LGE Means Better Selection of HCM Patients for Primary Prevention Implantable Defibrillators*

Barry J. Maron, MD, Martin S. Maron, MD

Since the first reports of hypertrophic cardiomyopathy (HCM) more than 55 years ago, sudden death has been the most highly visible and feared complication of this complex and heterogeneous genetic heart disease (1-4). Over this time, by virtue of numerous retrospective and observational cohort studies, a risk stratification algorithm has emerged in HCM (1-3) that has been effective in identifying many high-risk patients (Figure 1). Indeed, the assembly of reliable risk markers has now become a critical clinical tool given the availability of the implantable cardioverter-defibrillator (ICD) to the HCM patient population over the past 15 years (5,6), making primary prevention of sudden death a reality in this disease.

STATUS OF RISK STRATIFICATION

The current HCM risk factor strategy has been tested in many diverse patient populations in Europe, Australia, and North America, including the largest International Multicenter (ICD in HCM) Registry (1-3). In these studies, there has been general agreement that high-risk status in HCM patients can be based on the conventional markers, including (Figure 1): 1) family history of ≥1 HCM-related sudden death in close relatives; 2) ≥1 recent episode of unexplained syncope; 3) massive LV hypertrophy (wall thickness ≥30 mm); 4) multiple repetitive or prolonged nonsustained ventricular tachycardia (VT) on ambulatory 24-h (Holter) electrocardiography; and selectively 5) hypotensive or attenuated blood pressure response to exercise. In these cohort studies, HCM patients implanted for primary prevention experienced appropriate device therapy for VT/ventricular fibrillation at a rate of 4% per year (10% per year for secondary prevention) (5).

In addition, 1 of the major observations to emerge from these investigations was that appropriate ICD discharge rates did not differ significantly between patients implanted for 1, 2, or ≥3 risk factors, and that 1 major risk marker within the patient’s clinical profile can be sufficient to consider a prophylactic ICD (5). This observation underscores an important principle in HCM, i.e., that requiring a minimum of 2 risk factors in a given patient is unnecessary for recommending an implant, because it will leave many high-risk patients vulnerable, without the protection from an ICD (1,2).

More recently, the risk stratification algorithm in HCM has expanded to include other high-risk subgroups, such as patients with left ventricular (LV) apical aneurysm and regional scarring, and those who evolve to the “end-stage” phase associated with systolic dysfunction (ejection fraction <50%) (Figure 1) (1,2). As a result of this expanded risk stratification strategy, in accord with the United States/Canada Guidelines (2) and the penetration of ICDs into HCM practice, the natural history of this complex disease has been altered, as evidenced by reduction in HCM disease-related mortality across all ages to 0.5% per year (7). While this decrease in disease-related mortality represents substantial progress, nevertheless it is also apparent that not all patients at unacceptably high risk can be identified with the available conventional markers and that sudden death can occur occasionally in vulnerable patients without risk factors (8). Furthermore, in some HCM patients, sudden death risk may remain ambiguous even when using the conventional risk marker algorithm, such as in those patients with 1 risk factor who do not definitively fall into high- or low-risk categories (1).

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From the Hypertrophic Cardiomyopathy Institute, Division of Cardiology, Tufts Medical Center, Boston, Massachusetts. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.
For these reasons, the identification of additional risk markers to allow more precise selection of patients who may benefit from primary prevention ICD therapy represents a major clinical aspiration.

**THE ADDITIVE VALUE OF CMR**

Recently, contrast-enhanced cardiac magnetic resonance (CMR) has emerged as a powerful, advanced imaging technique that can identify structurally abnormal areas of the myocardial substrate, in particular replacement fibrosis identifiable by late gadolinium enhancement (LGE) (9). More than 50% of HCM patients demonstrate some LGE, in diverse patterns and location, and most commonly within hypertrophied segments of the LV wall (10).

Initial cross-sectional studies confirmed that HCM patients with LGE were at greater risk for VTs on ambulatory monitoring compared with those without LGE (11). Subsequently, several prospective CMR studies demonstrated that LGE was more common in patients who experienced sudden death (or an appropriate ICD discharge) than those patients who did not (12–15). However, the small size of these cohorts, and the relatively short follow-up, made it difficult to draw definitive conclusions regarding LGE and outcome.

More recently, an international prospective multicenter study of almost 1,300 consecutive HCM patients followed for >3 years after contrast-enhanced CMR considered the relationship between amount of LGE and sudden death events (10). In this study by Chan et al. (10), the frequency of LGE areas of any size was too great to allow the presence of LGE to be a practical strategy for judging outcome or clinical decision-making. However, extensive LGE occupying 15% or more of LV myocardial mass proved to be an independent predictor, conveying a 2-fold increase in sudden death risk for relatively young asymptomatic patients without conventional risk markers (Figure 2) (10). Also, in those patients with risk factors, the addition of extensive LGE identified HCM patients at greater risk with extensive LGE acting as an arbitrator to resolve complex ICD decision-making (Figure 2). Alternatively, absence of LGE was associated with low risk, providing a measure of reassurance to many patients, and evidence against ICD decisions (10).

In this issue of JACC, Weng et al. (16) provide further support for LGE as a novel sudden death risk marker with important prognostic value by assembling a meta-analysis derived from 5 of the previously noted contrast-enhanced CMR studies, totaling almost 3,000 HCM patients. In this pooled analysis, representing the largest combined experience with

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**FIGURE 1** Updated Risk Stratification Model to Identify HCM Patients at Highest Risk Who May Be Candidates for ICDs and Sudden Death Prevention

- **Primary Risk Markers**
  - Cardiac arrest/sustained VT
  - Family history of HCM-SD
  - Unexplained syncope
  - Multiple-repetitive NSVT (Holter)
  - Abnormal exercise BP response
  - Massive LVH

- **LGE ≥ 15% LV**

- **Potential Arbitrators**
  - End-stage phase
  - LV apical aneurysm
  - Marked LV outflow obstruction (rest)
  - Modifiable
    - Intense competitive sports
    - CAD
  - Alcohol septal ablation (?)

- **ICD**

**ICD**

**Highest**

**Intermediate**

**Lowest**

Primary risk markers and potential arbitrators appear in boxes at the left. *Extensive LGE, a primary risk marker, can also be used as an arbitrator when conventional risk assessment is ambiguous. BP = blood pressure; CAD = coronary artery disease; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LV = left ventricular; LVH = left ventricular hypertrophy; NSVT = nonsustained ventricular tachycardia; SD = sudden death; VT = ventricular tachycardia. Reprinted with permission from Maron et al.(4).
LGE in HCM, 55% of the HCM patients were LGE-positive and the extent of LGE was a strong independent predictor of disease-related outcome, including sudden death events (16). LGE (≥15% of LV mass) also conferred a 2-fold greater sudden death risk compared to HCM patients without LGE, even when taking into account other variables associated with sudden death risk, including systolic dysfunction.

These findings also support the principle that it is the amount or extent of LGE that is clinically relevant, with each 10% increase in LGE representing a 36% increase in relative sudden death risk (16). The continuous linear relationship between extent of LGE and heart failure incidence in HCM patients underscores the role that contrast-enhanced CMR now has in risk stratification and ICD decision-making (2,5). Of note, the European Society of Cardiology risk stratification strategy, based on mathematical and statistical modeling, does not include CMR-derived LGE as a marker for myocardial fibrosis (3), seemingly diminishing this approach as a contemporary risk prediction tool (17).

Weng et al. (16) also demonstrate a similar strong relationship between extent of LGE and heart failure death. The opportunity to identify HCM patients at risk for developing end-stage heart failure with systolic dysfunction may allow clinicians to anticipate revisions in management strategy, including tailored drug administration and timely consideration for heart transplant and prophylactic defibrillators for sudden death prevention (2,4).

CONCLUSIONS

Over the past several decades, the primary prevention risk stratification strategy in HCM has matured substantially and is largely responsible for the lower overall mortality now achievable in this genetic heart disease by the capability to prevent sudden death. The meta-analysis from Weng et al. (16) underscores the role that contrast-enhanced CMR now has in risk stratification and ICD decision-making. Indeed, diffuse and extensive LGE represents a novel powerful clinical tool that dictates HCM clinical course along 2 divergent adverse pathways: risk for sudden death and for advanced end-stage heart failure. For these and other reasons, it would seem justified to regard CMR as firmly integrated in the contemporary assessment of virtually all HCM patients.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Martin S. Maron, Tufts Medical Center, 800 Washington Street, #70, Boston, Massachusetts 02111. E-mail: mmaron@tuftsmedicalcenter.org.

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