JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2014 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 64, NO. 1, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.05.003

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Hypertrophic Cardiomyopathy

Present and Future, With Translation Into Contemporary Cardiovascular Medicine

Barry J. Maron, MD,* Steve R. Ommen, MD,† Christopher Semsarian, MBBS, PhD,‡ Paolo Spirito, MD,§ Iacopo Olivotto, MD,‖ Martin S. Maron, MD¶

ABSTRACT

Hypertrophic cardiomyopathy (HCM) is a common inherited heart disease with diverse phenotypic and genetic expression, clinical presentation, and natural history. HCM has been recognized for 55 years, but recently substantial advances in diagnosis and treatment options have evolved, as well as increased recognition of the disease in clinical practice. Nevertheless, most genetically and clinically affected individuals probably remain undiagnosed, largely free from disease-related complications, although HCM may progress along 1 or more of its major disease pathways (i.e., arrhythmic sudden death risk; progressive heart failure [HF] due to dynamic left ventricular [LV] outflow obstruction or due to systolic dysfunction in the absence of obstruction; or atrial fibrillation with risk of stroke). Effective treatments are available for each adverse HCM complication, including implantable cardioverter-defibrillators (ICDs) for sudden death prevention, heart transplantation for end-stage failure, surgical myectomy (or selectively, alcohol septal ablation) to alleviate HF symptoms by abolishing outflow obstruction, and catheter-based procedures to control atrial fibrillation. These and other strategies have now resulted in a low disease-related mortality rate of <1%/year. Therefore, HCM has emerged from an era of misunderstanding, stigma, and pessimism, experiencing vast changes in its clinical profile, and acquiring an effective and diverse management armamentarium. These advances have changed its natural history, with prevention of sudden death and reversal of HF, thereby restoring quality of life with extended (if not normal) longevity for most patients, and transforming HCM into a contemporary treatable cardiovascular disease. (J Am Coll Cardiol 2014;64:83-99) © 2014 by the American College of Cardiology Foundation.

More than 50 years have elapsed since the modern pathological description of hypertrophic cardiomyopathy (HCM) by Teare in 1958 (1), followed shortly thereafter by the first detailed clinical reports from Dr. Eugene Braunwald and colleagues at the National Institutes of Health (Bethesda, Maryland) in the early 1960s (2). For much of the early years, HCM was considered a rare, interesting, and perhaps odd (if not exotic) disease, with high mortality and little effective or safe treatment interventions. In particular, measures to prevent sudden death (SD), undoubtedly the most feared and visible complication of this complex genetic disease, were unavailable to young patients for decades. In a very early (1962) paper that defined left ventricular (LV) outflow tract obstruction in HCM, Dr. Braunwald wrote: "At this time, we are aware of no method of management that can specifically and favorably influence the course of a patient" (3).

As major reviews of HCM have appeared over the last decade (4-13), changes in the clinical profile, diagnostic methods, and management options have continued and accelerated, including: 1) recognition

From the *Hypertrophic Cardiomyopathy Center, Minneapolis Heart Institute Foundation, Minneapolis, Minnesota; †Mayo Clinic, Rochester, Minnesota; ‡Royal Prince Alfred Hospital and Centenary Institute, University of Sydney, Sydney, Australia; §Ente Ospedaliero Ospedali Galliera, Genoa, Italy; ‖Referral Center for Cardiomyopathies, Careggi University Hospital, Florence, Italy; and the ¶Tufts Medical Center and School of Medicine, Boston, Massachusetts. Dr. Barry J. Maron is a consultant for GeneDx. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received May 5, 2014; accepted May 5, 2014.

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AF = atrial fibrillation

AHA = American Heart Association

CAD = coronary artery disease

CMR = cardiovascular magnetic resonance

ECG = electrocardiography

HCM = hypertrophic cardiomyopathy

HF = heart failure

ICD = implantable cardioverter-defibrillator

LGE = late gadolinium enhancement

LV = left ventricle

LVH = left ventricular hypertrophy

SD = sudden death

of the full diversity of the disease spectrum, which is now recognized as associated with a relatively low adverse event rate (14–22); 2) definition of the molecular basis of the disease, with the opportunity for family screening and identification of relatives not at risk for developing HCM, as well as affected family members without clinical evidence of disease (12,23–26); 3) introduction of implantable cardioverter-defibrillators (ICDs) for prevention of SD (27–31); 4) development of a more reliable stratification model, expanding recognition and appreciation of the highest-risk patients who will most likely benefit from ICDs (8,32–34); 5) penetration of advanced imaging into HCM practice with high-resolution and tomographic cardiovascular magnetic resonance (CMR) imaging (**Fig. 1**), complementary to echocardiography, with improved diagnosis and identification of novel at-risk subgroups, expanding the scope of risk stratification (9,17,19,35); 6) advances in operative (myectomy) techniques, resulting in low-risk surgery that is highly effective in abolishing outflow obstruction and heart failure (HF) symptoms (10,13,36); 7) introduction of nonsurgical alternatives to myectomy for selected patients, such as percutaneous alcohol septal ablation (37); 8) recognition of the impact of patient age in dictating clinical course and management decisions (38); 9) publication of comprehensive guidelines offering concise and specific recommendations to the practicing community for diagnosis and management (39,40); 10) advances in refractory HF treatment, including transplantation (18); 11) recognizing the significant cardiovascular mortality benefit attributable to contemporary treatment options (27,28,41); and 12) evolution in the perception of HCM to a disease deserving of a more optimistic outlook, compatible with extended longevity for most patients and affording them with a measure of reassurance (42).

These advances for patients with HCM support this State-of-the-Art review, which is designed to provide the cardiovascular community with an opportunity to appreciate the important current approaches to this complex disease. This is a clinically relevant, patient care-related discussion formulated around contemporary HCM practice patterns, assembled by the efforts of 6 expert cardiologists with established dedication to HCM and care of these patients. The presentation is structured around 7 major areas: epidemiology; genetics and genetic testing; clinical diagnosis with imaging; natural history and impact of therapy; risk stratification and prevention of SD; HF management, septal reduction therapy, and transplantation; and the role and significance of atrial fibrillation (AF).

HCM remains a challenging disease, characterized by a heterogeneous clinical profile and considerable unpredictability in its natural history, with clinical decisions often made without absolute certainty on the basis of incomplete data.

EPIDEMIOLOGY

Although once considered rare, HCM is now more appropriately regarded as the most common inherited cardiac disease. A number of population studies estimate the prevalence of HCM in the general population to be at least 1 in 500, with the extrapolation that 700,000 Americans are affected by this disease (43).

HCM is a global disease, reported in >50 countries on all continents, including the most populous nations of India and China (7). Consequently, HCM is known to occur in a variety of races and ethnic groups (44), as well as equally in both sexes and with a generally similar clinical, phenotypic, and genetic expression (45).

Paradoxically, the estimated prevalence of HCM in the general population seems inconsistent with the persistent perception in cardiovascular practice that it is a distinctly uncommon disease. This apparent discrepancy strongly suggests that most affected individuals are not diagnosed clinically, probably achieving advanced longevity without HCM-related symptoms. Therefore, clinicians assess only a small fraction of the overall HCM population (likened to the "tip of the iceberg"), which often includes patients who are diagnosed only because of symptoms or clinical events (46). Fortuitous diagnosis of HCM during routine clinical or family screening and evaluation is increasing due to unexpected findings on electrocardiography (ECG) or advanced imaging (47).

GENETICS

GENERAL PRINCIPLES. It has been almost 25 years since the seminal work by the Seidman laboratory and others identified the first sarcomere gene mutations that cause HCM, bringing this genetic disease into the modern era of molecular investigation (25). HCM is inherited with an autosomal dominant Mendelian pattern, variable expressivity, and age-related (and incomplete) penetrance (12,25,48–50). Offspring of an affected individual have a 50% probability of inheriting a mutation and risk for the disease; alternatively, sporadic cases may be due to de novo