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JACC STATE-OF-THE-ART REVIEW

Management of Hypertrophic Cardiomyopathy

JACC State-of-the-Art Review

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ABSTRACT

Hypertrophic cardiomyopathy (HCM), a relatively common, globally distributed, and often inherited primary cardiac disease, has now transformed into a contemporary highly treatable condition with effective options that alter natural history along specific personalized adverse pathways at all ages. HCM patients with disease-related complications benefit from: matured risk stratification in which major markers reliably select patients for prophylactic defibrillators and prevention of arrhythmic sudden death; low risk to high benefit surgical myectomy (with percutaneous alcohol ablation a selective alternative) that reverses progressive heart failure caused by outflow obstruction; anticoagulation prophylaxis that prevents atrial fibrillation-related embolic stroke and ablation techniques that decrease the frequency of paroxysmal episodes; and occasionally, heart transplant for end-stage nonobstructive patients. Those innovations have substantially improved outcomes by significantly reducing morbidity and HCM-related mortality to 0.5%/y. Palliative pharmacological strategies with currently available negative inotropic drugs can control symptoms over the short-term in some patients, but generally do not alter long-term clinical course. Notably, a substantial proportion of HCM patients (largely those identified without outflow obstruction) experience a stable/benign course without major interventions. The expert panel has critically appraised all available data and presented management insights and recommendations with concise principles for clinical decision-making. (J Am Coll Cardiol 2022;79:390–414) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Hypertrophic cardiomyopathy (HCM) is now recognized as a relatively common contemporary and treatable disease, not inevitably progressive, with potential for low mortality, and compatible with normal or extended life expectancy.

INTRODUCTION

HCM is a relatively common inherited heart disease with diverse and complex phenotypic and genetic expression and clinical course, worldwide in its distribution, affecting both sexes and many races, cultures, and ethnicities.[1,2] HCM is now 60 years old since the original pathologic description by Teare[1] and the first comprehensive clinical description by the Braunwald group in the early 1960s.[3] It is now diagnosed with increasing frequency at virtually any time in life from infancy to advanced age.[4-6] Estimated prevalence is 1:500[7] in the general population

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HIGHLIGHTS

- Contemporary treatments have effectively transformed HCM into a highly treatable condition with relatively low morbidity/mortality.
- Sudden death in patients with HCM can be prevented through risk stratification and use of ICDs.
- Surgical myectomy has become a highly effective, low-risk operation in experienced centers to relieve outflow tract obstruction and symptoms.

based on the disease phenotype, and higher (1:200)[8] accounting for familial transmission, subclinical cases, and pathogenic sarcomere mutations, inferring that 750,000 or more Americans may be affected by HCM. However, only about 100,000 patients are identified clinically,[9] suggesting that HCM is underdiagnosed, and cardiologists may be exposed to only a small proportion of patients within the broad disease spectrum ("tip of the iceberg" phenomenon).

Not long ago considered a grim, unrelenting, and malignant disease entity with few effective treatment options, the clinical narrative of HCM has evolved substantially,[10] Over the last 20 years, in combination with increased clinical recognition including benign low-risk subgroups without significant symptoms or disability,[1,5,6,10] effective management strategies for major HCM complications have emerged which improve clinical course, resulting in substantially lower mortality and morbidity rates, with enhanced likelihood of achieving normal longevity with good quality of life for both adults and children with survival possible to age 70s to 90s[1,4-6,11-19] (**Central Illustration, Figures 1 and 2**).

Contemporary treatments and interventions, personalized to target adverse pathways, have significantly reduced HCM mortality >10-fold from 6%/y reported early on to 0.5%/y,[1,11,15,17] currently one of the lowest of all major disease-related risks to living (eg, cancer, neurological disorders, and congestive heart failure [HF])[14] (**Figure 3**). With currently available management options, mortality specifically attributable to HCM is now distinctly uncommon and largely limited to a minority of nonobstructive patients with progressive refractory HF.[20-22]

Recognition of such clinical advances in HCM, a condition less common in cardiovascular practice than ischemic or valvular heart disease, may not penetrate as rapidly and completely into consciousness of the physician and patient communities. Therefore, the enhanced understanding of this complex disease, often mired in controversy, represents the impetus and justification for assembling this consortium of experts to promote the most contemporary diagnostic and clinical management principles for HCM.

THE *JACC* EXPERT PANEL

The Expert Panel is comprised solely of clinicians and thought leaders, each with highest level of personal experience with HCM from major centers dedicated to this disease. This unique consensus document was the product of a systematic overview approach producing evidence-based recommendations and insights that reflect extensive practice experience (cumulative, 250 years), derived from direct interactions with HCM patients over decades, as well as knowledge acquired from personal research and the peer-reviewed literature.

It is our goal to create a concise but comprehensive best care model emphasizing decision-pathways for HCM scenarios commonly encountered in clinical practice, with reliance on the most up-to-date literature (including 2021), emphasizing the progress made in diagnosis and treatment. We also wish to underscore that an often nuanced disease such as HCM may not lend itself readily to adherence with rigid guideline-type categorizations that sometimes cannot adequately capture disease complexity or the realities of clinical practice.[4-6] Therefore, we have expressed key principles for HCM decision-making in "real world" clinical language. The flexibility afforded by the present state-of-the-art format represents a distinct advantage in this regard.

The present expert recommendations offer ease of interrogation to identify decision-making principles, while not restraining the diagnosis or management of individual patients. Although panel members support (and promote) the advantages of specialized and dedicated multidisciplinary HCM referral center programs as models of care,[1,4-6,13] an equally important objective is to more expansively inform cardiovascular practitioners caring for most HCM patients in general cardiology environments outside of referral centers.

Furthermore, we recognize that no set of recommendations can fully embrace all conceivable clinical scenarios and management decisions encountered in a disease such as HCM, and implementation of

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ASA = alcohol septal ablation

EF = ejection fraction

HCM = hypertrophic cardiomyopathy

HF = heart failure

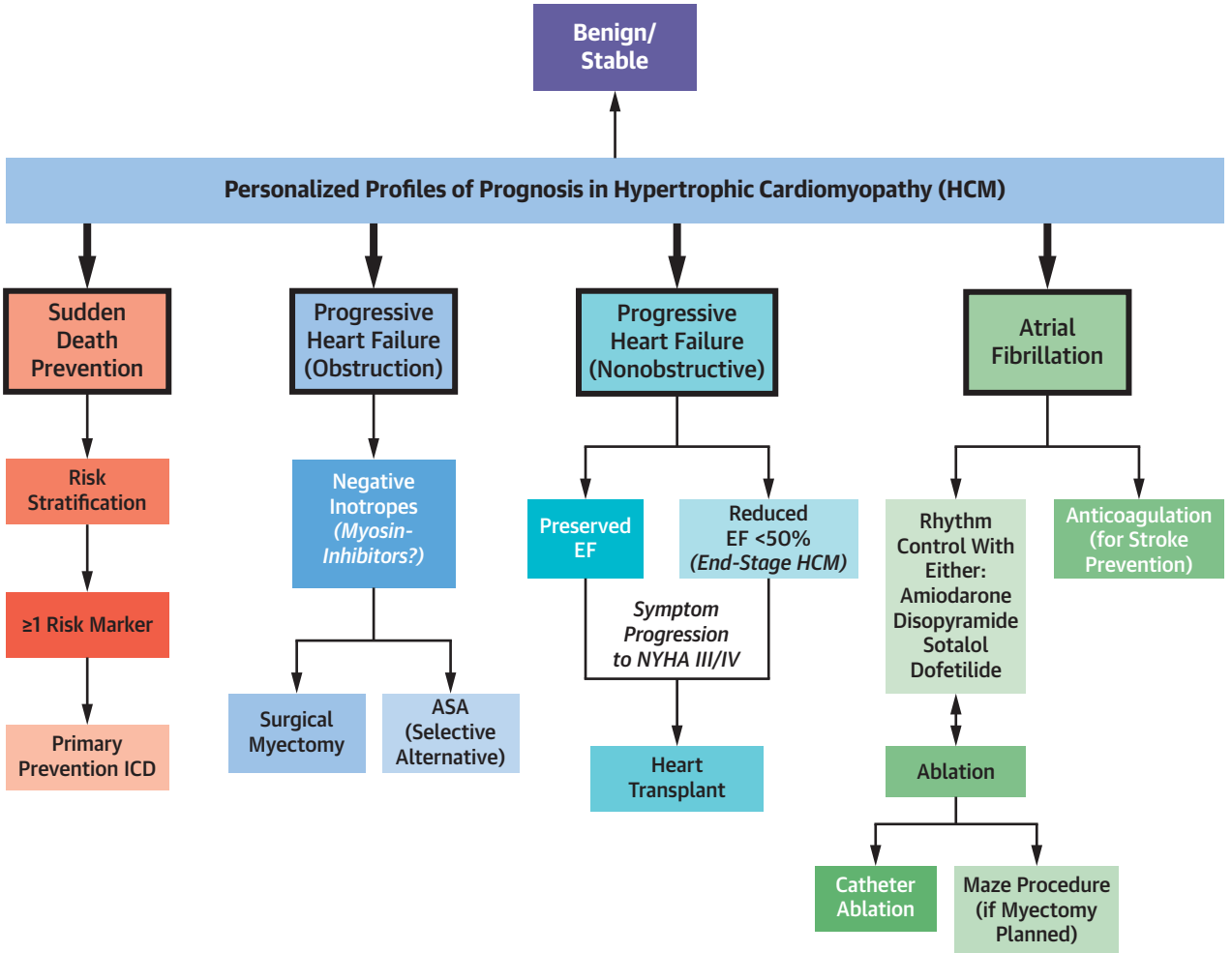
ICD = implantable cardioverter-defibrillator

LGE = late gadolinium enhancement

LV = left ventricular

NYHA = New York Heart Association

CENTRAL ILLUSTRATION Management Guidelines for Hypertrophic Cardiomyopathy



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Personalized profiles dictating prognosis and effective management strategies in HCM shown **below** that are aligned with the 4 specific adverse pathways. Only about 10% of patients incur >1 of these disease pathways. ASA = alcohol septal ablation; EF = ejection fraction; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association.

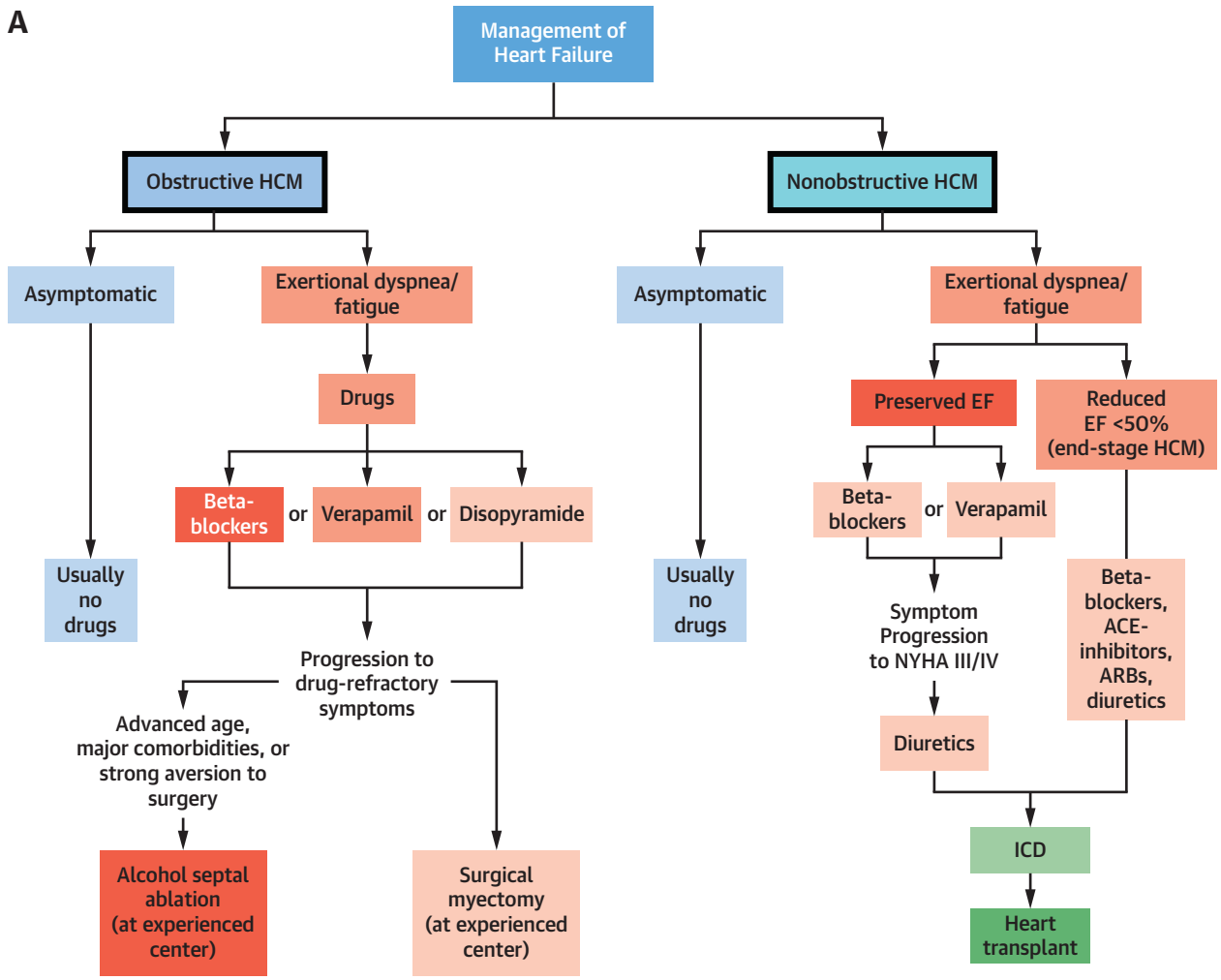
effective contemporary strategies may not yet be available for each and every patient or in all venues. Indeed, HCM is a heterogeneous and relatively low event rate condition comprised of numerous patient subgroups,[1] some of which may not lend itself easily to available data, particularly considering the often bewildering volume of information encountered in the literature, sometimes encumbered by contradictory messages.[1]

Our recommendations allow for personal preferences and active participation of fully informed patients, in conjunction with physician judgment (based on knowledge, experience, acumen, and intuition) to resolve ambiguities by medical reasoning that inevitably surround treatment decisions for a nuanced disease like HCM, which unavoidably relies largely on nonrandomized data from observational registries.

SUDDEN DEATH PREVENTION

Once considered the most common cause of sudden death in the young, prevention of these events is now a reality by virtue of a mature risk algorithm with predictive markers and penetration of ICDs into this patient population.

FIGURE 1 **Management Strategies for HCM**



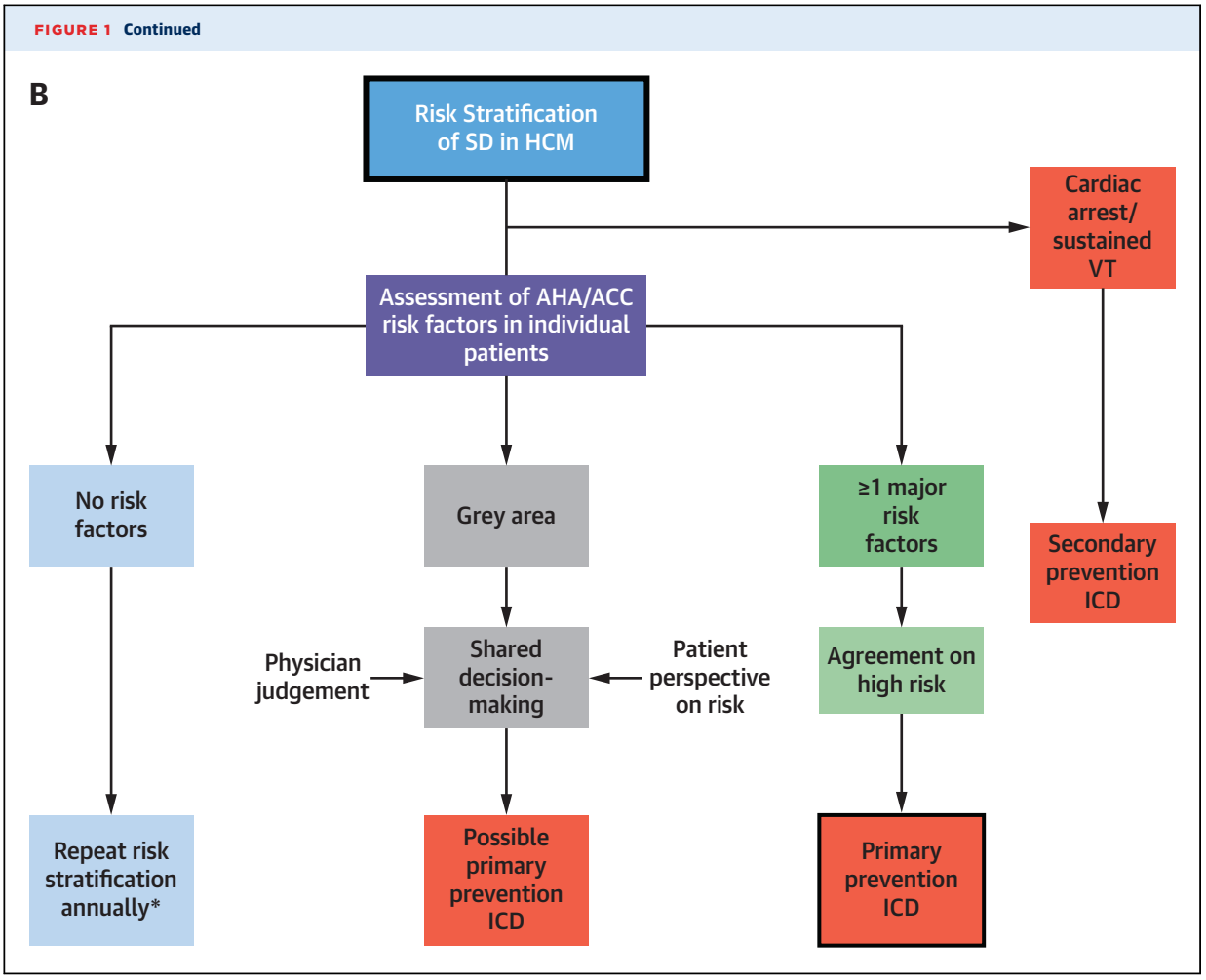
(A) Heart failure reversal; **(B)** risk stratification and prevention of sudden death; and **(C)** atrial fibrillation and stroke prevention. *Based on proposal by Carrick et al.[93] †With novel direct oral anticoagulants, or vitamin K antagonist warfarin (coumadin). ‡Usually after recurrent AF and unsuccessful trial of anti-arrhythmic drugs. ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CPAP = continuous positive airway pressure; EF = ejection fraction; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; SD = sudden death; VT = ventricular tachycardia.

Continued on the next page

BACKGROUND. The specter of unexpected sudden death has historically been the most visible and devastating complication of HCM for young patients, albeit relatively uncommon (0.9%/y) and >3-fold less prevalent than progressive HF or atrial fibrillation (AF) in HCM cohorts.[1,11,15,23,24] Notably, implantable cardioverter-defibrillators (ICDs) were introduced to HCM for primary prevention 20 years ago after a landmark clinical study[25] demonstrated that device therapy was effective in terminating sustained ventricular tachyarrhythmias likely triggered by re-entry circuits,[11,15] with an underlying substrate very different from coronary artery disease, ie, subject to left ventricular (LV) outflow obstructive, marked hypertrophy, diastolic dysfunction, and microvascular ischemia[1] (**Figure 4**).

Subsequently, dissemination of ICDs to thousands of HCM patients resulted in a management paradigm[11] in which there is general agreement that these devices are highly effective in preventing sudden death in high-risk patients and have reduced the number of these events, thereby

FIGURE 1 Continued



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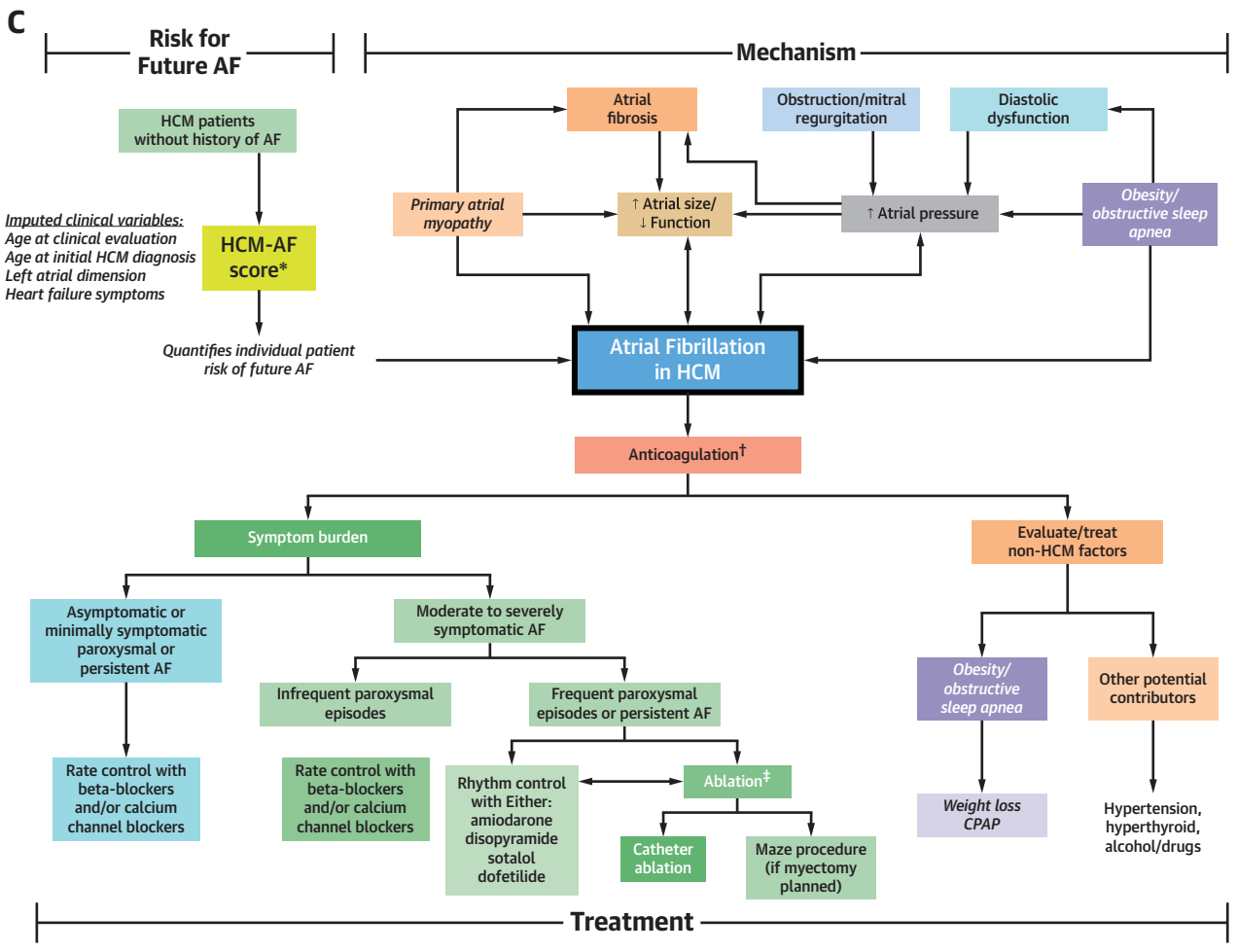
significantly decreasing the HCM mortality rate (now to 0.5%/y), which also includes benign and stable low-risk patient subsets.[1,10,13-15,17] Effectiveness of ICDs in hospital-based HCM populations coupled with apparent rarity of events in the community without prior diagnosis[26] suggests that HCM-related sudden death may not be as common as previously considered.

RISK STRATIFICATION. Studies of risk stratification have been carried out in diverse cohorts in several parts of the world, using the AHA/ACC individual risk marker strategy, ie, *identification of ≥1 conventional risk marker regarded as relevant and major within the individual patient clinical profile and sufficient to justify strong consideration for a primary prevention ICD implant* (**Central Illustration, Figure 1B, Tables 1 and 2**). Sudden death risk markers most commonly associated with ICD therapy in adult HCM patients have been repeatedly recommended in the HCM literature and guidelines (2003 American College of Cardiology [ACC]/European Society of Cardiology [ESC], 2011 ACC/American Heart Association [AHA] and 2020 AHA/ACC, 2017 AHA/ACC/Heart Rhythm Society [HRS], 2019 enhanced ACC/AHA algorithm, and 2020 AHA/ACC guidelines)[4-6,27] (**Table 1**): including recent unexplained syncope with or without outflow obstruction; family history of HCM-related sudden death in a close relative; thin-walled akinetic-dyskinetic LV apical aneurysm with regional scarring[28]; repetitive and/or prolonged episodes of nonsustained ventricular tachycardia on ambulatory monitoring; extensive late gadolinium enhancement (LGE) (fibrosis)[29] including end-stage progression; and massive left ventricular hypertrophy (LVH) (wall thickness ≥30 mm) (**Figure 5**), although individual patterns of LV wall thickness distribution do not per se predict sudden death (or HF). No single risk marker applies to all patients susceptible to sudden death.

Not uncommonly, risk stratification scenarios can involve a measure of ambiguity when data are insufficient to allow definitive recommendations. In

FIGURE 1 Continued



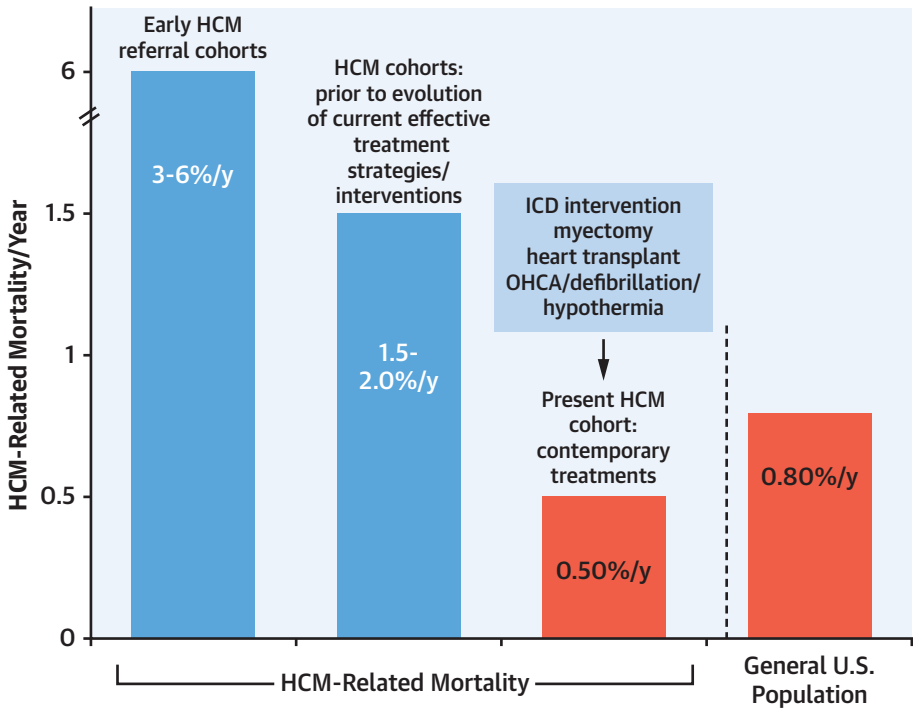
such inevitable "gray zones," ICD decision-making can rely on arbitrators including extensive LGE, coexistent ischemic heart disease, prior alcohol septal ablation (ASA), or marked resting outflow gradient[1,11,13,15,17,29,30] (Table 1). Predictive power of individual sudden death risk factors is also influenced by age, ie, with risk markers most relevant in young and middle-aged patients, but substantially less so in stable adults surviving >60 years (0.2%/y sudden death rate),[31] for whom prophylactic ICDs are discouraged or recommended on a case-by-case basis.[11]

ICD DECISIONS AND THERAPY. Notably, in studies from multiple centers in many countries, primary prevention ICD interventions terminating sustained malignant tachyarrhythmias (rapid VT/VF) occur at a rate of 3-4%/y (at mean age 45 years), and 10%/y for secondary prevention (after resuscitated cardiac arrest), with multiple interventions occurring in one-third of patients (Figure 6, Table 2).[1,15,16,25,32] In contrast to ischemic heart disease, device interventions in HCM are not associated with later disease-related morbidity/mortality such as HF, multiple hospitalizations, sudden death, psychological dysfunction.[33]

Of note, timing of appropriate ICD therapy is highly unpredictable likely attributable to the unique underlying HCM electrophysiologic substrate (Figure 4), ie, the time elapsed from implant (recognition of high risk status) to first ICD treatment is variable, including prolonged periods ≥10 years in more than one-third of patients (range to 17 years), and without objective evidence of increasing risk over that time interval.[32]

A 17-year clinical practice initiative carried out in a large cohort of >2,000 consecutive patients[13] used risk markers (in concert with 2020 AHA/ACC

FIGURE 2 Progress in the Management of HCM



Decrease in HCM mortality over 60 years from the early studies in the 1960s and 1970s, to those before introduction of the ICD in 2000[25] to the present (2022). OHCA = out-of-hospital cardiac arrest; other abbreviations as in Figure 1.

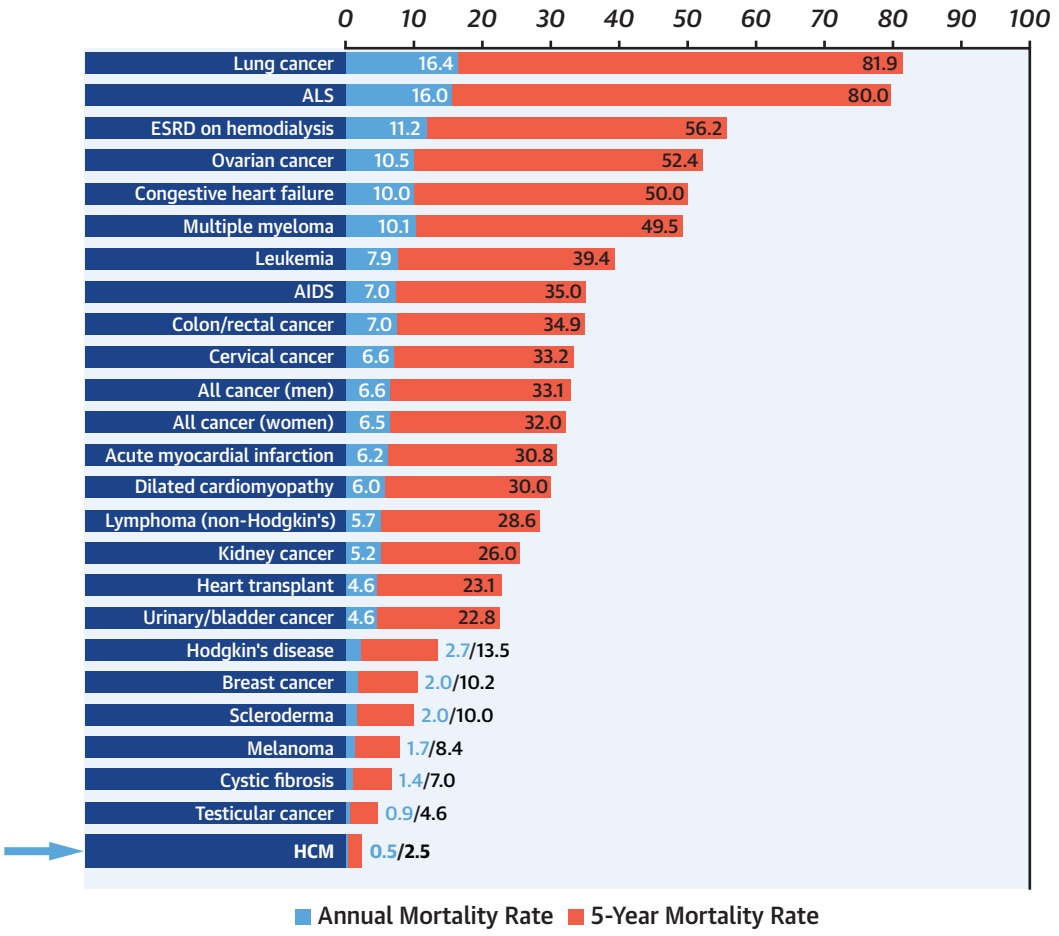
guidelines)[6] to make prospective ICD decisions for individual patients. With a sensitivity of 95%, this strategy reliably identified a high proportion of at-risk ICD candidates who subsequently benefited from prophylactic device therapy by terminating lethal ventricular tachyarrhythmias at a rate 50-fold greater than the small subset who died suddenly without ICDs,[13] of whom 40% had received an ICD recommendation with risk markers, but declined (Figure 6). The number of ICD implants needed to terminate VT/VF in 1 patient was 6:1, similar to that from randomized defibrillator trials in compromised patients with ischemic heart disease.[15]

Decisions to implant ICDs can be challenging, particularly when available evidence is insufficient to confidently assign risk level. Resolution of ambiguity may benefit from comprehensive physician clinical judgment/intuition and medical reasoning, as well as transparent interactions with fully informed patients and families weighing benefits and limitations of risk stratification and ICDs.[34] This process accounts for varying personal attitudes of patients toward sudden death risk and implanted devices, including perspectives in different countries and cultures. Sudden death risk in HCM does not differ by sex or race, although ICDs are less frequently implanted in minorities.[35,36]

For primary prevention, single-chamber devices are preferred to decrease likelihood of long-term lead problems. Indeed, ICD considerations should always be weighed against the possibility of device-related complications, including inappropriate shocks usually triggered by supraventricular or sinus tachycardias, and most common in younger patients.[11,15] However, inappropriate shocks have decreased in frequency (now 1%/y) because of standardized conservative adjustments in device programming after 2012 based on higher rate cutoffs/thresholds and longer detection intervals in accord with consensus recommendations.[11,15,32] About 10% of patients experience other significant device complications, including lead fractures and dislodgement, pocket or lead infections, or from lead extractions (rate, 1%/y).[32]

Despite potential device complications, net benefit of prophylactic ICDs favors sudden death prevention strategies for preservation of life.[1,11,15-17,28,32,37] Potential adverse consequences to the venous system from indwelling leads in young high-risk HCM patients

FIGURE 3 **HCM and the Risks of Living**



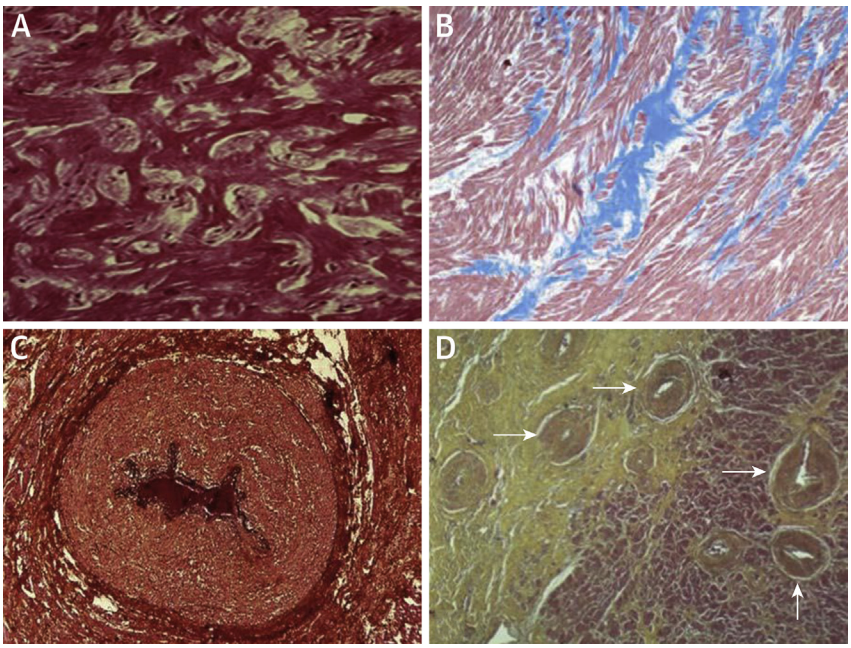
Annual and 5-year mortality rates for the most common chronic diseases that impact survival of the general population as of 2017. Reproduced with permission from Maron et al.[14] ALS = amyotrophic lateral sclerosis; ESRD = end-stage renal disease; HCM = hypertrophic cardiomyopathy.

has created interest in the subcutaneous ICD. This system has now been shown to be reliable in a small group of HCM patients with diverse disease phenotypes (interventions, 5%/y).[38] Limitations include: absence of pacing function, which would make transvenous implants more advisable in some subgroups such as LV apical aneurysm, and not uncommon inappropriate shocks caused by T-wave oversensing.

ICDs IN CHILDREN. Risk stratification in children with HCM has been encumbered by lack of general consensus for risk marker definitions and reports from relatively small heterogeneous patient populations that may include other diseases with LVH. The AHA/ACC ≥1 individual risk marker approach has also been most effective for selection of young patients for primary prevention implants and effective prevention of sudden death.[5,13,39,40] As in adults with HCM, appropriate therapy in children occurs at 3.5%-5%/y,[11,15,39-42] including 1 study reporting particularly high sensitivity and zero sudden deaths with ICDs.[40] In this age group, the predominant predictive sudden death markers reported have been: unexplained syncope, family history of HCM-related sudden death, massive LVH, and possibly nonsustained VT.[39-46] Notably, however, ESC risk scoring cannot be used below age 16 years to identify high-risk patients, even though sudden deaths not uncommonly occur in this age group.[4,47]

Due to the paucity of relevant outcome data in young rapidly growing patients with small body size, caution is advised in using the Z-score as a primary strategy instead of absolute wall thickness to define extreme LVH as a sudden death marker, as it could

FIGURE 4 Histopathology



Underlying HCM-myocardial substrate. **(A)** Disorganized architecture with myocytes arranged at oblique and perpendicular angles, possibly responsible for arrhythmogenicity. **(B)** Interstitial (matrix) fibrosis (stained **blue**) responsible in part for LV thickness. **(C)** Vasculopathy: thick-walled narrow-lumen intramural coronary arteriole (small-vessel disease), probably the basis for microvascular ischemia. **(D)** Intramural arterioles within and in close proximity to replacement fibrosis shown at lower power **(arrows)**.

lead to excessive implants in young low-risk patients, given that therapeutic interventions in children/adolescents most often occur at the absolute LV wall thickness threshold of ≥30 mm.[40]

ESC RISK SCORE. The ESC has promoted an online decision-making risk score derived from a multivariable logistic regression model that estimates sudden death risk, based on a complex formula comprising 7 clinical continuous or binary variables (only 4 of which are associated with sudden death in the literature).[4,47]

Relying on the C-(concordance) statistic, the ESC risk score attempts to distinguish high-risk vs low-risk patients who will (or will not) experience sudden death events over 5 years. However, this risk tool is associated with low sensitivity for predicting sudden death events in both adults and children (ie, sensitivity only 33%, compared with 95% for the AHA/ACC individual risk marker strategy), theoretically leaving many patients unprotected without ICDs.[11,13,15,45]

The ESC risk score has not been tested prospectively on an external independent HCM population for individual patient outcome and ICD efficacy. However, it has been repeatedly applied retrospectively to adult and childhood populations of known clinical outcome (in the United States, Canada, China, and Korea), with low sensitivity, consistently failing to identify most patients who experience arrhythmic events.[15,45]

Limitations of the ESC statistical risk score emanate from difficulty applying a rigid mathematical model to predicting sudden death for individual patients affected by a heterogeneous heart disease, with the inevitability of restricting physician judgment, or without the flexibility to evolve as new information emerges.[34] Absence of CMR data from the ESC formula is a major determinant of the low sensitivity of the score, given that CMR-based markers are associated with 20% of appropriate device therapies.[15]

The panel also questions the value of ESC scores for estimating risk level quantitatively in patient interactions,[6] given the imprecision in annual mortality estimates and difficulty patients have understanding and incorporating such numerical values into their personal clinical circumstance.

Nevertheless, the specificity attributable to the ESC score suggests it could modestly reduce the number of implants in low-risk patients mitigating excessive ICD use, albeit at the cost of lower sensitivity for identifying high-risk patients eligible for ICDs.[4,47] It is impractical to combine ESC scores with an individual

TABLE 1 Major Clinical Markers Recommended for Current HCM Risk Stratification[a]

Family history of sudden death[b]	Sudden death judged definitively or likely caused by HCM, generally considered when occurring in ≥1 first-degree, or other close relatives, <50 years of age.
Extreme LV hypertrophy[b]	Wall thickness ≥30 mm in any LV segment by echocardiography and/or CMR; consideration for this morphological marker is also given to borderline values of 28 or 29 mm in individual patients, at the discretion of the treating cardiologist.[c]
Unexplained recent syncope[b]	One or more recent and otherwise unexplained events involving loss of consciousness, judged by history unlikely to be neurally mediated (vasovagal) syncope[d]
Nonsustained ventricular tachycardia (NSVT)[e]	3 or more brief episodes of consecutive ventricular beats and/or ≥1 prolonged burst of ≥10 beats, at a rate of >130/min, usually over 24-48 h of continuous ambulatory ECG monitoring.
LGE (fibrosis)	Diffuse and extensive LGE distribution representing fibrosis, either quantified or estimated by visual inspection as comprising about ≥ 15% of LV mass, either alone or in association with other risk markers, and a likely source of ventricular tachyarrhythmias.[f]
End-stage HCM	Systolic dysfunction with ejection fraction <50% by echocardiography or CMR, usually in symptomatic patients without outflow obstruction who may be considered potential heart transplant candidates.
LV apical aneurysm	Of variable size, and characterized by akinetic-dyskinetic thinned wall. Usually Identified by CMR (or contrast-enhanced echocardiography), with contiguous "border-zone" myocardial scarring, often associated with apical hypertrophy and malignant ventricular tachyarrhythmias.

Recommendation from Ommen et al[6] and Maron et al.[13] [a]2 other variables, abnormal blood pressure response to exercise and LV outflow obstruction (gradient ≥50 mm Hg at rest), can be used to selectively support implantable cardioverter-defibrillator decisions in some patients with ≥1 other risk marker, but alone are not usually considered sufficient evidence to support implantable cardioverter-defibrillator recommendations. [b]Most important in risk stratification of children and adolescents. [c]Relationship between LV thickness and sudden death risk is linear, although mild LVH does not necessarily exclude sudden death risk; pattern of LVH does not predict HCM outcome, including development of heart failure. [d]Episodes of near-syncope can also be considered, if judged likely to be arrhythmic in origin. [e]Prognostic power of NSVT as a risk factor is probably greater when associated with other markers, particularly substantial LGE which can be responsible for ventricular tachyarrhythmias: it is also intuitive that long NSVT runs (≥10 beats) convey greater risk than brief runs.[15] Caution is appropriate when prognostic judgments rely solely on NSVT as an isolated risk factor because of its variability, and also the difficulty in standardizing for length of the monitoring period. Prolonged, frequent periods of palpitations can represent important ventricular tachyarrhythmias, particularly when associated with impaired consciousness, but require documentation by ECG monitoring. [f]In addition to the arbitrary cutoff of ≥15% of LV mass (exclusive of right ventricular insertion areas) a linear relationship is demonstrated between sudden death risk and LGE extent, suggesting that LGE of 10%-15% can be clinically relevant in some patients; absent or focal LGE (<5% of LV mass) is generally regarded as most consistent with low risk.

CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; LV = left ventricular; NSVT = nonsustained ventricular tachycardia.

TABLE 2 Global Experience With ICDs in HCM

First Author	Country	Year	Study	ICD Patients, n	Mean Age at Implant, y	Sudden Death Prevention Appropriate ICD Interventions/y)		
						Primary	Secondary	All
Maron et al[25]	United States, Italy	2000	Multicenter	128	40	5	11	7
Jayatilleke et al[101]	Australia	2004	Single center	22	N/A	10	17	11
Maron et al[16]	Italy, Australia, United States	2007	Registry	506	42	3.6	10	–
Woo et al[102]	Canada	2007	Single center	61	46	4	–	–
Kiernan et al[103]	United States	2008	Single center	69	43	4.3	–	–
Lin et al[104]	United States	2009	Single center	181	44	4	–	–
Bos et al[105]	United States	2010	2 centers	177	45	2.2-4.5	–	–
Syska et al[106]	Poland	2010	Single center	104	35	4	–	–
Prinz et al[107]	Germany	2010	Single center	50	43	–	–	4-5
Schinkel et al[12]	Netherlands	2012	Meta-analysis	2,190	42	3.3	–	–
Vriesendorp et al[19]	Netherlands	2013	Single center	134	44	5.1	–	6.8
Maron et al[41]	Italy, Greece, United States, Australia (children)	2013	Registry	224	14	3.1	14	4.5
Konstantinou et al[108]	Greece	2016	Single center	37	49	–	–	7.2
Maron et al[33]	Italy, United States, Australia	2018	Multicenter	486	44	3.7	–	10
Maron et al[13]	United States	2019	Single center	527	51	3.2	10	–
Rowin et al[32]	United States (Long-term follow-up)	2019	Single center	217	38	3.4	–	3.4
Rowin et al[42]	United States (children)	2020	Single center	146	15	3.4	–	3.4
Weissler-Snir et al[109]	Canada	2020	Single center	302	53	2.3[a]	–	–

[a]3.2%/y in patients ≤40 years at implant.

ICD = implantable cardioverter-defibrillator.

risk marker strategy in the same patient to make decisions.

GUIDE TO CLINICAL MANAGEMENT.

1. ***All patients with prior cardiac arrest or sustained VT should have secondary prevention ICDs.***
2. ***Noninvasive stratification of sudden death risk is recommended at initial evaluation and every 1-3 years thereafter (or when there is relevant change in clinical profile) to assess eligibility for primary prevention ICDs: personal/family history, echocardiography, contrast-CMR, 12-lead ECG, and ambulatory ECG monitoring.***
3. ***Identification of candidates for prophylactic ICDs relies on documentation of 1 or more conventional risk factors judged to be major and relevant within the individual patient clinical profile (Table 1).***
4. ***More recent markers based on CMR are part of an enhanced risk stratification algorithm—ie, LV apical aneurysm with regional scarring, LGE when extensive and/or associated with systolic dysfunction.***
5. ***Primary prevention ICDs are discouraged in clinically stable patients age ≥60 years, given the low event rate in this age group, but may be considered on a case-by-case basis (eg, with apical aneurysm).***
6. ***Subcutaneous ICDs can be recommended, particularly for younger patients, at the discretion of the implanting electrophysiologist in accord with patient wishes, assuming that the need for antitachycardia and antibradycardia pacing is unlikely.***
7. ***Electrophysiological testing with programmed ventricular stimulation is not predictive of sudden death and not part of standard HCM risk stratification.***
8. ***Mathematical risk scores (as proposed by ESC) are not recommended as the sole criterion to select HCM patients for prophylactic ICDs because this strategy is associated with low sensitivity (and would exclude some high-risk patients from ICDs).***

OBSTRUCTIVE HCM AND REVERSAL OF HEART FAILURE

Heart failure symptoms, usually caused by LV outflow obstruction, can be progressive but reversible by septal myectomy (or in selected patients by percutaneous alcohol ablation).

Dynamic LV outflow tract obstruction (gradient, ≥30 mm Hg), associated with mitral regurgitation, occurs at rest and/or with physiological (exercise) provocation in 70% of HCM patients evaluated at referral centers.[1,23,30] Indeed, subaortic gradients (and high intracavitary LV pressures) are a strong independent determinant of HF, the responsible mechanism in 90% of HCM patients who progress to severe functional limitation (New York Heart Association [NYHA] functional classes III/IV).[23,48-54]

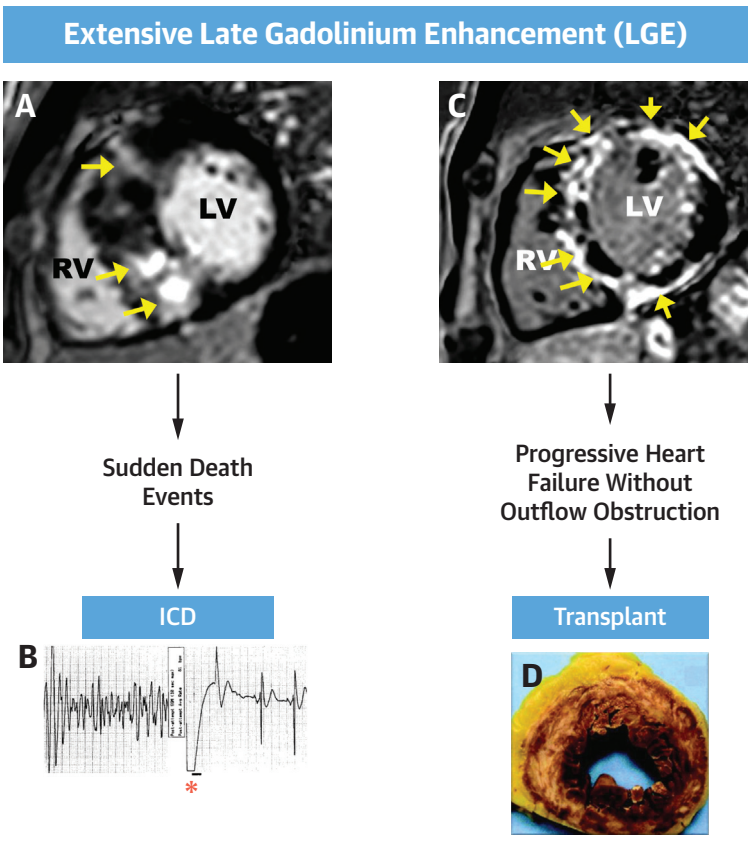
Symptoms of LV outflow obstruction are predominantly exertional dyspnea and fatigue with or without chest pain (sometimes typical of angina), and syncope/presyncope. Less common are orthopnea, PND, or fluid retention with peripheral/pulmonary edema, or renal dysfunction. In most patients, impedance to LV outflow is caused by mitral valve systolic anterior motion (SAM) with prolonged septal contact, although obstruction can emerge in the absence of SAM from midcavity muscular apposition, usually caused by anomalous papillary muscle insertion directly into anterior mitral leaflet in absence of interpositioned chordae.[53]

Although HCM is not a uniformly progressive disease, HF symptoms may occur or increase in severity at any age, most frequently in midlife caused by the accumulated effect of long-standing outflow obstruction and elevated LV pressures, and more advanced in women[1,23,30,35,48] (Figure 7). HF symptoms are typically variable and sensitive to ventricular loading and contractility, often differing in magnitude from day-to-day ("good and bad days") or within a given day, and not uncommonly after meals and alcohol consumption.[5,23] Functional disability is usually judged reliably by a targeted history-taking interview, although in some patients with an ambiguous or misleading personal history, treadmill or cardiopulmonary exercise testing may be informative in assessing limitation.[48]

Lifestyle comorbidities such as obesity can accentuate outflow obstruction, HF, and unsatisfactory clinical response.[55] In women and minorities, recognition of HF symptoms can be delayed or underestimated, and surgery underutilized or referral delayed.[35,36] Rarely, natural history of HCM in patients with dynamic outflow gradients can be punctuated by regional LV ballooning reminiscent of takotsubo syndrome, with abrupt HF exacerbation.[56]

PHARMACOLOGIC STRATEGIES FOR PATIENTS WITH OUTFLOW OBSTRUCTION. Established drugs. In obstructive patients, the objective of pharmacological therapy is palliation, mitigation, and control of HF symptoms, although there is little evidence that

FIGURE 5 Extensive LGE as Risk Marker for Adverse Complications in HCM



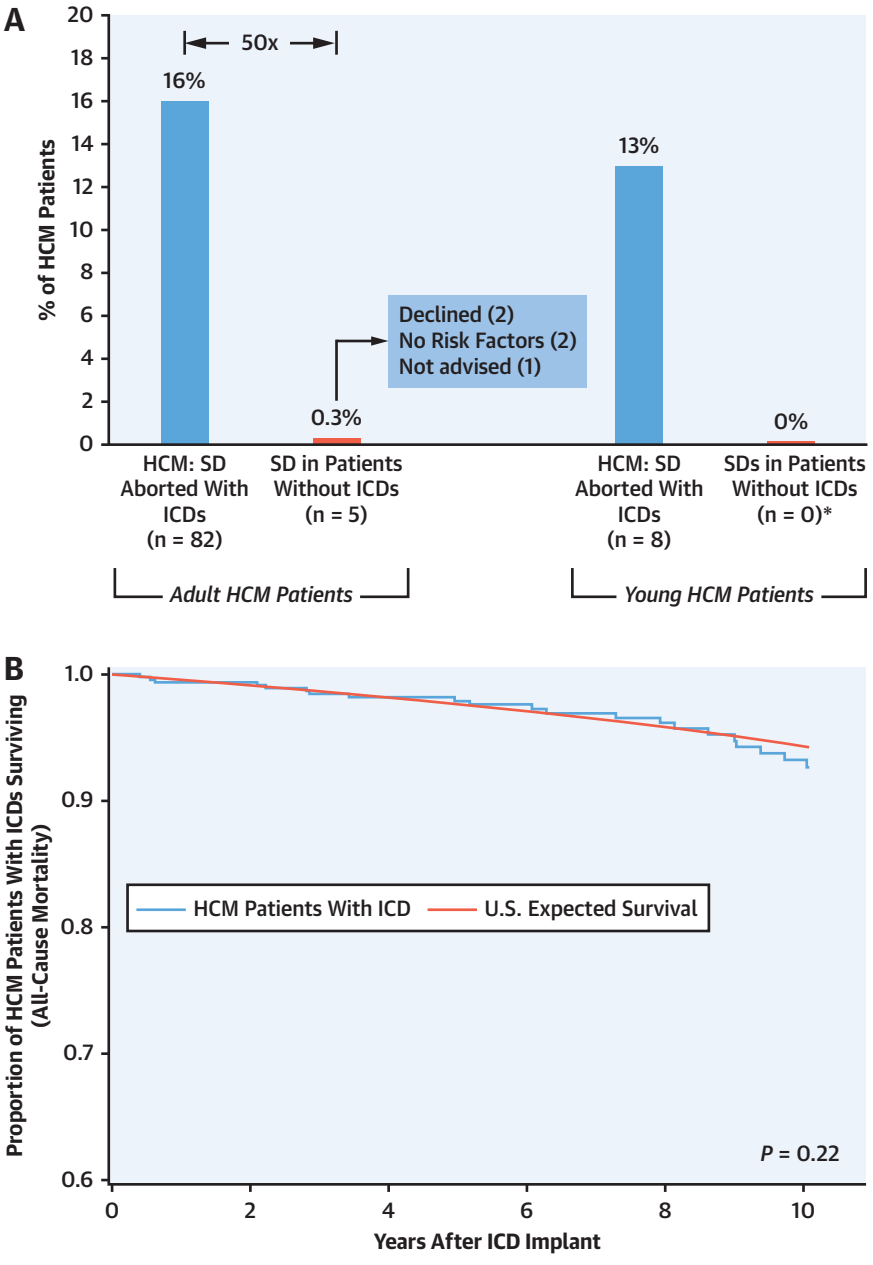
(A and B) LGE in ventricular septum **(arrows)** predisposing to sudden death events. **(C and D)** Diffuse LGE involvement of septum extending into LV free wall **(arrows)** predisposing to progressive HF in absence of obstruction. *Appropriate device therapy. LV = left ventricle; RV = right ventricle; other abbreviations as in Figure 1.

drugs reliably prevent disease progression over long-term clinical course, or reduce sudden death risk.[1,57,58] Administered in standard doses negative inotropic drugs (beta-blockers, verapamil, disopyramide), represent traditional medical therapy than can be titrated against HF symptoms.[57,58] Beta-blockers are usually the first-line option when symptoms intervene, albeit still administered prophylactically by some pediatric cardiologists to asymptomatic patients to improve LV filling and clinical course, but with little direct evidence of benefit. Caution is warranted in administrating verapamil to HCM patients with high resting gradients and advanced HF.[57]

In patients with outflow obstruction, palliative pharmacological strategies with traditional negative inotropic drugs can often control symptoms over the short-term. However, beta-blockers and verapamil are inconsistent and/or weak agents for reducing resting outflow gradients, although beta-blockers potentially blunt exercise provoked gradients,[3,48] and in nonobstructive disease, may be beneficial by reducing heart rate and improving diastolic dysfunction by prolonging LV filling. Disopyramide is the strongest negative inotropic drug, used in HCM for 40 years to reduce outflow gradient and symptoms (without significant proarrhythmia), as an option to delay elective myectomy (or alcohol ablation).[58]

Newer drugs. However, the panel recognizes that the landscape of medical therapy in HCM is evolving with emerging pharmacological options for obstructive HCM, including another strong negative inotropic drug similar to disopyramide, ie, mavacamten (MyoKardia, Bristol Myers Squibb).[59] Not yet approved by the U.S. Food and Drug Administration for use in HCM, mavacamten is a small molecule allosteric modulator of cardiac myosin and strong negative inotrope that reduces LV contractility and

FIGURE 6 Prevention of Sudden Death in HCM



(A) Prospective ICD decision-making using ≥1 risk marker (2020 AHA/ACC guidelines) in 2,094 consecutive adult patients. Reproduced with permission from Maron et al.[13] *146 patients <20 years of age at implant. Data from Rowin et al.[40] **(B)** Kaplan-Meier survival showing HCM patients with ICDs no different than the general population. **(C)** Events occurring in HCM patients ≥60 years. Advanced age per se offers sudden death protection, with such events uncommon at age ≥60 years. **(D)** Frequency of ICD therapy increases with time after implant; greater than one-third of patients have ≥10-year delay before initial therapy. Abbreviations as in Figure 1.

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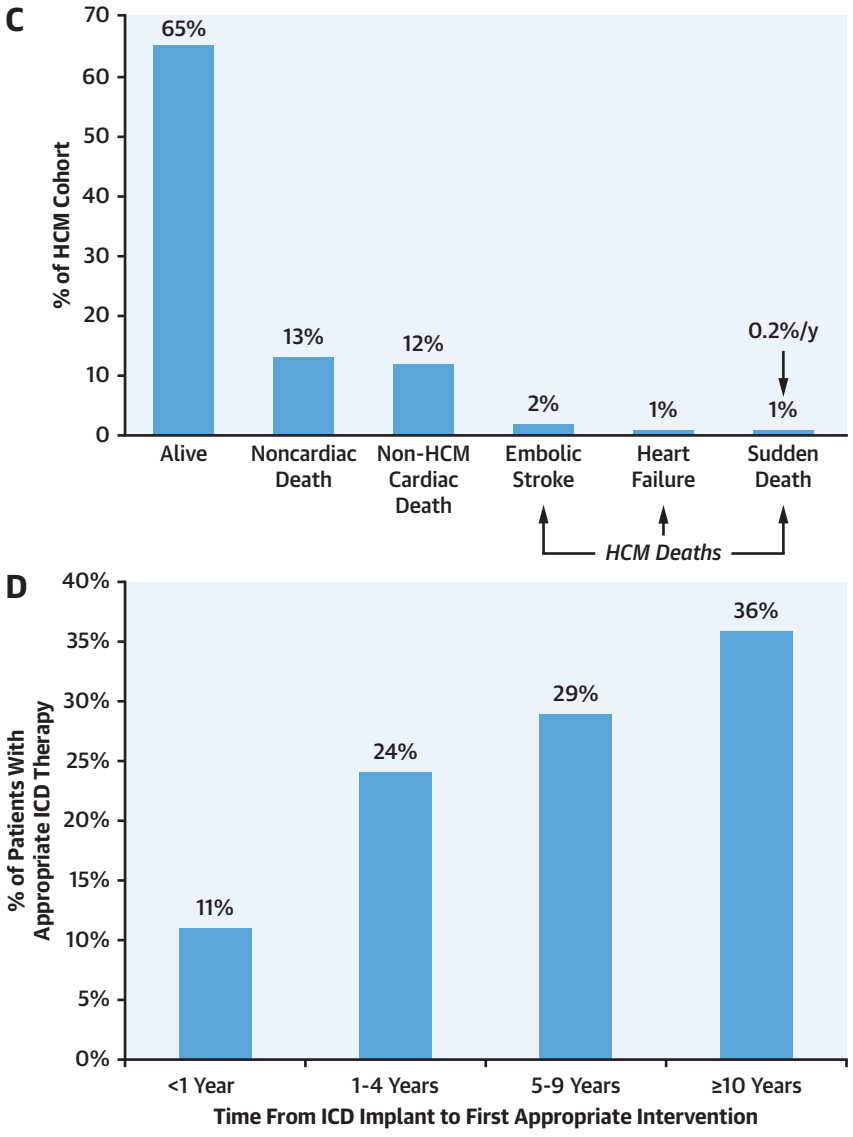
FIGURE 6 Continued



consequently outflow gradient and possibly HF symptoms. However, in a short-term and relatively small randomized phase 3 trial comprised largely of patients with mild symptoms (EXPLORER-HCM), only 37% achieved the combined beneficial endpoint of subjectively improved functional capacity (ie, NYHA functional class) and increased peak VO_2, with incomplete symptom and gradient relief evident in about one-half of patients.[59] Notably, risk for adverse clinical events and systolic dysfunction associated with LV remodeling[60] or HF approached 10%. Futuristic considerations for HCM have focused on genome editing techniques in human embryos such as CRISPR/Cas9 to correct underlying mutant genes considered disease-causing.[1,6]

Bacterial endocarditis. In 2007/2017, AHA/ACC guidelines for prevention of infective endocarditis have excluded HCM patients from recommendations for antimicrobial prophylaxis prior to dental procedures. However, the lack of consensus among HCM experts on this issue permits latitude for individual physician decisions, particularly for HCM patients with obstruction.

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GUIDE TO CLINICAL MANAGEMENT.

1. ***Magnitude HF symptoms and quality-of-life limitation can usually be judged reliably by standard history-taking interview, although cardiopulmonary exercise testing can be informative when uncertainty arises regarding exercise tolerance.***
2. ***Drug therapy should be initiated first to control HF symptoms caused by outflow obstruction, including beta-blockers (usual first choice), verapamil, or disopyramide.***
3. ***Combining beta-blockers with verapamil is usually discouraged because it can lead to excessive bradycardia and possibly hypotension.***
4. ***Disopyramide, a potent negative inotropic agent, may reduce resting outflow gradient (and symptoms), and is potentially an important option.***
5. ***Prophylactic administration of beta-blockers to asymptomatic patients is generally not recommended caused by the lack of evidence of benefit.***
6. ***Drugs to be avoided because of potential adverse effects on symptoms and outflow gradient: vasodilators, nitroglycerin, amlodipine, nifedipine, angiotensin-converting enzyme/angiotensin II receptor blockers; β-adrenergic receptor agonists, eg, dobutamine and dopamine; and stimulant medications used for attention-deficit/hyperactivity disorder.***
7. ***Patients with outflow obstruction should be advised to maintain proper hydration, healthy body weight, avoidance of excessive caffeine and alcohol.***

SURGERY. Operative strategies. Transaortic septal myectomy is the preferred treatment option for most patients with limiting HF symptoms refractory to medical therapy (NYHA functional classes III/IV) secondary to mechanical LV outflow tract obstruction, ie, peak instantaneous gradient ≥50 mm Hg at rest and/or with exercise provocation[4-6,27,49-52,61-66] (**Central Illustration**). However, symptom limitation justifying surgery has a generally lower threshold for children.[61]

Myectomy reliably results in immediate and also permanent abolition of outflow obstruction (with normalization of LV pressures and preservation of systolic function), and may also be responsible for reverse left atrial remodeling and modest regression of LV hypertrophy, and possibly reduced sudden death and AF risk.[51,63,65] In patients with rest obstruction (>30 mmHg), progression from NYHA functional class I/II to class III occurs at a rate of 7%/y[48] (**Figure 7**).

Surgery achieves the most favorable results and lowest perioperative mortality and morbidity when performed in high-volume HCM centers by surgeons highly experienced with the disease and its diverse outflow tract anatomy. Some HCM centers have selectively extended myectomy to patients with symptoms that limit quality of life without reaching the conventional NYHA functional class III/IV threshold.[64,67]

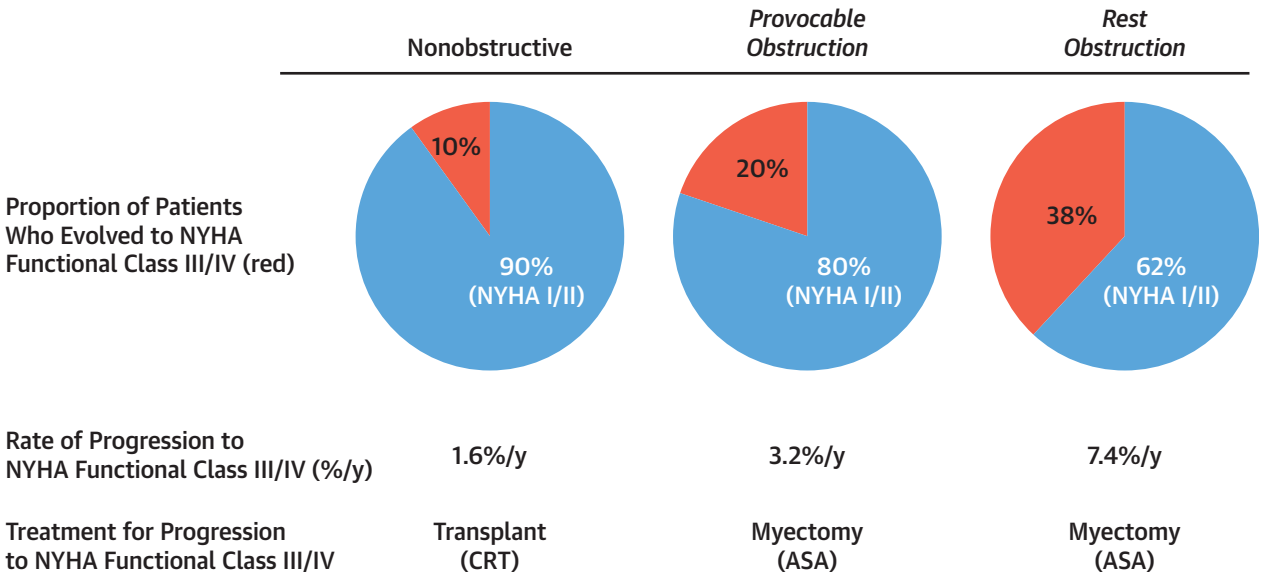
Myectomy relieves outflow obstruction by enlarging the cross-sectional area of LV outflow tract and redirecting flow away from the anteriorly positioned mitral valve to eliminate the pushing force of flow drag directly on the exposed leaflets that is responsible for systolic anterior motion and mitral regurgitation.[68] The classic Morrow procedure introduced in the 1960s[3] (muscle resected from basal anterior septum) has evolved to an extended septal excision well beyond the mitral-septal contact point and involving midventricular septum to level of papillary muscles and into posterolateral free wall.

In association with myectomy, some surgeons rely on remodeling or repair of the mitral valve apparatus and submitral structures to most effectively relieve outflow gradient and mitral regurgitation, now including patients with only mild septal thickening.[66,69] Such remodeling can include: plication or pericardial patch to stiffen and shorten a markedly elongated anterior mitral leaflet, or resection of residual leaflet tissue; mobilization/repositioning of mitral apparatus out of the flow stream by cutting secondary fibrotic chordae tendineae; and/or accessory muscular and fibrous structures connecting papillary muscles to septum or free wall.

Intrinsic mitral valve abnormalities such as myxomatous valves with prolapse and/or ruptured chordae, or leaflet and annular calcification are often amendable to mitral valve repair, although mitral valve replacement is likely in patients with mixed mitral stenosis/regurgitation, or sometimes with particularly mild septal hypertrophy. Complete heart block requiring permanent pacemakers, as a complication of myectomy, occurs in 1%-5% of patients[50,70]; ICDs may be implanted in such patients based on overall risk profile.

Results. Myectomy has matured considerably over the past >50 years. Surgery-related mortality has decreased strikingly from 6%-8% about 30 years ago to about 0.5%[62] currently, and can now be considered one of the safest open-heart operations and a low risk to high benefit procedure in experienced high-volume HCM centers. However, myectomy performed as a matter of convenience in community hospitals with less-experienced surgeons often

FIGURE 7 **Progression of Severe Heart Failure Symptoms With Respect to Hemodynamic State in HCM**



Demonstration that evolution to New York Heart Association (NYHA) functional class III symptoms are most common in obstructive patients (up to 38%) who may become candidates for surgical myectomy, and uncommon in nonobstructive patients (10%) who may become candidates for heart transplant. ASA = alcohol septal ablation; CRT = cardiac resynchronization therapy.

results in high perioperative mortality (≥6%) and technically inadequate operation attributable to an insufficient muscular resection.[71]

Indeed, there is an ongoing need for additional surgeons experienced with myectomy in the United States, Europe, and elsewhere to allow wider accessibility of this option.[72] Although operative volume is an important determinant of outcome (as with isolated mitral valve repair), defining the minimum number of patients required to guarantee operative safety and efficacy remains a challenge.[5,6,27]

Surgical myectomy has been consistent in ameliorating HF symptoms and improving quality of life by ≥1 NYHA functional class in ≥90% of patients, with restoration to normal activity in 75% at all ages,[42] independent of preoperative HF duration. Postoperative clinical state is usually judged subjectively by history-taking, but is also supported by objective data, eg, increased exercise duration and peak VO_2 (by 3-7 mL/kg/min). Third, a long-term survival benefit is attributable to myectomy, similar to longevity in the general population, and also possibly with reduced sudden death risk[63]: 98%, 96%, and 83% survival from all-cause mortality; and 99%, 98%, and 95% survival from HCM-related mortality at 1, 5, and 10 years[49,52] (**Figure 8**).

Clinical outcomes after myectomy (including survival) do not differ in men and women. Myectomy nonresponders with recurrent or persistent symptoms after hemodynamically adequate myectomy are uncommon (about 5% at HCM centers), and are most frequently related to comorbidities (eg, obesity), massive LVH, or diastolic dysfunction.[55,73] There is no compelling evidence for a causal linkage between myectomy and evolution to systolic dysfunction/end-stage HF.[1,22] Some surgeons have successfully combined septal myectomy with the Maze procedure, reducing both HF symptoms and AF episodes.[74]

Other subgroups. Surgery has proved effective within a wide range of septal thicknesses, including massive hypertrophy.[40] In an emerging subset with minimal septal thickening (ie, ≤15 mm), HF symptoms caused by dynamic subaortic obstruction can be reversed by combining shallow myectomy with remodeling of mitral valve apparatus,[69] usually without mitral valve replacement. A distal LV "debulking" operation via apical myectomy has been performed by a few experienced myectomy surgeons in selected nonobstructive patients with refractory HF and abnormally small distal LV cavity to improve filling by increasing chamber size.[75]

Mitral valve replacement, employed primarily outside HCM centers, is generally discouraged as a

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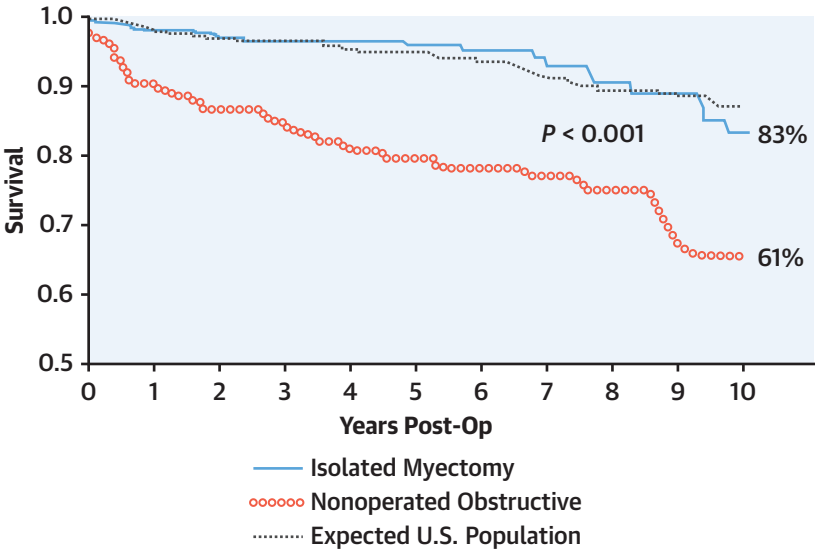
FIGURE 8 Surgical Septal Myectomy in HCM



Abolition of LV outflow gradient by surgical myectomy is associated with long-term survival (all-cause mortality), similar to expected in age- and sex-matched general U.S. population, exceeding a comparison group of symptomatic nonoperated obstructive patients. Adapted with permission from Ommen et al.[49]

primary treatment to relieve obstruction. Patients with midcavity muscular gradients caused by anomalous papillary muscle insertion into mitral valve benefit from extended myectomy and papillary muscle mobilization.[53] Despite early enthusiasm for dual-chamber pacing 30 years ago, this strategy has been largely abandoned.[76] Preliminary experience relieving HCM-outflow gradients with MitraClip as an alternative to septal reduction have to date yielded inconsistent results.[6]

Pulmonary hypertension is not uncommon in obstructive HCM and may contribute to symptoms before surgical myectomy.[77] In 1 report, pulmonary hypertension in HCM was associated with all-cause mortality, except in patients undergoing myectomy.[78] Pulmonary hypertension has also been a concern for outcome in nonobstructive transplant candidates.

GUIDE TO CLINICAL MANAGEMENT (SURGERY).

1. ***Patients with drug-refractory HF symptoms (NYHA functional class III/IV), and outflow gradient ≥50 mm Hg at rest or with physiological (exercise) provocation, should be considered candidates for surgical myectomy as the preferred treatment intervention.***
2. ***In patients unable to adequately exercise, it is reasonable to employ nonphysiological maneuvers to provoke gradients, eg, Valsalva maneuver, amyl nitrite inhalation, or possibly infused sympathomimetic drugs.***
3. ***Septal myectomy is performed safely and most effectively by surgeons in high-volume HCM programs experienced specifically with this disease and operation and its broad morphologic spectrum (including septal thicknesses from mild to massive), associated with diverse abnormalities of mitral valve apparatus.***
4. ***Myectomy should not be performed in low-volume HCM environments (including community hospitals) by surgeons with limited myectomy experience.***
5. ***In HCM centers, myectomy can also be considered for selected obstructive patients with less-severe symptoms, equivalent to NYHA functional class II.***
6. ***Transesophageal echocardiography provides vital anatomic guidance in the operating room to assess extent of muscular resection and advisability of mitral valve repair/remodeling.***
7. ***Mitral valve replacement should not be a primary treatment option in obstructive HCM unless severe mitral regurgitation caused by intrinsic valvular abnormalities is not amendable to repair.***
8. ***After successful myectomy, patients deserve continued outpatient HCM surveillance.***

ALCOHOL SEPTAL ABLATION

Percutaneous ASA has become the most frequent alternative to myectomy for reducing outflow gradient and HF symptoms in HCM[4-6,79-82] (**Central Illustration, Figure 1A**). Similar to surgery, ablation should also be performed by a HCM team in a high-volume center environment experienced with this interventional procedure and the morphological variability characteristic of the disease.

Alcohol ablation has the advantage of brief hospital stay and rapid recovery, with procedural mortality and risk of complications similar to those with myectomy. However, compared with myectomy, ablation is associated with: less uniform and slower reduction in gradient (>3 months vs immediate for myectomy); a high rate of complete heart block requiring permanent pacing (10%-15% vs <5% following myectomy); inconsistent results with extreme or mild septal hypertrophy or with associated abnormalities of mitral valve apparatus; and persistent concern for ventricular tachyarrhythmias from the alcohol-induced septal scar in susceptible patients.[5,6,79-82]

Given suitable septal perforator coronary anatomy and absence of structural abnormalities of mitral apparatus, alcohol ablation may be appropriate for patients of advanced age and/or with important comorbidities that could greatly increase surgical risk, or for patients with strong aversion to open-heart surgery.[5,6] Alcohol ablation should not be considered in children and young adults or patients with other cardiac abnormalities requiring operation (eg, valve repair or replacement, or coronary artery bypass grafting), or subaortic membrane resection.

GUIDE TO CLINICAL MANAGEMENT (ALCOHOL ABLATION).

1. ***Candidates for interventional relief of LV outflow obstruction should be fully informed regarding availability of surgery and ASA, including required operator skill/experience, and advantages/limitations of both***
2. ***ASA is the primary alternative to myectomy for severely symptomatic patients who are not optimal operative candidates, assuming septal perforator anatomy is appropriate to serve the targeted infarct area, important mitral valve abnormalities are absent, and basal septal hypertrophy is neither excessively thick or thin.***
3. ***ASA should not be performed in children, adolescents, and young adults.***
4. ***ASA should be performed by operators highly experienced with this interventional procedure.***
5. ***Prophylactic ICDs can be considered on a case-by-case basis after ASA, based on evidence of ventricular tachyarrhythmias caused by the septal scar, or pre-existing sudden death risk markers.***
6. ***Contrast echocardiography is necessary to guide ASA, ie, determine suitability of septal perforator.***
7. ***Dual-chamber pacing with short atrioventricular delay is not recommended as primary treatment to relieve obstruction and HF symptoms, but may be considered in selected older patients who are not optimal candidates for either myectomy or ASA.***
8. ***Primary prevention ICDs are not offered routinely to patients undergoing myectomy or ASA, unless they are independently judged to be at high sudden death risk based on conventional markers.***

NONOBSTRUCTIVE HCM

Nonobstructive HCM is common, and usually well-tolerated, but a small minority of patients progress to refractory end-stage HF requiring consideration for transplant.

BACKGROUND. The vast majority of nonobstructive HCM patients (no/small gradient both at rest and with exercise provocation) are asymptomatic or mildly symptomatic (NYHA functional classes I-II), and generally have low probability for advanced HF or other adverse consequences, without the need for major interventions.[20] In most such patients, exertional dyspnea likely results primarily from diastolic dysfunction, usually controllable by medical management with drugs (beta-blockers/verapamil), albeit without rigorous or randomized evidence.

Notably, nonobstructive patients are at low risk for developing progressive HF (2-4 times less than obstructive patients) with a minority (5%-10%) experiencing severe functional disability (NYHA functional classes III/IV) refractory to pharmacological management, often with elevated LV filling pressures and reduced oxygen consumption. This subgroup includes some considered for heart transplant as a definitive remedy to restore acceptable quality of life (about 2% of a referral cohort).[20-23,83]

ADVANCED HF. Advanced HF with end-stage progression is defined by refractory limiting symptoms consistent with NYHA functional classes III/IV usually presenting with transformation from a hypercontractile nondilated LV to one with systolic dysfunction (global ejection fraction [EF] 10%-50%; 25% with EF <35%), and with remodeling including

ventricular chamber enlargement and/or LV wall thinning caused by diffuse replacement scarring, involving up to 30% of LV myocardium[20-23,29,83] (**Central Illustration, Figure 5**). Patients with borderline EF (50%-60%) and LGE, but not yet with markedly limiting symptoms or remodeling, can be predisposed to progressive LV dysfunction.[84] Some HCM families have relatives with end-stage HF and others relatives with sudden death events.

Progression to NYHA functional class III/IV may also occur with preserved systolic function (EF >50%) in up to 50% of patients with advanced refractory HF, probably caused by diastolic dysfunction with restrictive physiology and without substantial LV remodeling or myocardial scarring.[85] This subset of patients phenotypically resembles non-HCM-related congestive HF with preserved EF.

When the end stage is associated with systolic dysfunction, management is converted to angiotensin-converting enzyme/angiotensin II receptor blockers, beta-blockers, spironolactone, and diuretic agents.[5,6,22] However, while these drugs often reduce symptoms and reverse LV remodeling in non-HCM patients with congestive HF and systolic dysfunction, such results have not been reported in HCM. Cardiac resynchronization therapy can prolong timing for transplant by reducing symptoms and increasing EF in some patients with intraventricular conduction delay.[86]

Although uncommon within a HCM referral cohort (2%-3%), paradoxically end stage is the most unfavorable complication of HCM and responsible for the majority (two-thirds) of disease-related deaths.[83,87] Nevertheless, outcome is not uniformly progressive, and many patients now experience extended stability with advanced therapies and a mortality rate 4-fold less than previously reported, ie, 85% survival at 10 years with or without heart transplant.[22]

An unmet need in HCM is to arrest progression of HF to NYHA functional class III and thereby alter natural history of nonobstructive HCM, otherwise potentially leading to transplant consideration. HF progression and systolic dysfunction in nonobstructive HCM can be anticipated by combining measures of global longitudinal strain and EF.[88]

TRANSPLANT. Heart transplant for refractory nonobstructive end-stage HF patients (with or without systolic dysfunction) is considered when lifestyle is unacceptable, and in the absence of other options. Although transplant is capable of extending longevity and restoring satisfactory quality of life to many patients,[20-23,83,89,88] HCM patients have been disadvantaged by selective heart allocation systems and listing. Notably, arbitrary reliance on peak oxygen consumption ≤14 mL/kg/min (or ≤50% predicted for age) with cardiopulmonary exercise testing as a major criterion for transplant candidacy can unfairly exclude some disabled HCM patients from this option. In the UNOS registry data, survival after heart transplant for HCM is 85%, 75%, and 61% at 1, 5, and 10 years, respectively, which is superior to patients transplanted for other end-stage cardiomyopathies, probably because of younger ages with less comorbidities in HCM.[87] Individual HCM centers have reported higher 5-year survival of >90%.[21,22] Listed patients survive to transplant supported by inotropic drugs (milrinone), prophylactic ICDs, and in some cases ventricular assist devices.[22]

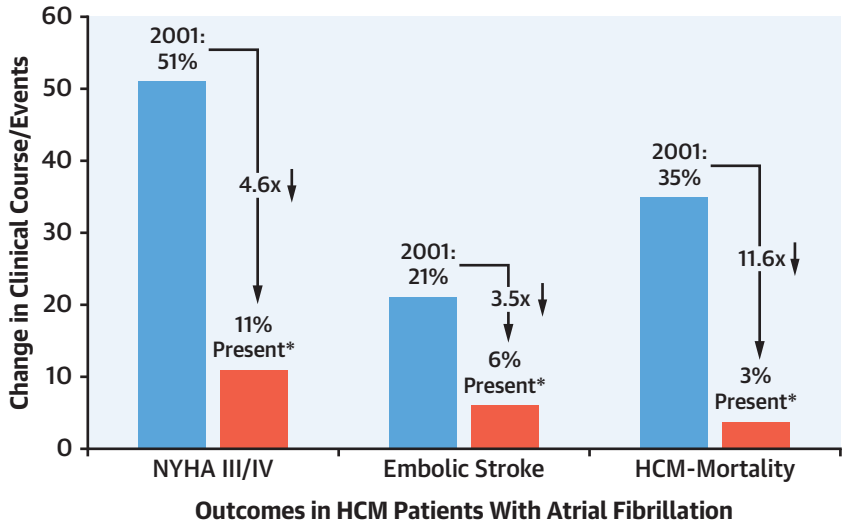
GUIDE TO CLINICAL MANAGEMENT.

1. ***Symptomatic patients without obstruction at rest should have stress echocardiography to identify physiologically provocable gradients that may be treated with septal reduction intervention.***
2. ***Nonobstructive HCM patients should have medical therapy (beta-blockers or verapamil) administrated at onset of HF symptoms and be monitored closely with history-taking and imaging, focused on changes in symptoms, LV morphology, or EF.***
3. ***Patients with global EF <50% should be evaluated with respect to eligibility and motivation for transplant listing, even if less than severely symptomatic, given the potential for rapid clinical deterioration.***
4. ***Peak VO_2 ≤14 ml/kg/min (or <50% predicted for age) on cardiopulmonary exercise testing should not be the sole criterion for transplant eligibility.***
5. ***Patients identified as end-stage HCM should have ICDs as bridge to transplant.***
6. ***It is reasonable to offer a trial of cardiac resynchronization therapy to end-stage patients with intraventricular conduction delay (QRS duration >120 ms) to improve symptoms and EF, and to potentially delay timing of transplant.***
7. ***High index of suspicion for pulmonary hypertension is recommended, particularly in nonobstructive patients with progressive HF who may become transplant candidates.***

ATRIAL FIBRILLATION

AF has low mortality risk in HCM, although paroxysmal episodes can impair quality of life. Control is achievable by drugs, catheter ablation, and surgical Maze. Embolic stroke death can be prevented by anticoagulation prophylaxis initiated after the first AF episode.

FIGURE 9 **Management and Outcome of AF in HCM Has Evolved**



Over 20 years with evolution of contemporary treatment, impact of AF on HCM appears less severe with reduced symptoms (NYHA), lower prevalence of embolic stroke, and greatly reduced HCM-related mortality (with preserved EF); 2001: Olivotto et al.[91] *2017 and at present; Rowin et al.[24]

DEMOGRAPHICS. Atrial fibrillation (AF) is the most common sustained arrhythmia in adult HCM patients and a major component of clinical profile and natural history[17,24,73,90-94] (**Central Illustration, Figures 1C and 9**). Symptomatic paroxysmal episodes occur in about 20% of patients evaluated at referral centers, 6-fold more common than in an age-matched general population, with onset at an average age of 57 years (and rarely <30 years). Paroxysmal AF episodes can evolve to permanent AF in many HCM patients for whom treatment strategies focus on pharmacological rate control. AF onset can be anticipated prospectively relying on left atrial enlargement and dysfunction as a predisposing substrate; a primary atrial myopathy has not been excluded as an AF determinant.

MANAGEMENT CONSIDERATIONS. Frequent paroxysmal AF episodes can impair quality-of-life, and may require acute intervention with electrical cardioversion. AF episodes can be suppressed over time by antiarrhythmic drugs (ie, amiodarone, disopyramide, sotalol, and dofetilide) and/or by catheter ablation performed when paroxysmal AF is uncontrolled and interferes with quality-of-life. At present, such intervention is associated with short-term (1 year) freedom from symptomatic AF in about 50% of patients, and a lower proportion over longer follow-up. Biatrial Cox-Maze IV when performed by highly experienced surgeons (with myectomy to abolish obstruction) can also result in significant freedom from AF (1 year, 85%; 3 year, 69%; 5 years, 64%).[74] Asymptomatic or minimally symptomatic patients with AF are usually managed successfully with rate control.

EVOLVING PRINCIPLES OF AF. Much of the older HCM literature characterizes AF as a decisive complication, inevitably a turning point and marker for excess mortality and morbidity, particularly when associated with outflow obstruction, given the loss of atrial contribution to LV filling.[90-92] However, much of these data include earlier more rudimentary treatment eras in which anticoagulation was underutilized and amiodarone was the sole antiarrhythmic drug, and before the introduction of catheter ablation, surgical Maze, and direct oral anticoagulant (DOAC) agents. Notably, recent analyses of HCM patients in the contemporary treatment era failed to show AF to be an independent determinant of HF-related morbidity or arrhythmic sudden death events, but rather associated with low disease-related mortality (0.7%/y)[24] (**Figure 9**).

A low threshold for aggressive anticoagulation prophylaxis to prevent thromboembolism is justified in HCM, usually following the first clinically overt AF episode.[4-6,24,90,93,94] Administration of vitamin K antagonist warfarin and more recently novel DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban),

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have greatly diminished embolic stroke and stroke death (now <1%/y). CHA_2DS_2-VAS_c score, used widely to identify at-risk patients for anticoagulation is unreliable in HCM.[24,94] Strategies have emerged to prospectively screen for likelihood of HCM progression to AF, largely dependent on increased left atrial size, including a novel point score algorithm (from Tufts).[93]

Because asymptomatic (subclinical) AF episodes fortuitously detected by ambulatory monitoring are common (in 25% of patients with implanted devices),[94] the overall burden of AF in an HCM population is probably underestimated. However, clinical implications of short asymptomatic AF episodes are largely unresolved, although predictive of future symptomatic AF. Data in HCM are insufficient to justify prophylactic anticoagulation for short subclinical AF episodes,[94] and decisions are made on a case-by-case basis when repetitive and/or prolonged.

GUIDE TO CLINICAL MANAGEMENT.

1. ***Low threshold of 1 or more symptomatic AF episodes is sufficient to recommend anticoagulation prophylaxis with DOAC agents (or warfarin) after balancing individual patient risks to these drugs; antiplatelet drugs alone do not provide adequate stroke prevention in HCM.***
2. ***CHA_2DS_2-VAS_c score, widely used in cardiovascular medicine for anticoagulation decisions, is not relevant to HCM.***
3. ***It is reasonable to administer antiarrhythmic drugs (eg, sotalol, disopyramide, dofetilide, or amiodarone) as first-line therapy to patients with paroxysmal AF.***
4. ***When patient and cardiologist agree that repetitive AF episodes unacceptably interfere with quality-of-life, catheter ablation is a reasonable option after considering antiarrhythmic drugs.***
5. ***In patients with a history of AF episodes undergoing myectomy to relieve obstruction and HF symptoms, concomitant biatrial Cox-Maze IV can reduce AF reoccurrences.***
6. ***Prophylactic anticoagulants for asymptomatic (clinically silent) AF are decided on a case-by-case basis after considering overall clinical profile and arrhythmia duration.***
7. ***Rate control strategy is appropriate for most asymptomatic patients with AF, using beta-blockers or calcium-channel blockers.***
8. ***Uncommonly, paroxysmal AF can cause acute HF decompensation requiring emergency care to restore sinus rhythm and/or reverse cardiogenic shock.***

CONCLUSIONS AND PERSPECTIVES

After more than one-half century, the narrative surrounding HCM has changed substantially. Advances in therapeutics, diagnostics, and understanding of the disease spectrum and its relevant mechanisms, pursued relentlessly by clinical investigators and practitioners using evidence-based and guideline-directed personalized treatment strategies, have transformed HCM into a starkly different disease entity (**Central Illustration, Figures 1, 2, 3, and 6**).

Once a condition considered uniformly progressive with poor prognosis and limited management options, HCM is now a contemporary highly treatable disease with low morbidity and mortality, offering potential for normal/extended longevity.[1,14,15,17,24] Evolution from primarily pharmacological management to device and interventional therapies with the capability to interrupt and alter HCM natural history has reduced mortality >10-fold from 6%/y to currently 0.5%/y (and 95% survival 10 years post-diagnosis), while substantially improving quality of life.

Furthermore, predictive algorithms anticipate: future progression to NYHA functional class III/IV HF caused by resting or provoked outflow gradients; arrhythmic sudden death events; or onset atrial fibrillation. Taken together, these paradigms dispute the historic misperception of HCM as an unrelenting and uniformly progressive disease.

Such significant progress has been achieved through the following: contemporary CMR imaging for diagnosis; low risk to high benefit surgical septal myectomy; percutaneous alcohol septal ablation as a selective alternative to surgery; pharmacological prevention of embolic stroke as well as ablation techniques to reduce atrial fibrillation episodes; and prevention of sudden death events relying on a mature predictive risk stratification algorithm and implementation of prophylactic ICDs.

In patients evaluated at referral centers, death specifically caused by HCM has become exceedingly uncommon and largely confined to nonobstructive patients with end-stage HF or related to comorbid conditions. Paradoxically, some European and other centers continue to report higher HCM mortality rates, apparently relying on older management strategies and/or historic data assembled before the advent of contemporary treatment strategies.[95,96]

HCM is a chronic condition with several management options, although unmet needs remain, including effective medical treatment for progressive

HF in nonobstructive patients with preserved EF or systolic dysfunction, or also for refractory AF. New medications for HCM patients have not emerged since verapamil and disopyramide 40 years ago. Since 2010, HCM patients have been encumbered by the failure of 8 clinical trials testing a variety of medications to relieve HF symptoms primarily in patients with nonobstructive disease, ie, losartan, diltiazem, valsartan, atorvastatin, trimetazidine, antioxidants, and ranolazine.

A negative inotropic agent and myosin inhibitor (mavacamten), has not shown a clinical efficacy for nonobstructive HCM, ie, without significant benefit measured by peak VO_2 and NYHA functional class in a phase 2 trial. Nevertheless, in the EXPLORER-HCM phase 3 trial,[59] mavacamten demonstrated promising short-term palliation of HF symptoms in some patients with obstructive HCM, albeit reducing outflow gradient less than demonstrated with septal myectomy or ASA. There is no evidence that new myosin-inhibitor drugs can be expected to modify the overall basic HCM disease process, and there are early questions regarding cost-efficacy.

All HCM patients do not experience the same access to advances in diagnosis and disease management, and inequities in care can be based on sex, race, ethnicity, culture, and country of residence. For example, HCM diagnosis in women is often delayed and HF under-recognized, whereas minorities (eg, African-Americans) are less likely referred for myectomy or ICD implantation.[35,36,97] Therefore, although treatment options that substantially extend survival with good quality of life are now available in HCM, more widespread implementation of these advances outside of dedicated HCM centers, in regional and community-based populations,[98] and also worldwide including populous countries (such as China and India),[99] remains an important challenge for this disease that has now emerged from the darkness.[100]

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