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*Heart* 2010 96: 510-515 originally published online November 1, 2009
doi: 10.1136/hrt.2009.178061

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Incidence of left ventricular function improvement after primary prevention ICD implantation for non-ischaemic dilated cardiomyopathy: a multicentre experience

Atul Verma,1 Zaev Wulffhart,1 Dhanunjaya Lakkireddy,2 Yaariv Khaykin,1 Alexander Kaplan,1 Bradley Sarak,1 Mazda Biria,2 Jayasree Pillarisetti,2 Pradeep Bhat,3 Luigi Di Biase,4 Otto Constantini,3 Kara Quan,3 Andrea Natale4

ABSTRACT

Background The SCD-HeFT study demonstrated a benefit of primary prevention implantable cardioverter-defibrillator (ICD) implantation in patients with non-ischaemic dilated cardiomyopathy (NIDCM). However, NIDCM may improve spontaneously, even after waiting 6–9 months on optimal medical treatment. Objective To assess the incidence of left ventricular (LV) function improvement in patients receiving primary prevention ICDs for NIDCM. Methods All patients with NIDCM receiving primary prevention ICDs (non-cardiac resynchronisation therapy) from 2005 to the present at our institutions were retrospectively studied. All patients had NIDCM confirmed by a lack of significant stenoses on coronary angiography, a lack of significant valvular abnormalities on echo, and LV dysfunction with ejection fraction (EF) <35%. All patients had to have had a diagnosis of NIDCM for at least 9 months and be receiving optimal medical treatment for at least 3 months before implant according to the guidelines. All patients had at least New York Heart Association (NYHA) II symptoms. Baseline and follow-up EF was documented by quantitative echo and/or multi-gated acquisition scan.

Results 332 patients were identified by a database search. Patients were aged 67±11 years, 75% of them were male, NYHA 2.3±0.7, with EF 25±13%, and LV diastolic diameter 61±10 mm. Time from initial NIDCM diagnosis to implant was 11±6 months and duration of medical treatment before implant was 8±5 months. Treatment at the time of implant included ACE inhibitors or ARBs (85%), β blockers (77%), spironolactone (53%), loop diuretic (63%) and digoxin (50%). Repeat EF assessment was available in 309/332 (93%) 8±6 months after implant. EF improved to >35% in 37/309 (12%) patients. Patients who improved had a shorter time from diagnosis to implant (9±3 vs 13±5 months respectively, p=0.03). No other significant predictors were identified for patients with improved EF. Conclusions In spite of following guidelines for implantation of primary prevention ICDs in patients with NIDCM, a substantial number of patients (12%) experience improvement in LV function to levels above those recommended for ICD implant. A shorter time from diagnosis to implant may predict post-implant improvement.

INTRODUCTION

The benefit of implantable cardioverter-defibrillator (ICD) treatment for primary prevention of sudden cardiac death has been long established in patients with ischaemic cardiomyopathy.1 Data demonstrating a similar benefit in patients with non-ischaemic dilated cardiomyopathy (NIDCM) has been more recent.2 Based on studies such as SCD-HeFT and DEFINITE, the most recent joint AHA/ACC/HRS guidelines for device-based treatment now categorises as a class I indication the implantation of an ICD in patients with NIDCM with ejection fraction (EF) ≤55% who are New York Heart Association (NYHA) functional class II or III.4 Although the guidelines suggest that it would be best to offer ICDs to patients who have “clinical profiles as similar to those included in the trials as possible,” they do not specify a minimum time between diagnosis of NIDCM and device implantation, nor is there a recommendation on the length of optimal medical treatment before implant.

Yet, it is well known that some patients with NIDCM may experience spontaneous improvement in their cardiac function over weeks, but sometimes over months.5 Furthermore, improved medical treatment may also reverse the cardiomyopathy over time.6–8 Even patients with severe, end-stage cardiomyopathy on mechanical ventricular support may resolve to the point of not requiring such support with medical treatment alone.9 This is different from the ischaemic cardiomyopathy population where previous scar due to infarction is unlikely to regain contractile function. Unfortunately, data on the incidence and predictors of such left ventricular (LV) improvement in NIDCM are limited.10–12 The incidence of improvement has important implications for ICD treatment in this population since patients who experience substantial improvements in EF may no longer be at sufficient risk of sudden cardiac death to warrant an ICD. Thus, the purpose of this study was to assess in multiple centres the incidence of LV function improvement in patients receiving primary prevention ICDs for NIDCM and to determine if there are any predictors of such improvement in this population.

PATIENTS AND METHODS

Patient population

Patient data were obtained from four different participating institutions. Consecutive patients
undergoing first-time implantation of either a single- or dual-chamber ICD at these institutions between January 2005 and January 2008 were identified and their data was studied retrospectively. Patients receiving cardiac resynchronisation therapy (CRT) ICD devices were excluded from this study.

All included patients had to have a diagnosis of NIDCM as defined by an EF ≤35%; a lack of ischaemic, hypertrophic, or other clear aetiology of cardiomyopathy and a lack of significant valvular abnormalities on pre-implantation echocardiography. Ischaemic cardiomyopathy was defined as patients with a low EF who had any one of the following: (a) >70% obstruction in one of the major epicardial coronary vessels; (b) a history of transmural myocardial infarction; (c) a history of coronary intervention, including angioplasty, stenting and/or bypass surgery or (d) exercise or pharmacological stress-induced perfusion abnormalities detected by nuclear scintigraphy typical of myocardial ischaemia. Significant valvular abnormalities included severe stenosis or regurgitation of either the mitral and/or aortic valves. All included patients also had to have NYHA functional class II or III heart failure symptoms before implantation according to established guidelines. Included patients also had to have a diagnosis of NIDCM for at least 9 months and be receiving optimal medical treatment for at least 3 months before implantation. Although current device implantation guidelines do not specify a minimum amount of time between diagnosis of NIDCM and ICD implantation, 9 months has been defined as a reasonable timeframe by the Centers for Medicare and Medicaid Services (CMS). Finally, included patients had to have a minimum follow-up time of 6 months.

Patients were excluded if they did not meet the above-mentioned criteria for diagnosis of NIDCM, if they had a CRT device implanted, if they had NYHA class I or IV functional class before implant, if they did not have a diagnosis of NIDCM for at least 9 months (with minimum of 3 months’ medical treatment) before ICD implant, or if they did not have at least 6 months of follow-up after implantation.

Baseline demographic data, clinical characteristics, data from electrocardiogram, echocardiogram and/or radionuclide studies were routinely collected within 1 month of ICD implantation. All patients gave informed consent for the procedures and all data were collected in accordance with institutional ethics guidelines for each participating centre.

Assessment of LV function
Both baseline and follow-up EF were documented either by radionuclide angiogram (RNA) scanning or quantitative echocardiography. Echocardiographic calculation of EF was performed using the modified Simpson' method, as described in detail elsewhere. Both echocardiograms and RNAs were read and reported by imaging specialists who were not directly involved in the decision-making about device implantation or in follow-up of the patients receiving a device. In other words, these specialists were blinded to patient outcome. However, random samples of echocardiographic studies were reviewed by an investigator at each site to confirm the reported EFs. If more than one EF determination was available before implantation, the measurement taken closest to the implant date was chosen. Furthermore, if more than one type of EF determination was taken within a month of implantation, RNA EF was used preferentially over echocardiography. Follow-up determinations of LV function were not performed according to a particular schedule, but were collected for all patients who had follow-up EF data available. If more than one type of EF determination was available after implant, we tried to match the same method used for EF determination before implantation. If multiple assessments of LV function were available after implantation, the latest EF was used for analysis.

Patients who experienced an improvement in EF to >35%, with a minimum increase of 5% compared with the initial pre-implantation EF, were defined to have improvement in LV function for the purposes of this study.

Follow-up
All patients were followed up routinely in the device clinic of their respective institution. Follow-up intervals at all participating institutions were according to the recommendations of the guidelines for ICD follow-up. A clinical assessment with device interrogation was performed within 1 month, at 3 months and then every 6 months thereafter. More frequent visits were scheduled if the patient experienced device problems, shocks, or other problems necessitating more follow-up. At one of the participating institutions, some of the device follow-up is done at remote locations from the hospital; however, complete records of those visits and all imaging data were available and were used.

Statistical analysis
All data are reported as a mean±SD for continuous variables and number of subjects (%) for categorical variables, unless otherwise indicated. Univariate analyses were carried out using the unpaired, independent samples t test for continuous variables, and the χ² test for categorical variables. All multivariate analyses were performed using logistic regression analysis with a determination of an OR and its 95% CI for each variable included in the model. Forward, stepwise regression was initially performed to identify those variables that most affected the odds ratio of LV function improvement, with a cut-off p value of ≤0.10 for entry into the model. These variables were then included in the multivariate analysis in a forward, stepwise fashion in order of significance on the outcome of LV functional improvement. A p value <0.05 was considered significant for all statistical determinations. All analysis was performed using SPSS software, version 11.0.

RESULTS
Patient characteristics
During the study period, 2690 ICDs were implanted at the participating institutions. Of this total number, 807 patients were identified as having NIDCM. Of these patients, 475 had a CRT device implanted and were therefore excluded. This left a total of 332 patients to be included in the study. All these patients had either NYHA functional class II or III heart failure and met the EF criteria of ≤35%. The mean NYHA class was 2.3±0.7 and the mean EF was 25±13% for the group. The LV end-diastolic diameter was 61±10 mm and the LV end-systolic diameter was 46±11 mm. All these patients also had a diagnosis of NIDCM for a minimum of 9 months before implantation with at least 3 months of optimal medical treatment. The mean time from diagnosis to ICD implant was 11±6 months and the mean duration of medical treatment before implant was 8±5 months. The mean follow-up time for patients was 19±7 months. Baseline characteristics for the group are specified in table 1.

Single-chamber ICD devices were implanted in 136/332 (41%) patients, whereas dual-chamber ICDs were implanted in the remaining 196/332 (59%) patients. Only 30 (9%) of these patients had pre-existing pacemaker devices which subsequently underwent upgrade to an ICD. Very few patients (13/332, 4%) had ventricular pacing more than 40% of the time. Only 55/332
(16%) had appropriate treatments for ventricular arrhythmia. Thirty-five of these 53 patients (66%) received a mean of 1.8±1.1 shocks (shock incidence of 35/332, 11%) while the other 18 patients received only anti-tachycardia pacing.

This was a well-treated group who had received medical treatment for heart failure before ICD implantation. A total of 282 (85%) were receiving an ACE inhibitor or an angiotensin receptor blocker, 256 (77%) were receiving a β blocker, 176 (53%) were receiving spironolactone, 209 (65%) were receiving a loop diuretic and 166 (50%) were receiving digoxin. Of those patients receiving an ACE inhibitor or angiotensin receptor blocker, 269 (95%) were taking more than half of the target dose of the drug and/or had a systolic blood pressure <100 mm Hg at the time of ICD assessment. Of those patients taking a β blocker, 257 (93%) had a heart rate <65 bpm and/or had a systolic blood pressure <100 mm Hg at the time of ICD assessment.

Incidence of LV function improvement

Of the 332 patients included in the study, 309/332 (93%) had repeat measurements of EF available after ICD implantation. Before implantation, RNA EF was available in 201/309 (65%) of patients while echo EF was available in 305/309 (98%) patients taken 1±2 months before implantation. After implantation, all 309 patients had echo EF available, while only 103/309 (33%) had RNA EF available. In order to match the method of EF assessment used after implantation with that used before implantation, 238/309 (77%) patients had pre- and post-implant EFs compared using echo EF, while RNA EF was used for comparison in 71/309 (23%).

The time from implant to the time of repeat EF assessment was 8±6 months after implantation. The EF before implantation was 25±13% and the EF after implantation was 29±11% (p=0.09) (figure 1). After implantation, the EF improved by at least 5% to >35% in 37/509 (12%) of patients. For these 37 patients, EF before implantation was 28±10% and after implantation, it was 45±14% (p=0.02) (figure 1). The absolute mean improvement in EF for these patients was 18±12%. Only 18/37 (49%) of these patients had multiple assessments of EF available after ICD implantation. In these 18 patients, the time from implant to the most recent EF was 9±45 months. However, improvement in EF was typically seen within 6 months after implantation in 14/18 (78%) of these patients with multiple post-implant EF assessments.

In the 37 patients experiencing improvement of LV function after implantation, none of them received any anti-tachycardia pacing or shocks from their device (appropriate or inappropriate) over a mean follow-up of 14±9 months.

Predictors of LV improvement

Characteristics of the patients who had no improvement in LV function versus those with improvement are detailed in table 2. There was no significant difference in age, sex, or EF of patients who did or did not have LV functional improvement. Medical treatment in both groups was also similar between the group without improvement versus the improvement group with 87% versus 86% taking ACE inhibitors or angiotensin receptor blockers (p=0.33) and 78% versus 70% taking β blockers (p=0.10), respectively. The duration of medical treatment was also similar in both groups (8±5 versus 9±6 months respectively, p=0.42). The incidence of comorbid conditions, specifically hypertension, diabetes and significant alcohol intake, was also similar between groups.

The time from initial diagnosis to implant was significantly shorter for patients who experienced improvement in LV function than for those who did not (9±5 vs 13±5 months.
respectively, p=0.05). Patients who did not experience improvement also tended to have a larger left ventricular end-diastolic diameter than those who experienced improvement (58±9 vs 63±8 mm), but this did not reach statistical significance (p=0.06).

Using logistic regression, time from initial diagnosis to implant, left ventricular end-diastolic diameter, alcohol history and β blocker use had p values ≤0.10. When these were included in a multivariable model, only time from initial diagnosis to implant was independently predictive of LV function improvement with an odds ratio of 1.21 (per month) (95% CI 1.07 to 1.50, p=0.04) (figure 2).

**DISCUSSION**

**Main findings**

This study demonstrates that in a typical, contemporary population of patients with dilated cardiomyopathy undergoing primary prevention ICD implantation, improvement in LV function can occur in up to 12% of patients over a follow-up period of 8±6 months. The improvement often occurred within 6 months of ICD implant. Furthermore, the magnitude of improvement was such that the post-implant EF no longer met the initial indication for primary prevention ICD. The improvement occurred despite patients meeting or exceeding the CMS guideline of a minimum of 9 months from diagnosis to implant (mean 11±6 months), and patients were receiving good medical treatment for at least 3 months (mean 8±5 months) before implant. By univariate analysis, there were no differences between patients whose EF improved and those who did not, except that the time from diagnosis to implant was shorter (9±5 vs 13±5 months, respectively, p=0.03), and there was a trend towards a smaller LV end-diastolic dimension (58±8 vs 63±9 mm, p=0.06). Only a shorter time from diagnosis to implant predicted EF improvement by multivariate analysis.

**Incidences of LV function improvement**

It has long been appreciated that patients with NIDCM may experience spontaneous improvement in LV function. Furthermore, as medical treatment for heart failure has improved, further increases in the rate of improvement may be possible. Even patients with very severe heart failure requiring mechanical ventricular support may experience spontaneous improvement with weaning of such support. However, many of the studies examining the rate of improvement have been limited by very small cohorts, single-centre experiences and a variety of different medical regimens. Thus, the incidence of LV improvement in this population is not well known, with studies reporting a wide range from 19% to 85%. Two of the larger cohorts reported improvement rates of 22% and 27% over follow-up periods of 9–12 months from the time of initial diagnosis. The rate of improvement seen in this study was only 12%, but this was in a preselected population of patients with NIDCM who already had a diagnosis of NIDCM for at least 9 months, and had been receiving medical treatment for a minimum of 5 months. Patients with earlier recovery of EF (before 9 months) would therefore have been excluded from our study cohort.

The timing of LV improvement in NIDCM is also not well known. From most of the studies quoted above, patients were typically followed up for 9–12 months. Recovery seems to occur as early as a few weeks with many showing substantial improvement within 6–9 months. It is probably on this basis that the CMS issued a recommendation that patients be considered for primary prevention ICD a minimum of 9 months after the initial diagnosis of NIDCM. However, some evidence suggests that further improvements may occur even after 9 months. In children with dilated cardiomyopathy, for example, substantial improvements in EF may occur even between 12 and 18 months after diagnosis in up to 50% of patients. Indeed, in our study of adult patients with multiple comorbidities, as many as 12% of patients may further improve beyond the 9-month suggestion made by CMS.

**Predictors of LV function improvement**

By univariate analysis, this study found that the duration from diagnosis to implant was the only significant predictor of LV functional improvement. There was a trend towards smaller LV end-diastolic diameter predicting improvement, but this did not
reach statistical significance. This is consistent with data from other studies looking at predictors of outcome in patients with NIDCM. In two of the larger cohort studies, a shorter duration of heart failure symptoms was identified as a significant predictor of EF improvement in patients with NIDCM. Several studies have also shown that a smaller LV end-diastolic diameter significantly predicts spontaneous LV functional improvement. Both of these would have apparent clinical correlations since patients with shorter duration of NIDCM are more likely to have acute aetiologies which may resolve, and patients with a smaller degree of dilatation may also have a milder, and potentially reversible, disease process.

However, previous studies have shown other variables to be important predictors of EF improvement, which this study did not. In particular, high systemic blood pressure has consistently been identified by numerous studies as a negative predictor of improvement, whereas the incidence of hypertension in our population was not significantly different between groups. However, many of the previous studies were done in an era when use of medical treatment, particularly β blockers, was not nearly as widespread. Our population had high usage of both ACE inhibitors and β blockers, which perhaps explains why blood pressure was not a significant predictor. EF has also been consistently reported as a predictor, which was not the case in our study, but our population was already preselected to include only patients with EF <35%. Thus, patients with lesser degrees of NIDCM were not included. Finally, the presence of diabetes and left atrial dilatation have also been previously reported by more than one study, but in both cases, we did not observe any differences in this population. Whether this has to do with the preselected nature of this population, or just a small sample size is not known.

Clinical implications
In spite of fairly rigorous criteria for the implantation of primary prevention ICDs in patients with NIDCM, there still exists a small, but substantial, percentage of patients who will have late EF improvement to the point where they no longer meet ICD implant criteria. Thus, this study emphasises the need for further investigation into identifying characteristics of those patients with NIDCM who will most benefit from ICD treatment in the long term. This will be important for providing ICD treatment to the NIDCM population in the most tailored and cost-effective manner possible. Based on this study’s findings, it might be argued that the waiting time between diagnosis to ICD implant should be lengthened beyond 9 months to filter out those few patients who will have late EF improvement. However, the longer wait time must be balanced against the incidence of sudden cardiac death earlier in the course of NIDCM, which may be significant. Furthermore, the ongoing arrhythmic risk of patients with NIDCM with EF improvement (but not necessarily normalisation) is not well known.

Study limitations
This was a retrospective study and it is therefore subject to limitations inherent in retrospective analysis. The study may also be limited by size. Our ability to detect statistically significant differences in both univariate and multivariate analysis may have been limited by the small number of patients in some of the subgroups. However, this was a multicentre study with a relatively large NIDCM cohort compared with older studies examining the prognosis of patients with NIDCM without ICDs. Furthermore, the study assessed serial EFs using echocardiographic data in a number of patients, a method which is subject to both inter- and intraobserver variability. However, the variability using the modified Simpson method is small relative to the changes in EF seen in this study and correlates well with RNA values. Finally, this study did not assess other potential predictors of LV functional improvement, such as advanced echocardiographic parameters (filling patterns), haemodynamic criteria (wedge pressures, contractility), or biochemical criteria (such as brain natriuretic peptide). There may also be other electrophysiological criteria that may identify those at highest risk of sudden cardiac death regardless of EF status.

CONCLUSIONS
In spite of following guidelines for implantation of primary prevention ICDs in patients with NIDCM, a substantial number of patients (12%) experience improvement in LV function to levels above those recommended for ICD implantation. A shorter time from diagnosis to implantation may predict post-implant improvement.

Competing interests None.

Ethics approval This study was conducted with the approval of the participating institutions.

Provenance and peer review Not commissioned; externally peer reviewed.

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Heart failure and cardiomyopathy


