

## EDITORIAL COMMENT

# Say No to Primary Prophylaxis With Implantable Cardioverter-Defibrillators in Asymptomatic Nonischemic Dilated Cardiomyopathy?\*

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Nonischemic dilated cardiomyopathy (NIDCM) is a common cause of congestive heart failure (CHF) and is a risk factor for sudden cardiac death (1,2). Although an asymptomatic patient with *ischemic* cardiomyopathy can now be approached with a reasonably established strategy (e.g., risk stratification using an electrophysiologic [EP] study in those with moderately reduced left ventricular [LV] function and non-sustained ventricular tachycardia [NSVT] [3]; a prophylactic implantable cardioverter-defibrillator [ICD] in those with severely reduced LV function [4]), the optimal management of asymptomatic patients with NIDCM has been less rigorously defined.

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Inducibility of VT at EP study in these patients correlates poorly with past or future episodes of VT (5,6). The only antiarrhythmic drug shown to be of possible use in preventing ventricular tachyarrhythmias, amiodarone, has not been evaluated in depth. The often-quoted GESICA study of empiric amiodarone therapy in dilated cardiomyopathy (DCM) comprised a very heterogeneous population group, of which 40% of the patients had ischemic heart disease (7). In the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (CHF-STAT) (70% of these patients had ischemic heart disease), amiodarone therapy was associated with a trend toward reduced mortality in the non-ischemic cardiomyopathy group (8).

The only published randomized trial employing ICDs for primary prophylaxis of sudden cardiac death in patients with NIDCM studied 104 asymptomatic patients with a recent onset of NIDCM (<9 months) (the Cardiomyopathy Trial [CAT]). Patients were randomized to ICD or control, and cumulative survival at four years was 86% and 80%, respectively ( $p = ns$ ) (9).

In this issue of the *Journal*, Strickberger et al. (10) results of a randomized multicenter trial, Amiodarone versus Implantable Defibrillator Randomized Trial (AMIOVIRT), in patients with NIDCM and asymptomatic NSVT are reported. One hundred and three patients with NIDCM and asymptomatic NSVT (no prior syncope, sustained VT, or sudden death) were randomized to either amiodarone (52 patients) or ICD (51 patients). The study was terminated at interim analysis because of lower than expected mortality. Analysis of outcomes by intention to treat found that survival at three years was approximately 88%, with no significant difference between the groups assigned to either initial amiodarone or ICD therapy. A trend toward lower initial cost and improved arrhythmia-free survival was noted in the amiodarone group.

Before generalizing the results of AMIOVIRT as a therapeutic strategy, one must consider all features of the patient population as well as the design of the study, which is the focus of this editorial.

First, the significance of NSVT in these patients still remains unclear as a risk marker of future arrhythmic events. The prevalence of NSVT in patients with DCM is high (>50%) (9,11), and while some studies have found this to be a marker of high risk of death (12), others have not (11). In the recent CAT study, survival was no different in patients with NSVT from those without NSVT (9). Even the prognosis of rapid (>220/min) polymorphic "bursts" or monomorphic episodes that last 20 to 25 s is not clearly determined. Thus clinically, it has been difficult to establish a level of risk according to the presence or type of NSVT.

Second, patients with NIDCM form an extremely heterogeneous group. The present study appeared to include all forms of NIDCM. The risk of sudden death could be different in those with DCM caused by sarcoidosis (13) or hypertrophic cardiomyopathy (14) from such risk in those whose DCM is, for example, "idiopathic/post viral," hypertensive, or alcoholic. The CAT study that found no benefit for ICDs was comprised largely of patients with idiopathic DCM (9).

Third, the mortality rate was significantly lower in these recent NIDCM studies than previously reported. Whereas previous studies noted NIDCM mortality rates as high as 31% within one year (15), patients in AMIOVIRT had a mortality of  $\leq 10\%$  at one year and 12% to 13% at three years. This low mortality rate was observed despite the likely inclusion of patients referred to tertiary care centers, who traditionally have a higher mortality than community-based patients (15). It is reasonable to assume that this is largely due to the dramatic effect of treatment with angiotensin-converting enzyme (ACE) inhibitor therapy and other drugs. This reduced mortality, however, raises the issue of what the true mortality rate is in patients currently treated with optimal medical therapy. In AMIOVIRT, approximately 50% of the patients were receiving beta-blockers in

\*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.

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addition to ACE inhibitors at final follow-up. Because the trial began in 1996, it is possible that beta-blocker use was lower earlier in the trial. It is likely that more widespread beta-blocker usage would have provided an incremental benefit to ACE inhibitors in this population, possibly reducing mortality rates further.

Bradycardia has long been implicated as a cause of mortality in patients with CHF. A telemetry study of patients admitted with advanced CHF found that all patients with NIDCM in fact died with *bradycardia* (sinus bradycardia, AV block, pulseless electrical activity), whereas all those who suffered VT/VF as the terminal event had ischemic DCM (16). One indirect inference that may be drawn from the present study is that "backup ventricular pacing" to prevent death from bradyarrhythmia may not influence mortality outcome in NIDCM, because mortality rates were similar in the amiodarone arm and the implanted-device arm.

Nevertheless, the overall effect of implanted device therapy on mortality due to CHF (non-arrhythmic mortality) in patients with NIDCM is unknown. Although it is counter-intuitive to think that an ICD could worsen survival, a population that has a relatively low incidence of sudden death might be significantly affected by any intervention that worsens LV "pump function." At the present time the effect of right ventricular pacing (automatic cardiac *desynchronization*) from a prophylactic ICD in this population is not well defined. In patients with ischemic cardiomyopathy, prophylactic ICD insertion appeared to result in a slightly higher rate of hospital admissions for CHF (4). The advent of biventricular pacing is likely to influence the natural clinical history of these patients further and may favorably modify our ability to use beta blockers and ACE inhibitors aggressively.

Thus, at the present time, while improbable, it is unclear whether medical therapy with widespread use of beta-blockers, spironolactone, and ACE inhibitors results in a lower total mortality rate than either amiodarone or prophylactic ICD. In addition, widespread adoption of a strategy using amiodarone in these asymptomatic patients may be a futile exercise, granted the relatively high rate of discontinuation of amiodarone in this trial (25 of 52 patients; almost 50%) in the amiodarone arm.

Despite these issues, the present study highlights the contrast of disease substrate between ischemic and NIDCM, and in concert with CAT (9), raises the possibility that *prophylactic* ICD implantation in asymptomatic patients with NIDCM may be futile.

This is in sharp contrast to patients with NIDCM who have either syncope or an aborted sudden cardiac death. Patients with unexplained syncope who undergo ICD implantation experience a rate of resuscitative shocks by the ICD similar to patients who undergo implantation for cardiac arrest (17). From meta-analysis of Antiarrhythmics Versus Implantable Defibrillators (AVID), Cardiac Arrest Study Hamburg (CASH), and Canadian Implantable De-

fibrillator Study (CIDS) data, sudden death/symptomatic VT survivors with NIDCM have a similar rate of recurrence of sudden death as patients with ischemic cardiomyopathy and thus a similar benefit (18). Therefore, the weight of evidence is in favor of implantation of ICDs in patients who have any form of DCM and either unexplained syncope or aborted sudden death.

One non-invasive test that appears to show promise in the risk stratification of NIDCM is T-wave alternans (TWA). The negative predictive value of TWA is high, and in concert with ejection fraction, specific features of TWA such as a low onset heart rate of TWA can be predictive of future cardiac events (19). One potential strategy in the asymptomatic patient with NIDCM might be to assign TWA negative patients to "best medical" CHF therapy and TWA positive patients to that plus amiodarone therapy. Naturally, this must be tested prospectively.

Despite these criticisms, the authors of the present study should be commended for their efforts in clarifying rational therapy for patients with NIDCM. At the present time, when confronted with a patient who fits this study profile, we believe that our existing position would be not to empirically implant an ICD, and this study confirms that this strategy is reasonable. It is probably also reasonable to offer amiodarone therapy with the understanding that this is a strategy unproven to be superior to usual medical therapy (beta-blockers, ACE inhibitors). For a more definitive approach in managing these patients, we await further clinical trial data, including that from Sudden Cardiac Death in Heart Failure Trial (SCD-HEFT).

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