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VIEWPOINT
Heart failure and cardiomyopathies

Hypertrophic cardiomyopathy evolving management: American Heart Association/ American College of Cardiology vs. European Society of Cardiology guidelines

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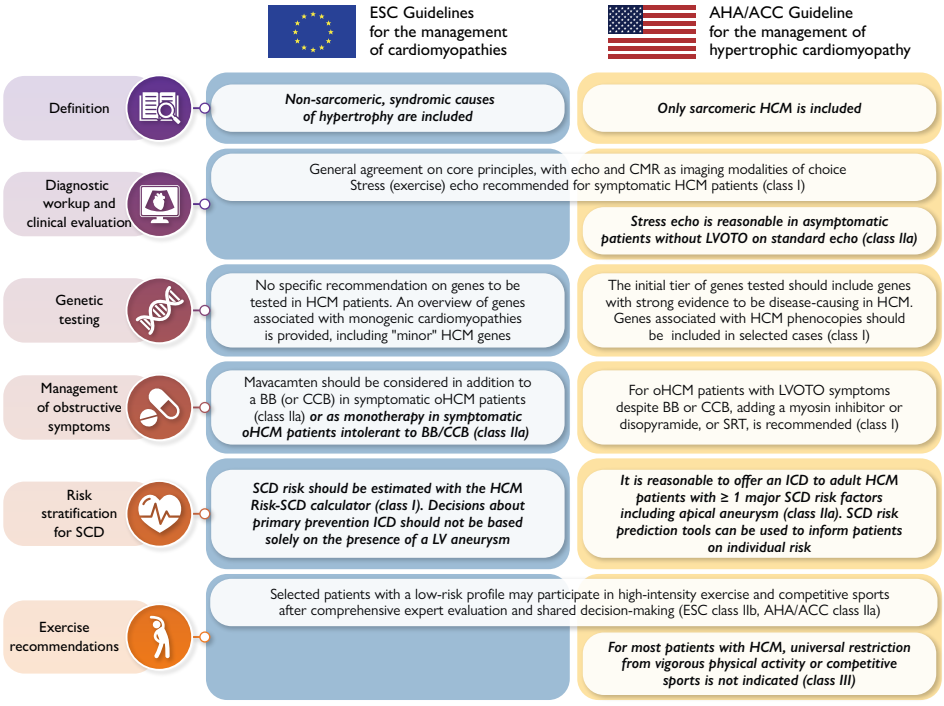
Graphical Abstract



Text in bold and italics indicates differences between ESC and AHA/ACC guidelines. AHA/ACC, American Heart Association/American College of Cardiology; BB, beta-blocker; CCB, calcium channel blocker; CMR, cardiac magnetic resonance; HCM, hypertrophic cardiomyopathy; ESC, European Society of Cardiology; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVOTO, left ventricular outflow tract obstruction; oHCM, obstructive hypertrophic cardiomyopathy; SCD, sudden cardiac death; SRT, septal reduction therapy.

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The availability of cardiac myosin inhibitors (CMI) to treat symptomatic left ventricular outflow tract obstruction (LVOTO) and the evolving recommendations on exercise in patients with hypertrophic cardiomyopathy (HCM) have prompted the need for updated guidelines. The European Society of Cardiology (ESC) guidelines for the management of cardiomyopathies, which provide a focused updated of the 2014 HCM guidelines,[1] and the American Heart Association/American College of Cardiology/Multisociety (AHA/ACC) guideline on the management of HCM[2] offer revised recommendations that largely agree on core principles, but also present some differences worth revisiting. In this viewpoint, we explore some of the novelties and the main points of divergence between European and American recommendations on key areas of HCM diagnosis, evaluation, and management (*Graphical Abstract*).

Diagnostic workup and clinical evaluation

One fundamental difference is that the AHA/ACC guideline defines HCM as a disease whose morphologic expression is confined to the heart,[2] whereas the ESC guideline adopts a broader, phenotype-based approach that includes non-sarcomeric, syndromic causes of cardiac hypertrophy, such as Fabry disease, under the HCM definition.[1] This divergence reflects the philosophy of the European guideline, which advocates an approach to disease diagnosis based on the phenotypic manifestation of cardiomyopathy.[1]

Both ESC and AHA/ACC guidelines concur on the central role of echocardiography and cardiac magnetic resonance (CMR) for diagnosis and guiding clinical decision-making in HCM. However, a minor difference exists on recommendations on stress (exercise) echocardiography to unmask latent LVOTO. The AHA/ACC recommends stress echocardiography for both symptomatic (class I) and asymptomatic patients (class IIa).[2] In contrast, in the ESC guideline, stress echocardiography is recommended in symptomatic patients with a maximum provoked gradient < 50 mmHg.[1] This discrepancy reflects uncertainties regarding the real prevalence and prognostic implication of labile LVOTO in asymptomatic patients. Retrospective analyses indicate that LVOTO in minimally symptomatic HCM patients is associated with only a slight excess mortality compared with the general population,[3] and labile obstruction might even portend a better prognosis compared with non-obstructive HCM.[4] However, physicians should not be hesitant to perform stress echocardiography in asymptomatic subjects, as the identification and characterization of obstructive physiology with stress echocardiography can inform both lifestyle recommendations and treatment choices, and should be actively pursued in most HCM patients.

Genetic testing

There is universal consensus that genetic testing should be offered to patients with a confirmed diagnosis of HCM, but the panel of genes tested varies between different centres. According to the AHA/ACC guideline, the initial tier of genes tested should include the eight sarcomeric genes with a strong association with HCM (i.e. *MYH7*, *MYBPC3*, *TNNI3*, *TNNT2*, *TPM1*, *MYL2*, *MYL3*, and *ACTC1*) and should be expanded to genes associated with HCM phenocopies if there is clinical suspicion of another genetic disorder manifesting with cardiac hypertrophy.[2] The ESC guideline does not provide specific recommendations on gene panels, but features a list of genes associated with monogenic, non-syndromic cardiomyopathies based on ClinGen validation efforts, implying that genetic testing should be routinely expanded beyond the eight sarcomeric genes.[5] According to ClinGen, there is sufficient evidence to establish a definitive association between recently identified variants in genes encoding non-sarcomeric proteins, such as *ALPK3* and *CSRP3*, and HCM. These minor HCM-associated genes and the encoded proteins are attracting significant attention due to their potential to provide new insights into the genetic basis of HCM.[6] While evaluating these genes may not significantly increase the yield of genetic testing, their inclusion in diagnostic gene panels is especially important in regions or populations in which high rates of consanguinity and/or the presence of founder effects could increase the prevalence of these non-sarcomeric gene variants.[5]

Management of obstructive symptoms

Cardiac myosin inhibitors offer an additional pharmacological option to alleviate symptoms of LVOTO. In the EXPLORER-HCM trial, mavacamten improved symptoms and functional capacity in symptomatic patients with obstructive HCM (oHCM) receiving background therapy with beta-blockers (BB) or non-dihydropyridine calcium channel blockers (non-DHP CCB), but not disopyramide.[7] Therefore, the ESC guideline recommends mavacamten alongside (but not in combination with) disopyramide, in patients with significant LVOTO who remain symptomatic despite first-line treatment with BB or non-DHP CCB.[1,2] We estimated that about half of real-world oHCM patients have these characteristics and may be eligible to mavacamten.[8] Following the publication of the ESC guideline, the benefit of CMI was confirmed in the SEQUOIA-HCM trial, which demonstrated a significant improvement in exercise capacity in symptomatic oHCM patients treated with aficamten, another agent of the same class.[9] On these grounds, the AHA/ACC guideline includes a class I recommendation (rather than class IIa, as in the ESC guideline) for treatment with CMI in patients with oHCM who do not respond to BB or non-DHP CCB.

A number of questions on CMI remain to be addressed. First, it is unclear whether their use in combination with disopyramide is safe and confers additional symptomatic relief in oHCM patients. Furthermore, symptomatic, non-obstructive HCM remains a therapeutic challenge. The ongoing phase 3 ODYSSEY-HCM and ACACIA-HCM trials will assess the efficacy of mavacamten and aficamten, respectively, on symptoms and functional capacity of this patient population (NCT05582395, NCT06081894). Most importantly, long-term studies will reveal whether CMI hold potential to modify the natural history of HCM, as supported by preclinical evidence showing that these agents prevent the development of cardiac hypertrophy, cardiac myocyte disarray, and myocardial fibrosis in mouse models of the disease.[10] If so, CMI might become the cornerstone of HCM treatment, and radically change the management of HCM patients. As of now, their use as a monotherapy is mentioned only in the ESC guideline,[1] and they are recommended as a second-line therapy, with the same strength of recommendation of disopyramide and septal reduction therapy, in a context where the patient's preference is key to determine the treatment approach.[2]

Risk stratification for sudden cardiac death

The strategy for sudden cardiac death (SCD) risk stratification remains the main point of divergence between the ESC and AHA/ACC guidelines. The ESC guideline endorses an approach based on risk estimation with the HCM Risk-SCD tool as the first step to identify candidates for primary prevention implantable cardioverter-defibrillator (ICD) placement.[1] The HCM Risk-SCD takes into account multiple SCD risk factors, but does not factor in the presence of extensive late gadolinium enhancement (LGE) on CMR, left ventricular systolic dysfunction, and the presence of an apical aneurysm, which are instead included among major SCD risk factors by the AHA/ACC guideline.[2] According to the ESC guideline, evidence on the SCD risk conferred by an apical

aneurysm is insufficient to guide decisions about primary prevention ICD, whereas LGE extension > 15% and left ventricular systolic dysfunction should be considered in SCD risk stratification, but only for patients with a low estimated 5-year risk of SCD (<4%). The recommendation class for primary prevention ICD in this scenario is IIb, which is the same for patients with an intermediate risk (≥4% and <6%).[1] Conversely, the AHA/ACC guideline recommends considering ICD placement in primary prevention in the presence of a single risk factor, based on the fact that each of the major risk factors is independently associated with an increased risk of SCD.[2] Within this paradigm, the HCM Risk-SCD tool can be used to inform patients on their individual risk in a shared decision-making process for ICD placement. Data from the international Sarcomeric Human Cardiomyopathy Registry (SHaRe) indicate that the difference in approaches to SCD risk stratification resulted in a two-fold higher rate of primary prevention ICD utilization in the USA vs. non-USA, which however did not translate into differences in SCD or resuscitated cardiac arrest, but rather decreased the rate of appropriate ICD therapies in US vs. non-US sites.[11]

The same difference applies to SCD risk stratification in children and adolescents, for whom the ESC guideline recommends using dedicated risk prediction models (e.g. HCM Risk-Kids), whereas the AHA/ACC guideline advocates a single risk factor-based approach.[1,2] Moreover, the updated AHA/ACC guideline considers a positive genotype status a clinical SCD risk factor in children, which is in contrast to the ESC guideline and a recent position statement of the Association for European Paediatric and Congenital Cardiology (AEPC) on indications of ICD therapy in childhood HCM.[12] This difference highlights a measure of uncertainty regarding the predictive role of a positive genetic test with regard to SCD risk in HCM patients, in any age group. The positive gene test criterion is widely felt to be too crude to inform clinical practice, and might lead to unnecessary implant of ICDs in many patients who are otherwise at low risk of events. Overall, it should be noted that paediatric-specific information on SCD risk is scant, and that SCD risk stratification in children is partly based on risk markers derived from adult HCM populations.

In spite of these fundamentally different strategies, both ESC and AHA/ACC guidelines emphasize that the decision to implant an ICD in primary prevention should not be guided solely by prespecified thresholds, but should take into account the patient's own level of risk tolerance. Within this framework, a thorough discussion of the potential benefits and risks related to ICD placement is of paramount importance, as it ensures the patient's active participation in a shared decision-making process.

Exercise recommendations

A key message from both guidelines is that accumulating evidence supports the safety and beneficial effect of low- and moderate-intensity exercise in patients with HCM,[13] which should therefore be encouraged. The guidelines' task forces agree that selected patients with a low-risk profile may participate in high-intensity exercise and competitive sport after comprehensive expert evaluation and shared decision-making,[1,2] as supported by registry data showing that HCM is an uncommon cause of SCD during competitive sports.[14] This point is further underscored by what is possibly the most noteworthy addition to the AHA/ACC guideline, i.e. a class III recommendation that vigorous physical activity and competitive sports should not be universally contraindicated in most HCM patients.[2] This implies that a physician's contraindication to physical exercise for an HCM patient, particularly when it significantly impacts the patient's lifestyle and health, could expose the physician to legal challenges.

In conclusion, the updated AHA/ACC and ESC guidelines capture paradigm-changing novelties in the evolving landscape of HCM management, encompassing not only CMI but also a revised approach to exercise recommendations. While some differences remain, particularly regarding the strategies for SCD risk stratification, both guidelines share the same fundamental philosophy that grounds the best clinical care on shared decision-making across all domains of HCM management.

Declarations

Disclosure of Interest

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