Editorial

Comments on the 2014 ESC Guidelines on the Diagnosis and Management of Hypertrophic Cardiomyopathy. A Critical View From the Perspective of Spanish Cardiology

Comentarios a la guía de práctica clínica de la ESC 2014 sobre el diagnóstico y manejo de la miocardiopatía hipertrófica. Una visión crítica desde la cardiología española

SEC Working Group for the 2014 ESC Guidelines on Diagnosis and Management of Hypertrophic Cardiomyopathy, Expert Reviewers for the ESC 2014 Guidelines on the Diagnosis and Management of Hypertrophic Cardiomyopathy, and SEC Clinical Practice Guidelines Committee

INTRODUCTION

In line with the policy on clinical practice guidelines of the Executive Committee of the Spanish Society of Cardiology,¹ the present document aims to debate the most important and novel aspects of the guideline on the diagnosis and management of hypertrophic cardiomyopathy (HCM) issued by the European Society of Cardiology (ESC).²

In Europe, the current guidelines replace the 2003 consensus document of the American College of Cardiology (ACC) and the ESC,³ which in the United States had been substituted by the clinical practice guidelines of the ACC and the American Heart Association (AHA) in 2011.⁴ The present guidelines are highly relevant, given the need to update the knowledge presented in the 2003 document, as well as to the numerous and substantial discrepancies between European cardiological practice and the recommendations of the 2011 ACC/AHA guidelines.⁴

METHODS

The Clinical Practice Guidelines Committee of the SEC created a working group composed of cardiologists with expertise in distinct fields, nominated by the Clinical Cardiology and Heart Failure and Transplant Sections and by the Working Group on Familial Heart Disease of the SEC. The general aim of this working group was to review the evidence and recommendations provided by the European guidelines on the diagnosis and management of HCM, which are the guidelines accepted by the SEC. A translation to Spanish is published in the current issue of Revista Española de Cardiología. All members of the working group were asked to analyze the guidelines. Specifically, they were asked to comment on: a) the most novel or important features for clinical practice; b) the most positive and most debatable aspects of these novel contributions; c) implications for clinical practice in Spain and elsewhere in our environment. A document was then drafted that included the information from the participants. The draft was then reviewed by 14 external expert reviewers and, after a definitive review by the working group, was submitted to the journal for evaluation and eventual simultaneous publication with the Spanish translation of the European guidelines.

GENERAL COMMENTS AND METHODOLOGICAL ANALYSIS

Hypertrophic cardiomyopathy is the most common genetic heart disease and is the most frequent cause of sudden cardiac death (SCD) in young persons.⁵,⁶ There are no data on the prevalence of HCM in Spain, but numerous studies conducted in diverse populations have reported that the prevalence of HCM is 1 out of every 500 persons in the general population.⁷

Extrapolation of these prevalence data shows that more than 90 000 persons have HCM in Spain. The guidelines are therefore particularly useful, given the large number of patients with HCM in our country and the particular features of the management of the various complications of this disease (left ventricular outflow tract obstruction, thromboembolism, and risk of sudden cardiac death [SCD]). Moreover, because of advances in the field of genetics in the last decade and its eruption in clinical practice, a framework of recommendations for general cardiologists is particularly timely.

Despite the existence of familial heart disease units and referral units designated by the Ministry of Health for patients with HCM in Spain,³ most patients receive care elsewhere, making a general, up-to-date guideline on the diagnosis and management of HCM particularly welcome. Although the guidelines are aimed at cardiologists who are not specialists in this disease, they document makes several references to the advisability of sending patients to referral units with demonstrated experience in particular aspects of their management (genetic studies, familial and reproductive counseling, invasive management of left ventricular outflow tract obstruction, etc).

The guideline is fairly long and detailed (55 pages, with 506 references, and 36 tables listing recommendations).

SEE RELATED ARTICLE:

¹A list of all the authors is provided in the Appendix.

²Corresponding author: Unidad de Insuficiencia Cardiaca y Cardiopatías Familiares, Servicio de Cardiología, Hospital Universitario Puerta de Hierro-Majadahonda, Manuel de Falla 2, 28222 Madrid, España.
E-mail address: paulogpavia@yahoo.es (P. García-Pavia).
The overall methodology is similar to that of other ESC guidelines: first there is an up-to-date description of the topic, followed by a series of recommendations on the topic (I, IIa, IIb, or III) and the strength of the evidence (A, B, or C) supporting the recommendations. Given the lack of clinical trials on HCM, it is unsurprising that, of the 132 recommendations in the guideline, 96 (73%) are supported by level C evidence, that is, these recommendations based on registries, retrospective studies, or expert consensus. Thirty-six (27%) are supported by level B evidence (derived from a single randomized trial or from numerous nonrandomized studies) and there are no recommendations with level A evidence (based on multiple randomized trials and meta-analyses).

This situation should lead to reflection on the need to carry out clinical trials designed to provide scientific answers to many questions related to HCM that are currently resolved through expert consensus.

**EVALUATION OF THE MOST IMPORTANT POINTS**

The most important or novel points identified by the working group are the following: etiologic diagnosis, diagnostic criteria, diagnostic work-up, genetic testing and family screening, management of left ventricular outflow tract obstruction, management of symptoms in the absence of obstruction, atrial arrhythmias, prevention of SCD, reproduction and contraception, and special issues.

**Etiologic Diagnosis**

The most novel contribution in this section is that it describes a detailed approach to the various causes of the disease.

In line with the ESC classification of cardiomyopathies, the classification of HCM is based on morphological criteria, and the causes are grouped into familial/genetic and nonfamilial/non genetic.

The document underscores that the disease has a genetic basis in most patients. These causes can be classified into 3 groups:

1. Sarcomere protein gene mutations (40%-60%), the most frequent of which are the MYBPC3 and MYH7 mutations.

2. Mutations in nonsarcomere genes (5%-10%), which include distinct metabolic disorders (such as Fabry disease, Danon disease, etc.), neuromuscular diseases, familial amyloid polyneuropathy (related to transthyretin), and congenital disorders (Noonan syndrome, LEOPARD syndrome, etc).

3. Other causes with no genetic basis, such as some amylloidoses and endocrine disorders.

A detailed description of the genes involved in HCM is provided in the tables in appendix II. In all, there is no causative genetic defect in 25% to 30% of patients, who may have developed the disease due to mutations in genes not yet described.

While the guideline briefly reviews the distinct etiologies, it does not describe treatment regimens in diseases with specific treatments (eg, Fabry disease, familial amyloidosis).

Importantly, both this section and others provide a detailed description of the signs, symptoms, and particular features that guide the etiologic diagnosis. Thus, numerous characteristics are listed that should be investigated in all patients with HCM to identify the potential phenocopies of the disease (Table 1).

**Diagnostic Criteria**

The new guideline clarifies the definition of HCM in children and adults. The disease is defined by wall thickness ≥ 15 mm in the absence of a known cause in adults and by wall thickness ≥ 2 standard deviations above the predicted mean in children.

The simplification adopted for the definition of the disease is important for the diagnosis in relatives. The major and minor diagnostic criteria for relatives have been abandoned and a wall thickness of ≥ 13 mm is diagnostic of HCM in the first-degree relatives of patients with HCM.

Although other subtle signs in imaging tests (crypts in magnetic resonance imaging, etc) or on electrocardiography can help to indicate that a relative is affected, the proposed simplification will help standardize which relatives are considered affected or unaffected.

**Diagnostic Work-up**

The guideline provides a detailed evaluation of the distinct tests used to assess patients with HCM, establishes their usefulness, and indicates how often they should be performed.

Some of the most important features related to these tests are discussed below.

**Holter Monitoring**

Holter monitoring should be carried out for 48 hours. In Spain, most centers have only 24-hour monitoring, requiring the test to be performed on 2 distinct days. Although some classical studies have conducted Holter monitoring for more than 24 hours, importantly, 24-hour Holter monitoring continues to be valid. Moreover, the equation proposed by the guideline for calculating the risk of SCD was mostly obtained from 24-hour Holter monitoring and a detailed analysis of the studies associating the presence of nonsustained ventricular tachycardia with SCD shows that many performed recordings > 48 hours (Table 2).
indicate ICD implantation. However, this study has been criticized because enhancement > 15% of the ventricular mass could be sufficient to cause ventricular fibrillation even in patients without risk criteria for SCD, the presence of late gadolinium enhancement may be sufficient to indicate a higher risk. Moreover, a recent publication postulated that, in patients with HCM, late gadolinium enhancement is a factor influencing implantable cardioverter defibrillator (ICD) implantation in patients with extensive enhancement is a factor influencing implantable cardioverter defibrillator (ICD) implantation in patients with cardiomyopathy.

### Late Atrial Size

The guideline recommends measurement of the anteroposterior left atrium (LA) diameter. There is wide interoperator-and even intraoperator-variability, in LA diameter measurement. Many centers dispense with this measurement and use LA volume, not only in HCM patients but also in routine practice. Because the anteroposterior diameter has been included in SCD risk stratification, it is important to stress that measurements be the most exact possible.

### Late Gadolinium Enhancement in Magnetic Resonance Imaging

The usefulness of late gadolinium enhancement as a risk marker for SCD is controversial and is one of the most important discrepancies with the ACC/AHA guideline. The US guideline established that extensive enhancement is a factor influencing implantable cardioverter defibrillator (ICD) implantation in patients with nonsustained ventricular tachycardia or an abnormal blood pressure response to exercise. Moreover, a recent publication postulated that, in patients without risk criteria for SCD, the presence of late enhancement > 15% of the ventricular mass could be sufficient to indicate ICD implantation. However, this study has been criticized for its design and its findings are based on a very small number of participants.

To date, there are no studies that demonstrate an association between late gadolinium enhancement and SCD, although the presence and extension of enhancement has been related to the development of heart failure. Given these findings and the lack of well-designed multicenter studies, late gadolinium enhancement is not currently included in SCD risk stratification.

### Genetic Testing and Family Screening

Management of the family, genetic counselling, and family are essential in the care of patients with HCM. Genetic testing is recommended in patients with HCM to allow cascade genetic screening of their relatives. The guideline specifies that tests should be performed by “trained health care professionals” forming part of a “multidisciplinary team”, but do not specify who should form part of such teams or what training is required of their members.

In Spain, this recommendation should support the creation of specialized consultations in familial heart diseases and the modification of the approach to these diseases. The family tree and family study are essential when attending patients with HCM. This “working method” should be routine and not exclusive to referral centers.

The most important part of this section is undoubtedly the clear message on the usefulness of genetics. Genetic testing receives a class IB indication but the guidelines indicate that, although it allows genetic counselling, it rarely helps in the clinical management of the proband. Those who derive greatest benefit from genetic testing are the relatives, since carriers (who will require genetic counselling and follow-up) can be distinguished from noncarriers. The document also stresses that genetic testing is of doubtful usefulness in probands whose relatives cannot be traced or who do not wish to be screened.

In our environment, a recent study has demonstrated the usefulness of genetic testing in these patients and their relatives, both from the clinical and economic points of view. The guideline shows prudence when approaching current routine practice regarding the method of genetic testing. It does not advocate any particular method, although, in our opinion, next generation sequencing currently seems to be the best choice, given that it allows a higher number of genes to be studied more efficiently. In clinical practice, targeted next generation sequencing, ie, analysis of a particular group of genes, rather than of the complete exome, seems the strategy most in line with current knowledge. Study of the exome can imply low coverages (poor-quality studies) and identification of gene variants unrelated to HCM that may be difficult to interpret.

In line with the ESC position statement on genetic testing, once a causative mutation has been identified in the proband, genetic analysis should proceed to clinical assessment of the proband’s family. In our opinion, this is erroneous. Both evaluations should be carried out simultaneously and clinical assessment should always be performed, given that the phenotype found in relatives can support (or exclude) the pathogenicity of the mutation identified in the proband. Moreover, almost 5% of patients with HCM carry 2 mutations, which could be important in the family study. Our experience indicates that failure to systematically perform a clinical assessment can sometimes lead to misdiagnosis.

The message of the guideline on clinical and genetic screening in relatives younger than 18 years is fairly nonspecific (class IIa). Clinical follow-up may begin at the age of 19 years, when genetic testing may also be considered. The spirit of this latter recommendation is rooted in the belief that DNA testing is not appropriate in minors if a positive result will not change the clinical approach. Furthermore, a positive result can affect children and their families psychologically, possibly affecting their development. The members of the working group differ in their opinions on this point and there is no clear evidence on the optimal approach in this situation.

However, it is obvious that establishing the age of 10 years as the cut-off for protecting children does not resolve the controversy. The working group recommends an individualized approach to genetic testing, depending on the child’s personal circumstances and the family context, and always after appropriate genetic counselling.

Given that the expressivity of HCM varies widely, the possibility of offering prenatal or preconception genetic diagnosis is rarely indicated. Because the legal framework of these techniques varies from country to country, it is difficult to establish recommendations. According to the current legal framework in Spain for preconception diagnosis (detection of severe hereditary diseases that develop early and have no curative treatment), prior approval for preconception diagnosis is required from the National Commission for Assisted Reproduction.

Finally, 2 additional recommendations on DNA testing deserve mention. The first concerns postmortem genetic analysis of stored tissue or DNA samples. In this case, the indication is only Ila. This is...
striking, since the benefit for relatives is the same as in living relatives (grade I indication). In our opinion, the indication for postmortem DNA testing should also be grade I. Moreover, joint protocols between clinicians and forensic pathologists should be created that would allow preservation and subsequent analysis of samples from patients who die suddenly if autopsy reveals HCM. Such protocols have already been created in several autonomous communities in Spain and should be extended to the entire country.

Management of Left Ventricular Outflow Tract Obstruction

In this section, the guideline basically consolidates current recommendations, outlining a systematic approach to aid the management of obstruction. The document also makes some novel contributions, discussed below.

Medical Treatment

Beta-blocker therapy at the maximum tolerated dose is the mainstay of the treatment of symptomatic obstruction. Propranolol receives special mention, despite the lack of comparative studies that would allow recommendation of specific beta-blockers. A new addition is the inclusion of sotalol, due to its ability to treat obstruction and arrhythmias. Disopyramide is recommended as second-line treatment and always in combination with a beta-blocker (not sotalol) or sometimes with verapamil. It is important to monitor the QTC interval, which should not exceed 480 ms. Disopyramide is contraindicated with other antiarrhythmic agents.

Patients with obstruction usually tolerate atrial fibrillation (AF) poorly and consequently it is important to restore sinus rhythm (IIa-C). Digoxin is contraindicated for the treatment of AF in patients with obstruction (III-C), although this recommendation is based on very few clinical data.

Invasive Treatment

The guideline underscores the importance of heart team discussions and of operator experience. Operators should carry out a minimum of 10 interventions per year (20 per operator in the ACC/AHA guidelines). Application of this recommendation is not feasible in Spain, where there are fewer cases per center and operator. The only solution would be to make referral circuits mandatory, an option that has been much discussed but never implemented in our environment.

The indication for invasive treatment remains unchanged in patients with significant obstruction (baseline or provoked gradient > 50 mmHg) and moderate-to-severe symptoms (New York Heart Association functional class III-IV) or recurrent exertional syncope (I-B and IIa-C, respectively).

For the first time, septal alcohol ablation is assigned the same class of recommendation (I-B) as myectomy in expert centers. There are no randomized trials, but meta-analyses have shown that the 2 procedures have similar efficacy and complications rates. Septal alcohol ablation has a higher rate of atroventricular block than surgery (12% vs 5%).

Myectomy is the procedure of choice in patients with severe hypertrophy (> 30 mm), extensive fibrosis on magnetic resonance imaging, and in children and adolescents. Pacemaker implantation or mitral valve surgery may be considered in mild hypertrophy (< 16 mm).

Some randomized controlled trials on the value of pacemakers show a reduction in obstruction and varying degrees of clinical improvement. The benefit of dual chamber pacing seems to be greater in persons older than 65 years; however, the guideline does not specify which patient groups could derive the greatest benefit from this technique (unlike the ACCF/AHA guidelines). The authors leave the recommendation for pacemaker implantation for patients with sympotomatic obstruction who refuse myectomy or septal alcohol ablation, with an indication for pacemaker implantation, or who require an ICD (IIb-C).

Left Ventricular Midcavity Obstruction

For the first time, the guideline devotes a section to midcavity obstruction, which occurs in 10% of patients; of these patients, apical aneurysms will develop in one-fourth. These aneurysms seem to be associated with a higher risk of ventricular arrhythmias and embolization. Nevertheless, ICD implantation is not recommended in the absence of other risk predictors. There is little experience with transaortic or transapical myectomy for the treatment of midcavity obstruction.

MANAGEMENT OF SYMPTOMS IN PATIENTS WITHOUT LEFT VENTRICULAR OUTFLOW OBSTRUCTION

In patients with a left ventricular ejection fraction < 50%, the new guideline adheres to the recommendations on drug therapy of the guidelines on chronic heart failure. Importantly, the recommendation assumes that there are benefits in terms of mortality, hospital admissions, and symptom improvement, without demonstrated evidence in this specific group of patients. Reference is made to the complexity of the management of these patients, as they do not usually tolerate high doses of vasodilators and diuretics due to the presence of reduced ventricular volumes.

With regard to cardiac resynchronization therapy, the guideline accepts the recommendations of general pacing guidelines (IIa-C). Moreover, cardiac resynchronization therapy is recommended in patients in New York Heart Association functional class II-IV, left ventricular ejection fraction < 50%, a QRS duration > 120 ms, and left bundle branch block; this controversial recommendation is based on the results of a small, single-center observational study. These recommendations on cardiac resynchronization therapy are a novel contribution and are not present in the ACCF/AHA guidelines. The document does not mention—and therefore adopts no position on-novel antianginal drugs agents such as ivabradin and ranolazine.

ATRIAL ARRYTHMIAS

Atrial fibrillation is the most common arrhythmia in patients with HCM, with a prevalence of 22.5% and an annual incidence of 3.1, according to a recent systematic review, which identified age and LA enlargement as the clinical features most closely associated with AF. Stroke is a frequent complication. The prevalence of thromboembolism (stroke and peripheral embolism) in patients with HCM and AF in this review was 27.1%, with an annual incidence of 3.8.

Patients with HCM were not included in studies of risk stratification of stroke risk in nonvalvular AF. The stroke risk in patients with HCM and AF is equivalent to a CHA2DS2-VASc (congestive heart failure, hypertension, age ≥ 75 years [doubled], diabetes, stroke [doubled], vascular disease, age 65–74 years, and female sex) score of 3, even though the HCM population is much younger. The authors of the present document do not consider CHA2DS2-VASc applicable in HCM. In contrast, we recommend the HAS-BLED ((Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score to estimate the rate of hemorrhagic complications.

Based on these data, the guideline issues the first recommendations on AF in HCM:

- It is important to identify AF early, if necessary, through periodic Holter monitoring (every 6–12 months) in patients with LA enlargement (> 45 mm).
• The CHA2DS2-VASc score is not recommended and anticoagulation should be prescribed to all patients with HCM and any form of AF.

There is no mention of anticoagulation self-monitoring. In contrast, the use of the new anticoagulants is discussed as an alternative when difficulties arise with vitamin K antagonists. The use of aspirin and clopidogrel can be considered when anticoagulant therapy is not feasible or is refused, even though there are no studies of their effectiveness in HCM (Ia-B).

Importantly, there is no recommendation on anticoagulation in patients with severe LA enlargement, even though anticoagulation therapy in these patients is widely used in various referral centers. This absence is probably motivated by the lack of robust data supporting this practice.

In contrast, the document discusses the option of AF ablation in selected patients (not very enlarged LA) refractory to antiarrhythmic therapy (Ia-B) but does not make clear the approach to be adopted in patients with postablation AF recurrence, nor does it mention the low effectiveness rates of ablation in these patients.

PREVENTION OF SUDDEN CARDIAC DEATH

This is one of the most novel and important sections of the guideline and includes relevant information from a recent study proposing and validating a formula for SCD risk stratification.9

The previous European guideline considered that patients with 2 or more classical risk factors were at high risk and, therefore, recommended ICD implantation in primary prevention.7 The ACCF/AHA guideline is less demanding and defines high-risk patients as those with at least 1 risk factor. The 5-year predictive ability of both guidelines is moderate, with an area under the curve of 0.64 and 0.63 for the ACC/ESC and ACCF/AHA guidelines, respectively.20

The new proposed formula is the result of a complex statistical analysis based on a population of 3675 patients with HCM from 6 European centers, including 2 Spanish centers.8 Each of the factors has a specific relative “weight”. These factors include age, unexplained syncope, the gradient of left ventricular outflow tract obstruction, LA diameter, and maximum ventricular thickness. Some of the classical risk factors, such as an abnormal blood pressure response, are excluded and 2 new factors have been added: age and left atrial thickness. Other possible risk factors have not been evaluated, such as the presence of fibrosis on cardiac magnetic resonance, myocardial ischemia, and genetic mutations.

Implantable cardioverter-defibrillator implantation is recommended for secondary prevention (I-B) or high estimated annual risk of SCD (≥ 6%) (Ia-B). Risk should be assessed individually in patients with an intermediate annual risk of 4% to 5% (IIb-B). The formula has not been tested and, therefore, should not be used in persons younger than 16 years, athletes, persons with phenocopies (Fabry) and in syndromic cases (eg, Noonan), and provides paradoxical redistribution.

SPECIAL ISSUES

The last section of the guideline discusses several scenarios requiring special considerations in the diagnosis and management of MCH. This section discusses the differential diagnosis between HCM and the normal training effect in athletes or hypertensive heart disease, as well as the management of basal septal hypertrophy in elderly people and associated valve diseases.

In line with the guideline on valvular heart disease, antibiotic prophylaxis for systemic endocarditis is not recommended in patients with HCM. Although there are no robust data to support antibiotic prophylaxis, this recommendation is controversial, especially in patients with left ventricular outflow tract obstruction.

Lastly, the guideline makes no clear recommendations on recreational sports activities (a question frequently asked by MCH patients) and there is still no consensus on competitive sports activities in carriers without phenotypic disease expression (IIb-C). These
activities were advised against in previous ESC recommendations but were allowed by the AHA/ACC.

CONCLUSIONS

The ESC guideline on the diagnosis and management of HCM is the most recent update on the topic. The document provides basic and general information on the management of these patients, and recommendations are classified into 4 categories that allow clinical cardiologists to adopt the most appropriate approach in each patient.

The most important points of the guideline refer to the etiologic diagnosis of HCM, genetic testing, structured management of left ventricular outflow tract obstruction, atrial arrhythmias, and SCD prevention. The document should encourage the creation of specialized units for the care of these patients and their families.

APPENDIX. AUTHORS

SEC Working Group for the ESC 2014 Guidelines on Diagnosis and Management of Hypertrophic Cardiomyopathy: Pablo García-Pavia (Coordinator), Josep Comín-Colet (Coordinator), Roberto Barriales-Villa, Vicente Climent, Enrique Galve, José Manuel García-Pinilla, Juan Ramón Gimeno-Blanes, Tomás Ripoll-Vera, and Maite Tomé-Esteban.


SEC Clinical Practice Guidelines Committee: Manuel Anguita Sánchez (President), Ángel Cequier Fillat, Lina Badimón Maestro, José Antonio Barrabés Riu, Josep Comín Colet, Ignacio Fernández Lozano, José Juan Gómez de Diego, Manuel Pan-Alvarez-Osorio, Luis Rodríguez Padial, José Alberto San Román Calvar, and Pedro Luis Sánchez Fernández.

CONFLICTS OF INTEREST

None declared.

REFERENCES


5. Centros, Servicios y Unidades de Referencia del Sistema Nacional de Salud [Cited 28 Sept 2014]. Available at: https://www.msssi.gob.es/profesionales/CentrosDeReferencia/CentrosCSUR.htm


