Progress in Cardiovascular Diseases 62 (2019) 212–216

Contents lists available at ScienceDirect

Progress in Cardiovascular Diseases

journal homepage: www.onlinepcd.com

Sudden death related cardiomyopathies - Hypertrophic cardiomyopathy☆

Zackary D. Goff [a], Hugh Calkins [a,b,*]

[a] Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, United States of America
[b] Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD, United States of America

ARTICLE INFO

Article history:
15 April 2019
15 April 2019

Keywords:
Cardiomyopathy
Hypertrophic cardiomyopathy
Sudden cardiac death

ABSTRACT

Hypertrophic cardiomyopathy (HCM) is a form of inherited cardiomyopathy. Most individuals with HCM experience minimal symptoms throughout their lifetime. However, those with HCM are at risk of ventricular arrhythmias and sudden cardiac death (SCD), the most feared complication of HCM. Implantable cardioverter defibrillator (ICD) implantation has played a large role in transforming this disease from one with an ominous prognosis to one with mortality rates that are on par with the general public. Since the early 2000s, balance between SCD prevention and unnecessary ICD placement has been sought, this is reflected in the evolution of SCD risk stratification models for patients with HCM. This review discusses key concepts pertaining to HCM, with emphasis on prevention of SCD, and summarizes and compares the recommendations for ICD implantation in current guidelines.

Contents

Hypertrophic Cardiomyopathy (HCM) was initially described in living patients in 1959 by Marrow and Braunwald in a case series of 3 patients, documenting significant pressure gradients in the absence of valvular outflow obstruction observed during open-heart surgery.[1]

HCM is the most common sudden cardiac death (SCD)-related cardiomyopathy. The long-standing estimated prevalence has been 1 in 500,[2] with one study estimating the prevalence as high as 1 in 200.[3] HCM is one of the most common causes of SCD in young athletes.[4,5] Four studies of SCD etiology in young athletes show that HCM accounts for 6–13% of SCD cases.[4–7] The largest of these reviewed SCD in 1866 athletes over 27 years. HCM was confirmed in 251 cases (13%) and suspected in another 57 cases (3%).[5] Fig. 1 shows the cause of SCD in the 690 cases confirmed to be of cardiac etiology, with HCM accounting for 36% of cases.

HCM is a familial cardiomyopathy that is inherited in an autosomal dominant pattern. The pathologic hallmark of HCM is myocyte disarray.[8] Mutations in eight genes, encoding sarcomeric proteins, have been determined to cause HCM: beta myosin heavy chain (MYH7), cardiac myosin binding protein-C (MYBPC3), cardiac troponin T (TNNT2), cardiac troponin I (TNNI3), alpha tropomyosin (TPM1), cardiac alpha actin (ACTC1), myosin regulatory light chain (MYL2), and myosin essential light chain (MYL3). Mutations in the genes encoding beta myosin heavy chain and cardiac myosin binding protein account for nearly 50% of all cases of HCM. As many as 11 additional genes have been less definitively linked to HCM.[9–12] Data from the Sarcomeric

Abbreviations: AF, Atrial fibrillation; BP, Blood pressure; CMR, Cardiac magnetic resonance; HCM, Hypertrophic cardiomyopathy; HF, Heart failure; ICD, Implantable cardioverter defibrillator; LGE, Late gadolinium enhancement; LV, Left ventricular; LVOT, Left ventricular outflow tract; LVH, Left ventricular hypertrophy; NSVT, Non-sustained ventricular tachycardia; SAM, Systolic anterior motion; VA, Ventricular arrhythmia.

☆ Conflict of interest statement: see page 216.

* Address reprint requests to: Hugh Calkins, Sheikh Zayed Tower, Room 7125R, 1800 Orleans Street, Baltimore, MD 21287, United States of America.
E-mail address: hcalkins@jhmi.edu (H. Calkins).

https://doi.org/10.1016/j.pcad.2019.04.001
0033-0620/

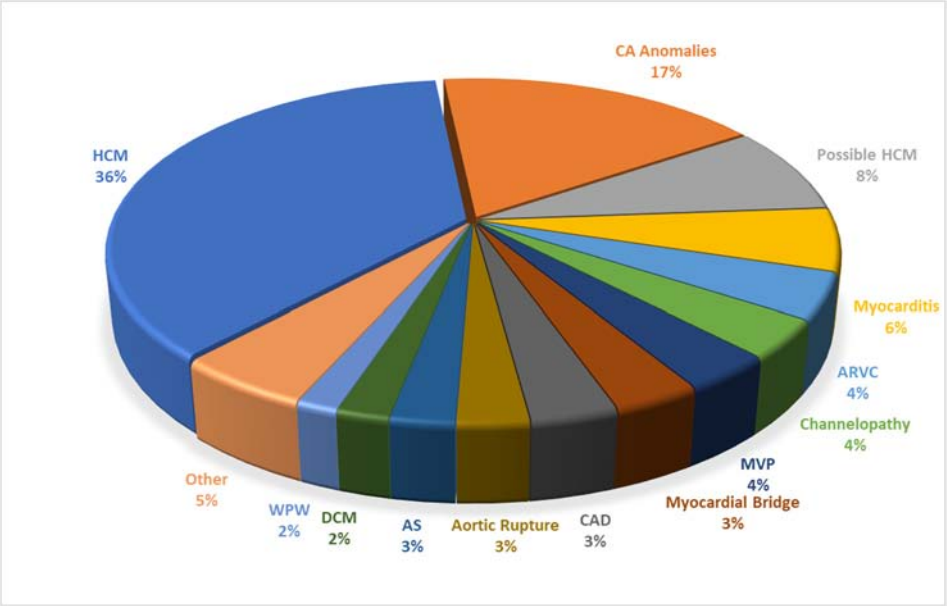

Fig. 1. Etiology of SCD due to cardiovascular events. Cause of sudden death in 690 young competitive athletes who died as a consequence of a cardiovascular event. ARVC – Arrhythmogenic right ventricular cardiomyopathy; AS – Aortic stenosis; CA – Coronary artery; CAD – Coronary artery disease; DCM – Dilated cardiomyopathy; HCM – Hypertrophic cardiomyopathy; MVP – Mitral valve prolapse; WPW – Wolff-Parkinson-White. Adapted from Maron BJ, Doerer JJ, Haas TS, et al. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980–2006. Circulation. 2009;119[8]:1085–1092.

Human Cardiomyopathy Registry (SHaRe), the largest HCM cohort to date, report 46% of 4591 patients carried a pathogenic or likely pathogenic mutation.[12] Genetic testing is recommended (Class I) for patients who meet clinical criteria for HCM and have family members who are available and willing to consider cascade genetic screening. Genetic testing is also recommended (Class I) when the diagnosis is equivocal. Given the lack of genotype-phenotype association in the current data, genetic testing may be of limited value when cascade screening is not possible.[9,10]

HCM is diagnosed by three criteria: 1) left ventricular (LV) wall thickness ≥15 mm, by any cardiac imaging modality, 2) absence of LV cavity dilation, 3) LV hypertrophy (LVH) unable to be explained by cardiac or systemic disease.[9,10] However, given disease heterogeneity and overlap with other causes of LVH, these criteria should be considered in the entire clinical context of the patient, including morphology of LVH, family history, electrocardiography, multi-modality cardiac imaging, and genetic testing. These other considerations are of particular importance when diagnosis is equivocal, such as LV wall thickness 13–15 mm. Measurement of LV wall thickness is primarily from transthoracic echocardiogram, however cardiac magnetic resonance imaging (CMR) is increasingly being used. LVH is generally asymmetric with the basal interventricular septum being affected to the greatest degree.

Although not necessary for diagnosis of HCM, identification of a sarcomeric gene mutation, severe LV wall thickness (>25 mm), or systolic anterior motion (SAM) of the mitral valve leaflets support the diagnosis of HCM, when the diagnosis is unclear.[10] SAM is the most common cause of LV outflow tract (LVOT) obstruction in HCM and is present at rest in approximately one third of patients with HCM, another third develop SAM with physiologic stress, the final third have no obstructive physiology.[9,10] Identification of LVOT obstruction is an important prognostic indicator; it is associated with increased symptoms and risk of atrial fibrillation (AF), stroke, and SCD.[13,14]

The differential diagnosis for HCM in adults most commonly includes LVH due to increased afterload and physiologic cardiac remodeling secondary to athletic training ("athlete heart").[10] Evaluation of the patient's medical history and degree of physical involvement are important in determining the cause of LVH. The morphology of LVH secondary to conditions of increased afterload is typically symmetric and <15 mm. These patients will have an identifiable cause of increased afterload, such as systemic hypertension or aortic stenosis. Athletic training typically causes symmetric LVH with enlarged LV end-diastolic diameter (>55 mm), without associated left atrial enlargement. During periods of deconditioning, the severity of LVH will decrease, if the hypertrophy is secondary to athletic conditioning.[15] Other less common causes of LVH are mitochondrial, metabolic, neuromuscular, and infiltrative diseases.

Natural history and risk of sudden death

The natural history and clinical manifestation of HCM can be highly variable, even within members of the same family, carrying the same genetic mutation – ranging from completely asymptomatic to heart failure and/or sudden death.[16] Most patients remain asymptomatic or minimally symptomatic throughout their lives. The most common complications of HCM leading to morbidity and mortality are AF (20–25%), heart failure (HF; 22%), end-stage HF (3%), and SCD (1%).[12,17] Symptoms of HCM include dyspnea, exertional chest pain, palpitations, light headedness and syncope, with dyspnea and angina being the most common and syncope the least common.[18]

As described above, HCM is accountable for a considerable portion of SCD in young athletes. Bagnall and colleagues showed that HCM is also a significant cause of SCD in young non-athletes. They reported that in 490 cases of SCD between ages 1 and 35 years, HCM was the cause of SCD in 20 cases (4%).[19] In non-athlete adult populations of all ages, the incidence of SCD due to HCM is less significant. A study of 2661 cases of SCD in a province of Northern Finland identified 15 individuals (0.6%) with HCM.[20] Of 525 cases of SCD that underwent autopsy in San Francisco county, 6 (1%) had HCM.[21]

Early mortality rates for HCM were estimated to be 3–6% per year, though this estimate came from tertiary referral centers, whose population may not be representative of the entirety of the HCM population. Later, pre-implantable cardioverter defibrillator (ICD) estimates of 1.5% per year were thought to more representative.[22] More recently, a large cohort of 744 patients with HCM, 44 (6%) experienced SCD over an average of 8 years, yielding and annual mortality of 0.7% due to SCD.[23] Another study reported 17 of 1000 (2%) patients with HCM died of SCD, for an annual SCD mortality of 0.23%.[24] The total mortality rates for HCM from these two studies were 0.2% and 0.5% per year,

Table 1
Summary of recommendations for ICD implantation in patients with HCM.

2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death[31]	Class I • Survival of cardiac arrest due to VT or VF • Spontaneous sustained VT causing syncope or hemodynamic compromise Class IIa • Presence of ≥1 of the following risk factors: o Maximum LV wall thickness ≥30 mm o SCD due to HCM in 1 or more first-degree relatives o ≥1 episode of unexplained syncope in the last 6 months • Spontaneous NSVT AND ≥1 risk modifier or patient from high-risk subset • Abnormal blood pressure response with exercise AND ≥1 risk modifier or patient from high-risk subset Class IIb • Spontaneous NSVT or abnormal blood pressure response with exercise, without additional risk factors Class III • HCM genotype and no other SCD risk factors
2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy[9]	Class I • Survival of cardiac arrest due to VT or VF • Spontaneous sustained VT causing syncope or hemodynamic compromise Class IIa • Estimated 5-year risk ≥6% by HCM Risk-SCD model Class IIb • Estimated 5-year risk ≥4% and <6% by HCM Risk-SCD model • Estimated 5-year risk <4% by HCM Risk-SCD model AND ≥1 clinically important feature: o Multiple family members with sudden death o Abnormal blood pressure response with exercise Class III • Estimated 5-year risk <4% by HCM Risk-SCD method
2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy[10]	Class I • Survival of cardiac arrest due to VT or VF • Hemodynamically significant VT Class IIa • Presence of 1 or more of the following risk factors: o ≥1 first-degree relative with HCM-related sudden death o Maximum LV wall thickness ≥30 mm o ≥1 episode of unexplained syncope • NSVT AND ≥1 risk factor or risk modifier • Abnormal blood pressure response to exercise AND ≥1 risk factor or risk modifier Class IIb • NSVT or abnormal blood pressure response to exercise without additional risk factors Class III • HCM genotype without risk factors • Strategy to allow patients with HCM to participate in competitive athletics
2008 guidelines for device-based therapy of cardiac rhythm abnormalities[30]	Secondary prevention • Survival of cardiac arrest due to VT or VF • Spontaneous sustained VT causing syncope or hemodynamic compromise Primary prevention • Presence of at least one established risk factor

Table 2
Clinical features of HCM associated with increased risk of SCD.

Established risk factors	• Survival of cardiac arrest due to VT or VF • Spontaneous sustained VT causing syncope or hemodynamic compromise • Family history of HCM-related SCD • Maximum LV wall thickness ≥30 mm • Unexplained syncope within 6 months • Non-sustained VT ≥3 beats • Abnormal blood pressure response to exercise
Potential risk modifiers	• Age <30 years • Delayed hyperenhancement on cardiac MRI • Left ventricular outflow tract obstruction • Unexplained syncope >5 years prior
High-risk subsets	• Left ventricular aneurysm • Left ventricular ejection fraction <50%

Modified from Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2018;72(14):e91-e220.

respectively, both less than the annual mortality rate of the general United States population (0.8%).[23,24] This improvement in mortality is attributed to implantation of ICDs, which have been shown to be highly effective in preventing SCD, and heart transplantation.[25,26]

Prevention of SCD and other management considerations

SCD is the most devastating complication of HCM and can be the initial presentation of HCM. Indications for ICD implantation, to prevent SCD, have evolved over the last 2 decades.[17,27–29]

Shown in Table 1 is a summary of current recommendations for ICD implantation from four current guidelines: 2017 AHA/ACC/HRS guidelines on ventricular arrhythmias (VA) and prevention of SCD, 2014 ESC HCM guidelines, 2011 ACCF/AHA HCM guidelines, and 2008 ACCF/AHA/HRS cardiac device guidelines. New guidelines, to replace the 2011 ACCF/AHA HCM guidelines, are currently in process but not available for discussion in this review. ICD implantation for secondary prevention in patients who have experienced hemodynamically unstable VA or survived SCD is recommended (Class I) unanimously. The decision for primary prevention ICD implantation utilizes two risk stratification models: identification of established risk factors or calculation of individual risk estimates.

The three current guidelines from US societies all endorse the classic risk factor model, which is shown in Table 2. ICD implantation is reasonable (Class IIa) in patients with family history of premature sudden death, unexplained syncope, or LV thickness greater than or equal to 30 mm. Two additional risk factors, which have been deemphasized in current AHA/ACC/HRS guidelines, abnormal blood pressure (BP) response to exercise (decrease in systolic BP by 20 mm Hg or inability to increase systolic BP by 20 mm Hg during exercise) and nonsustained ventricular tachycardia (NSVT), now require the presence of another established or potential risk factor for ICD implantation to be considered reasonable (Class IIa). Presence of only abnormal BP with exercise or NSVT, in the absence of additional risk factors, should only lead to consideration of ICD on a case-by-case basis (Class IIb).[10,30,31]

The 2014 ESC HCM guidelines endorse a novel model for estimation of SCD risk developed by Mahony and colleagues (HCM Risk-SCD) to predict individualized estimates of SCD for patients with HCM.[32] This model addressed concerns that use of a single risk factor to identify patients at high risk for SCD, as recommended by the 2011 ACCF/AHA HCM guidelines, may overestimate the risk of SCD and lead to unnecessary ICD implantation.[33] The HCM Risk-SCD model utilizes 8 predictors (age, maximal LV wall thickness, left atrial diameter, LVOT gradient, family history of SCD, NSVT, and unexplained syncope) to calculate an individualized 5-year estimate of SCD. The ESC guidelines consider ICD implantation reasonable (Class IIa) for patients with an estimated 5-year risk of SCD ≥6%. Those with 5-year estimated SCD risk of 4–6% may benefit from ICD implantation (Class IIb). ICD is not recommended for those with an estimated risk <4%.[9] Efforts have since been made to validate this model, with mixed results.[34–39] This online risk calculator can be accessed at http://www.doc2do.com/hcm/webHCM.html.

Late gadolinium enhancement (LGE) on CMR is thought to represent areas from which VA arise. Both presence of LGE and the extent of LGE have been shown to be associated with increased risk of sudden death, however this has yet to be validated in large prospective studies, therefore the predictive value remains indeterminant.[40,41]

Additional risk factors have been reported, including: extracellular volume on CMR,[42] high T2-weighted signal intensity,[43] Global longitudinal strain,[44] left atrial volume,[43] fragmented QRS patterns,[45] J waves,[45] and LV mechanical dispersion.[46]

Beta-blockers are first-line treatment for symptomatic patients; this is thought to be a class effect and there are little data to support use of individual beta-blockers. They should be up-titrated to a goal heart rate of 60 beats per minute, to decrease myocardial oxygen demand and attenuate sympathetic-induced VA.[9,10] Non-dihydropyridine calcium channel blockers, verapamil and diltiazem, can also be useful in symptomatic relief for patients that do not tolerate beta-blockers. Dihydropyridine calcium channel blockers can exacerbate obstruction and should not be used in patients with outflow tract obstruction.[9,10] Disopyramide may be considered as add-on therapy for patients whose symptoms are refractory to beta-blocker or calcium channel blocker therapy.[9,10] There are limited data to suggest that ranolazine may be beneficial in providing symptomatic relief, however further study is required to establish the role of ranolazine in HCM.[47] Mavacamten (MYK-461) interacts with cardiac myosin ATPase to impair myosin binding and to decrease intensity of sarcomeric contraction.[48] Two trials are currently investigating the role of Mavacamten in obstructive and nonobstructive HCM: EXPLORER-HCM (NCT03470545) and MAVERICK-HCM (NCT03442764).

Septal myectomy and alcohol septal ablation are invasive therapies that can be beneficial to select patients with symptoms refractory to medical management. Minimum criteria for consideration of these procedures are: severe dyspnea or angina that interferes with daily activity, septal hypertrophy causing a LVOT gradient of ≥50 mm Hg at rest or with exertion, and sufficient septal thickness to perform the procedure.[9,10] Septal myectomy has been reported to reduce the LVOT gradient and provide symptomatic relief in 90% of HCM patients.[49] There have been no randomized trials comparing myectomy and alcohol ablation, but both have been shown to improve functional status with similar risk of procedural mortality.[50] There is risk of developing both left and right bundle branch blocks and, less commonly, atrioventricular block with either of these procedures.[50,51]

Conclusions and future perspective

HCM is the most common and well-studied inherited cardiomyopathy. In the last two decades, remarkable progress has been made in disease management and prevention of SCD. The role of medical management, namely Mavacamten, is being studied in current trials. Risk stratification for SCD continues to evolve, current data suggest that CMR may have value, but its definitive role in risk stratification for SCD is yet to be determined. Recent data have shown that patients diagnosed before the age of 40 years and those with pathogenic mutations were more likely to experience malignant arrhythmias and SCD.[12] Further investigation of the value of genotype in prognostication and SCD risk stratification is underway in an observational prospective study, Hypertrophic Cardiomyopathy Registry (HCMR) - Novel Markers of Prognosis in Hypertrophic Cardiomyopathy (NCT01915615). The study aim is to use CMR and genetic mutations, in addition to clinical and demographic variables, to develop a predictive scoring model for SCD risk.[52]

Conflict of interest statement

None of the authors have any conflicts of interests with regard to this publication.

References

1. Morrow AG, Braunwald E. Functional aortic stenosis; a malformation characterized by resistance to left ventricular outflow without anatomic obstruction. Circulation 1959;20:181-189.
2. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. Circulation 1995;92:785-789.
3. Semsarian C, Ingles J, Maron MS, Maron BJ. New perspectives on the prevalence of hypertrophic cardiomyopathy. J Am Coll Cardiol 2015;65:1249-1254.
4. de Noronha SV, Sharma S, Papadakis M, Desai S, Whyte G, Sheppard MN. Aetiology of sudden cardiac death in athletes in the United Kingdom: a pathological study. Heart 2009;95:1409-1414.
5. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980–2006. Circulation 2009;119:1085-1092.
6. Finocchiaro G, Papadakis M, Robertus JL, et al. Etiology of sudden death in sports. insights from a United Kingdom Regional Registry J Am Coll Cardiol 2016;67:2108-2115.
7. Harmon KG, Asif IM, Maleszewski JJ, et al. Incidence, cause, and comparative frequency of sudden cardiac death in National Collegiate Athletic Association Athletes: a decade in review. Circulation 2015;132:10-19.
8. Maron BJ, Anan TJ, Roberts WC. Quantitative analysis of the distribution of cardiac muscle cell disorganization in the left ventricular wall of patients with hypertrophic cardiomyopathy. Circulation 1981;63:882-894.
9. Elliott PM, Anastasakis A, Borger MA, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;35:2733–2779.
10. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2011;58:e212–260.
11. Sabater-Molina M, Perez-Sanchez I, Hernandez Del Rincon JP, Gimeno JR. Genetics of hypertrophic cardiomyopathy: a review of current state. Clin Genet 2018;93:3-14.
12. Ho CY, Day SM, Ashley EA, et al. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). Circulation 2018;138:1387-1398.
13. Maron MS, Olivotto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med 2003;348:295-303.
14. Efthimiadis GK, Parcharidou DG, Giannakoulas G, et al. Left ventricular outflow tract obstruction as a risk factor for sudden cardiac death in hypertrophic cardiomyopathy. Am J Cardiol 2009;104:695-699.
15. Maron BJ, Pelliccia A, Spirito P. Cardiac disease in young trained athletes. Insights into methods for distinguishing athlete's heart from structural heart disease, with particular emphasis on hypertrophic cardiomyopathy. Circulation 1995;91:1596-1601.
16. Alcalai R, Seidman JG, Seidman CE. Genetic basis of hypertrophic cardiomyopathy: from bench to the clinics. J Cardiovasc Electrophysiol 2008;19:104-110.
17. Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol 2003;42:1687-1713.
18. McKenna W, Deanfield J, Faruqui A, England D, Oakley C, Goodwin J. Prognosis in hypertrophic cardiomyopathy: role of age and clinical, electrocardiographic and hemodynamic features. Am J Cardiol 1981;47:532-538.
19. Bagnall RD, Weintraub RG, Ingles J, et al. A prospective study of sudden cardiac death among children and young adults. N Engl J Med 2016;374:2441-2452.
20. Hookana E, Junttila MJ, Puurunen VP, et al. Causes of nonischemic sudden cardiac death in the current era. Heart Rhythm 2011;8:1570-1575.
21. Tseng ZH, Olgin JE, Vittinghoff E, et al. Prospective countywide surveillance and autopsy characterization of sudden cardiac death: POST SCD study. Circulation 2018;137:2689-2700.
22. Maron BJ, Casey SA, Poliac LC, Gohman TE, Almquist AK, Aeppli DM. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. Jama 1999;281:650-655.
23. Maron BJ, Olivotto I, Spirito P, et al. Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. Circulation 2000;102:858-864.
24. Maron BJ, Rowin EJ, Casey SA, et al. Hypertrophic cardiomyopathy in adulthood associated with low cardiovascular mortality with contemporary management strategies. J Am Coll Cardiol 2015;65:1915-1928.
25. O'Mahony C, Lambiase PD, Quarta G, et al. The long-term survival and the risks and benefits of implantable cardioverter defibrillators in patients with hypertrophic cardiomyopathy. Heart 2012;98:116-125.
26. Maron BJ, Rowin EJ, Casey SA, et al. Hypertrophic cardiomyopathy in children, adolescents, and young adults associated with low cardiovascular mortality with contemporary management strategies. Circulation 2016;133:62-73.
27. Maron BJ, Shen WK, Link MS, et al. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. N Engl J Med 2000;342:365-373.
28. Gregoratos G, Cheitlin MD, Conill A, et al. ACC/AHA guidelines for implantation of cardiac pacemakers and antiarrhythmia devices: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation). J Am Coll Cardiol 1998;31:1175-1209.
29. Maron BJ, Spirito P, Shen WK, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. JAMA 2007;298:405-412.
30. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society J Am Coll Cardiol 2013;61:e6-75.
31. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2018;72:e91-e220.
32. O'Mahony C, Jichi F, Pavlou M, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). Eur Heart J 2014;35:2010-2020.
33. O'Mahony C, Tome-Esteban M, Lambiase PD, et al. A validation study of the 2003 American College of Cardiology/European Society of Cardiology and 2011 American College of Cardiology Foundation/American Heart Association risk stratification and treatment algorithms for sudden cardiac death in patients with hypertrophic cardiomyopathy. Heart 2013;99:534-541.
34. Fernandez A, Quiroga A, Ochoa JP, et al. Validation of the 2014 European Society of Cardiology sudden cardiac death risk prediction model in hypertrophic cardiomyopathy in a reference center in South America. Am J Cardiol 2016;118:121-126.
35. Liebregts M, Faber L, Jensen MK, et al. Validation of the HCM Risk-SCD model in patients with hypertrophic cardiomyopathy following alcohol septal ablation. Europace 2018;20:f198-f203.
36. O'Mahony C, Jichi F, Ommen SR, et al. International external validation study of the 2014 European Society of Cardiology guidelines on sudden cardiac death prevention in hypertrophic cardiomyopathy (EVIDENCE-HCM). Circulation 2018;137:1015-1023.
37. Vriesendorp PA, Schinkel AF, Liebregts M, et al. Validation of the 2014 European Society of Cardiology guidelines risk prediction model for the primary prevention of sudden cardiac death in hypertrophic cardiomyopathy. Circ Arrhythm Electrophysiol 2015;8:829-835.
38. Maron BJ, Casey SA, Chan RH, Garberich RF, Rowin EJ, Maron MS. Independent assessment of the European Society of Cardiology sudden death risk model for hypertrophic cardiomyopathy. Am J Cardiol 2015;116:757-764.
39. Ruiz-Salas A, Garcia-Pinilla JM, Cabrera-Bueno F, et al. Comparison of the new risk prediction model (HCM Risk-SCD) and classic risk factors for sudden death in patients with hypertrophic cardiomyopathy and defibrillator. Europace 2016;18:773-777.
40. Maron MS. Clinical utility of cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Cardiovasc Magn Reson 2012;14:13.
41. Weng Z, Yao J, Chan RH, et al. Prognostic value of LGE-CMR in HCM: a meta-analysis. JACC Cardiovasc Imaging 2016;9:1392-1402.
42. Avanesov M, Munch J, Weinrich J, et al. Prediction of the estimated 5-year risk of sudden cardiac death and syncope or non-sustained ventricular tachycardia in patients with hypertrophic cardiomyopathy using late gadolinium enhancement and extracellular volume CMR. Eur Radiol 2017;27:5136-5145.
43. Debonnaire P, Thijssen J, Leong DP, et al. Global longitudinal strain and left atrial volume index improve prediction of appropriate implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy patients. Int J Cardiovasc Imaging 2014;30:549-558.
44. Kang KW, Janardhan AH, Jung KT, Lee HS, Lee MH, Hwang HJ. Fragmented QRS as a candidate marker for high-risk assessment in hypertrophic cardiomyopathy. Heart Rhythm 2014;11:1433-1440.
45. Tsuda T, Hayashi K, Konno T, et al. J waves for predicting cardiac events in hypertrophic cardiomyopathy. JACC Clin Electrophysiol 2017;3:1136-1142.
46. Jalanko M, Tarkiainen M, Sipola P, et al. Left ventricular mechanical dispersion is associated with nonsustained ventricular tachycardia in hypertrophic cardiomyopathy. Ann Med 2016;48:417-427.
47. Gentry 3rd JL, Mentz RJ, Hurdle M, Wang A. Ranolazine for treatment of angina or dyspnea in hypertrophic cardiomyopathy patients (RHYME). J Am Coll Cardiol 2016;68:1815-1817.
48. Green EM, Wakimoto H, Anderson RL, et al. A small-molecule inhibitor of sarcomere contractility suppresses hypertrophic cardiomyopathy in mice. Science 2016;351:617-621.
49. McCully RB, Nishimura RA, Tajik AJ, Schaff HV, Danielson GK. Extent of clinical improvement after surgical treatment of hypertrophic obstructive cardiomyopathy. Circulation 1996;94:467-471.
50. Agarwal S, Tuzcu EM, Desai MY, et al. Updated meta-analysis of septal alcohol ablation versus myectomy for hypertrophic cardiomyopathy. J Am Coll Cardiol 2010;55:823-834.
51. Talreja DR, Nishimura RA, Edwards WD, et al. Alcohol septal ablation versus surgical septal myectomy. comparison of effects on atrioventricular conduction tissue J Am Coll Cardiol 2004;44:2329-2332.
52. Kramer CM, Appelbaum E, Desai MY, et al. Hypertrophic Cardiomyopathy Registry: the rationale and design of an international, observational study of hypertrophic cardiomyopathy. Am Heart J 2015;170:223-230.