EDITORIAL COMMENT

Timing the Implantation of Implantable Cardioverter-Defibrillators in Patients With Nonischemic Cardiomyopathy*

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The prophylactic use of implantable cardioverter-defibrillators (ICDs) in selected patients with nonischemic cardiomyopathy (NICM) is unequivocally valuable (1). Clinicians are nevertheless confronted with decision making related to two fundamental aspects in the selection of patients for an ICD. First is the use of a single and poorly reproducible dichotomous variable, left ventricular ejection fraction (LVEF) above or below 35%, as the sole means by which to stratify risk. Second is the difficulty in distinguishing patients with a cardiomyopathy, who might benefit from early device implantation, from those in whom a marked improvement of left ventricular function averts the need for an ICD.

The arbitrary selection of LVEF <35% as the major inclusion criterion in the Sudden Cardiac Death-Heart Failure Trial (SCD-HeFT) and Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial designs is confounded by the variability of LVEF measurement even during stable clinical conditions (1,2). There are no supplementary criteria in these patients to further stratify risk for lethal tachyarrhythmia if their LVEF value is ambiguous. Unfortunately, the scope of those trials makes it improbable that repeat studies with different inclusion parameters will be undertaken. A well-designed registry of patients with NICM, an LVEF <35%, and a prophylactic ICD could result in data collection that identifies supplementary parameters associated with a high arrhythmia risk. These parameters, applied prospectively, may prove sufficiently robust to narrow the scope of ICD use in patients with LVEF <35% and incorporate a larger denominator of patients with LVEF >35%.

In this issue of the Journal, Kadish et al. (3) address the second difficult decision—the timing of ICD implantation. This post hoc analysis of the DEFINITE trial was undoubtedly provoked by the Center for Medicare and Medicaid Services’ decision to restrict prophylactic ICD implantation in patients with NICM for nine months after initial diagnosis (4). This restriction is absolute for patients within three months of the diagnosis, and permitted only as part of a registry for patients diagnosed within three to nine months. It is noteworthy that in both the SCD-HeFT and DEFINITE trials, inclusion criteria did not specify a time limit for study entry but required the exclusion of patients with a reversible cardiomyopathy (1,2). Despite the limits of a post hoc analysis, the current report documents the benefit of ICD implantation in patients with a more recent diagnosis of NICM in the DEFINITE study population. These results are provocative and focus the clinical imperative to identify the likelihood of reversibility of the cardiomyopathy. Parameters that define the likelihood of reversibility, as opposed to a biologically implausible time interval after diagnosis, should dictate ICD implantation.

It seems that the DEFINITE investigators identified persistent arrhythmia risk because the two treatment arms continued to diverge in the early diagnosis group. However, the report does not substantiate whether they identified the irreversibility of the cardiomyopathy with their exclusion/inclusion criteria. Follow-up LVEF information in the DEFINITE population should be ascertained so that the relationship of improvement in LVEF to the time of entry in the study could be explored. Better-defined, objective parameters to identify patients with the possibility of improvement must be confirmed and stipulated.

Reversible cardiomyopathy, such as that produced by a persistent tachycardia, or fulminant myocarditis is easily identified, but accounts for only a small fraction of the total patients symptomatic with NICM (5). Our ability to identify the reversibility of the cardiomyopathy in other less obvious settings is more uncertain. New observations related to the potential for reversible cardiomyopathy caused by paroxysmal arrhythmias, frequent ventricular ectopy, and intermittent right ventricular pacing highlight this difficulty, suggesting that the arrhythmia burden that adversely affects LVEF may vary from patient to patient and over the clinical course of the disease (6–8). Currently, aggressive management to limit the patient’s arrhythmia burden and/or right ventricular pacing with repeat assessment of LVEF is the appropriate approach before ICD implantation.

The reversibility of left ventricular dysfunction is also well recognized in many patients with NICM in response to medical treatment with angiotensin-converting enzyme inhibitors and beta-blockers (9). Over 50% of patients with dilated cardiomyopathy may experience substantive (>10%) improvement in LVEF. This improvement in left ventricular function represents reverse remodeling of a time-dependent nature. Indeed, the question is not whether the

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LVEF improves in some patients with newly diagnosed NICM in response to optimized medical therapy, but rather how to identify the nonresponder so that an interval of observation is not required before ICD implantation.

There are available biologic parameters that have prognostic significance in patients with NICM. Patients with an increased expression of Fas, a transmembrane cell surface receptor that plays a critical role in apoptosis, are more likely to show minimal recovery in LVEF (10). One of the best biologic markers for irreversibility seems to be related to the development of significant cardiac fibrosis. Fibrosis serves as an arrhythmogenic substrate and site of origin for most sustained ventricular arrhythmias in NICM and reflects the chronicity of the process (11). Fibrosis in the setting of nonischemic right and left ventricular cardiomyopathy tends to be predominantly perivascular. This fibrosis can be identified by sinus rhythm and bipolar-voltage catheter mapping, and may also be identified with noninvasive contrast-enhanced imaging techniques (11–13). Other indirect indices for the presence of perivascular fibrosis include persistent atrioventricular block or proximal left bundle branch block. Subsequent observations need to confirm that patients who show these abnormalities have both a higher arrhythmia risk and a lower likelihood of improvement in LVEF. Ideally, evidence of significant fibrosis will add prognostic information to identify patients who warrant ICD therapy despite a recent diagnosis of NICM.

There are also clinical parameters with prognostic significance in patients with NICM. These clinical factors could also be tested prospectively as markers for the severity and chronicity of the disease process and the likelihood of irreversibility in left ventricular dysfunction. These factors include the presence of pulmonary hypertension, marked impairment in LVEF to <20%, left ventricular end-diastolic dimension of >7.0 cm, coexistent right ventricular dysfunction, and an increased degree of left ventricular sphericity (14). Clinical findings such as a persistent S3 gallop, signs of right-sided heart failure, hyponatremia, increased B-type natriuretic peptide, and elevated troponin levels may also be associated with a decreased likelihood of reversibility (15). Provocative maneuvers, such as dobutamine stress testing, have also been used to predict persistent left ventricular dysfunction during follow-up (16). Importantly, although improvement in left ventricular function with medical therapy may take more than six months to optimize, evidence of some improvement within one to three months after initiating therapy is usually observed (9). The absence of any substantive improvement in LVEF after two months of optimum medical therapy also may serve as a marker for the absence of a long-term response.

Finally, there is yet another group of patients with NICM that needs to be identified early after diagnosis, i.e., those patients unable to respond to medical treatment because the drugs cannot be tolerated (17). Whether such patients benefit from implantation of an ICD has not been substantiated. Thus, the mandate raised by the current report in the Journal is not only to identify patients with an irreversible abnormality not likely to respond to medical intervention, but also to identify patients in whom such evidence-based therapy cannot be used.

In summary, enough doubt is present to question the wisdom of requiring a nine-month observational period in patients with NICM before the implantation of an ICD. The clinical imperative is to identify which patients are likely to have irreversible LV dysfunction at the time of initial presentation. Collecting follow-up data on LVEF from patients enrolled in the DEFINITE and SCD-HeFT trials is an important effort to initiate. The results may provide insight into how common left ventricular dysfunction is reversed when patients are excluded with known reversible causes of cardiomyopathy. Parameters for defining a high likelihood of reversible myopathy should be incorporated into the guidelines for implantation. Patients who show biological, electrophysiological, imaging, or clinical parameters that suggest a high likelihood of irreversibility of left ventricular dysfunction should be considered for early implantation. This could be done in conjunction with a compulsory registry incorporating serial follow-up of LVEF as part of the implantation strategy. An active strategy that couples evidence-based medicine with sound, hypothesis-testing, prospective data collection and recognizes the importance of distinguishing reversible and nonreversible forms of NICM should be the norm.

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REFERENCES


