Leading with Innovation
Serving with Compassion
ST. MICHAEL'S HOSPITAL
A teaching hospital affiliated with the University of Toronto

Cardiology

UNIVERSITY OF TORONTO

Special New Feature
Visit us at www.cardiologyupdate.ca for PowerPoint teaching slides on this topic

A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

Preventing Sudden Death: Have Prophylactic Implanted Defibrillators Finally Arrived?

A Report on the Preliminary Results of the SCD-HeFT Trial

Originally presented by: Dr. Gust Bardy, Principal Investigator for the SCD-HeFT Trial

A Report on a Presentation at the 53rd Annual Scientific Session of the American College of Cardiology

March 7-10, 2004 New Orleans, Louisiana

Reported and discussed by:
PAUL DORIAN, M.D.

Over 20 years ago, the first defibrillator designed by Dr. Michel Mirowski was implanted. Although it may be hard to believe today, this revolutionary idea was met with considerable skepticism. These original defibrillators were large, clumsy devices that required a thoracotomy for implantation, only delivered painful shocks for detected arrhythmias, and were frequently associated with complications related to the hardware and to inaccurate detection of tachyarrhythmias.

Since then, the technology has improved considerably. Today, implantable cardioverter defibrillators (ICDs) are the same size as pacemakers for bradycardia were 5-10 years ago, and they are implanted in conjunction with 1 or 2 transvenous leads. The morbidity of surgery is virtually identical to that of implanting a pacemaker and most patients are discharged the same day or the following day after the implant. Over 80% of detected arrhythmias can be treated with painless antitachycardia pacing and shocks are reserved for failed pacing or ventricular fibrillation. Furthermore, 98% or more of detected arrhythmias can be successfully reverted and the incidence of inappropriate shocks has declined from 30%-40% to 5%-10%.

These considerable technical improvements have been accompanied by several randomized clinical trials of defibrillator therapy allowing accurate assessments of the effectiveness of these devices in preventing sudden death, as well as comparisons to other available therapies. This issue of *Cardiology Scientific Update* discusses the results of previous trials in light of the preliminary results from the latest examination of implanted defibrillator effectiveness, the SCD-HeFT trial.

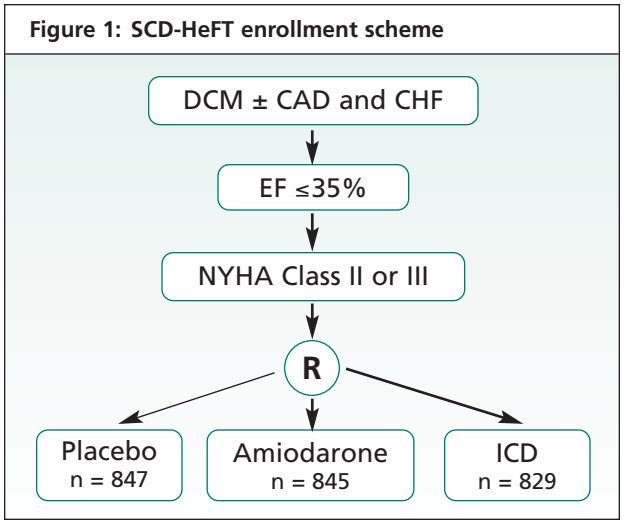
Original studies with defibrillators tested the benefit of ICDs versus antiarrhythmic drug therapy in patients with a prior history of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). In these very high-risk patients, an annual mortality of 10% to 15% was reduced by 28% with implanted defibrillator therapy as compared to amiodarone therapy.[1] As a result, there is widespread agreement that most patients with a history of sustained VT in the presence of left ventricular (LV) dysfunction, or with a history of resuscitated cardiac arrest, should be treated with an implanted defibrillator unless there is some major contraindication.

Proof that defibrillators were effective at prolonging life in these patients led to investigations testing their effectiveness in patients with no previous serious ventricular arrhythmias, but who were perceived to be at high risk ("primary prophylaxis"). These studies arose from the clinical observation that almost half of the deaths in patients with heart failure and severe LV dysfunction occurred suddenly, presumably from VT. The initial studies attempted to identify high-risk patients by selecting those with low LV ejection fraction (EF) *and* by performing tests to look for features thought to predict a high future risk of VT or VF.[2] These included inducible VT at electrophysiologic study, the presence of nonsustained VT on Holter or in-hospital monitoring, positive signal-averaged ECGs, or the failure to suppress VT inducibility by antiarrhythmic drugs.

Studies of primary prophylaxis, including the MADIT I and MADIT II studies and the MUSTT study, showed a reduction of all-cause mortality in patients receiving ICDs. On the other hand, the CABG-Patch study in which patients had their implants immediately after successful bypass surgery, was unable to show superiority of defibrillators over controls.

St. Michael's Hospital, 30 Bond St., Suite 7049, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5941

Figure 1: SCD-HeFT enrollment scheme



DCM = dilated cardiomyopathy; CAD = coronary artery disease; CHF = congestive heart failure; EF = ejection fraction; NYHA = New York Heart Association

A meta-analysis in these patients selected to be at very high risk, suggested an approximate 30% mortality reduction at about 3 years; however, these early studies had considerable limitations.[3] They studied only patients with coronary artery disease and prior myocardial infarction (MI), excluding dilated cardiomyopathy patients. In addition, they required the performance of additional tests that were sometimes expensive or not relatively accessible. As a result, there was great interest in the concept of a trial with primary prophylactic ICDs in patients selected only according to clinical characteristics, without complicated "filters" for patient selection. The question of whether amiodarone was superior to placebo in preventing all-cause mortality in these patients had not really been settled. For these reasons, the SCD-HeFT investigators planned a large, relatively simple study to answer these questions.

The SCD-HeFT study

The SCD-HeFT study[4] was designed to investigate the effectiveness of implanted defibrillators in a simpler fashion than previous studies, requiring no investigations beyond those used to objectively identify LV dysfunction. The first study patient was enrolled in September, 1997 and the last patient follow-up occurred October 31, 2003. The enrollment schemes are illustrated in Figure 1. Any patient with either dilated cardiomyopathy of any etiology or coronary artery disease with previous MI and LV dysfunction, was potentially eligible for the study. Patients had to have a history of congestive heart failure, be in NYHA functional class II or III, and have an EF ≤35%. Following informed consent, they were randomized into a 3-arm study to either treatment with an implanted defibrillator (829 patients), amiodarone (845 patients), or matching placebo (847 patients). By primary intent, there were 2 studies embedded in SCD-HeFT: a comparison of ICD versus placebo and a comparison of amiodarone versus matching placebo. All patients were intended to have optimal pharmacological therapy for their underlying cardiac disease. The primary endpoint was total mortality.

Inclusion criteria also required a more than 3-month history of symptomatic heart failure and an appropriate dose of angiotensin converting enzyme (ACE) inhibitors, if they were tolerated and beta-blocker therapy if it was tolerated. Patients had to be over 18-years-old and, if they had permanent atrial fibrillation, they were required to be on warfarin anticoagulation. Patients were excluded if they had NYHA class I or IV heart failure symptoms on the day of randomization, a history of spontaneous sustained VT or VF not associated with an acute Q-wave MI (ie, eligible for secondary prophylaxis), unexplained syncope within the previous 5 years, poor prognosis (eg, expected cardiac transplant within the year), contraindications to amiodarone, or a likely requirement for amiodarone or atrioventricular (AV) node ablation for atrial fibrillation. Rare forms of heart disease such as restrictive or hypertrophic cardiomyopathy, complex congenital heart disease, and surgically-correctible valvular disease were also criteria for exclusion. Patients could not have current pacemaker therapy, or be treated with class I or class III antiarrhythmic drugs at the time of randomization. The study was supported by the National Institutes of Health, National Heart, Lung, and Blood Institute (NHLBI), and grants from Medtronic Inc. and Wyeth-Ayerst Inc.

The defibrillators in the study were single-chamber defibrillators (Medtronic Inc. model 7223 VVI-ICD), programmed to VF therapy only, with settings to detect tachyarrhythmias at cycle lengths <320 ms (about 185 bpm), and the pacemaker was programmed to VVI back-up at 50 bpm. Amiodarone was started as out-patient therapy, with a loading dose of 800 mg/day for 1 week, 400 mg/day for the next 3 weeks, followed by long-term dosing, ranging from 200 mg to 400 mg/day depending on body weight.

There was a predicted control mortality rate of 10% per year and the study had a 90% power to detect a 25% decrease in mortality in either the ICD or the amiodarone arm, compared to placebo. All analyses were by intention-to-treat.

Baseline characteristics

The median age of the patients was 60.1 years (25th and 75th percentile 51.7, 68.5); 23% were female. The median EF was 25.0% (20.0, 30.0); 52% had ischemic and 48% nonischemic cardiomyopathy. The most recent MI occurred >1.5 years prior to enrollment in 75% of the patients. Other baseline enrollment characteristics are illustrated in Table 1.

Patients were consistently treated respecting optimal pharmacological therapy for heart failure and coronary disease. Background medications at baseline and last follow-up are illustrated in Table 2.

Results

In terms of the primary endpoints, defibrillator implantation reduced all-cause mortality by 23%, with a hazard ratio of 0.77 and a 97.5% confidence interval (CI), 0.62-0.96. Amio-

Table 1: Baseline enrollment characteristics

Age (yrs)	60.1 (51.7, 68.5)*
Female	23%
Heart rate	73 bpm (63, 84)*
CHF duration (mo)	24.5 (20, 30)*
NYHA II, III	70%, 30%
LVEF	25.0 (20.0, 30.0)*
Ischemic, non-ischemic	52%, 48%
6-minute walk (m)	342 (255, 412)*
Diabetes mellitus	30%
Prior CABG/PCI	37%
History of hypertension	56%
History of NSVT	23%
QRS duration (ms)	112 (96, 140);* 41% ≥ 120 msec

* Expressed as median (25th and 75th percentile)

darone therapy did not reduce mortality, with a hazard ratio versus placebo of 1.06 (97.5% CI, 0.86-1.30) over a median follow-up of 45.5 months (Figure 2). Control (placebo) mortality was 7.2% per year, for a 36.1% mortality over the approximate 5-year maximum follow-up. Absolute mortality reduction by the ICD was thus 7.6% over 5 years, approximately 1.5% per year. In other words, treating nearly 13 patients over 5 years resulted in 1 life saved by the defibrillator versus placebo.

Among patients assigned to ICD treatment, 2.2% were not implanted, and 4.0% had their device removed and not replaced. At implant, there were 4.6% serious complications, none fatal, and there were 9.4% serious complications during follow-up. On average, there were 7.4% high-energy shocks/patient/year, with 5.0% appropriate shocks/patient/year in the ICD group.

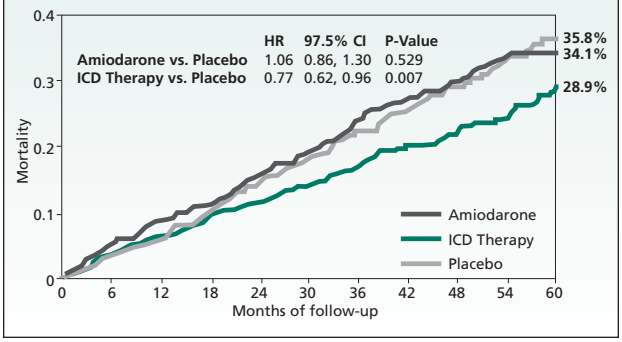
Subgroup analyses in the defibrillator patients

Defibrillator therapy was superior to placebo therapy in both the ischemic and nonischemic groups, with hazard ratios for mortality of 0.79 (97.5% CI, 0.60-1.04) and 0.73 (97.5% CI, 0.50-1.04), respectively. In NYHA class II patients, the hazard ratio for ICD versus placebo was 0.54 (97.5% CI, 0.40-0.74); in class III patients, the hazard ratio was 1.16 (97.5% CI, 0.84-1.61); however, there were only 516 patients in this latter category.

Table 2: Background medications

	Baseline	Last follow-up
ACE Inhibitor	85%	72%
ACE-I or ARB	96%	87%
Beta-blocker	69%	78%
Spironolactone	19%	31%
Loop diuretics	82%	80%
Aspirin	56%	55%
Statin	38%	47%

Figure 2: Mortality by intention to treat



Many subgroups were analyzed with respect to ICD versus placebo. In virtually all subgroups, the point estimate of the hazard ratio for mortality with respect to ICD versus placebo was <1, indicating that the defibrillators were superior to placebo, although almost all of these hazard ratios crossed the value of 1.0, given the multiple analyses and the reduced sample size in the subgroups. Interestingly, the hazard ratio for patients with EF ≤30% was 0.73 (97.5% CI, 0.57-0.92), while those with EF >30%, the hazard ratio was 1.08 (97.5% CI, 0.57-2.07). Patients with a QRS duration ≥ 120 ms had a hazard ratio of 0.67 (97.5% CI, 0.49-.93), and those <120 ms, a hazard ratio of 0.84 (97.5% CI, 0.62-1.14). Although these results have to be interpreted extremely cautiously in view of the small numbers involved, the 164 patients enrolled from Canada and New Zealand had a hazard ratio for the defibrillator versus placebo of 0.37 (97.5% CI, 0.17-0.82).

In the amiodarone versus placebo portion of the study, no subgroups benefited significantly from amiodarone. In particular, the hazard ratio for mortality was >1 for both ischemic and nonischemic etiologies of heart failure, and there was no evidence for amiodarone benefit in any subgroup (ie, those with or without beta-blocker, those with EF <30% or >30%, or those with QRS duration <120 ms or >120 ms). In the subgroup with NYHA class III, there appeared to be a trend for harm from amiodarone, with a hazard ratio of 1.44 (97.5% CI, 1.05-1.97) for mortality; however, the subgroup only contained 497 patients.

Discussion

SCD-HeFT is the largest in a series of trials examining the benefit of ICDs for primary prophylaxis of sudden death. The results were unambiguous, consistent with previous trials such as the MADIT-II trial, and indicated a substantial mortality reduction in patients with severe structural heart disease and LV dysfunction. These results need to be interpreted in light of prior studies, as well as recent studies that have been presented or very recently published.

• The DINAMIT study randomized patients with recent MI (<40 days), LVEF <35%, and low heart rate variability (a risk marker for death) to ICD versus control. There was no benefit in ICD implantation; although arrhythmic deaths were reduced in the ICD group, there was an offsetting increase in nonarrhythmic cardiac death.[5]

• The DEFINITE study randomized patients with dilated non-coronary cardiomyopathy, LVEF < 35%, and frequent ventricular premature beats (VPBs) or nonsustained VT, to ICD versus control. There was a reduction in all-cause mortality of 34%, but this did not reach statistical significance (p=0.08).[6]

• The recently published COMPANION study had 3 arms: control, resynchronization pacemaker [CRT] (biventricular pacemaker), and CRT with an ICD. In patients with severe and symptomatic LV dysfunction (LVEF < 35%, prior CHF hospitalization, class 3 congestive heart failure) and prolonged QRS duration, the CRT + ICD group had an all-cause mortality reduction of 36% (p=0.003) compared to control.[7]

There can no longer be any doubt that defibrillators are both effective at treating spontaneous potentially life-threatening ventricular arrhythmias when they occur and in prolonging life in patients with severe LV dysfunction and heart failure symptoms, regardless of etiology.

On the other hand, oral amiodarone, previously suggested to reduce mortality in a meta-analysis of mostly post-infarction trials, does not appear to be beneficial in patients with long-standing coronary disease remote from MI, or in those with non-ischemic cardiomyopathy. There is thus no indication for amiodarone in patients without symptomatic cardiac arrhythmias for the prevention of sudden death.

There are many patients potentially eligible for defibrillator implantation. The number of possible candidates for this therapy seems overwhelming considering the resources available for treatment and follow-up. How does one deal with these difficulties?

First, it needs to be emphasized that the SCD-HeFT and other primary prophylaxis trials refer only to those patients with severe LV dysfunction (LVEF < 35%) who are treated with optimal pharmacological therapy (beta-blockers, ACE inhibitors, angiotensin receptor blockers, spironolactone [as appropriate], and statins [as appropriate]). The role of nonsustained VT and electrophysiologic studies as a risk stratifier is unclear and probably limited. Importantly, the majority of patients in all of the large trials including SCD-HeFT (and the MADIT II and MUSTT trials) were enrolled at least 1 year, and usually many years, after their index MI (for the CAD patients). In view of the recently reported results of the DINAMIT study, it is required to wait for at least 40 days and it seems reasonable to wait longer after an MI before evaluating patients for prophylactic ICD implantation.

It must also be emphasized that the SCD-HeFT patients represent a relatively select segment of the heart failure population. The median age was 60 years, and three-quarters of the patients were <69-years-old. The median heart failure duration was >2 years, indicating a relatively stable population with long-standing heart failure; 70% were NYHA class II, suggesting that they did not have extremely severe heart failure, at least at the time of evaluation (although all had **some** heart failure symptoms). Median EF was 25%, and three-quarters of the patients had an EF ≤30%. In general, all of these observations suggest that the SCD-HeFT results apply to patients who are younger, have worse structural heart disease, but are clinically relatively stable. In comparison, many of the heart failure patients seen in everyday practice are usually elderly (>70-years-old), may have somewhat less severe LV dysfunction, and are generally identified at the time of severe symptoms as NYHA class III or IV.

Patient selection for ICDs is and will remain quite a considerable challenge. However, difficulties in patient selection and insufficient resources for implantation should not paralyze the practitioner or impede a careful consideration of referral for defibrillator implantation in each and every patient who might be destined to benefit from this very effective technology.

References

1. Connolly SJ, Hallstrom AP, Cappato R, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH, and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg, Canadian Implantable Defibrillator Study. *Eur Heart J* 2000;21(24):2071-8.
2. Ezekowitz JA, Armstrong PW, McAlister FA. Implantable cardioverter defibrillators in primary and secondary prevention: a systematic review of randomized, controlled trials. *Ann Intern Med* 2003;138(6):445-52.
3. Lee DS, Green LD, Liu PP, Dorian P, et al. Effectiveness of implantable defibrillators for preventing arrhythmic events and death: a meta-analysis. *J Am Coll Cardiol* 2003; 41(9):1573-82.
4. Bardy GH, et al. SCD-HeFT: The Sudden Cardiac Death in Heart Failure Trial. A Presentation at the Late-breaking Clinical Trial Session; 53rd Annual Scientific Session of the American College of Cardiology, New Orleans, March 2004.
5. Connolly SJ, Hohnloser SH, on behalf of the DINAMIT Steering Committee and Investigators. DINAMIT: Randomized trial of prophylactic implantable defibrillator therapy versus optimal medical treatment early after myocardial infarction: The Defibrillator IN Acute Myocardial Infarction Trial. Late-breaking Clinical Trial Session; 53rd Annual Scientific Session of the American College of Cardiology, New Orleans, March 2004.
6. Kadish A, Dyer A, Daubert JP, et al; Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004; 350(21):2151-8.
7. Bristow MR, Saxon LA, Boehmer J, et al; the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; 350:2140-2150.

SNELL Medical Communication acknowledges that it has received an unrestricted educational grant from Medtronic Inc. to support the distribution of this issue of *Cardiology Scientific Update*. Acceptance of this grant was conditional upon the sponsors' acceptance of the policy established by the Division of Cardiology and SNELL Medical Communication guaranteeing the educational integrity of the publication. This policy ensures that the author and editor will at all times exercise unrestricted, rigorous, scientific independence free of interference from any other party.