Contemporary Insights and Strategies for Risk Stratification and Prevention of Sudden Death in Hypertrophic Cardiomyopathy

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After 50 years of recognition and study, it is evident that hypertrophic cardiomyopathy (HCM) is a particularly heterogeneous and unpredictable disease with respect to its clinical expression and natural history.[1–5] Sudden death (SD) continues to be the most devastating complication of HCM, dating from its modern description.[6] However, there were virtually no effective strategies for SD prevention until recently when HCM entered the implantable cardioverter-defibrillator (ICD) era,[7–9] creating an enhanced focus on risk stratification and reliable identification of high-risk patients.[8–14] Consequently, it is timely to summarize what has been learned about HCM-related SD over these 5 decades, including the electrophysiological substrate, epidemiology, risk markers, and ultimately the role of ICDs, which have changed the natural course of this complex disease.

This discussion emphasizes the clarification of areas in which disagreement and divergent views arise, by using available information to achieve a balanced assessment of SD in HCM. However, these observations ultimately represent only a "snapshot" in time for what undoubtedly will prove to be an evolving area of investigation and understanding.

Epidemiology of SD

The specter of SD has been intertwined with the diagnosis of HCM, which is now regarded as the most common cause of these events in young people, including competitive athletes[2,3,5,10–15] (Figure 1). Although the most visible complication of HCM,[2,3,7–9,13] SD occurs in only a small minority of patients and is less common than other adverse disease consequences, including atrial fibrillation and progressive heart failure.[3,11,16]

HCM occurs at a frequency of 1 of 500 in the general population,[17] affecting an estimated 600 000 people in the United States. However, only a small proportion of such individuals are recognized clinically. Because a truly general unselected HCM population is not available for study, the precise proportion of all HCM patients with a significant SD risk remains elusive.

SD rate estimates unavoidably emanate from hospital-based cohorts, and in the older literature were as high as 6%/y, which we now understand is an overestimate based on tertiary center data contaminated by preferential referral of higher-risk patients.[18] Reports over the last 15 years from less selected regional or community-based cohorts placed HCM mortality rates at a much more realistic $\leq$1% annually.[2,3,19,20]

Nevertheless, the traditional profile of SD in HCM remains unchanged, ie, usually occurring without warning largely in asymptomatic or mildly symptomatic young patients (predominantly $<$25 years of age)[1–3,5,6,10–15] (Figure 1). Although the SD risk is lower in midlife and beyond, achieving a measure of longevity does not confer immunity to SD[11] (Figure 1). No relation between SD risk and gender is evident.[21] Although no differences in risk according to race are reported, HCM-related SD is not uncommon in black competitive athletes.[15]

Arrhythmogenic Substrate

Considerable data assembled from stored electrograms document that SD events in HCM are caused by sustained ventricular tachyarrhythmias (ie, rapid ventricular tachycardia [VT] and/or ventricular fibrillation [VF]).[7–9,22] There is no evidence that bradyarrhythmias play a role in these SDs. Triggers for potentially lethal ventricular tachyarrhythmias are poorly understood, although sinus tachycardia has been identified as an initiating rhythm in some cases, suggesting that high sympathetic drive can be proarrhythmic[23] and providing a possible clue to the mechanisms of SD in athletes with HCM.[15]

The underlying pathology of the myocardial substrate consists of extensive myocardial disarray in which numerous myocytes (and myofilaments) are arranged at oblique and perpendicular angles, constituting a disorganized architecture (Figure 2).[24] HCM is also characterized by small-vessel disease in which structurally abnormal intramural coronary arterioles with thickened media and narrowed lumina are responsible for bursts of silent microvascular ischemia and myocyte death and ultimately repair as replacement fibrosis (Figure 2).[25] It has been hypothesized that architectural disorganization and scarring (and possibly the expanded interstitial matrix)[26] represent the unstable electrophysiological substrate that creates susceptibility to reentry arrhythmias.

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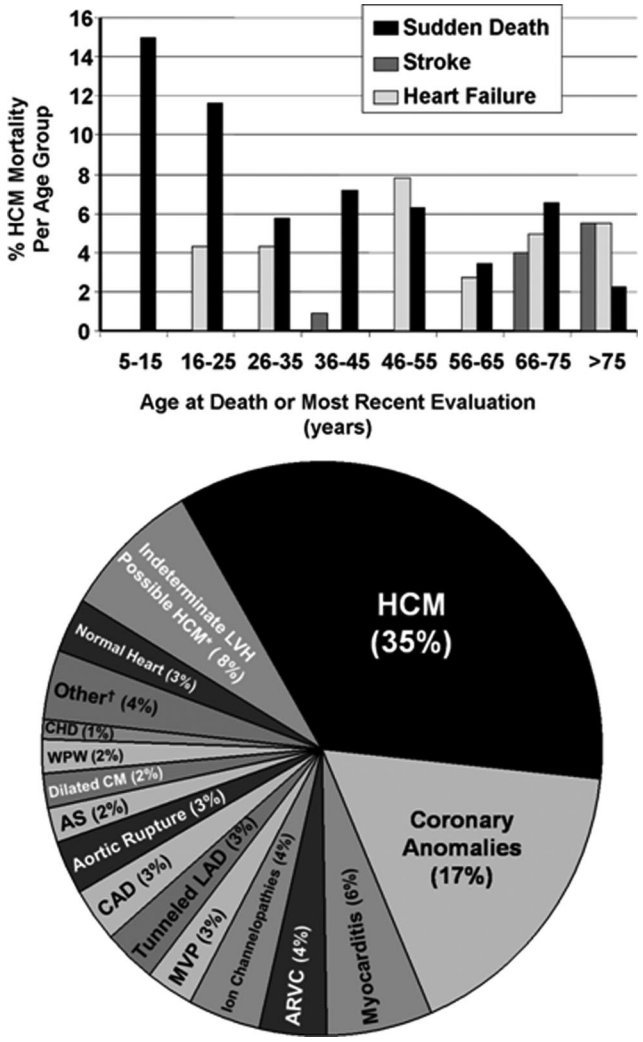

Figure 1. SD and age in HCM. Top, SD is most common before ≈25 years of age, whereas heart failure and stroke generally occur later in life. From Maron et al.[11] Used with permission from the American Heart Association, copyright © 2000. Bottom, Single most frequent cause of SD in young competitive athletes in the United States. ARVC indicates arrhythmogenic right ventricular cardiomyopathy; AS, aortic valve stenosis; CHD, congenital heart disease; LAD, left anterior descending; MVP, mitral valve prolapse; and WPW, Wolff-Parkinson-White. *Regarded as possible (but not definitive) evidence for HCM at autopsy with mildly increased LV wall thickness and heart weight (447±76 g). †Includes Kawasaki disease, sickle cell trait, and sarcoid.

SD Prevention: Historical Context

Drugs

For much of the modern history of HCM, efforts directed at the prevention of SD were pharmacological and empirical, over time including β-blockers, procainamide, quinidine, verapamil, and amiodarone.[27] However, pharmacological strategies, popular in the pre-ICD era, failed to achieve absolute protection from SD or from ventricular tachyarrhythmias triggering appropriate ICD interventions, and are now regarded as obsolete.[28]

ICD Evolution

The ICD was introduced for SD prevention >25 years ago,[29] creating a paradigm shift from pharmacological and ablation strategies to sophisticated implanted devices that recognize and automatically terminate lethal ventricular tachyarrhythmias.[30–34] Notably, 2 of the initial 3 patients implanted with defibrillators and studied in the laboratory had HCM.[29] Nevertheless, patients with genetic heart diseases (including HCM) were largely overlooked for the following 20 years as the ICD was assessed in several randomized trials, largely in patients with ischemic heart disease.[30–34] In HCM, ICDs were used sparingly until 2000, when the first substantial series of patients was reported, demonstrating the efficacy of device therapy,[7] and thereby contributing to greater numbers of subsequent prophylactic implantations in this and other genetic heart diseases.[9]

HCM Versus Coronary Artery Disease

Major distinctions between HCM and coronary artery disease (CAD) with regard to SD prevention are often unappreciated. Randomized trials in patients with CAD and nonischemic cardiomyopathy have demonstrated reduced all-cause mortality or SD[30–34] when the ICD was compared with standard antiarrhythmic agents. Such evidence is an unrealistic aspiration for HCM because of the unique obstacles of low prevalence and infrequent events in cardiologic practice, and heterogeneous clinical presentation.[2,3] Randomized patient selection in HCM would raise major ethical considerations by potentially excluding young at-risk patients from SD prevention.

ICD candidates with CAD average 65 years of age at implantation, usually with systolic dysfunction and compromised left ventricular (LV) substrate, and often extracardiac organ disease.[30–34] The future period of risk is relatively short, with prolongation of life the objective. In contrast, high-risk HCM patients are 25 years younger at implantation, with intact substrate unencumbered by multisystem disease,[7–9] and potentially long risk periods with the possibility of achieving substantial longevity with the ICD.

ICD Experience in HCM

Evidence assembled over the last 10 years substantiates that appropriate ICD interventions occur not uncommonly in HCM and are highly effective in terminating potentially lethal ventricular tachyarrhythmias[3,7–9,22,35,36] (Figure 3). Indeed, ICDs have created a new strategy within the HCM armamentarium, and represent the most reliable treatment available for SD prevention.

Most ICD reports comprise a small number of HCM patients (ie, <50) and device interventions.[9] The most reliable data are found largely in an international multicenter registry of 506 HCM patients from 42 centers with ICDs implanted on the clinical judgment of the managing cardiologist[8,9] (Figure 3). This study has >2-fold the number of participants in the Multicenter Automatic Defibrillator Implantation Trial I (MADIT I)[33] and is larger than many randomized ICD trials.[30–34]

Several important principles relative to ICD therapy in HCM are derived from this registry.[8] Over an average follow-up of 3.7 years, 20% of patients experienced appropriate device therapy for VT/VF, equivalent to 5 ICDs implanted per intervention. Discharge rates were 5.5%/y

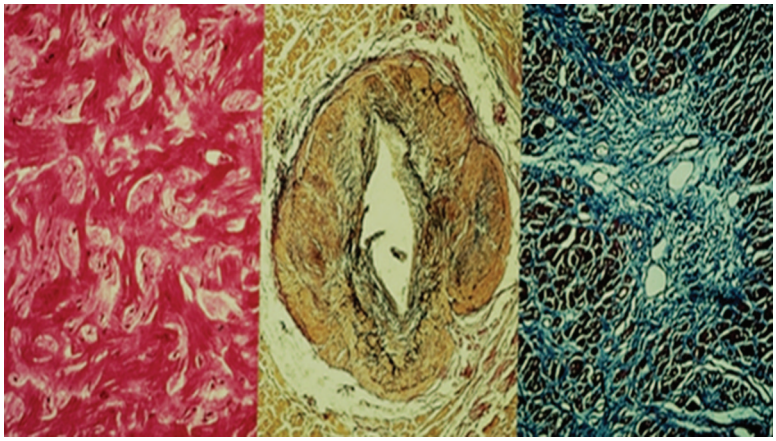

Figure 2. Arrhythmogenic myocardial substrate. Left, Disorganized myocyte arrangement and LV architecture. Center, Small-vessel disease; remodeled intramural coronary arteriole with thickened media and narrowed lumen. Right, Repair process with replacement fibrosis, the consequence of silent ischemia and myocyte death.

overall, 11%/y for secondary prevention (after cardiac arrest or sustained VT), and 4%/y for primary prevention (≥1 risk factors) (Figure 3). ICD therapy was most common in young patients (average, 40 years of age), with the highest rates in children and adolescents (11%/y), consistent with the predilection of SD for young HCM patients.[2–6,10–14] Of note, primary prevention intervention rates (ie, 4%) are similar to those previously reported for SD in tertiary HCM centers, with referral patterns skewed to high-risk patients[2,3,18] and 4-fold that in community-based cohorts.[19] Conversely, SD appears particularly uncommon in HCM patients judged to be at low risk without conventional risk factors. In preliminary data from the Minneapolis Heart Institute over the last 15 years, SD events occurred in only 2% of patients (0.5%/y) considered to be low risk without ICDs.

Furthermore, the ICD was effective in terminating VT/VF despite the complex HCM phenotype, which may include extreme LV hypertrophy, subaortic obstruction, microvascular ischemia, and diastolic dysfunction.[2,3] An exception is the emerging lysosomal-associated membrane protein 2 (LAMP2) cardiomyopathy, an X-linked lysosomal storage disease and HCM phenocopy with massive LV hypertrophy that is largely refractory to ICD therapy (Figure 4).[37]

Unpredictable Substrate

An important principle related to ICDs in HCM surrounds the highly unpredictable timing of life-threatening ventricular tachyarrhythmias with varying periods of dormancy (Figures 3 and 5).[7–9,38–40] Substantial delays of many years between implantation and initial device intervention[7–9] are not uncommon (Figure 5), and circadian patterns of ICD-terminated events show no discrete hourly predilection, and a not uncommon occurrence during sleep.[38,39] Furthermore, long-term survival after VT/VF for up to 30 years without recurrence of life-threatening arrhythmias has been reported.[41] Notably, the development of disabling heart failure symptoms after major arrhythmic events appear to be rare in HCM[41] and without evidence that ICDs merely shift demise from SD to competing modes (eg, progressive heart failure), as suggested in CAD.[33]

Initial recognition of high-risk status in an HCM patient may be fortuitous (eg, SD of a family member) and removed significantly in time from the unpredictable onset of a life-threatening arrhythmias (Figures 3 and 5). Nevertheless, when increased SD risk is recognized (independently of the precise circumstances), the physician and patient are obligated to consider an ICD.

Device interventions triggered by VT/VF may occur relatively early in HCM, within 12 to 18 months after implantation[7–9,40] (Figure 5). Similar observations in CAD raised speculation that device-related proarrhythmia could be responsible for some defibrillation shocks, possibly as a result of local mechanical lead effects,[42] and that some ICD interventions may not be lifesaving, particularly when triggered by potentially self-terminating VT episodes.[42] However, there is currently no evidence specifically in HCM that such ICD interventions are irrelevant to the disease process.

Selection of Patients for ICDs

Conventional Risk Markers

There is virtually universal agreement that HCM patients should be afforded secondary prevention after cardiac arrest or sustained episodes of VT,[31,32] including the American College of Cardiology/European Society of Cardiology 2003 consensus HCM panel.[3] However, the selection of patients most likely to benefit from ICD therapy for primary prevention has been less certain,[14] with guidelines a long-evolving and sometimes contentious issue for which definitive resolution has been elusive.

Risk stratification in HCM is predicated on the assessment of several noninvasive risk markers, usually in clinically stable patients, that have emerged from observational studies and achieved general acceptance.[2,3,5,7–10,12–14,43–51] In this respect, the strategy differs from that used in patients with CAD; ie, in which primary prevention is based largely on a single predominant risk marker demonstrated by randomized trials and emanating from a major clinical event (myocardial infarction) leading to LV remodeling and impaired function (ejection fraction ≤30% to 35%), often associated with adverse disease progression.[30–34]

The conventional primary prevention risk factors for HCM assume greater weight in patients <50 years of age (Figure 6): (1) family history of ≥1 HCM-related SD, (2) ≥1 episode of unexplained recent syncope, (3) massive LV hypertrophy (thickness ≥30 mm) (Figures 6 and 7A), (4) nonsustained VT on ambulatory 24-hour (Holter) ECG, and (5) hypotensive or

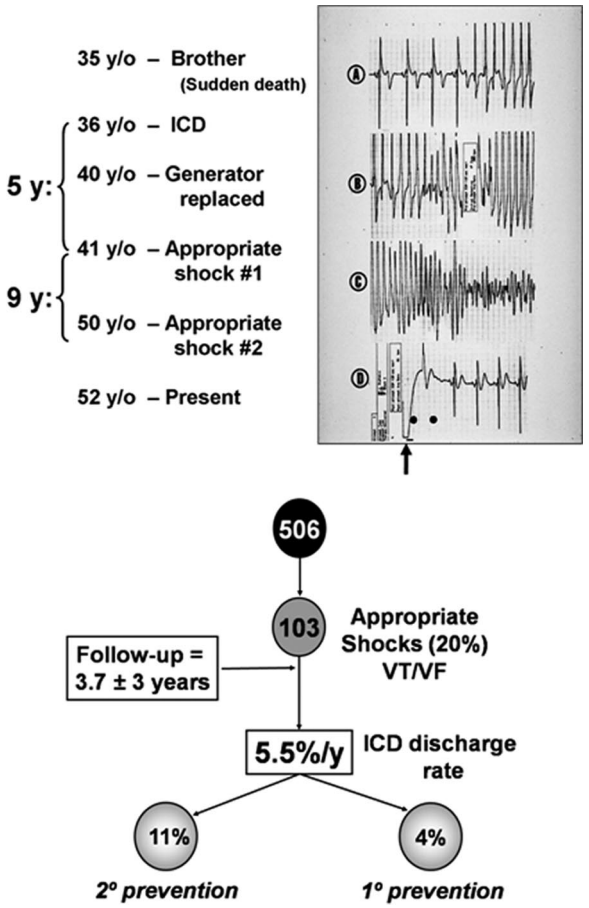

Figure 3. Prevention of SD. Top, Intracardiac electrogram obtained at 1:20 AM in a patient while asleep 5 years after implantation. From 35-year-old man with HCM who received prophylactic ICD because of family history of SD and marked ventricular septal thickness (31 mm). A, VT begins abruptly at 200 bpm. B, Defibrillator senses VT and charges. C, VT deteriorates into VF, and defibrillator issues 20-J shock (D; arrow), restoring sinus rhythm. Virtually identical sequence occurred 9 years later during sleep; the patient is now 53 years of age and asymptomatic. Reprinted from Maron et al.[7] Copyright © 2000 Massachusetts Medical Society. All rights reserved. Bottom, Flow diagram summarizing ICD-related outcome in 506 high-risk HCM patients from an international multicenter ICD registry.[8]

attenuated blood pressure response to exercise. However, the exercise blood pressure response is tested less commonly than other risk factors[8] and rarely represents the sole indicator for a prophylactic implant in clinical practice.[8] It is used more frequently as an arbitrator when risk assessment by echocardiography and history-taking is ambiguous. Nonsustained VT on ambulatory ECG is the risk marker that most directly explores the arrhythmogenic substrate. However, as a matter of practice, isolated brief runs of nonsustained VT on random 24-hour Holter ECGs have not usually triggered decisions for prophylactic ICDs, whereas frequent and/or prolonged (>10 beats) bursts of nonsustained VT identified over serial monitoring periods (as a matter of practice) intuitively carry greater weight as a risk factor.

Potential Arbitrators

A number of disease features can be regarded as arbitrators when the level of risk based on conventional markers is ambiguous. They may be useful in resolving otherwise uncertain ICD decisions on a case-by-case basis (Figures 6 and 7):

- LV apical aneurysms are associated with a 10% annual event rate, largely because of the arrhythmogenic substrate created by the fibrotic thin-walled aneurysm and scarring of the contiguous distal LV[47] (Figure 7B and 7B[1]).
- The end-stage phase with widespread LV scarring (morphologically similar to CAD after myocardial infarction) leads to slowly evolving and irreversible systolic dysfunction, often associated with wall thinning and cavity dilatation (Figure 7D), and inevitably an adverse course that may involve atrial and ventricular tachyarrhythmias.[48] In the end-stage phase, the ICD is used as a bridge to heart transplant.
- LV outflow obstruction with gradient ≥30 mm Hg at rest is a highly visible quantitative measure of elevated intraventricular pressures and wall stress.[49] In 2 studies,[40,50] obstruction had a modest although statistically significant relation to SD risk in patients without severe heart failure (positive predictive value, only 5% to 10%), but showed no relation in another investigation.[51]

  Other obstacles to obstruction as a primary risk factor include its dynamic nature and frequency, with 70% of patients capable of generating outflow gradients at rest or with physiological exercise,[52] thus creating the potential for unnecessary ICD implantation in the majority of HCM patients. Reducing the gradient by surgical myectomy (or alcohol ablation) is not a primary strategy for mitigating SD risk.[3]
- Alcohol septal ablation is a therapeutic alternative to surgical myectomy for selected patients to relieve outflow obstruction and progressive heart failure,[2,3,53–60] which produces a transmural infarction of ventricular septum that occupies 10% of the overall LV chamber[61,62] (Figure 7C). Although there is concern, no definitive evidence is yet available at this relatively early juncture that the alcohol septal ablation scar per se increases (or does not increase) the long-term risk for SD in absolute terms, and resolution will require greatly extended follow-up studies in large patient cohorts.[63]

  There is, however, a documented risk for potentially life-threatening sustained ventricular tachyarrhythmias largely over the short-term[8,55–62] (with reported postprocedural annual event rates of 3% to 5%[58,61]) presumably resulting from electrical instability potentiated by the scar in certain susceptible patients. On the basis of this consideration and a measure of concern that alcohol-imposed infarcts could compound preexisting and underlying myocardial electric instability,[8,9,54,55,57,59] some practitioners have considered alcohol septal ablation a risk arbitrator and prudently implanted ICDs in selected patients with commonly accepted risk markers after the ablation procedure.[59]
- Delayed enhancement (DE). Because current risk stratification cannot reliably guide SD prevention for each HCM patient and SD occasionally occurs in patients without evidence of risk, there is an aspiration to identify more sensitive or specific clinical markers. Ideally, this could

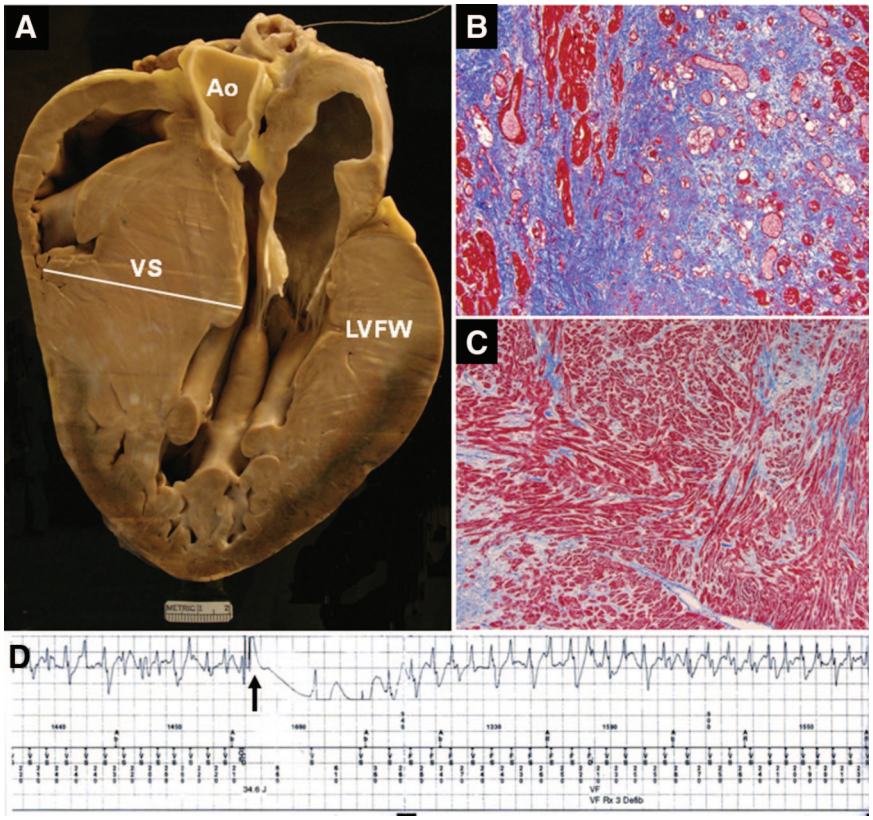

Figure 4. LAMP2 cardiomyopathy, a phenocopy of HCM. A, From 14-year-old boy with SD and septal thickness of 65 mm (heart weight, 1425 g). B, Clusters of myocytes with vacuolated sarcoplasm (stained red) embedded in area of scar (stained blue; Masson trichrome). C, Disorganized arrangement of myocytes most typical of sarcomeric HCM. D, Intracardiac electrogram. ICD elicited 5 defibrillation shocks that failed to interrupt VF (280 bpm). Reprinted from Maron et al.[37] Used with permission from the American Medical Association, copyright © 2009.

lead to a single, noninvasive, repeatable quantitative test that does not add to patient risk.

Hence, there is considerable interest surrounding in vivo detection of LV myocardial fibrosis (as DE) by contrast-enhanced cardiovascular magnetic resonance (CMR) imaging and its relation to SD risk.[64–67] DE has been linked to the underlying electrical substrate by recognition that ventricular tachyarrhythmias (including nonsustained VT) on ambulatory Holter ECG are most common in patients with DE[66] (Figure 8). However, whether extensive DE can be regarded as a bona fide risk marker in HCM will ultimately require adequately powered studies in large populations with sufficient numbers of events accrued over many years.[65]

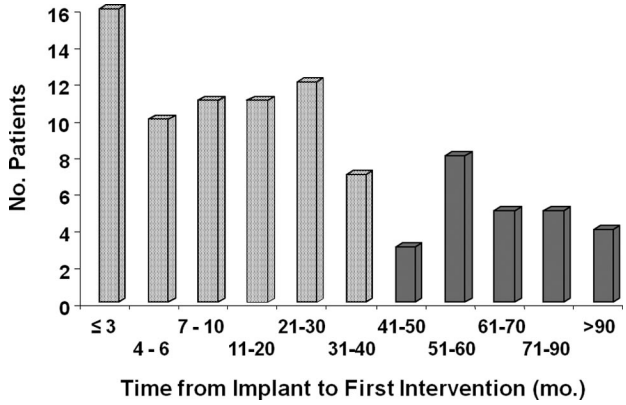

Figure 5. Time interval between implantation and first appropriate intervention. Variable time delay after implantation is considerable, with some device discharges occurring relatively early and others after 5 to 10 years (darker bars).

Uncertain Contributors to Risk

Atrial fibrillation is the most common arrhythmia occurring in HCM (20% to 25% of patients) and is associated with progressive heart failure and embolic stroke.[16] However, there is no compelling evidence that paroxysmal atrial fibrillation is specifically a predictor of SD in cohort analyses, although it has been reported occasionally as a trigger for ventricular tachyarrhythmias causing ICD interventions.[23]

Recognition that mutations in genes encoding proteins of the cardiac sarcomere cause HCM[68] created substantial enthusiasm for identifying malignant or benign genetic substrates in order to facilitate assignment of SD risk level.[69] Genotyping, although now widely available, has not proved to be a reliable strategy for predicting future prognosis with sufficient precision to justify a widespread role in selecting patients for primary-prevention ICDs.[70] The gene-based hypothesis for risk stratification[69] became clinically impractical, largely because of the heterogeneity of HCM, now with >1000 mutations (in 11 genes), including many that are novel with unresolved pathogenicity.[68] However, selected clinical situations in which molecular diagnosis may predict prognosis are emerging, including nonsarcomeric LAMP2 cardiomyopathy[37] (Figure 4) and possibly double sarcomere mutations.[71]

Laboratory electrophysiological testing with programmed ventricular stimulation, while directly probing electric properties of the heart, is an impractical prognostic strategy that has been abandoned in HCM clinical practice as nonspecific, expensive, irrelevant to the clinical arrhythmia environment, and without advantage over noninvasive risk stratification.[3] Paced ventricular electrogram fractionation is capable of distinguishing components of reentry with accuracy in risk

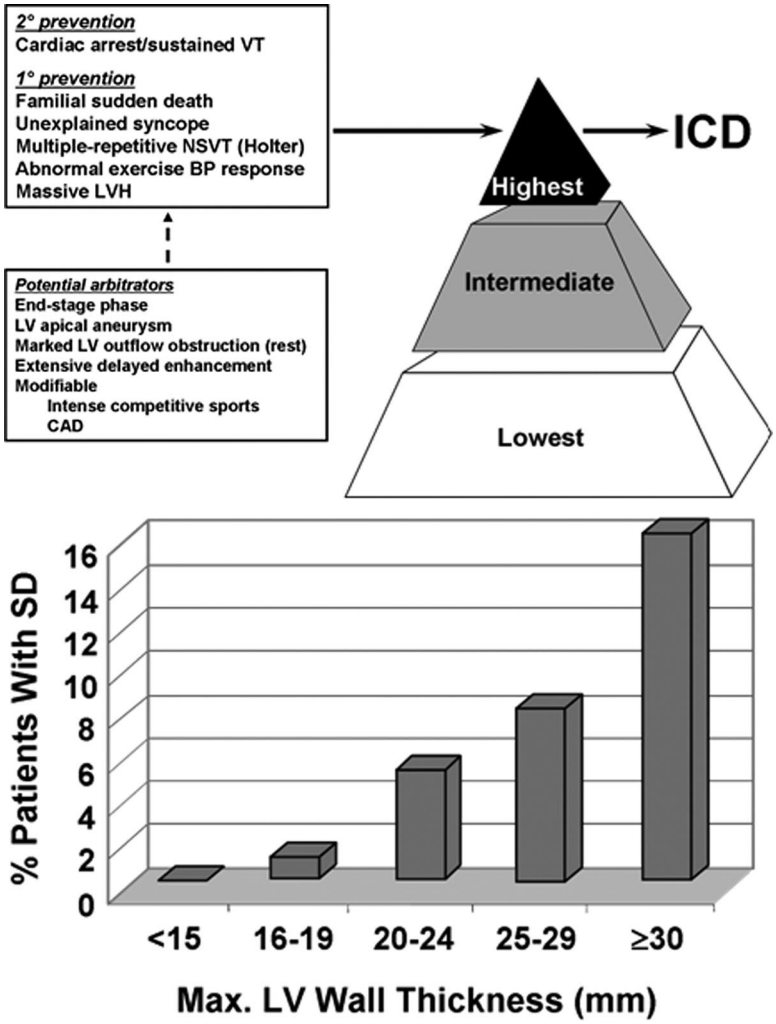

Figure 6. SD risk stratification. Top, Pyramid profile currently used to identify those patients at highest risk for SD who are potential candidates for ICDs. BP indicates blood pressure; LVH, LV hypertrophy; NSVT, nonsustained VT. Sustained ventricular tachyarrhythmias have been reported in a significant minority of patients (≈10%) over the short term after alcohol septal ablation. Bottom, Direct relation between magnitude of LV hypertrophy (maximum [max] wall thickness by echocardiography) and SD risk. Mild hypertrophy conveys generally lower risk; extreme hypertrophy (wall thickness ≥30 mm) conveys the highest risk as a marker for SD. Reprinted from Spirito et al.[43]

prediction,[72] but is encumbered by practical constraints similar to standard electrophysiological testing. Evidence is insufficient for coronary arterial bridging,[73] or ECG patterns[74] to be regarded as specific risk markers in HCM. Microvascular ischemia is a common pathophysiological component of HCM, but appears to be a determinant largely of progressive heart failure (rather than SD).[75]

Modifiable Risk Markers

Linkage between intense physical exertion and risk for sudden arrhythmic death has established participation in competitive sports as a potential HCM risk factor even in the absence of conventional markers.[15] The generally accepted recommendation of Bethesda Conference 36, to reduce SD risk in athletes with HCM[76] is withdrawal from the intense training and competition associated with most competitive sports. After sports disqualification, some athletes with HCM may be judged to be at high risk on the basis of their clinical profile and to be candidates for prophylactic ICDs.[7,8] However, the ICD is not a preferred strategy if its sole purpose is continued participation in intense competitive sports.[15,76] In older HCM patients, coexistent obstructive CAD[77] may increase overall SD risk, potentially modifiable by coronary intervention.

Translating Risk Factors to Clinical Practice

Limitations

First, much of the uncertainty surrounding risk stratification in HCM can be traced to some imprecision in defining the risk markers. For example, multiple definitions appear in the literature for family history of HCM-related SD, including: 1 first-degree relative, ≥2 relatives <40 years of age, ≥1 first-degree relatives <40 years of age, or ≥1 relatives <50 years of age[2,3,5,9,10,12–14,78]; this problem is further encumbered by adoption, small pedigree size, or frequent uncertainty regrading the precise cause of death in relatives. Syncope as a risk factor has been defined alternatively as 1 or 2 prior events occurring at a variety of time intervals before evaluation.[10,12,46] Recognition of these limitations related to definitions weakens the reliability of risk stratification strategies based on simple numeric summation of risk factors or "major-minor" scoring systems.[10,12,78]

Second, the independent weight of each risk factor with respect to all others remains unknown, and the interplay between markers in individual patients is likely complex. Third, although each of the conventional risk factors is associated with high negative predictive value (≥90%), risk markers individually or collectively are limited by positive

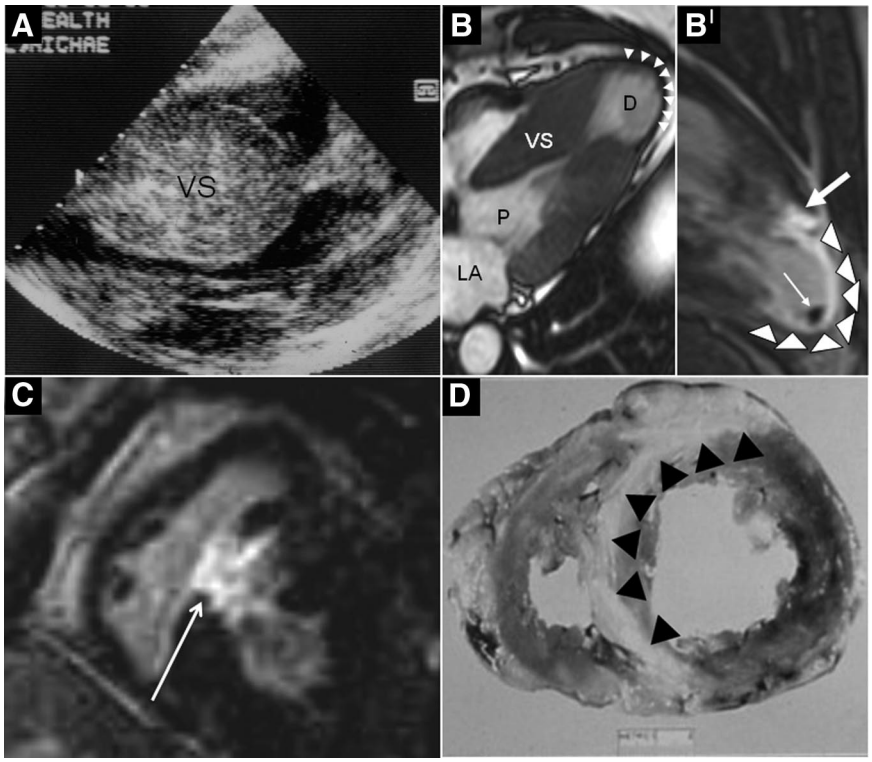

Figure 7. Morphology of patient subgroups associated with possible risk for sustained ventricular tachyarrhythmias. A, Massive hypertrophy with ventricular septal (VS) thickness of 55 mm. B, Akinetic thin-walled LV apical aneurysm with midcavity muscular apposition. D indicates distal (cavity); LA, left atrium; and P, proximal (cavity). B, Contrast CMR shows DE (ie, scar) involving the thin aneurysm rim (arrowheads) and also contiguous myocardium (large arrow); small apical thrombus is evident (small arrow). C, Typical large transmural ventricular septal scar (arrow) resulting from alcohol ablation. Reprinted from Valeti et al.[61] Used with permission from the American College of Cardiology, copyright © 2007. D, "End-stage" heart showing extensive and transmural septal scarring extending into anterior wall (arrowheads).

predictive value in the range of only 15% to 30%, largely resulting from the low event rate that is characteristic of HCM.[78] Fourth, risk factors are not static disease components and can change with time (toward higher levels), underscoring the importance of ongoing clinical surveillance. For example, LV wall thickness can increase abruptly and substantially in young patients; syncope may occur for the first time; a family member may experience an SD; or nonsustained VT bursts can appear on routine ambulatory ECGs.[43,44,46,79] Finally, the HCM risk factor algorithm is most applicable to patients 18 to 50 years of age. Some stratification markers for adults cannot be easily extrapolated to young children,[80] including the difficulty encountered in using an arbitrary cut-point of ≥30 mm for massive LV hypertrophy in small patients.

Risk Factor Counting

There is considerable evidence that a single strong, established marker of increased risk within the clinical profile of an individual patient is sufficient for both physician and patient to recognize SD risk as unacceptably increased, resulting in the proposal for a primary-prevention ICD.[2,3,9–11,43,44,46,79] In the ICD in HCM registry,[8,9] an important proportion of appropriate ICD interventions for VT/VF occurred in patients implanted for only 1 risk factor (ie, 35%), and device therapy was as common in patients with 1 risk marker as in those with ≥2 markers (Figure 9). Appropriate intervention rates were substantial for each of the single risk factors for which patients were implanted, and highest in those with syncope (Figure 9).

However, the 1–risk-factor ICD model is complicated by recognition that the proportion of patients in tertiary center cohorts with only 1 conventional risk marker (estimated to be 15% to 35%) may exceed the number of patients expected to die suddenly.[9,10,12,13,78] Indeed, not all patients with 1 risk factor are at the same magnitude of risk, and universal device implantation in this patient subgroup is not recommended.[8,9] For example, clinically stable survival to advanced age (eg, >65 years) probably excludes many patients with only 1 risk factor from mandatory consideration for ICD therapy. The low HCM-related SD rate in this age group[11] and the reasonable expectation for uncomplicated survival and tolerance for presumed risk over decades (sometimes virtually a lifetime), common in this disease, become mitigating circumstances declaring lower risk status for such older patients.

Patients with multiple risk factors are at increased SD risk,[8–10,12,14,78] although it is unresolved whether such clinical profiles consistently convey excessive risk over that found in many patients with 1 risk factor. Assessment of SD risk level in HCM can be encumbered by an overemphasis on numeric summing of risk markers in individual patients, which can represent an artificial strategy.[10,12,14,78] Indeed, should this approach convey the impression that rigid adherence to a minimum of 2 risk markers is mandatory before recommending a primary-prevention ICD,[78] there is the possibility that some deserving patients with 1 risk factor will be relegated to a lower level of consideration for ICD therapy or left unprotected.

Decision-making dilemmas inevitably occur because many patients fall into ambiguous gray zones in which risk level cannot be assessed with precision, and individual clinical judgment and experience are advantageous, even necessary, for making judgments about ICDs. Indeed, the model of transparency, full disclosure, and informed consent, linked with autonomous input from the well-informed patient, is necessary for resolving decisions in which there are gaps in

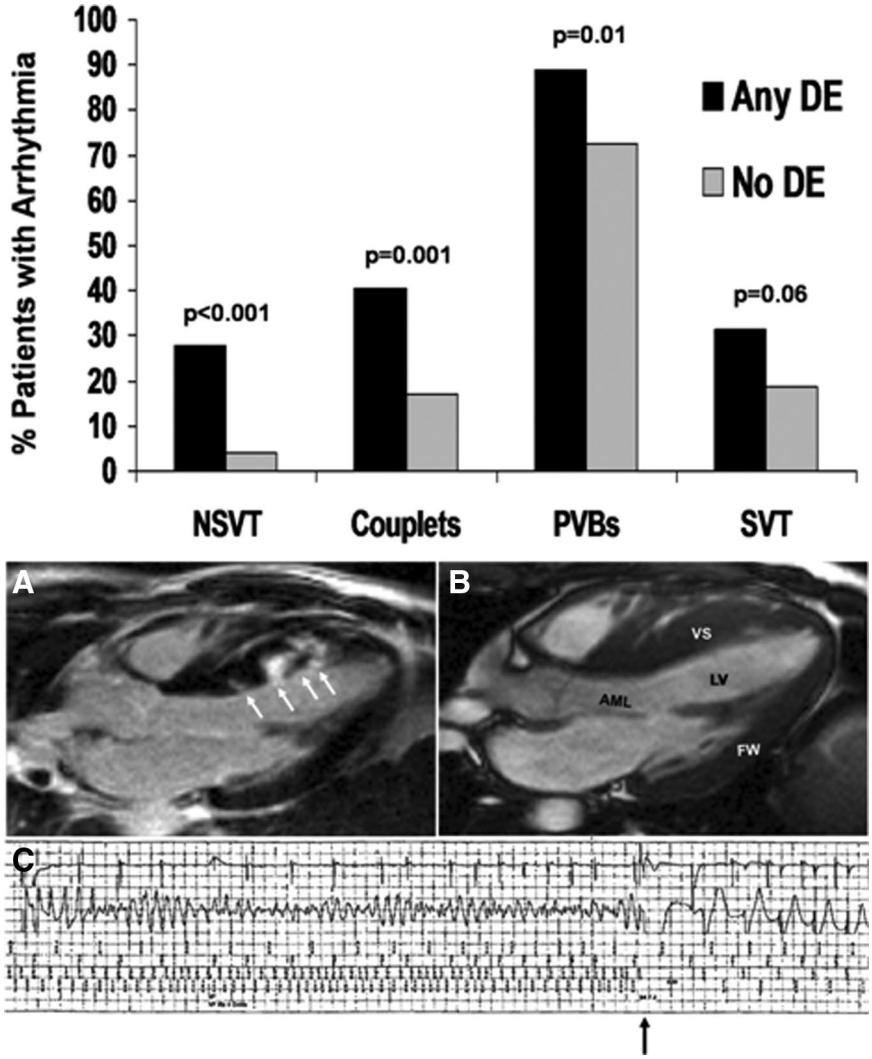

Figure 8. CMR DE as an arrhythmogenic substrate. Top, Ventricular tachyarrhythmias on ambulatory (Holter) ECG, including nonsustained VT (NSVT), are significantly more frequent in the presence of DE. PVBs indicates premature ventricular beats; SVT, supraventricular tachycardia. Reprinted from Adabag et al.[66] Used with permission from Elsevier, copyright © 2008. Bottom, A 21-year-old man with HCM and septal scarring without conventional risk factors who survived an episode of VF because of ICD intervention. A, CMR image showing transmural DE of high signal intensity occupying a substantial proportion of septum (arrows). B, Without contrast, asymmetrical hypertrophy of ventricular septum (VS; 21 mm). C, Intracardiac electrogram showing VF interrupted by defibrillation shock (arrow). AML indicates anterior mitral leaflet; FW, free wall. Reprinted from Maron et al.[67] Used with permission from Elsevier, copyright © 2008.

knowledge or an absence of data, and when sufficient clarity cannot be achieved solely with the conventional risk factor algorithm.

Other Considerations Affecting ICDs

Complications

Decisions to implant ICDs prophylactically for SD prevention in HCM patients involve consideration of the potential complications and inconvenience incurred by a permanent device versus obvious lifesaving benefit should it terminate a lethal arrhythmia. Clearly, these 2 scenarios are not of equal weight, given the capability of ICDs to preserve life. However, a measure of hesitancy toward lifelong ICDs may arise in pediatrics when physicians are confronted by the clinical paradox in which active and healthy-appearing HCM patients (exposed to greatest SD risk by age) have the highest device complication rates over long time periods.[9,81–83]

Although ICD components have proved generally safe and effective, device-related complications, including infection, pocket hematoma, pneumothorax, and venous thrombosis, are well documented.[7–9,35,36,81–84] More frequently, ≈25% of HCM patients[8] experience inappropriate shocks (5.3%/y)[83] resulting from lead fracture or dislodgement, oversensing, double counting, and programming malfunctions, or triggered inadvertently by sinus tachycardia or atrial fibrillation (although reports of multiple shock "storms" are rare).[7,8,83] Such complications occur most commonly in younger patients, primarily because their activity level and body growth place continual strain on leads, considered the weakest link in this system.[84] Indeed, extended lead survival is crucial to young HCM patients, given that many will have their ICDs for decades (if not most of their lives), and possibly even subjected to the risk of lead extraction.

Although repetitive or increased shock frequency may create psychological trauma and impair quality of life in some patients,[85] we have observed that the presence of the ICD itself often contributes substantially to the psychological well-being of HCM patients who are acutely aware of their unpredictable SD risk. Finally, in HCM, the implant procedure itself has been largely free of significant risk with no reported deaths,[86] although selected patients with extreme LV hypertrophy may require high-energy-output generators or epicardial leads.[86]

Recently, ICD industry–related problems have directly affected HCM patients, for whom device components either failed to terminate lethal arrhythmias[87] or were responsible

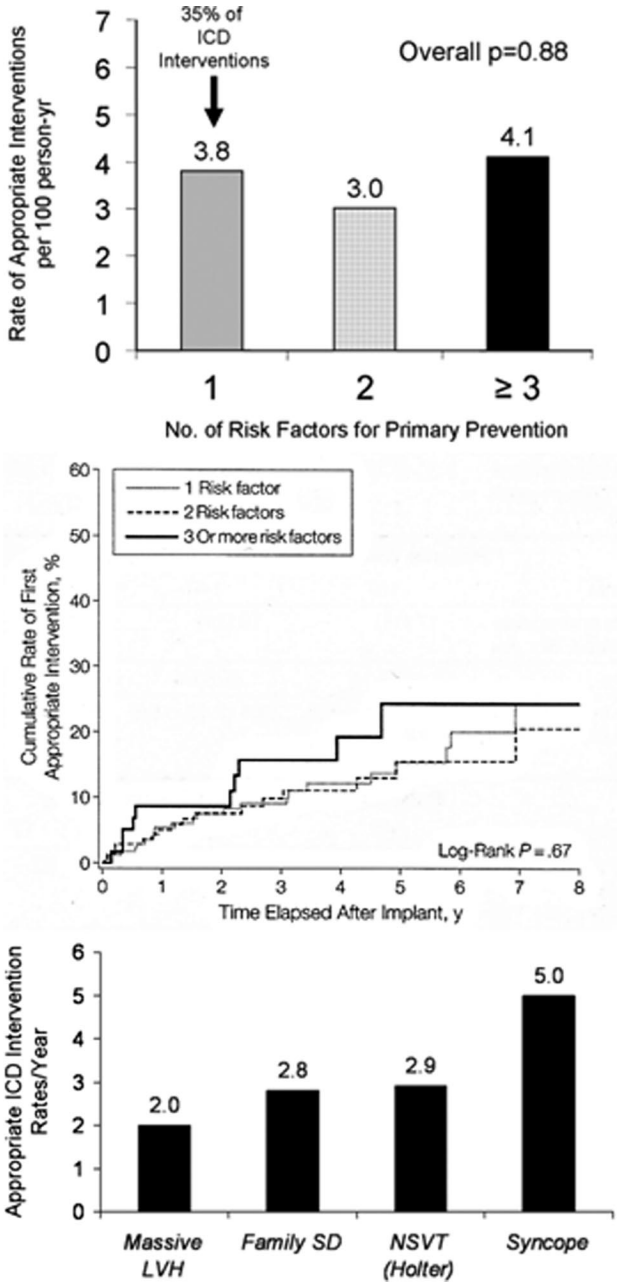

Figure 9. Number of risk factors. Top, Appropriate ICD intervention rates (per 100 person-years) are not significantly different with respect to 1, 2, or ≥3 risk factors. Center, Cumulative rates for first appropriate device intervention in patients with 1, 2, or ≥3 risk factors. Reprinted from Maron et al.[8] Used with permission from the American Medical Association, copyright © 2007. Bottom, ICD intervention rates in those patients with only 1 risk factor. LVH indicates LV hypertrophy; NSVT, nonsustained VT.

for serious injury or death,[88] unavoidably affecting the decision-making process surrounding prophylactic implantations. Recent recalls have most prominently included defective, short-circuiting generators that resulted in several deaths[87] and small-diameter high voltage leads that offered technologically advanced maneuverability but were prone to fracture.[89]

Implants Worldwide

Overall ICD implant rates differ considerably with regard to country and healthcare system because of a number of cultural, societal, and economic factors that unavoidably influence strategies for primary prevention of SD in HCM. Rates in the United States far exceed those in Western European countries (2- to 5-fold)[90] and are also much higher than in Far East, Middle Eastern, and Eastern European nations. Although these gaps are closing, such differences in ICD use raise the distinct possibility that HCM patients with a similar level of risk living in different countries may not have the same access to prophylactic ICDs and the opportunity for SD prevention.

Strategies for SD Prevention: Targeting Patients for ICD Therapy

Secondary Prevention

- ICDs are indicated in those patients surviving cardiac arrest or sustained episodes of VT.

Primary Prevention

- A single strong and unequivocal risk marker in accordance with the patient's clinical profile can represent sufficient evidence to justify the ICD option, particularly when family history of SD, unexplained syncope, or massive LV hypertrophy is present.
- Patients with multiple risk markers (≥2) have an increased arrhythmia burden and most deserve strong consideration for an ICD.
- Strict adherence to the model requiring ≥2 risk factors for ICD consideration is not sustainable.
- Patients in select HCM subsets such as the end-stage phase with systolic dysfunction or LV apical aneurysm with regional scarring may be at increased risk and are potential ICD candidates.
- Routine implantation of ICDs after alcohol septal ablation would appear unnecessary at present although consideration on a case-by-case basis is advisable, particularly in patients with conventional risk factors.
- Advanced age is a factor in judging SD risk level, with clinically stable patients >65 years of age deserving a higher threshold for consideration of prophylactic ICDs.
- Because assignment of risk level in HCM is not uncommonly ambiguous and because the conventional risk factor algorithm is not always definitive, ICD decision making, particularly in patients with 1 risk factor, may take into account other considerations. These include using additional disease variables as arbitrators, eg, LV outflow obstruction, and marked contrast-CMR delayed enhancement, as well as the clinical judgment of managing physicians with direct knowledge of the patient's overall clinical profile and desires.

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None.

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