Primary Prevention of Sudden Death as a Novel Treatment Strategy in Hypertrophic Cardiomyopathy

Barry J. Maron, MD; N.A. Mark Estes III, MD; Martin S. Maron, MD; Adrian K. Almquist, MD; Mark S. Link, MD; James E. Udelson, MD

Case Report: A 20-year-old asymptomatic man was diagnosed with hypertrophic cardiomyopathy (HCM) after routine physical examination during which a systolic heart murmur was detected. Echocardiography showed massive left ventricular (LV) hypertrophy with ventricular septal thickness of 36 mm extending into the anterolateral wall (30 mm); outflow obstruction was absent. Ambulatory (Holter) ECG showed 3 isolated premature ventricular contractions, and blood pressure response to exercise was normal. Echocardiographic examinations in parents and siblings were negative for HCM. Although 2 centers advised against an implantable cardioverter-defibrillator (ICD) based on the presence of only 1 risk factor for sudden death (ie, extreme hypertrophy), a prophylactic device was recommended by a third cardiac consultant. After an uneventful 16-month period during which the ICD neither detected nor treated arrhythmias, an unprovoked episode of ventricular fibrillation triggered a defibrillation shock that immediately restored sinus rhythm (Figure 1).

Background
HCM is the most common genetic cardiovascular disease, and since its description 45 years ago, sudden death has been its most visible and devastating consequence. Indeed, HCM is the most common cause of sudden cardiac death in young people (including trained athletes). Such events usually occur in previously healthy individuals without significant symptoms or as the initial clinical manifestation of the disease, thus generating considerable anxiety and a sense of vulnerability among patients and families. Identification of high-risk patients and efforts at prevention of sudden death represent important clinical challenges in HCM.

The ICD was introduced 25 years ago as a treatment strategy for lethal ventricular tachyarrhythmias. Several large, randomized, multicenter trials have shown the superiority of the ICD over antiarrhythmic drug therapy for both primary and secondary prevention of sudden death in patients with ischemic heart disease. However, application of ICD therapy to relatively young-risk patients with genetic diseases such as HCM has only recently become a focus. Although there is general consensus that HCM patients who survive cardiac arrest with ventricular fibrillation should be offered an ICD as secondary prevention, this subset of patients represents a small proportion of the at-risk population. It is our view that the availability of ICD technology underscores the need for strong consideration of more aggressive treatment strategies in high-risk HCM patients who have not experienced sustained arrhythmic events.

Role of the ICD in Primary Prevention
The ICD represents the most effective prophylactic treatment for prevention of sudden death in HCM. This contention is supported by several investigations, including a multicenter retrospective investigation of high-risk HCM patients. ICDs reliably aborted potentially lethal ventricular tachyarrhythmias in almost 25% of patients over a 3-year period, despite the substantial LV mass characteristic of this disease. Appropriate device interventions occurred at 11%/year for secondary prevention and about 5%/year for primary prevention. The mean age at initial appropriate shock (and also implant) was only 40 years, underscoring the relative youth of these HCM patients.

From the Hypertrophic Cardiomyopathy Center, Minneapolis Heart Institute Foundation, Minneapolis, Minn (B.J.M., A.K.A.), and the Hypertrophic Cardiomyopathy Center, Division of Cardiology, Tufts-New England Medical Center, Boston, Mass (N.A.M.E., M.S.M., M.S.L., J.E.U.).

Correspondence to Barry J. Maron, MD, The Hypertrophic Cardiomyopathy Center, Minneapolis Heart Institute Foundation, 920 E 28th St, Suite 60, Minneapolis, MN 55407. E-mail hcm.maron@mhif.org

(Circulation. 2003;107:2872-2875.)

© 2003 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org

DOI: 10.1161/01.CIR.0000072343.81530.75
There was only a 4:1 ratio of devices implanted to lives saved.

The fact that the first appropriate ICD intervention for ventricular tachycardia/fibrillation was often delayed for as much as 10 years emphasizes the unpredictable nature of the electrically unstable substrate in HCM (ie, disorganized myocardial architecture and ischemia-related replacement scarring).\(^2,3,10\) Indeed, the time at which high-risk status is identified in a given HCM patient may not bear a direct relationship to the future timing of a life-threatening arrhythmia. Consequently, a 20-year-old, high-risk HCM patient with a prophylactic ICD will still be relatively young even if the device first triggers appropriately 15 years later when the patient is 35. However, the potential life-saving implications of device implantation in young patients should always be weighed against possible ICD-related complications, including the risk for inappropriate shocks and other lead-related problems, as well as the negative psychological impact that can be associated with implants early in life.

The premise of primary prevention of sudden death in HCM is unique compared with that in high-risk coronary artery disease patients who have sustained a prior myocardial infarction, may have congestive heart failure,\(^9\) and are generally of advanced age, often with limited life expectancy (even with the ICD). In contrast, patients with HCM who are candidates for ICDs\(^2,3,10–14\) are usually asymptomatic (or only mildly symptomatic) and represent a much younger population for whom potential risk extends over many decades. By extrapolation, it is estimated that within 20 years, at least 40% of the defibrillators implanted prophylactically in young high-risk HCM patients could intervene and abort sudden death.\(^15\) Of note, this event rate in HCM does not differ greatly from the event rate used to design medical primary prevention strategies to reduce the incidence of myocardial infarction caused by coronary artery disease in asymptomatic populations.\(^16\)

The American College of Cardiology/American Heart Association/North American Society of Pacing and Electrophysiology 2002 guidelines\(^11\) designate the ICD as a class IIb indication for primary prevention of sudden death in HCM. Availability of sufficient data to support a higher classification is unlikely, given that it is impractical (and possibly unethical) to contemplate prospective randomized clinical trials of sufficient size to definitively prove benefit for the ICD in a genetic heart disease such as HCM.

Finally, in HCM, there is little evidence to support a role for pharmacological therapy (with \(\beta\)-blockers, calcium channel blockers, class I-A antiarrhythmic agents, or amiodarone), for the prevention of lethal arrhythmias; indeed, many sudden death events in HCM have been reported during treatment with amiodarone.\(^3,10\) Furthermore, the long risk period over many decades in HCM generally precludes treatment with amiodarone, given its cumulative toxicity.

**Risk Stratification**

In HCM, although there is a predilection for sudden death in the young (<30 years of age), such events can also occur in middle-age and beyond; therefore, achieving a particular age does not appear to confer immunity to
Strongest Risk Factors for Sudden Death in HCM

- Cardiac arrest (ventricular fibrillation)
- Spontaneous sustained ventricular tachycardia
- Familial sudden HCM-related death (particularly in a first degree relative and/or multiple in occurrence)
- Syncope (one or more episode, and particularly if recurrent, exertional, or in the young)
- Nonsustained ventricular tachycardia (NVST) on Holter ECG (frequent, repetitive, or prolonged; arbitrarily defined: ≥3 bursts of NSVT at ≥120 bpm on ≥2 Holters within 6 months, or any runs ≥10 beats)
- Abnormal blood pressure response with exercise (a fall or sustained failure to rise ≥20 mm Hg during exercise or recovery, in patients <50 years of age)
- Extreme LV hypertrophy (maximum LV thickness ≥30 mm from echocardiogram)

sudden death. To create a risk profile, all HCM patients (especially those <60 years old) should undergo an initial comprehensive ambulatory risk-stratification assessment, including detailed personal and family history and physical examination, 12-lead ECG, 2-dimensional echocardiogram, Holter ECG monitoring, and exercise testing. Subsequent risk analysis should be performed periodically and when there is a perceived change in clinical status.

Clinical parameters currently used to assess risk level for sudden death in HCM are summarized in the Table. Other HCM disease features such as LV outflow tract obstruction, inducible myocardial ischemia, and atrial fibrillation, although not strong independent predictors of sudden death in cohort analyses, may nevertheless contribute to an increased risk profile in individual patients.2,17 Electrophysiological testing with programmed ventricular stimulation has been largely abandoned as a routine strategy in HCM because of the non-specificity of provoked ventricular tachyarrhythmias. Laboratory-based genotyping for mutations indicative of high (or low) risk is not currently available for routine clinical practice and is largely confined to research centers.

Although multiple risk factors convey greater likelihood for future sudden death events,4 it is the predominant clinical practice to offer patients strong consideration for a prophylactic ICD on the strength of one or more risk factors regarded as major (such as family history of sudden death). As illustrated by the case report (Figure 1), massive LV hypertrophy (thickness ≥30 mm), even in the absence of important arrhythmias, may represent a sole and independent marker for future sudden death.2,15 Some investigators (largely European) are more restrictive, requiring 2 or more risk factors before considering a prophylactic ICD.18 However, it is important to underscore that many “gray-zones” unavoidably persist in reaching decisions to implant defibrillators prophylactically in HCM patients who are possibly at increased risk. This necessitates considerable clinical judgment in conjunction with the desires of the individual patient.

Whereas almost 50% of clinically identified HCM patients have some evidence for increased risk (Figure 2), almost 5% of those without any risk factors nevertheless experience sudden death.4 This indicates that the current risk stratification algorithm for HCM is incomplete and that no single disease feature or test can reliably stratify all patients. Also, because the overall sudden death event rate in HCM is low, most of the clinical risk markers have low positive and high negative predictive values.2,4,18

Therefore, a future challenge is more precise identification of those HCM patients who should be targeted for primary prevention. Prudent management decisions are currently based on the known risk factors, and in many instances are made by integrating all relevant clinical data with individual physician judgment and in accord with the risk level acceptable to patient and family.

Future Perspectives

On the basis of the reported prevalence of HCM in the general population (1 in 500), we can infer that as many as 500 000 patients in the United States have this disease at any time. However, a substantial proportion (including many at high-risk for sudden death) either remain undiagnosed, are not exposed to risk stratification assessments sufficient to define their prognosis, or die suddenly before clinical recognition.

The introductory case report underscores that the powerful technology of the ICD is now available to patients with genetic heart diseases such as HCM for the primary prevention of sudden death, as well as the importance of proper risk stratification in this complex disease. Of note, our patient exhibited an extreme degree of LV hypertrophy as the sole marker of sudden death risk, emphasizing that the decision to prophylactically implant an ICD can be predicated on the strength of only 1 major risk factor. Therefore, the ICD now affords the possibility to intervene early in the clinical course of HCM, alter its natural history, and afford many decades of productive life (if not normal or near-normal longevity) to those patients for whom the adverse consequences of HCM are largely confined to electrical instability (ie, ventricular fibrillation). It is our expectation that this contem-
porary treatment strategy will prevent most of the devastating events that have plagued HCM patients over the past 4 decades.

References
Primary Prevention of Sudden Death as a Novel Treatment Strategy in Hypertrophic Cardiomyopathy

Barry J. Maron, N. A. Mark Estes III, Martin S. Maron, Adrian K. Almquist, Mark S. Link and James E. Udelson

*Circulation*. 2003;107:2872-2875
doi: 10.1161/01.CIR.0000072343.81530.75

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/23/2872

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org/subscriptions/