

EDITORIAL COMMENT

Prevention of Sudden Death for Patients With Cardiomyopathies

Another Step Forward*

Barry J. Maron, MD,†

Christopher Semsarian, MBBS, PhD‡

Minneapolis, Minnesota; and Sydney, Australia

It has now been >30 years since the implantable cardioverter-defibrillator (ICD) was introduced to the cardiovascular community for the prevention of sudden cardiac death (1). Perhaps it is no longer common knowledge that the defibrillator was conceived and initially developed >40 years ago by Drs. Michel Mirowski and Morton Mower, not in an eminent medical institution with the robust support of industry and the National Institutes of Health, but rather in the basement of a small, private hospital (Sinai Hospital, Baltimore, Maryland), initially with no formal funding. This entirely novel concept was initially met with substantial skepticism and even antagonism (2), but eventually moved forward, driven by the vision of Mirowski and Mower, until it became the acknowledged treatment to

See page 493

prevent sudden death due to ventricular tachyarrhythmias, largely for high-risk patients with coronary artery disease (CAD) and myocardial infarction. Certainly, it was not unexpected that this large group of patients would become the impetus for developing the ICD, as well as the core recipients of this technology, as it evolved over the decades with numerous randomized trials documenting its efficacy and superiority over pharmacologic strategies (3–5).

However, it is not generally appreciated that most of a small group of exceptionally high-risk patients selected for initial clinical testing of the ICD in the laboratory setting

(to assess its defibrillation capability to automatically abort ventricular fibrillation) did not have ischemic heart disease but, rather, a much less common genetic heart disease, hypertrophic cardiomyopathy (HCM). During the ensuing 2 decades of ICD development, while there were important advances such as transvenous lead systems, which permitted these devices to be employed more widely for primary prevention, nevertheless, genetic cardiomyopathies were largely ignored.

Not until 2000 was the ICD introduced to HCM patients with nonatherosclerotic genetic heart disease as a systematic, effective strategy for sudden death prevention in an international, multicenter registry study (6). This translation of the ICD to HCM was logical and necessary, given that HCM is the most common cause of sudden death in young people (7) who have many years of potentially productive life ahead. Indeed, over the last decade, the ICD has proven life-saving for many HCM patients, with primary prevention appropriate intervention rates of 4% per year (10% per year for secondary prevention). After the initial experience with HCM, the ICD has proved effective in patients with other genetic heart diseases such as arrhythmogenic right ventricular cardiomyopathy/dysplasia, an entity very different morphologically, but with similar reported ICD intervention rates (10–12).

Notably, in this issue of the *Journal*, van Rijsingen et al. (13) expand the role of the ICD for prevention of sudden death by reporting outcomes of an observational study from 8 centers in 6 European countries (Netherlands, Italy, Denmark, United Kingdom, France, and Germany). The study population includes 269 patients and relatives (from 109 families) with pathogenic lamin A/C (*LMNA*) gene mutations responsible for dilated cardiomyopathy and systolic dysfunction (some with muscular dystrophy). Approximately 20% of the patients had demonstrated malignant ventricular tachyarrhythmias manifest by either resuscitated cardiac arrest, sudden cardiac death, or (for approximately half) appropriate interventions from primary prevention ICDs. Indeed, of 107 patients implanted prophylactically with an ICD, 25 (or 23%) experienced an intervention for ventricular tachycardia/fibrillation over a 29-month follow-up, for a particularly substantial intervention rate of about 9% per year. Unfortunately, while there is abundant demographic data provided for the overall study group of 269 patients, some information of interest for this specific ICD subset appears to be lacking, such as the age at implant or time from implant to ICD shock, and the level of limiting symptoms experienced prior to device intervention.

It is now apparent that the ICD will intervene reliably in genetic cardiomyopathies such as HCM, arrhythmogenic right ventricular cardiomyopathy/dysplasia, and now *LMNA*-mediated dilated cardiomyopathy to terminate life-threatening ventricular arrhythmias and abort catastrophe. However, the key remaining clinical issue (and often dilemma) is the proper selection of patients who will benefit

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the †Hypertrophic Cardiomyopathy Center, Minneapolis Heart Institute Foundation, Minneapolis, Minnesota; and the ‡Agnes Ginges Centre for Molecular Cardiology, Centenary Institute, Sydney Medical School, University of Sydney, and Department of Cardiology, Royal Prince Alfred Hospital, Camperdown, Australia. Dr. Semsarian is the recipient of a Practitioner Fellowship from the National Health and Medical Research Council, Canberra, Australia. This work is funded in part by a grant from the Hearst Foundations, New York (Dr. Barry Maron).

most from ICD therapy through risk stratification. Rijsingen et al. (13) have used a noninvasive risk stratification algorithm including a variety of clinical variables to select patients for prophylactic ICDs similar in principle to that previously promoted in HCM (7–9). The authors' novel multivariate model identified 4 variables as independent risk factors: nonsustained ventricular tachycardia (on 24-h ambulatory [Holter] electrocardiogram), ejection fraction <45%, male gender, and non-missense mutations.

However, the most notable differences from HCM in this regard are the exclusion of family history of sudden death as a predictor, and the inclusion of a predictive genotype, namely, non-missense mutations such as insertions/deletions, truncating or mutations affecting splicing, which can lead to significant alterations in the encoded protein. In contrast, while the majority of disease-causing mutations in HCM are missense (single amino acid substitutions), there is little evidence that either missense or non-missense mutations predict clinical course and prognosis in that disease.

Two or more of the risk markers in *LMNA* mutation carriers predicted malignant ventricular tachyarrhythmias and permitted effective primary prevention of sudden death through reliable selection of patients for ICDs. The 2 risk factor model has been favored by European investigators in defining high risk status in genetic cardiomyopathies (e.g., HCM), whereas others have promoted the principle that 1 major risk factor in the clinical profile of an individual patient can be sufficient to consider the option of a primary prevention ICD. Therefore, it would be of interest to learn whether 1 risk factor was predictive in at least some of the authors' *LMNA* patients, i.e., are the 4 risk markers of equal weight in a given *LMNA* mutation carrier? Is a reduced ejection fraction alone sufficient to justify an ICD? These are among the many questions remaining in this early experience with sudden death prevention for patients with genetic dilated cardiomyopathy that will require studies in larger patient cohorts. It is also of interest that a family history of sudden death did not prove to be a risk factor in the *LMNA* mutation carriers (13), consistent with the experience in long-QT syndrome (14) and Brugada syndrome (15), but in contrast to HCM (16).

This is a complex paper to read, with much data, but the readership should not be dissuaded from an appreciation of its most important message—namely, that by virtue of a clinical-genetic risk stratification model, those *LMNA* mutation carriers most likely to benefit from ICD therapy have been identified, thereby saving many lives with another inherited heart disease. Indeed, the multicenter report of van Rijsingen et al. (13) makes a major contribution to the

management of such patients, and in a historical context, one that was certainly unforeseen 4 decades earlier by the visionary investigators who created the ICD.

Reprint requests and correspondence: Dr. Barry J. Maron, Hypertrophic Cardiomyopathy Center, Minneapolis Heart Institute Foundation, 920 East 28th Street, Suite 620, Minneapolis, Minnesota 55407. E-mail: hcm.maron@mhif.org.

REFERENCES

1. Mirowski M, Reid PR, Mower MM, et al. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. *N Engl J Med* 1980;303:322–4.
2. Lown B, Axelrod P. Implanted standby defibrillators. *Circulation* 1972;46:637–9.
3. Moss AJ, Zareba W, Hall WJ, et al., for the Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877–83.
4. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Eng J Med* 2005;352:225–37.
5. Epstein AE. Benefits of the implantable cardioverter-defibrillator. *J Am Coll Cardiol* 2008;52:1122–7.
6. Maron BJ, Shen W-K, Link MS, et al. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. *N Engl J Med*;342:365–73.
7. Maron BJ. Contemporary insights and strategies for risk stratification and prevention of sudden death in hypertrophic cardiomyopathy. *Circulation* 2010;121:445–56.
8. Maron BJ, Spirito P, Shen W-K, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *JAMA* 2007;298:405–12.
9. Maron BJ, Spirito P. Implantable defibrillators and prevention of sudden death in hypertrophic cardiomyopathy. *J Cardiovasc Electro-physiol* 2008;19:1118–26.
10. Corrado D, Calkins H, Link MS, et al. Prophylactic implantable defibrillator in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and no prior ventricular fibrillation or sustained ventricular tachycardia. *Circulation*. 2010;122:1144–52.
11. Corrado D, Leoni L, Link MS, et al. Implantable cardioverter-defibrillator therapy for prevention of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circulation* 2003;108:3084–91.
12. Wichter T, Paul M, Wollmann C, et al. Implantable cardioverter/defibrillator therapy in arrhythmogenic right ventricular cardiomyopathy: single-center experience of long-term follow-up and complications in 60 patients. *Circulation* 2004;109:1503–8.
13. van Rijsingen IAW, Arbustini E, Elliott PM, et al. Risk factors for malignant ventricular arrhythmias in lamin A/C mutation carriers: a European cohort study. *J Am Coll Cardiol* 2012;59:493–500.
14. Kaufman ES, McNitt S, Moss AJ, et al. Risk of death in the long QT syndrome when a sibling has died. *Heart Rhythm* 2008;5:831–6.
15. Sarkozy A, Sorgente A, Boussy T, et al. The value of a family history of sudden death in patients with diagnostic type I Brugada ECG pattern. *Eur Heart J* 2011;32:2153–60.
16. Bos JM, Maron BJ, Ackerman MJ, et al. Role of family history of sudden death in risk stratification and prevention of sudden death with implantable defibrillators in hypertrophic cardiomyopathy. *Am J Cardiol* 2010;106:1481–6.

Key Words: cardiomyopathy ■ implantable cardioverter-defibrillator ■ lamin A/C ■ risk factors ■ sudden cardiac death.