cannot be obtained from the clinical and noninvasive imaging examinations and when such information will alter patient management. Consequently, selected patient subsets will benefit from these evaluations. It is crucial that the operator who performs the assessment be experienced in such cases and use appropriate catheters while avoiding pitfalls such as catheter entrapment.Recommendation-Specific Supportive TextIn patients with a clinical history of significant limiting HF symptoms (NYHA class II to class IV) but in whom there is ambiguity regarding presence or magnitude of an LVOT gradient on cardiac imaging, invasive hemodynamic studies can clarify the presence of resting or latent outflow tract obstruction as well as provide information on cardiac output and filling pressures. Such circumstances may arise if the reliability of echocardiographic imaging is limited by poor acoustic windows, or if the Doppler profile cannot be reliably distinguished between increased velocity from outflow tract obstruction versus contamination of the profile by MR or reflect the fact that outflow gradients can be extremely dynamic, with spontaneous variability influenced by altered myocardial contractility and loading conditions at the time of cardiac imaging testing.A number of provocative maneuvers have been used in the catheterization laboratory to identify the presence of a latent gradient, including Valsalva maneuver, inducing a premature ventricular contraction to assess for the Brockenbrough-Braunwald-Morrow sign (post-extrasystolic augmentation in LVOT gradient and reduction in aortic pulse pressure), upper or lower extremity exercise, and inhalation of amyl nitrate. Low-dose isoproterenol infusion may be used to assess for latent obstruction as its use is generally limited to those invasive cardiologists with expertise in the hemodynamic evaluation of HCM. Dobutamine has previously been used for this purpose; however, the dosing protocols used for dobutamine stress studies can induce gradients even in patients without HCM, leading to a significant false-positive rate.7Another common clinical scenario that may support invasive hemodynamic assessment in a patient with obstructive HCM is coexistent valvular aortic stenosis.In clinical situations such as those noted previously, it is crucial that the operator performing the assessment be experienced in such cases and use appropriate catheters (eg, endhole pigtail, halo) while avoiding pitfalls such as catheter entrapment. Documentation of the LVOT gradient at rest and, if not severe (≥50 mm Hg), after provocative maneuvers helps guide clinical care.Chest discomfort is a common symptom in patients with HCM. For those patients with atherosclerotic coronary risk factors or in whom chest pain does not respond to medical therapy, the possibility of epicardial coronary artery disease (CAD) needs to be considered. Epicardial CAD may also be suspected based on noninvasive testing, although high false-positive rates are associated with nuclear stress testing. Coronary angiography is useful in patients with HCM when findings of CAD could aid in patient management.Coronary angiography is usually performed in patients who are scheduled for surgical myectomy and have risk factors for coronary atherosclerosis. Findings of extensive CAD would inform decision-making regarding altering the strategy to surgical myectomy combined with coronary bypass surgery. Coronary angiography is a requisite component of alcohol septal ablation, to assess septal anatomy and for the presence of CAD that can be addressed at the time of septal ablation.6.7. Exercise Stress TestingSynopsisThere is evidence to show that exercise stress testing, particularly when combined with simultaneous analysis of respiratory gases (ie, cardiopulmonary exercise test [CPET]), is safe in patients with HCM and provides information on the severity and mechanism of functional limitation. The value of exercise testing in assessing myocardial ischemia is limited because of resting ECG and wall motion abnormalities. Myocardial perfusion imaging using single-photon or positron emission tomography shows perfusion abnormalities in >50% of patients, most of whom have no significant epicardial CAD.Recommendation-Specific Supportive TextLVOT gradients can be dynamic, and maneuvers performed during a resting TTE to provoke an LVOT gradient (such as Valsalva) can be variable because of inconsistencies in instruction and patient effort. Stress echocardiography, representing the most physiologic form of provocation, can be most helpful for those patients where the presence or severity of LVOTO is uncertain after the baseline echocardiogram.5–9 LV outflow gradients in the postprandial state are higher than when fasting,11 and treatment with beta-blockers often reduces the severity of exercise-induced LVOTO. Although there are few data comparing treadmill and bicycle ergometry, both are acceptable when performed in experienced laboratories. Exercise testing is only useful in older children, typically >7 to 8 years of age, because young children are often unable to cooperate with exercise testing.CPET is a standard part of the evaluation for patients with severe symptoms, including those being considered for cardiac transplantation.3,4 CPET can be helpful in differentiating HCM from other causes of ventricular hypertrophy, for example, athletic adaptation.CPET, with simultaneous measurement of respiratory gases, provides objective data on the severity and mechanism of functional limitation.3,4 Data from >3000 patients show that reduced peak oxygen consumption and submaximal exercise parameters, such as ventilatory efficiency and anaerobic threshold, are associated with progression to advanced HF and all-cause mortality.In patients who are asymptomatic, understanding whether they have LVOTO at rest or provocation provides a comprehensive understanding their individual pathophysiology. Even in asymptomatic patients, knowing that they have provocable obstruction can influence health advice (eg, regarding hydration), or choices of therapies for concomitant conditions (eg, diuretics or vasodilators for patients with hypertension).5–10 Latent LVOTO, as an explanation for exertional or postural syncope, can be revealed by exercise stress echocardiography. Up to one-third of adults with HCM have hypotension or a failure to augment the systolic blood pressure during exercise caused by an inappropriate fall in systemic vascular resistance or low cardiac output reserve. An abnormal exercise blood pressure response (failure to increase systolic blood pressure by at least 20 mm Hg, or a drop in systolic blood pressure during exercise of >20 mm Hg from the peak value obtained) may be associated with a higher risk of SCD in patients ≤40 years of age. Its value as an independent marker of sudden death risk is confounded by the emergence of newer risk markers.CPET, with simultaneous measurement of respiratory gases, provides objective data on the severity and mechanism of functional limitation.3,4 Data from >3000 patients show that reduced peak oxygen consumption and submaximal exercise parameters, such as ventilatory efficiency and anaerobic threshold, are associated with progression to advanced HF and all-cause mortality.Exercise testing can provide objective evidence regarding an individual patient's functional capacity. This information can impact decisions on whether to escalate therapies, particularly if the symptom status of the patient is unclear on the basis of clinical history.6.8. Genetics and Family ScreeningSynopsisGenetic testing plays an important role in the diagnosis and management of HCM in patients and their families. HCM is inherited as an autosomal dominant trait in most cases, with offspring having a 50% chance of inheriting the same disease-causing genetic variant.3 A discussion about the role of genetic testing is considered a standard part of the clinical engagement of patients with HCM, including appropriate pre- and posttest genetic counseling performed either by a trained cardiac genetic counselor or by someone knowledgeable in the genetics of cardiovascular disease. It is essential to take a multigenerational (preferably at least 3 generations) family history of HCM and suspected SCD events. The importance of potential psychological, social, legal, ethical, and professional implications of having a genetic disease36 should be conveyed. Genetic assessment should ideally be performed in a specialized multidisciplinary HCM center with experience in all aspects of the genetic counseling and testing process.1Recommendation-Specific Supportive TextTaking a family history facilitates the identification of other clinically affected and at-risk family members, patterns of disease transmission, consanguinity within the family, and a history of SCD in a relative. These findings may be relevant to both the diagnosis and management of individuals with HCM in the family and subsequent clinical and genetic screening of at-risk family members.25–27Genetic testing in HCM has several clinical benefits, including confirmation of the diagnosis, preclinical diagnosis, cascade genetic testing in the family, and in guiding reproductive decisions.8–11 Cascade genetic testing in the family identifies those who carry the disease-causing variant and require ongoing surveillance, while those who do not carry the variant can be released from lifelong clinical surveillance.Genes associated with HCM phenocopies may be included in first-tier genetic testing if there is clinical suspicion based on phenotype evaluation of a systemic disorder, including PRKAG2 (glycogen storage disease), LAMP2 (Danon disease),13GLA (Fabry disease),39 transthyretin amyloid cardiomyopathy, and disease genes related to RASopathies. In some circumstances, the genetic test result may alter the management of the index case, such as enzyme replacement therapy in patients with Fabry disease or more aggressive clinical management of patients with Danon disease.Pretest genetic counseling is important to ensure the patient undergoing genetic testing fully understands and is informed of the benefits and potential harms (including psychosocial, ethical, and insurability) of finding a genetic cause of disease. Posttest genetic counseling allows a clear explanation to be provided for the genetic testing findings, regardless of whether a pathogenic or likely pathogenic variant is identified and the implications of both a positive and a negative result for the individual and for the family.1–3,16HCM is predominantly a disease of the sarcomere and, therefore, first-line genetic testing primarily includes panel testing for genes with strong evidence for being disease-causing in HCM.11 Genetic testing can be performed using various technological platforms, including gene panels, exome sequencing, or whole genome sequencing.9 Gene panels generally include 8 sarcomere genes, including MYH7, MYBPC3, TNNI3, TNNT2, TPM1, MYL2, MYL3, and ACTC1, and typically identify a disease-causing variant in approximately 30% of sporadic and 60% of familial cases.4,8–10 At this time, expanding to larger panels usually does not add diagnostic value.8,18 Initial genetic testing is usually performed in the index case (proband).8 If targeted gene panel testing does not reveal a causal variant, exome sequencing may provide a second-tier test on a clinical or research basis with genetic counseling that explains the often low diagnostic yield on exome sequencing at this time and the chance of incidental finding of susceptibility variants for diseases other than the disorder under study. In up to 40% of patients with HCM, no sarcomere variant is identified, and there is no family history of disease.28 Identification of a variant of uncertain significance (VUS) is not a clinically actionable result but can be investigated further at either a clinical or research level, to further clarify variant pathogenicity (eg, through cosegregation analysis in family members, DNA testing in parents to determine whether the VUS is de novo, functional studies) (Figure 1 and Figure 2).After genetic testing, a clinically actionable result (ie, likely pathogenic or pathogenic) can provide diagnostic clarification in the proband and offers the potential for cascade (predictive) testing of at-risk family members.3,7,12,19,20 Cascade testing involves targeted testing of first-degree relatives for the pathogenic or likely pathogenic variant found in the proband. When cascade testing is performed in an at-risk relative, those who are found not to carry the disease-causing gene variant can be released from further (lifelong) clinical surveillance. Those who are found to carry the disease-causing gene variant should undergo clinical screening at regular intervals (Table 6). Family members of a patient where genetic testing is not done or is negative (ie, no likely pathogenic or pathogenic variant is identified) also require clinical screening at regular intervals because there is considerable phenotypic heterogeneity in age of onset and disease progression within members of the same family.Postmortem testing for HCM-associated variants using blood or tissue collected at autopsy has been reported, particularly in instances where the family variant is unknown and no other affected family members are still living.23,41,42 Access to a molecular autopsy as well as considerations related to costs and insurance coverage for this testing can vary between jurisdictions. Nevertheless, identification of a likely pathogenic or pathogenic variant not only confirms the diagnosis of HCM but allows cascade genetic testing of other at-risk relatives as outlined previously (Figure 1 and Figure 2).Determining pathogenicity of variants relies on a weight of collective evidence based on American College of Medical Genetics and Genomics criteria17 and may change over time. In particular, there are fewer high-quality genetic data in a non-White HCM population. This highlights the importance of periodic reevaluation of variants every few years in case the variant has been reclassified (ie, either upgraded to likely pathogenic or pathogenic), in which case family cascade genetic testing can be initiated, or downgraded to a VUS, likely benign, or benign variant, whereby family screening would revert to regular clinical surveillance.25–27 In 1 report, 11% of HCM variants were either downgraded or upgraded over 6 years into a category that would necessitate a change in cascade screening of family members.31 This highlights the importance of having the necessary expertise within a specialized multidisciplinary clinic setting to not only perform genetic testing and interpret the genetic information but to continue to reevaluate the pathogenicity of variants during follow-up.25,26 The American College of Medical Genetics and Genomics published guidelines for clinical laboratories to implement policies to reevaluate variants based on new information about the variant and the patient or family phenotype.35 The American College of Medical Genetics and Genomics also stressed the importance of notifying a patient undergoing genetic testing that the genetic interpretation may change over time, and that recontacting the patient with updated results is a shared responsibility of the healthcare provider, clinical geneticist, clinical laboratory, patient, and family, while acknowledging that laboratories currently do not have a mechanism to receive reimbursement for such efforts.34In autosomal dominant HCM, there is a 1 in 2 (50%) chance of passing on the disease-causing gene variant to an affected individual's offspring, although variable penetrance can result in differences in onset and severity of clinical manifestations.43 Prenatal genetic counseling is helpful in explaining the risk of transmission of disease, as well as discussing potential reproductive options.1–3,16 These options include in vitro fertilization with preimplantation genetic diagnosis, prenatal genetic screening, and postnatal genetic testing. The benefits and potential harms can be discussed for each of these options, such that the individual or couple can make a fully informed decision.Although there is some evidence that individuals who carry >1 likely pathogenic or pathogenic variant may have more severe disease, including SCD, the role of the genetic test result in the determination of risk in SCD remains uncertain and is therefore not clinically used for this purpose. Similarly, a genetic result in isolation does not influence decisions related to implanting an ICD in patients with HCM. Several studies have reported that patients with HCM who carry pathogenic/likely pathogenic sarcomere variants have a worse prognosis compared to sarcomere variant-negative patients with HCM. This includes earlier onset of disease, higher incidence of SCD, higher incidence of AF and ventricular arrhythmias, HF, and overall mortality.10,12,27,29,44 However, there remains considerable heterogeneity within and between families with variants in the same gene that currently limits the application of genetic information for clinical decision-making, including risk stratification for SCD in the proband.Genetic testing for HCM is first performed in an individual in the family with clear phenotypic evidence of HCM, usually the proband (index case). If a definitive likely pathogenic or pathogenic variant is identified, then cascade genetic testing in at-risk relatives can be offered (Figure 1 and Figure 2). Genetic testing in a phenotype-negative relative without a known genetic diagnosis in the proband has a very low yield of identifying a genetic cause of HCM, and a negative test in this situation will not change recommendations for ongoing clinical screening.4,7,8,30 Identification of a VUS in a proband is not a clinically actionable result. In select circumstances only, family member testing may be offered at either a clinical or research level to further clarify the pathogenicity of the variant (eg, through cosegregation analysis in family members, determine de novo status through parental testing, functional studies). However, this is most appropriate in the setting of guidance from a cardiovascular genetics expert (Figure 1 and Figure 2).If genetic testing does not identify a pathogenic variant in a patient with HCM (ie, only identifies benign/likely benign variants), there is no indication to do genetic testing in family members as the identification of such variants will not change clinical management, including the need for continued clinical screening.4,8–10In genotype-negative relatives of individuals with genotype-positive HCM, no further clinical follow-up is required (Figure 1 and Figure 2). Over time, as more knowledge is gained, some variants previously thought to be likely pathogenic or pathogenic may be downgraded to a VUS or benign category.25,31,32 In such instances, family relatives who were released from clinical surveillance on the basis of the previous gene result need to be notified and regular clinical screening recommended.34,35Figure 2. Genetic testing process in HCM. Colors correspond to the Class of Recommendation in Table 2. HCM indicates hypertrophic cardiomyopathy; LB/B, likely benign/benign; LP/P, likely pathogenic or pathogenic; and VUS, variant of unknown significance.6.9. Genotype-Positive, Phenotype-NegativeSynopsisGenotype-positive, phenotype-negative individuals are those who carry a pathogenic or likely pathogenic HCM-causing variant but are asymptomatic without evidence of LVH on cardiac imaging. These individuals are also described as having preclinical HCM. They need ongoing cardiac surveillance for development of clinical HCM, although the time from genetic diagnosis to clinical HCM varies considerably within and between families.1,5,7 Studies have reported alterations in myocardial strain, LV relaxation abnormalities, myocardial crypts, mitral valve leaflet abnormalities, abnormal trabeculae, myocardial scarring, electrocardiographic abnormalities, and abnormal serum NT-proBNP concentrations even in the absence of LVH.9–12 However, the clinical significance of these subclinical structural and functional abnormalities is unclear and, therefore, treatment decisions are usually not made based on these findings alone.Recommendation Specific Supportive TextThe ongoing screening of genotype-positive, phenotype-negative family members of all ages is important. Previous small studies reported onset of clinical HCM in adolescence or young adulthood for most genotype-positive cases.1,5 However, recent large studies suggest that clinical HCM can develop in younger family members, with 5% to 10% being phenotype-positive at first screening and another 3% to 5% before 18 years of age.2,4,7 A third of patients who developed clinical HCM required medical, surgical, or device therapy before 18 years of age.4 Phenotype conversion can occur in young adults and, therefore, continued screening into adulthood is warranted,1 although frequency of screening can be lowered because disease penetrance is lower in individuals who are >18 years of age.3 Although there is an absence of systematic evidence, most physicians continue clinical screening until mid-life (age 50s) because disease can manifest in adults, albeit at a lower frequency.Sudden death in genotype-positive, phenotype-negative individuals is rare.6 There are no accurate risk prediction models for SCD in genotype-positive, phenotype-negative individuals at this time. Decisions about participation in competitive sports are usually made jointly with the patient and family taking into consideration family history of SCD, type of sports activity, and patient and family risk tolerance. Because of the low risk of sudden death, phenotype-negative individuals are not restricted from competitive sports and are not routinely monitored with ambulatory electrocardiography and exercise stress testing unless the family history indicates a high risk for SCD or as part of precompetitive athletic screening (eg, athletics involving intense, burst-sprint activity). This is appropriate every 1 to 2 years to assess safety of ongoing competitive athletics participation.ICDs are not offered for primary prevention in genotype-positive, phenotype-negative individuals given low risk of SCD. Similarly, preemptive medical therapy is not offered in genotype-positive, phenotype-negative individuals. In a small pilot randomized trial, preemptive treatment of sarcomere variant-positive, phenotype-negative individuals with diltiazem was associated with a small improvement in LV diastolic function and thickness: dimension ratio on 3-year follow-up.13 However, the trial was not powered to detect effects on clinical outcomes.7. SCD Risk Assessment and Prevention7.1. SCD Risk AssessmentSynopsisHCM has been regarded as the most common cause of SCD in young people in North America, a highly visible and devastating complication of this genetic heart disease.1,2,21,22,26–32 Among patients with HCM, younger patients are at higher risk for SCD than older patients.6,26–30,33,34 The 5-year cumulative proportion of SCD events in childhood HCM from diagnosis was 8% to 10% for SCD events in childhood.35,36 There appears to be no sex- or race-based differences in SCD risk.28,29Over several decades, a multitude of studies have focused on identification of major clinical risk markers that stratify patients according to level of risk to identify high-risk patients who may be candidates for SCD prevention with ICDs.1–22,26–33,37–61 This risk stratification strategy and the penetration of ICDs into clinical practice has substantially reduced disease-related mortality rates.31,32 A predictive risk score is also available that can derive individualized estimated 5-year SCD risk to aid in risk stratification and ICD decision-making in adult patients.2,22 The evolution of SCD risk assessment, including the addition of new risk markers, has resulted in the removal of abnormal blood pressure response to exercise as a routine part of the SCD risk evaluation.The current conventional noninvasive SCD risk markers (Table 7) used to estimate increased risk level in individual patients with HCM, and to identify those patients most likely to benefit from primary prevention ICD therapy,1,26,27,30–32 are based on personal and family history,1,3,5,6 noninvasive testing including echocardiography.1,7–9 ambulatory electrocardiographic monitoring,13,14 and CMR imaging.15–20 Given that the risk of SCD extends over many decades of life, periodic reassessment of SCD risk is an integral component of the longitudinal evaluation of most patients with HCM1,2,6,22,31,32Table 7. Established Clinical Risk Factors for HCM Sudden Death Risk StratificationFamily history of sudden death from HCMSudden death judged definitively or likely attributable to HCM in ≥1 first-degree or close relatives who are ≤50 y of age. Close relatives would generally be second-degree relatives; however, multiple SCDs in tertiary relatives should also be considered relevant.Massive LVHWall thickness ≥30 mm in any segment within the chamber by echocardiography or CMR imaging; consideration for this morphologic marker is also given to borderline values of ≥28 mm in individual patients at the discretion of the treating cardiologist. For pediatric patients with HCM, an absolute or z-score threshold for wall thickness has not been established; however, a maximal wall that corresponds to a z-score ≥20 (and >10 in conjunction with other risk factors) appears reasonable.Unexplained syncope≥1 Unexplained episodes involving acute transient loss of consciousness, judged by history unlikely to be of neurocardiogenic (vasovagal) etiology, nor attributable to LVOTO, and especially when occurring within 6 mo of evaluation (events beyond 5 y in the past do not appear to have relevance).HCM with LV systolic dysfunctionSystolic dysfunction with EF 20% is considered significant.Risk Stratification Considerations in Pediatric PatientsHistorically, risk stratification for SCD in children has been based on risk markers derived from adult HCM studies. Several studies suggest that adult risk factors have limited ability to predict SCD in pediatric patients.35,44,46,59,60 More recent collaborative studies suggest some, but not all, of the adult risk factors are important in pediatric patients with HCM.35,54,57,59,60 Risk prediction models for children with HCM have been developed but have not yet been used widely in clinical practice.35,36 The risk factors proposed in these guidelines remain based on adult risk factors and current available pediatric specific information.33,36–64 Ultimately, decisions regarding ICD placement must be based on individual judgment for each patient, taking into account all age-appropriate risk markers, strength of the risk factor(s) identified, the overall clinical profile, the level of risk acceptable to the patient and family, and the potential complications related to device implants, including psychological impact and inappropriate ICD shock.Recommendation-Specific Supportive TextOver the past several decades, numerous retrospective observational studies of patients with HCM have identified components of personal and family history as well as results from cardiovascular imaging and ambulatory monitoring to be associated with increased risk for future potentially life-threatening ventricular tachyarrhythmias.1–22 For this reason, SCD risk assessment at the initial visit and repeated every 1 to 2 years1,2,31 is a critical part of the evaluation of patients with HCM and includes: 1) previous history of cardiac arrest or sustained (>30 seconds or associated with hemodynamic compromise) ventricular arrhythmias1,3; 2) family history of sudden death, cardiac arrest, or sustained ventricular arrhythmias judged definitively or likely attributable to HCM in ≥1 first-degree or other close family members ≤50 years of age1,2,5,6; 3) continuous (24- to 48-hour) ambulatory electrocardiographic monitoring to detect NSVT or sustained VT1,2,6,13,14,22; 4) history of recent episode(s) of syncope (transient loss of consciousness) considered likely to be caused by arrhythmia (eg, episodes occurring in the previous 6 months because they carry the most prognostic importance, whereas those occurring >5 years in the past have little significance)1,2,4,22; and 5) cardiac imaging that helps determine maximal LV wall thickness in all segments of the LV chamber,7,9 EF,10,21,24,25 and presence of apical aneurysm.11,12 In pediatric patients, LV wall thickness is commonly reported both as an absolute measurement and standardized z-score adjusted for body surface area. As data suggest a lower SCD event rate in stable, older patients with HCM (>60 years of age),32 the decision regarding ongoing risk assessment is individualized in this subset of patients.Compared with CMR imaging, echocardiography can underestimate maximal LV wall thickness and may not detect LV apical aneurysm in some patients with HCM.11,12,15–17 In addition, extensive myocardial fibrosis, as detected by CMR-derived LGE, is associated with increased risk for potentially life-threatening ventricular arrhythmias.18–20 For these reasons, if a patient with HCM does not have evidence of increased SCD risk after assessment with family/personal history, echocardiography, and ambulatory monitoring, or risk stratification otherwise remains uncertain, contrast-enhanced CMR imaging can provide further characterization of maximum LV wall thickness measurement in any segment, EF, presence of LV apical aneurysm, and presence/extent of LGE.1,10–12,15–21,24,25,31 Although CMR imaging may be helpful in pediatric patients with HCM, this may require sedation, the risk of which may outweigh the benefits in an otherwise asymptomatic child. The use of CMR imaging should be determined by the physician and family after evaluating the child's individual risk.To calculate estimated SCD 5-year risk estimates for adults with HCM, echocardiographic left atrial diameter and maximal instantaneous LVOT gradient with continuous-wave Doppler technique are needed.2,22 The SCD risk estimate does not take into account the impact of newer markers of SCD risk, including systolic dysfunction (EF 6 as representing higher risk were based on association with a composite endpoint of cardiac death or transplant rather than SCD alone.40 It is therefore the consensus of this writing committee that a z-score of only 6 is inappropriately low and would overclassify children as high risk for SCD.Unexplained syncope: Judged by history as unlikely to be neurocardiogenic (vasovagal), unexplained syncope has a strong association with SCD risk in pediatric patients with HCM.7,22–24,28,29Family history of early SCD related to HCM: In pediatric patients, data regarding family history of SCD are conflicting, with many studies not finding an association with SCD in children.8,22,23,27–29 However, data from these studies may be confounded by incomplete ascertainment of genetic risk profile (de novo versus familial variant), relationship to the patients, and age of SCD in family members. SCD in a family member may be more relevant if the death occurred at a very young age (ie, during childhood or teenage years), or if SCD has occurred in multiple family members.NSVT: NSVT, identified on ambulatory monitoring performed over 24 to 48 hours, is associated with an increase in SCD risk, with stronger association as an independent risk factor in younger patients with HCM.2,4,5,16,17,19,22,23,25,28,29 As normal sinus rates in children can exceed adult proposed VT rate guidelines, VT is typically defined when the ventricular rate exceeds 20% of the baseline age-adjusted sinus rate.Other considerations: Recent multicenter studies report that left atrial diameter z-score is positively associated,27,37 while resting LVOT gradient is not associated with SCD risk in children.29,39 Risk estimate scores that incorporate several of these risk factors along with left atrial diameter z-score have been developed in children with HCM but have not yet been used prospectively in clinical ICD decision-making. Although LV systolic dysfunction and apical aneurysms are uncommon in children, it would seem prudent based on adult evidence to consider these as potentially increasing SCD risk in children but should be considered in the context of the entire risk profile of the individual patient. Finally, the complexity and potential psychological impact of ICD decision-making in this age group must be underscored, given the long periods of time with exposure to ICD therapy in young patients, and the relatively higher complication rates of long-term device therapy in this subgroup of patients.2,4,5,13,14,17,18,22,28In patients with HCM who are ≥16 years of age with ≥1 major SCD risk factors, estimating 5-year SCD risk may aid patients in understanding the magnitude of their individual risk for SCD to further assist in ICD decision-making.3,19 Because individual patients may consider the impact of SCD risk estimates differently, it is the consensus of this writing committee that prespecified risk thresholds should not be the sole arbiter of the decision to insert an ICD. Contemporary SCD risk markers in HCM, including LV apical aneurysm, LGE, and systolic dysfunction (EF 16 years of age, 5-year risk estimates can be considered to fully inform patients during shared decision-making discussions. ‡It would seem most appropriate to place greater weight on frequent, longer, and faster runs of NSVT. CMR indicates cardiovascular magnetic resonance; EF, ejection fraction; FH, family history; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death; VF, ventricular fibrillation; and VT, ventricular tachycardia.Figure 4. Management of symptoms in patients with HCM. Colors correspond to the Class of Recommendation in Table 2. GL indicates guideline; HCM, hypertrophic cardiomyopathy; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and SRT, septal reduction therapy.Figure 5. Heart failure algorithm. Colors correspond to the Class of Recommendation in Table 2. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitors; CRT, cardiac resynchronization therapy; EF, ejection fraction; GDMT, guideline-directed management and therapy; HCM, hypertrophic cardiomyopathy; LBBB, left bundle branch block; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; and NYHA, New York Heart Association.Table 8. Antiarrhythmic Drug Therapy Options for Patients With HCM and AFAntiarrhythmic DrugEfficacy for AFSide EffectsToxicitiesUse in HCMDisopyramideModestAnticholinergic HFProlonged QTcParticularly with early onset AFFlecainide and propafenone?ProarrhythmiaNot generally recommended in the absence of an ICDSotalolModestFatigue BradycardiaProlonged QTc Prolonged QTc ProarrhythmiaReasonableDofetilideModestHeadacheProarrhythmiaReasonableDronedaroneLowHFProlonged QTc?AmiodaroneModest-highBradycardiaLiver, lung, thyroid, skin, neurologicReasonable7.3. Device Selection ConsiderationsSynopsisThe decision of which type of ICD to implant is very important and nuanced. There are risks and benefits to consider. Considerations include transvenous versus subcutaneous ICD, single-chamber versus dual-chamber versus CRT devices, and number of defibrillation coils when using a transvenous approach. Patients with HCM receiving ICDs are usually younger than those with ischemic and even nonischemic cardiomyopathies who receive a device and, thus, life-long complications are likely to be higher in those with HCM.Pediatric ConcernsICD implantation in children raises additional concerns and challenges.30–32 Although selection for who should receive ICDs is discussed in the preceding section, the approach to implantation will vary based on body size. Epicardial leads will often be necessary in smaller children, usually 35%.25–29 Approximately half of patients will clinically respond to CRT with an improvement in their NYHA functional class or evidence of reverse LV remodeling. The benefit appears to be greater in those with LBBB and very prolonged QRS duration. Responders show a modest improvement in LVEF. One study found a significantly longer time to the combined endpoint of LVAD, heart transplantation, or death,27 while 2 other studies did not identify a survival benefit.25,29 RV pacing shares a similar physiology to LBBB so that this recommendation may be extended to those with LVEFs between 35% and 50% and expected to be paced >40% of the time, similar to the recommendation in the 2018 AHA/ACC/HRS pacing guidelines.36An atrial lead may provide better discrimination between ventricular and supraventricular arrhythmias, although data are modest regarding reduced inappropriate therapy in those with dual-chamber devices, and there are data that the complication rate is higher with dual-chamber devices.15–20 However, in pediatric patients with atrial tachyarrhythmias, the rates of which can approach typical VT rates, a dual-chamber device may aid in distinguishing supraventricular tachycardia from VT. This potential advantage must be weighed against the higher complication risk with the additional hardware.8. Management of HCM8.1. Management of Symptomatic Patients With Obstructive HCM8.1.1. Pharmacologic Management of Symptomatic Patients With Obstructive HCMSynopsisThe principal role of pharmacologic therapy targeted at the dynamic left ventricular obstruction is that of symptom relief, because there are not convincing data to suggest that pharmacologic therapy alters the natural history of HCM. Because the outflow tract obstruction is remarkably variable throughout daily life, the success of a given medication is determined by the patient's symptom response and not the measured gradient. In general, nonvasodilating beta-blockers are considered first-line therapy. The calcium channel blockers, verapamil, or diltiazem are reasonable alternatives to beta-blocker therapy. For patients who do not respond to trials of ≥1 of these drugs, advanced therapies with disopyramide or septal reduction are often the next step. One of the other key steps in managing symptomatic, obstructive HCM is to eliminate medications that may promote outflow tract obstruction, such as pure vasodilators (eg, dihydropyridine class calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) and high-dose diuretics. Low-dose diuretics, when added to other first-line medications, are sometimes useful for patients with persistent dyspnea or congestive symptoms. The principles of pharmacologic management outlined here also apply to patients with obstruction at the midventricular level.Recommendation-Specific Supportive TextBeta-blockers were the first studied medication for treatment of dynamic outflow tract obstruction and are generally considered the first-line agent for most patients with obstructive HCM. Medications should be titrated to a dose where there is symptom benefit but not declare failure of beta-blockade until there is demonstrated physiologic evidence of beta-blockade (ie, suppression of resting heart rate).1–3Diltiazem and verapamil have both been demonstrated to provide relief of symptoms in patients with obstructive HCM. Both of these agents can have vasodilating properties, in addition to the negative inotropic and negative chronotropic effects, which can be limiting. The use of calcium channel blockers in combination with beta-blockers, as therapy directed at HCM, is unsupported by evidence4–6; however, these may have a role in management of concomitant hypertension.Patients with HCM who did not respond to beta-blockers or non-dihydropyridine calcium channel blockers are candidates for more advanced therapies, including disopyramide and SRT when performed by experienced operators in comprehensive centers (Table 3 and Table 4). The choice among these options should be approached through a comprehensive shared discussion with the patient that includes the success rates, benefits, and risks of each of the options. Disopyramide has been shown to provide symptomatic benefit in patients with obstructive HCM who have failed first-line therapy with beta-blockers, verapamil, or diltiazem.7–9 This agent is an important option, particularly in those patients who are not candidates for SRTs. As disopyramide can enhance conduction through the atrioventricular node, which could lead to rapid conduction with the onset of AF, this medication should be used in combination with another medication that has atrioventricular nodal blocking properties (eg, beta-blocker, verapamil, or diltiazem). The anticholinergic side effects that can be seen with disopyramide can be mitigated with pyridostigmine. In patients with obstructive HCM who remain severely symptomatic despite optimal medical therapy, SRT, when performed by experienced operators in comprehensive centers (Table 3 and Table 4), is very effective for relieving LVOTO.10 Survival of patients with LVOTO is reduced compared with those without obstruction, and relief of obstruction may mitigate this incremental risk.11,12Acute hypotension in patients with obstructive HCM is a medical urgency. Maximizing preload and afterload, while avoiding increases in contractility or heart rate, is the critical focus in treating acute hypotension. Intravenous vasoconstrictors, such as phenylephrine, can also reverse this dangerous situation. Beta blockade can also be useful in combination with the vasoconstrictor as it dampens contractility and improves preload by prolonging the diastolic filling period.In the presence of signs or symptoms of congestion, cautious use of low-dose diuretics may provide some symptom relief. Aggressive diuresis can be problematic, as decreasing the preload can augment LVOTO.Caution should be exercised when introducing therapies in patients with HCM who will be treated for coexisting conditions. Some medications can cause or worsen symptoms related to LVOTO. Examples include the use of diuretics and vasodilators to treat hypertension or protect renal function. Those medications can be used in asymptomatic patients. However, if symptoms are present, or emerge after the initiation of the medication, it may be necessary to up-titrate medications being used for obstructive HCM or consider alternative therapies for the comorbid condition. As a result, positive inotropic agents, pure vasodilators, and high-dose diuretics can be considered relatively contraindicated in patients with symptomatic obstructive HCM.Although verapamil and diltiazem can be very effective medications to relieve symptoms attributable to LVOTO, in some patients, they have been reported to have a more prominent vasodilatory action. This afterload-reducing effect can be particularly dangerous in patients with very high resting gradients (>80 to 100 mm Hg) and signs of congestive heart failure. There are several reports of life-threatening bradycardia and hypotension in newborns of 6 months of age) can be used safely as an alternative to beta-blockers.10Loop or thiazide diuretics may be used to improve dyspnea and volume overload in nonobstructive HCM when volume overload is present. Aldosterone antagonists are also used in some patients. Cautious use of any of these diuretics is needed, usually as intermittent dosing as needed or chronic low-dose therapy, to prevent symptomatic hypotension and hypovolemia.17,18Although several pilot trials suggested that angiotensin receptor blockers and angiotensin-converting enzyme inhibitors may have benefits on myocardial structure and function, a larger placebo-controlled trial of 124 patients with nonobstructive and obstructive HCM (112 with LVOT gradient 24 hours increased stroke risk,15 other evidence suggests that shorter duration episodes may pose risk in patients with traditional risks factors.16 In ASSERT, the absolute stroke risk increased with increasing CHADS2 score, reaching a rate of 3.78 per year in those with score >2.18 Botto stratified risk according to AF duration and CHADS2 score, with a CHADS2 score of 1 increasing the risk only if AF duration was >24 hours, whereas for CHADS2 scores ≥2, episodes >5 minutes increased risk.19 Similar risk stratification is unavailable in HCM, yet risk factors for stroke in the population with HCM have been identified and include advancing age, previous embolic events, NYHA functional class, left atrial diameter, vascular disease, and maximal LV wall thickness.30 When very short AF duration is observed, continued surveillance should be maintained as the burden of AF is likely to progress.Recent studies suggest that with current therapies, AF in patients with HCM can be managed effectively, leading to low morbidity and mortality compared with historical controls.9,10 In general, drug selection for rhythm control in patients with HCM is based on extrapolation from studies of the AF population at large. Yet, reports suggest several drugs are safe and effective in a population with HCM (Table 8). Amiodarone has been used over many years and is generally deemed a favored option.10,20 Disopyramide has been safely prescribed for reduction of LVOTO, but its efficacy in AF is not well established.21,31 Data on NYHA class IC antiarrhythmic agents are limited because of concerns regarding their use in patients with structural heart disease. When used, therapy with class IC agents is safest in the presence of an ICD.10 Class III agents have been used as well. A recent report in 25 patients with HCM showed dofetilide to be well tolerated and facilitated AF management.13 Sotalol has also been shown to be safe and is commonly used in pediatric patients as well, either in oral or intravenous forms.23,32–34 The US Food and Drug Administration–mandated safety precautions should be adopted when prescribing antiarrhythmic drugs.Catheter ablation plays an important role in the management of AF and typical atrial flutter. Although no RCTs exist in this area, a number of meta-analyses have been published in patients with HCM undergoing catheter ablation for drug refractory AF, including one that compared catheter ablation between patients with HCM versus a cohort without HCM.12,25 In general, the procedure is safe and remains an important tool. However, the results seem less favorable compared with patients without HCM, with a 2-fold higher risk of relapse, more frequent need of repeat procedures, and higher use of concomitant antiarrhythmic drugs. This is attributed to the fact that patients with HCM have a greater degree of electrophysiologic and structural remodeling than the population without HCM.25 Contributing factors for atrial remodeling include LVOTO, diastolic impairment, MR, and other factors. It can be postulated that aggressive intervention in the earlier stages of disease would be more effective, but this is unproven, and ongoing remodeling is expected. With that in mind, some authors have suggested the need for a more extensive ablation approach, with linear lesions and ablation of triggers not associated with the pulmonary veins often required to improve the long-term durability of the procedure.26AF in patients with HCM is often poorly tolerated; therefore, aggressive rhythm control strategies are at times required. In view of the lower success rate of catheter ablation in HCM compared with the general AF population, surgical AF ablation is a potential rhythm management option, especially in patients already undergoing open heart surgery for a surgical myectomy. In combination with surgical relief of the LVOT gradient and MR, which can limit or even reverse negative atrial remodeling, concomitant surgical AF ablation may be successful in decreasing AF burden. Several studies have reported satisfactory midterm efficacy, yet these reports universally include a small number of patients, and the durability of the procedure appears to decrease with time.27,29 In a recent study that represents the largest series of patients with AF treated surgically, freedom from AF recurrence at 1 year was 44% for ablation patients (n=49) and 75% with the maze procedure (n=72) (P

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