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REVIEW

Diagnosis and management of hypertrophic cardiomyopathy: European vs. American guidelines

Alberto Aimo[1,2] · Giancarlo Todiere[2] · Andrea Barison[1,2] · Daniela Tomasoni[4] · Giorgia Panichella[3] · Ahmad Masri[5] · Martin S. Maron[6]

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Abstract

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, affecting 1:200 to 1:500 individuals worldwide. Guidelines on the diagnosis and management of HCM have been recently published by the European Society of Cardiology (ESC) and American societies. The ESC guidelines cover a broad range of cardiomyopathies, including HCM, with 119 recommendations, whereas the American guidelines focus exclusively on HCM with 141 specific recommendations. Both guidelines emphasize a comprehensive diagnostic approach, including imaging and genetic testing, but differ in some specific aspects. For example, sudden cardiac death (SCD) risk assessment is a primary point of divergence. The ESC guidelines advocate for the use of a validated Risk-SCD calculator, while the American guidelines rely on specific risk markers for individualized risk evaluation. Management strategies also vary: both guidelines prioritize beta-blockers and calcium channel blockers in patients with resting or provocable left ventricular outflow tract (LVOT) obstruction. If beta-blockers (or verapamil/diltiazem) are ineffective, either disopyramide or the myosin inhibitor mavacamten may be an option with slightly different indications among the two guidelines. Septal reduction therapy is recommended in ESC guidelines for symptomatic patients with significant LVOT gradients, while American guidelines suggest earlier myectomy for certain clinical factors and emphasize shared decision-making. The ESC guidelines recommend sequential atrioventricular pacing and dual-chamber defibrillators for reducing LVOT gradients. The American guidelines focus on genetic testing for risk assessment and suggest periodic cardiac magnetic resonance imaging. This paper provides a detailed comparison of these guidelines, highlighting key differences and areas needing further research and expert debate.

Keywords Hypertrophic cardiomyopathy · HCM · Guidelines · Recommendations · Diagnosis · Management · Therapy

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, affecting 1:200 to 1:500 individuals worldwide [1]. HCM presents with various patterns and locations of hypertrophy, with a significant proportion of patients exhibiting left ventricular outflow tract obstruction (LVOTO) due to mitral valve–ventricular septal contact, either at rest or with provocation [2, 3]. For symptomatic obstructive HCM, cardiac myosin inhibitors represent a novel pharmacologic opportunity as an alternative to invasive septal reduction to alleviate outflow tract gradients and HF symptoms [4, 5]. Around one-third of the HCM population do not have LVOTO [6]. Of these, 40% are symptomatic, requiring drug therapy, although therapeutic strategies remain limited up to now, and 10% progress to end-stage HF, necessitating advanced treatments like heart transplantation [6]. The ongoing phase 3 ODYSSEY-HCM and ACACIA-HCM trials are investigating the efficacy of

✉ Alberto Aimo
a.aimo@santannapisa.it; aimoalb@ftgm.it

1 Interdisciplinary Center for Health Sciences, Scuola Superiore Sant'Anna, Piazza Martiri Della Libertà 33, 56124 Pisa, Italy

2 Cardiology Division, Fondazione Toscana Gabriele Monasterio, Pisa, Italy

3 Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

4 Cardiology Division, University Hospital of Brescia, Brescia, Italy

5 Hypertrophic Cardiomyopathy Center, Oregon Health & Science University, Portland, OR, USA

6 Hypertrophic Cardiomyopathy Center, Lahey Hospital, Burlington, MA, USA

mavacamten and aficamten, respectively, on symptoms and functional capacity of patients with non obstructive HCM (NCT05582395, NCT06081894). Both obstructive and non-obstructive HCM patients have an increased risk of sudden cardiac death (SCD) and atrial fibrillation (AF) [6, 7].

Accumulating evidence highlights the need for standardized and "updated" HCM management. The first American College of Cardiology/American Heart Association (ACC/AHA) guidelines were published in 2011 [8], with updates in 2020 [9] and 2024 [10]. The first ESC guidelines for the management of HCM were published in 2014 [11], and the latest in 2023 covering various cardiomyopathies, including HCM [12]. Comparing these guidelines is crucial for clinicians to understand differences and identify areas needing further research and debate.

Diagnosis, initial evaluation, and follow-up

Diagnosis of HCM

The ESC guidelines provide general recommendations about the need for assessment by multidisciplinary tems and a systematic approach to diagnosis, including a comprehensive evaluation of cardiac dimensions and LV function [12]. The American guidelines recommend clinical evaluation and transthoracic echocardiography (TTE) in all patients with suspected HCM, but do not mention laboratory exams [10]. Cardiac magnetic resonance (CMR) is either recommended in all patients with cardiomyopathy (ESC), or when echocardiography is inconclusive or alternative diagnoses are possible (American) [10, 12]. The American guidelines also identify TTE with intravenous ultrasound agents as a possible alternative to CMR [10]. Both guidelines propose contrast-enhanced cardiac computed tomography (CT) when TTE is inconclusive and CMR is contraindicated or not available [10, 12]. In children, a maximum LV wall thickness > 2 standard deviations (SD) above the mean is indicated in ESC guidelines [12], while the American guidelines consider a threshold of > 2.5 SD, or > 2 when there is a clear family history or a positive genetic test [10].

Genetic testing in affected individuals

Both guidelines recommend an evaluation of family history and the creation of a 3- to 4- generation (ESC) or 3-generation (American) family tree [10, 12].

According to the ESC guidelines, genetic testing should be performed in all patients with cardiomyopathy when it has implications on diagnosis, risk prediction, therapy decision-making, reproductive management or cascade screening (I B). Other possible indications are "a borderline phenotype" (IIb C), or the finding of a cardiomyopathy during autopsy examination (I C). The ESC guidelines do not provide specific recommendations on the gene panel or result interpretation [12].

The American guidelines recommend genetic testing for cascade screening or differential diagnosis between HCM and phenocopies in cases with an atypical presentation (1 B). These guidelines provide the initial tier of genes to be tested that should include at least the following sarcomeric genes (i.e., MYH7, MYBPC3, TNNI3, TNNT2, TPM1, MYL2, MYL3, and ACTC1), and should be expanded to genes associated with HCM phenocopies when other aetiologies for cardiac hypertrophy are suspected. When a variant of uncertain significance is found, searching the same variant in family members with no disease phenotype for the purpose of variant reclassification is recommended with a weak level of evidence (2b). Both guidelines stress the need for genetic counseling [10, 12].

Detection and characterization of LVOTO

TTE with provocative maneuvers (detailed only in ESC guidelines) is recommended at initial evaluation for all HCM patients (ESC, I B), or only when the resting peak LVOT gradient is < 50 mmHg (American, 1 B) [10, 12]. Both guidelines agree on exercise TTE for symptomatic patients with a resting or provocable LVOT peak gradient < 50 mmHg (I B/1 B) [10, 12]. The American guidelines add that exercise TTE may also be considered for asymptomatic patients (2a C) [10]. Both guidelines recommend TEE for unclear LVOTO mechanisms or assessing the mitral valve apparatus before septal reduction procedures (ESC, IIa C; American, 2a C) [10, 12]. When uncertainty about the presence of LVOTO persists, both guidelines recommend invasive hemodynamic assessment (ESC, IIb C; American, 1 B) [10, 12]. Only the American guidelines propose CMR to clarify the mechanisms of LVOTO (1 B) [10]. Differences between guidelines are summarized in Table 1.

Additional indications to exercise stress testing

American guidelines provide additional recommendations for exercise TTE or cardiopulmonary exercise stress testing. Exercise stress testing may be reasonable for patients with obstructive HCM and ambiguous functional capacity (2b C), pediatric patients with HCM (1 B), or when the decline in functional capacity is unclear (2b C-EO). CPET is recommended for patients with nonobstructive HCM and advanced HF to aid selection of candidates for heart transplantation or mechanical circulatory support (1 B) [10].

Table 1 Recommendations about the detection and characterization of left ventricular outflow tract obstruction (LVOTO)

	ESC guidelines	American guidelines
TTE with provocative maneuvers	**For all HCM patients (I B)**	**Only when the resting peak LVOT gradient is < 50 mmHg (1 B)**
Exercise TTE for symptomatic patients	*For all patients without a resting or provocable LVOT peak gradient ≥ 50 mmHg (I B)*	*For all patients without a resting or provocable LVOT peak gradient ≥ 50 mmHg (1 B)*
Exercise TTE for asymptomatic patients	-	***May be considered (2a C)***
TEE for unclear LVOTO mechanisms or assessing the mitral valve apparatus before SRT	*May be considered (IIa C)*	*May be considered (IIa C)*
Invasive hemodynamic assessment	*When uncertainty about the presence of LVOTO persists (IIb C)*	*When uncertainty about the presence of LVOTO persists (1 B)*
CMR to clarify the mechanisms of LVOTO	-	***It is recommended (1 B)***

The degree of agreement between the European Society of Cardiology and AHA/ACC/AMSSM/HRS/PACES/SCMR (American) guidelines is schematically reported as substantial agreement (in italics), slightly heterogeneous positions (in bold), and relevant differences (in bold-italics)

CMR cardiac magnetic resonance, *HCM* hypertrophic cardiomyopathy, *TTE* transthoracic echocardiogram

Follow-up exams

The ESC guidelines endorse a follow-up protocol for stable patients with cardiomyopathies including ECG and TTE every 1 to 2 years (I C). In the ESC guidelines serial CMR are also recommended, but their timing is not specified (IIa C) [12], while the American ones recommend every 3–5 years in stable clinical conditions. The American guidelines recommend TTE every 1 to 2 years (1 B-NR in children, 1 C-LD in adults) and whenever there is a change in clinical status or a new clinical event (1 B-NR) [10]. Both guidelines recommend 12-lead ECG and 24- to 48-h ECG Holter monitoring every 1 to 2 years [10, 12].

Management

Medical therapy for obstructive HCM

The ESC guidelines recommend beta-blockers as first-line therapy in patients with obstructive HCM. These drugs should be titrated to the highest tolerated dose (I B). Verapamil or diltiazem are recommended when beta-blockers are not tolerated or contraindicated (I B) [12]. The American guidelines provide nearly identical recommendations [10].

The main novelty of both ESC and American guidelines compared to previous versions is probably the inclusion of myosin inhibitors as a possible treatment option when beta-blockers (or verapamil/diltiazem) alone are ineffective [10, 12]. The ESC guidelines mention mavacamten only [12], while the American guidelines mention myosin inhibitors as a class [10], thus potentially including also aficamten, on the light of the positive results of the SEQUOIA-HCM trial [7]. Specifically, the ESC guidelines recommend either disopyramide (I B) or mavacamten (IIa A), or even mavacamten as monotherapy for patients who are intolerant or have contraindications to beta-blockers, verapamil/diltiazem, or disopyramide (IIa B) [12]. Conversely, the American guidelines propose the following second-line therapies with the same class and level of evidence: a myosin inhibitor, disopyramide, or septal reduction therapy (1 B). The European guidelines affirm that cardiac myosin inhibitors should not be used with disopyramide, but may be coadministered with beta-blockers or calcium antagonists [12]. In the American guidelines, cardiac myosin inhibitor and dysopiramide are used as alternative second-line strategies and their concomitant use is not considered. Given that disopyramide may enhance conduction through the atrioventricular node, which could lead to rapid conduction with the onset of AF, the American guidelines recommend using this medication in combination with another medication that has atrioventricular nodal blocking properties (e.g., beta blocker, verapamil, or diltiazem) [10].

As for other medical therapies, both guidelines recommend cautious use of low-dose diuretics (ESC, IIb C; American, 2b C) [10]. Only the American guidelines recommend valsartan for younger patients with non-obstructive HCM and a mild phenotype, to slow adverse cardiac remodeling. This marks the first inclusion of this approach in HCM guidelines, based on findings from the phase 2 VANISH trial [13]. This randomized, double-blind, placebo-controlled study enrolled 178 patients aged 8 to 45 years with non-obstructive HCM, mild symptoms, normal ejection fraction, and no history of ICD interventions or SRT. The study showed significant reductions with valsartan in a composite of adverse remodeling markers, including LV wall thickness, LV mass, LV volume, left atrial size, diastolic parameters, and biomarkers [13].

Both guidelines also recommend avoiding digoxin and arterial and venous dilators in patients with LVOTO (IIa

C/2b C) [10, 12]. According to the ESC guidelines, oral nitrates may be considered to improve symptoms in patients with angina-like chest pain, even in the absence of obstructive coronary artery disease (CAD), provided no LVOTO is present (IIb C) [12]. Ranolazine is another option to improve symptoms in patients with angina-like chest pain without LVOTO or obstructive CAD (IIb C) [12]. The American guidelines do not include specific recommendations on these drugs [10].

Septal reduction therapy

The ESC and American guidelines provide comprehensive recommendations for SRT, with slightly different approaches [10, 12] (Table 2). The ESC guidelines recommend SRT for patients with a resting or maximum provoked LVOT gradient ≥ 50 mmHg in NYHA or Ross functional class III-IV despite maximum tolerated medical therapy (I B) [12]. While the ESC guidelines recommend SRT only after maximum tolerated medical therapy has been implemented [12], according to the American guidelines SRT might be considered also in symptomatic HCM patients as an alternative to escalation of medical therapy, after shared decision making (2b C) [10]. Both guidelines suggest considering SRT also in patients with recurrent exertional syncope with a resting or maximum provoked LVOT gradient ≥ 50 mmHg (ESC, IIa C; American, 1 B) [10, 12]. SRT may be considered even in less symptomatic patients (NYHA II) when the procedure is performed in expert centers with low rates of procedural complications (ESC, IIb C) [12], or when additional risk factors are present, including severe pulmonary hypertension attributable to LVOTO or associated mitral regurgitation (MR), left atrial enlargement with at least one previous episode of AF, poor functional capacity attributable to LVOTO, or resting LVOT gradients > 100 mmHg (American, 2b B) [10]. Both guidelines emphasize the importance of performing SRT in experienced centers [10, 12].

Based on the ESC guidelines, mitral valve repair or replacement should be considered in patients with moderate-to-severe MR that cannot be corrected by SRT alone (IIa C), and mitral valve repair or replacement in patients with LVOTO gradient ≥ 50 mmHg and moderate-to-severe MR after isolated myectomy (IIa C for repair, IIa C for replacement) [12]. The American guidelines do not provide any recommendations about mitral valve repair or replacement. They recommend instead SRT in patients with "associated cardiac disease requiring surgical treatment" and remind that patients with LVOTO obstruction should not undergo mitral valve replacement for the sole purpose of relieving LVOTO [10].

SRT should be preferred to alcohol septal ablation (ASA) in children and in adult patients requiring other surgical interventions (ESC, I C) [12]. The American guidelines provide specific indications to ASA, i.e., contraindications to surgery or unacceptably high surgical risk because of age or comorbidities (I C) [10]. ASA should be performed in experienced centers [10].

Atrial fibrillation

The ESC guidelines recommend anticoagulation for all patients with HCM and AF or atrial flutter unless contraindicated (I B) [12], while the American guidelines specifically recommend direct oral anticoagulants as the first-line option and vitamin K antagonists as the second-line option, extending this recommendation to subclinical AF detected by cardiac devices for more than 24 h (1 C) and possibly for shorter episodes depending on AF burden and risk factors (2a C) [10].

The ESC guidelines advocate catheter ablation to improve symptoms after one failed or intolerant antiarrhythmic drug (I B) and to reverse LV dysfunction when a tachycardia-induced component is probable (I B). They also suggest catheter ablation as a first-line therapy for selected patients with paroxysmal or persistent AF without major recurrence risk factors (IIa C), and for patients with AF and heart failure or reduced LVEF to prevent recurrences and improve outcomes (IIa B) [12]. The American guidelines recommend catheter ablation for symptomatic AF when drug therapy is ineffective, contraindicated, or not preferred (2a B), and suggest considering it during surgical myectomy (2a B) [10].

The ESC guidelines suggest early sinus rhythm maintenance for AF patients without major recurrence risk factors, regardless of symptoms (IIa C) [12]. The American guidelines recommend a rhythm-control strategy with cardioversion or antiarrhythmic drugs for poorly tolerated AF, tailored to the patient's symptoms, preferences, and comorbidities (2a B), and recommend rate control using beta-blockers, verapamil, or diltiazem based on patient preferences and conditions (1 C) [10].

Pacing

The ESC guidelines recommend sequential pacing with an optimal atrioventricular interval to reduce the LVOT gradient or facilitate treatment with beta-blockers and/or verapamil. This is suggested for patients with resting or provocable LVOTO ≥ 50 mmHg, sinus rhythm, and drug-refractory symptoms who have contraindications for ASA or septal myectomy or are at high risk of developing heart block after these procedures (IIb C). A biventricular pacemaker is recommended to reduce the LV outflow tract gradient with no differences between European and American guidelines (IIb C/2a B) [10, 12].

Table 2 Recommendations about septal reduction therapy (SRT)

	ESC guidelines	American guidelines
SRT indication	*SRT to improve symptoms is recommended in patients with a resting or maximum provoked LVOT gradient of ≥ 50 mmHg who are in NYHA/Ross functional class III–IV, despite maximum tolerated medical therapy (I B)*	*In patients with obstructive HCM who remain symptomatic despite GDMT, SRT in eligible patients, performed at experienced HCM centers, is recommended for relieving LVOTO (1 B)*
SRT indication factors	*NYHA III-IV*	*NYHA III-IV*
	Recurrent exertional syncope (IIa C)	*Recurrent exertional syncope (1 B)*
	Resting or maximum provoked LVOT gradient of ≥ 50 mmHg	*Dynamic LVOT gradient at rest or with physiologic provocation with approximate peak gradient of > 50 mmHg, associated with septal hypertrophy and SAM*
	-	***Targeted anterior septal thickness sufficient to perform the procedure safely and effectively in the judgment of the individual operator***
SRT indication in less symptomatic patients	**SRT may be considered in expert centres with demonstrable low procedural complication rates in patients with mild symptoms (NYHA class II) refractory to medical therapy who have a resting or maximum provoked (exercise or Valsalva) gradient of ≥ 50 mmHg and** **(a) moderate-to-severe SAM-related mitral regurgitation; or** **(b) AF; or** **(c) moderate-to-severe left atrial dilatation (IIb C).8**	**In patients with obstructive HCM, earlier (NYHA class II) surgical myectomy may be considered in the presence of:** **(a) Severe and progressive pulmonary hypertension thought to be attributable to LVOTO or associated MR** **(b) LA enlargement with > 1 episodes of symptomatic AF** **(c) Poor functional capacity attributable to LVOTO as documented on treadmill exercise testing** **(d) Children and young adults with very high resting LVOT gradients (> 100 mmHg) (2b B)**
Contemporary MV repair or replacement	***MV repair or replacement should be considered in patients with moderate-to-severe MR that cannot be corrected by SRT alone (IIa C), and mitral valve repair or replacement in patients with LVOTO gradient ≥ 50 mmHg and moderate-to-severe MR after isolated myectomy (IIa C for repair, IIa C for replacement)***	-
Other surgical indications	*Septal myectomy, rather than ASA, is recommended in children with an indication for SRT, as well as in adult patients with an indication for SRT and other lesions requiring surgical intervention (e.g. mitral valve abnormalities) (I C)*	*In symptomatic patients with obstructive HCM who have associated cardiac disease requiring surgical treatment, surgical myectomy, performed at experienced HCM centers, is recommended (1 B)*
SRT contraindication	-	***For patients with HCM who are asymptomatic and have normal exercise capacity, SRT is not recommended (3 C)***
Choice between SRT and ASA	**SRT should be preferred to ASA in children and in adult patients requiring other surgical interventions (ESC, I C)**	**In adult patients with obstructive HCM who remain severely symptomatic, despite GDMT and in whom surgery is contraindicated or the risk is considered unacceptable because of serious comorbidities or advanced age (I C)**

The degree of agreement between the European Society of Cardiology and AHA/ACC/AMSSM/HRS/PACES/SCMR (American) guidelines is schematically reported as substantial agreement (in italics), slightly heterogeneous positions (in bold), and relevant differences (in bold-italics)

AF atrial fibrillation, *ASA* alcohol septal ablation, *GDMT* guideline directed medical therapy, *HCM* hypertrophic cardiomyopathy, *LA* left atrium, *LVOTO* left ventricular outflow tract obstruction, *MV* mitral valve, *MR* mitral regurgitation, *NYHA* New York Heart Association, *SAM* systolic anterior movement

Heart transplantation and mechanical circulatory support

The American guidelines recommend assessing HCM patients with recurrent, poorly tolerated life-threatening ventricular tachyarrhythmias refractory to maximal antiarrhythmic drug therapy and ablation for heart transplantation (1 B). They also advise that patients with nonobstructive HCM and advanced HF (NYHA class III to IV despite GDMT) undergo CPET to quantify functional limitation and help select candidates for heart transplantation or mechanical circulatory support (MCS) (1 B), with heart transplantation assessment recommended for those with advanced HF or life-threatening ventricular arrhythmias refractory to GDMT (1 B) [10]. The ESC guidelines support heart transplantation for eligible patients with advanced HF or intractable ventricular arrhythmias refractory to other treatments (I C). Additionally, the ESC guidelines recommend considering MCS in selected patients with advanced HF despite optimal treatment who are suitable for heart transplantation (IIa B), and for those not eligible for transplantation and without severe right ventricular dysfunction (IIa B) [12]. The American guidelines do not provide specific indications on MCS beyond recommending CPET [10].

Risk assessment and prevention of SCD

Both guidelines address the indications to ICD (Table 3). There is an agreement on ICD implantation for secondary prevention [10, 12]. For primary prevention, the ESC guidelines suggest using validated SCD risk prediction models, such as the HCM Risk-SCD calculator for those aged 16 and older (I B) and HCM Risk-Kids for those under 16 (I B). They advise comprehensive SCD risk stratification at initial evaluation and every 1–2 years or with any change in clinical status (I C) [12]. CMR is recommended if the need for ICD placement remains uncertain (ESC, I B) [12], or every 3–5 years to evaluate changes in LGE, LV wall thickness, and other morphological changes (American, 2b C) [10].

In the American guidelines, primary prevention ICD implantation is recommended in HCM patients with any established risk factors (maximum LV wall thickness > 30 mm, family history of sudden death, nonsustained VT, unexplained syncope, LGE extent > 15%, of LVEF < 50% or LV apical aneurysm) (2a B), while left atrial size and LVOTO are not considered independent risk factors, but may be useful during shared decision-making for ICD placement in order to calculate an estimated 5-year sudden death (2a B). The presence of a pathogenic or likely pathogenic mutation is not considered as an independent risk factor, but is included in one of the risk calculators only in children (2a B), while their utility for risk prediction in adults is uncertain [10].

According to the ESC guidelines, primary prevention ICD implantation should be performed in HCM patients with a 5-year risk score ≥ 6% (IIa B), and might be performed in HCM patients with a 5-year risk between 4 and 6% (IIb B). The HCM risk score takes into account 7 parameters (age at clinical evaluation, maximum LV wall thickness, left atrial diameter, maximal LVOT gradient, family history of SCD, nonsustained VT, and unexplained syncope). The presence of LGE extent > 15% or LVEF < 50% which are not included in the risk calculator, make the ICD implantation indicated (IIb B) even in low-risk patients (those with a 5-year risk score < 4%) [12]. Although many of the risk factors are overlapping with those in the American guidelines (e.g., family history, nonsustained VT, unexplained syncope), some notable differences exist. In the European guidelines, maximal wall thickness is considered as a continuum value, while the American guidelines specify a cutoff of 30 mm, based on previous studies [14, 15]. Furthermore, age is not explicitly considered in the American guidelines; however, they note that, given the very low SCD event rate observed in patients > 60 years of age with HCM, the risk stratification strategy with major markers is most applicable to young adults and middle-aged patients. Additionally, left atrial diameter and maximal LV outflow tract gradients are not considered in the American guidelines; however, their predictive value is supported by the retrospective multi-center longitudinal cohort study that developed and validated the HCM SCD risk score [16]. Notably, the C-index for the HCM SCD risk calculator was 0.69 (95% CI 0.68, 0.71), indicating moderate predictive accuracy [16].

Unlike the American guidelines, which recommend LV apical aneurysms as a significant independent risk factor for SCD and consider them a sufficient indication for an ICD in selected cases, the ESC guidelines adopt a more conservative approach highlighting that current evidence on apical aneurysms is primarily derived from retrospective studies with a limited number of events [12]. Additionally, many patients with adverse outcomes had other established risk factors, such as prior sustained ventricular arrhythmias. Therefore, the ESC guidelines recommends that ICD decisions for patients with LV apical aneurysms be individualized, based on a comprehensive risk assessment [12].

The ESC guidelines emphasize that ICD implantation should only be performed in patients with a good quality of life and life expectation of more than 1 year (I C), with decisions guided by shared decision-making considering individual preferences and thorough understanding of treatment options (I C). Patients should be informed of the risks of inappropriate shocks, implant complications, and the social, occupational, and driving implications of the device prior to implantation (I C) [12].

Both guidelines prefer single-chamber transvenous ICDs or subcutaneous ICDs, particularly when pacing for

Table 3 Recommendations about risk assessment and prevention of sudden cardiac death (SCD)

	ESC guidelines	American guidelines
Primary prevention risk factors	**The HCM Risk-SCD calculator* (or the HCM Risk-Kids for those under 16) is recommended as a method of estimating risk of sudden death at 5 years (I B)** ***The HCM risk score considers: age, maximum LV wall thickness, left atrial size, LVOT gradient, family history, NSVT, and unexplained syncope**	**In adult patients with HCM, SCD risk assessment should include evaluation of** **(a) Personal history of syncope suspected by clinical history to be arrhythmic** **(b) Family history in close relative of premature HCM-related sudden death, cardiac arrest, or sustained VAs** **(c) Maximal LV wall thickness, LVEF, LV apical aneurysm** **(d) NSVT episodes on continuous ambulatory electrocardiographic monitoring (1 B)**
Primary prevention ICD implantation indications	**ICD implantation should be performed in HCM patients with a 5-year risk score* ≥ 6% (IIa B), and might be performed in HCM patients with a 5-year risk between 4 and 6% (IIb B)** ***The HCM risk score takes into account: age, maximum LV wall thickness, left atrial size, LVOT gradient, family history, NSVT and unexplained syncope**	**For adult patients with HCM with ≥ 1 major risk factors for SCD, it is reasonable to offer an ICD. Risk factors include:** **(a) Sudden death judged definitively or likely attributable to HCM in ≥ 1 first-degree or close relatives who are ≥ 50 years of age** **(b) Massive LVH ≥ 30 mm in any LV segment** **(c) ≥ 1 recent episodes of syncope suspected by clinical history to be arrhythmic** **(d) LV apical aneurysm with transmural scar or LGE** **(e) LVEF < 50% (2a B)**
SCD risk stratification timing	*It is recommended that the 5-year risk of SCD be assessed at first evaluation and re-evaluated at 1–2-year intervals or whenever there is a change in clinical status (I C)*	*A comprehensive, systematic noninvasive SCD risk assessment at initial evaluation and every 1 to 2 years thereafter is recommended (1 B)*
Role of CMR	**For patients who are in the low-risk category (< 4% estimated 5-year risk of SCD), the presence of extensive LGE (≥ 15%) on CMR may be considered in shared decision-making with patients about prophylactic ICD implantation (IIb B)**	**For adult patients with HCM who are not otherwise identified as high risk for SCD, or in whom a decision to proceed with ICD placement remains uncertain, CMR imaging is beneficial to assess for maximum LV wall thickness, LVEF, LV apical aneurysm, and extent of myocardial fibrosis with LGE (1 B)**
Genotype status	-	***For patients < 16 years of age with HCM, it is reasonable to calculate an estimated 5-year sudden death risk that includes echocardiographic parameters (IVS thickness in diastole, LV posterior wall thickness in end-diastole, left atrial diameter, maximal LVOT gradient) and genotype, which may be useful during shared decision-making for ICD placement (2a, b-NR)***
ICD implantation for secondary prevention	*Implantation of an ICD is recommended in patients who have survived a cardiac arrest due to VT or VF, or who have spontaneous sustained VT with haemodynamic compromise (I B)*	*For patients with HCM and previous documented cardiac arrest or sustained VT, ICD placement is recommended (1 B)*
CRT	-	***For adult patients with HCM with NYHA class II to ambulatory class IV HF, LBBB, and LVEF < 50%, CRT-defibrillator is considered reasonable for symptom reduction (2a C-LD)***

The degree of agreement between the European Society of Cardiology and AHA/ACC/AMSSM/HRS/PACES/SCMR (American) guidelines is schematically reported as substantial agreement (in italics), slightly heterogeneous positions (in bold), and relevant differences (in bold-italics)

AF atrial fibrillation, *CRT* cardiac resynchronization therapy, *HCM* hypertrophic cardiomyopathy, *ICD* implantable cardiac defibrillator, *IVS* interventricular septal, *LA* left atrium, *LBBB* left bundle branch block, *LGE* late gadolinium enhancement, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *LVOT* left ventricular outflow tract, *MV* mitral valve, *MR* mitral regurgitation, *NSVT* non-sustained ventricular tachycardia, *NYHA* New York Heart Association, *SAM* systolic anterior movement, *SCD* sudden cardiac death, *SRT* septal reduction therapy, *VA* ventricular arrhythmias, *VF* ventricular fibrillation, *VT* ventricular tachycardia

bradycardia, cardiac resynchronization, or antitachycardia pacing is not anticipated [10, 12]. For adult patients with HCM with NYHA class II to ambulatory class IV HF, LBBB, and LVEF < 50%, CRT-defibrillator is considered reasonable for symptom reduction (2a C-LD) [10]. ESC guidelines do not specifically mention CRT-defibrillators [12].

Sports activity

Recommendations about sports activity are summarized in Table 4. There is a general agreement between the two guidelines regarding the safety and beneficial effect of low- and moderate-intensity exercise in patients with HCM, which is therefore recommended for all patients, with a stronger level of evidence in the American guidelines (ESC, I C; American 1 B) [10, 12]. ESC guidelines recommend an individualized risk assessment for all patients [12], while American guidelines emphasize the importance of "comprehensive evaluation and shared decision-making" for athletes [10]. Compared to previous versions, both guidelines open to high-intensity exercise and competitive sports in genotype-positive/phenotype-negative individuals (ESC, IIa C; American, 2a B) [10, 12]. The ESC guidelines allows for high-intensity exercise or competitive sports also in asymptomatic low-risk individuals with morphologically mild HCM in the absence of LVOTO and exercise-induced ventricular arrhythmias (IIb B), but not in those with LVOTO and/or ventricular arrhythmias (III C) [10, 12]. The American guidelines provide a broader recommendation ("…may be considered after review by an expert provider with experience managing athletes with HCM who conducts an annual comprehensive evaluation and shared decision-making"; 2b B) [12]. Overall, the American guidelines seem globally more favorable to exercise activity in patients with HCM, as also reflected by the specific recommendation that "universal restriction from vigorous physical activity or competitive sports is not indicated" (3 B) [10]. Nonetheless, American guidelines remind that ICD placement solely for participation in competitive sports is not recommended (3 C) [10].

Family screening

Both guidelines recommend clinical screening and genetic testing for first-degree relatives when a pathogenic variant is identified, including postmortem genetic testing in cases of sudden unexplained death (1 B-NR) [10]. Both guidelines stress the importance of genetic counseling and multidisciplinary expertise in genetic testing [10, 12]. The American guidelines also highlight that cascade genetic testing is not

Table 4 Recommendations about sports activity

	ESC guidelines	American guidelines
Regular mild- to moderate-intensity recreational exercise	*For all patients (I C)*	*For all patients (1 B)*
High-intensity exercise and competitive sport in		
Genotype-positive/phenotype-negative individuals	*Should be considered (IIa C)*	*It is reasonable (2a B)*
Asymptomatic low-risk individuals with morphologically mild HCM	**May be considered in the absence of resting or inducible LVOTO and exercise-induced complex VAs (IIb B)**	-
High-risk individuals and in individuals with LVOTO and exercise-induced complex VAs	**Is not recommended (III C)**	-
Participation in vigorous recreational activities or competitive sports	-	***For patients with HCM, participation in vigorous recreational activities (2a B) or competitive sports (2b B) is reasonable after an annual comprehensive evaluation and shared decision-making with an expert professional who balances potential benefits and risks. (2a B)***
Universal restriction from vigorous physical activity or competitive sports in HCM	-	***It is not indicated (3 B)***
ICD placement for the sole purpose of participation in competitive sports	-	***Should not be performed (3 C)***

The degree of agreement between the European Society of Cardiology and AHA/ACC/AMSSM/HRS/PACES/SCMR (American) guidelines is schematically reported as substantial agreement (in italics), slightly heterogeneous positions (in bold), and relevant differences (in bold-italics)

HCM hypertrophic cardiomyopathy, *ICD* implantable cardiac defibrillator, *LVOTO* left ventricular outflow tract obstruction, *VA* ventricular arrhythmias

useful if the proband has benign variants and recommend serial reevaluation of variant significance (3 B) [10]. Moreover, the American guidelines suggest that a VUS can be further investigated at either a clinical or research level to clarify variant pathogenicity (e.g., through cosegregation analysis in family members, DNA testing in parents to determine whether VUS is de novo, functional studies) [10]. Both guidelines agree on echocardiography and clinical assessments for genotype-positive, phenotype-negative individuals every 1–2 years for children/adolescents and 3–5 years for adults [10, 12]. Finally, in both guidelines, there is no minimum age for childrens' assessment [10, 12].

Reproductive issues

For families considering pre-natal diagnostic testing, the ESC guidelines recommend early testing in pregnancy to facilitate decisions regarding continuation or coordination of the pregnancy (I C) [12], while the American guidelines advise offering reproductive and genetic counseling (1 B) [10]. Both advocate for vaginal delivery as the first choice (I C/1 C) [10, 12]. The American guidelines also suggest administering selected beta-blockers for symptoms related to LVOTO or arrhythmias while monitoring fetal growth (1 C) [10], similar to the ESC guidelines (IIa C) [12].

ESC vs. American Guidelines: an overview

The ESC and American guidelines provide extensive recommendations for diagnosing and managing HCM, with several elements of novelty compared to previous versions (most notably, the introduction of myosin inhibitors and a more permissive approach to sports activity). Some differences in the approaches proposed by the two guidelines may be remarked (Fig. 1).

The main difference between the European and American guidelines regards risk assessment and prevention of SCD. For primary prevention of SCD, the ESC guidelines emphasize validated SCD risk prediction models, recommending ICD implantation based on risk scores and specific factors like left atrial size and LVOTO [10, 12]. The American guidelines highlight genetic testing and periodic CMR imaging, recommending ICD placement for various established risk factors and stressing shared decision-making [10].

For the detection and characterization of LVOTO, both European and American guidelines recommend TTE; however, the indications are slightly different. The ESC

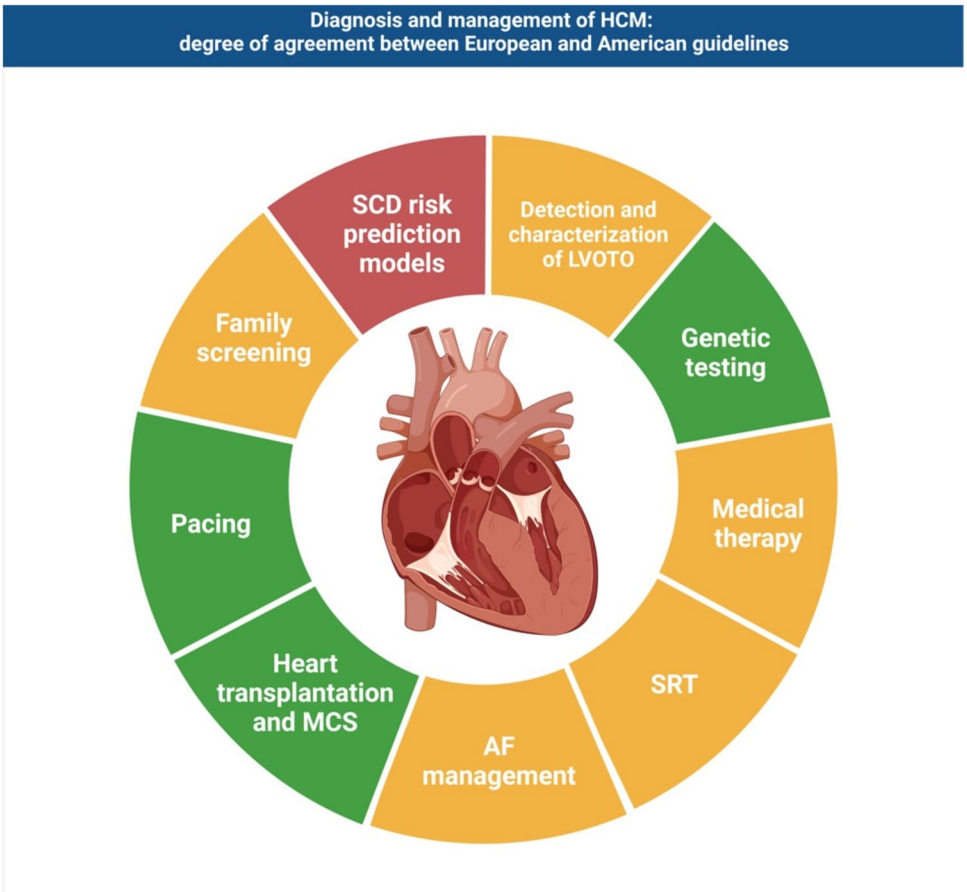

Fig. 1 Agreement between European and American guidelines. The degree of agreement between European Society of Cardiology and AHA/ACC/AMSSM/HRS/PACES/SCMR guidelines is schematically reported as green (substantial agreement), yellow (slightly heterogeneous positions), and red (relevant differences). See text for further details

recommends TTE for all HCM patients, while the American guidelines suggest it only if the resting LVOT gradient is < 50 mmHg. Both agree on exercise TTE for symptomatic patients and also recommend TEE for unclear LVOTO mechanisms or before septal reduction procedures. Invasive hemodynamic assessment is advised if uncertainty about LVOTO persists, with the American guidelines uniquely recommending CMR for further clarification.

Both guidelines prioritize beta-blockers and calcium channel blockers as first-line treatments for obstructive HCM [10, 12]. An element of novelty compared to previous versions is the introduction of myosin inhibitors (only mavacamten in the ESC guidelines, and possibly also aficamten in the American guidelines) [10, 12] as a second-line treatment option.

The ESC guidelines recommend SRT for symptomatic patients with significant LVOT gradients, emphasizing the need for experienced operators [10, 12]. The American guidelines suggest earlier myectomy as a possible second-line approach and stress shared decision-making for SRT, advising against the procedure for asymptomatic patients with normal exercise capacity [10].

Both guidelines recommend anticoagulation for HCM patients with AF and catheter ablation for AF if medications fail, though the ESC allows it as a first-line option for select patients. The American guidelines also suggest ablation during surgical myectomy. Both emphasize rhythm control, but the ESC prioritizes early sinus rhythm maintenance, while the American guidelines tailor rhythm or rate control based on individual patient needs.

Regular mild- to moderate-intensity recreational exercise is recommended for all patients, with a stronger level of evidence in American guidelines [10, 12]. The ESC guidelines advise individualized risk assessments, while American guidelines stress comprehensive evaluations and shared decision-making for athletes [10, 12]. Both guidelines now accept high-intensity exercise and competitive sports for genotype-positive/phenotype-negative individuals. The ESC allows high-intensity exercise for asymptomatic low-risk individuals without certain conditions, whereas American guidelines are more broadly supportive of exercise in HCM patients but advise against ICD placement solely for sports participation [10, 12].

No significant differences in genetic testing and family screening were noted, with both guidelines recommending comprehensive cascade genetic testing and clinical evaluation for first-degree relatives of HCM patients, stressing genetic counseling and long-term follow-up [10, 12]. Both guidelines support heart transplantation for advanced HF and intractable arrhythmias [10, 12].

Overall, while both the ESC and American guidelines offer detailed recommendations for HCM management, the ESC adopts a broader approach by addressing general cardiomyopathies, whereas the American guidelines focus exclusively on HCM, providing more specific recommendations in certain areas. Both emphasize specialized care, genetic counseling, and patient-centered management to optimize outcomes for HCM patients.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests AM, consultant activity for Attralus, BioMarin Pharmaceutical, Bristol Myers Squibb, Cytokinetics, Eidos, Ionis, Pfizer and Lexicon Pharmaceuticals, Inc. and grants/contracts from Pfizer, Ionis, Cytokinetics and Attralus; MSM reports consultant activity for Cytokinetics, BioMarin Pharmaceutical Inc., Edgewise, Imbria; the other authors have no relevant conflicts of interest to disclose.

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