SCD-HeFT: Sudden Cardiac Death in Heart Failure Trial

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Sudden cardiac death (SCD) is the leading cause of death in the United States and in most developed nations. Patients with impaired left ventricular function and congestive heart failure (CHF) are most susceptible to SCD, with a risk 6-9 times that in the general population. Antiarrhythmic drug therapy dominated early attempts to prevent SCD; however, several trials with sotalol and amiodarone revealed an unacceptably high rate of recurrent arrhythmic events. Beginning over 10 years ago, several large, well-controlled, randomized trials have documented the mortality benefits of ICDs for both the primary and secondary prevention of SCD.

Ventricular fibrillation (VF) is the most common initial rhythm in survivors of cardiac arrest, and the ICD trials have shown that the most important factor in determining survival from VF is the time from collapse to administration of the first defibrillation shock, whether it is delivered using an automated external defibrillator or implantable cardioverter defibrillator (ICD). Furthermore, the primary prevention trials, including the Multicenter Unsustained Tachycardia Trial (MUSTT)[1] and the first and second Multicenter Automatic Defibrillator Implantation Trial (MADIT I and II),[2,3] suggest that the number of patients who may actually benefit from prophylactic ICD therapy is much larger than originally estimated.

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), a placebo-controlled, 3-arm study, was designed to determine, by intention-to-treat analysis, whether amiodarone or a conservatively programmed shock-only ICD reduces all-cause mortality compared with placebo (double-blind to drug therapy) in patients with:

- Ischemic or nonischemic dilated cardiomyopathy;
- New York Heart Association (NYHA) class II and III heart failure;
- Ejection fraction (EF) ≤ 35%; and
- No history of prior sustained ventricular tachycardia (VT)/VF.

Conducted in 148 centers in Canada, New Zealand, and the United States between September 1997 and July 2001, SCD-HeFT involved a total of 2521 patients with dilated cardiomyopathy, with or without coronary artery disease, who were categorized as NYHA class II or III and had an EF ≤ 35%. Study subjects underwent the 6-minute hall walk testing and Holter monitoring and were then randomized on a 1:1:1 ratio based on NYHA class and etiology to optimal medical therapy (OMT) (angiotensin converting enzyme [ACE] inhibitors, diuretics, digoxin, beta-blockers, and spironolactone) as follows:

- Placebo (n = 847)
- Amiodarone (standard oral loading and maintenance dose) (n = 845)
- ICD (VF therapy only) (n = 829)

Patients categorized as NYHA class I or class IV, as well as those with a history of sustained VT/VF and those with an indication for pacemaker implantation, were excluded from the study.

All-cause mortality was the primary endpoint, and the study was designed with a 90% power to detect a 25% reduction in mortality in either the amiodarone or ICD group compared with the placebo arm.

Aim Study Design and Methods Results Table 1. SCD-HeFT: Baseline Characteristics (mean values) Table 2. SCD-HeFT: Medications at Baseline and Follow-up Conclusions Comment References

Presenter: Gust H. Bardy, MD, Seattle Institute for Cardiac Research (Seattle, Washington) Aim Study Design and Methods Results Table 1. SCD-HeFT: Baseline Characteristics (mean values)

Baseline characteristics, reported as mean values, are listed in Table 1. The majority of patients were male (77%), mean age was 60 years (range 19-90), and mean EF was 25%. The majority of patients enrolled in the trial had NYHA class II heart failure, and, importantly, both patients with ischemic and nonischemic etiology were well represented (52% and 48%, respectively). The average QRS duration was 112 msec, but 41% of patients had a QRS duration ≥ 120 msec.

Characteristic	Mean (N = 2521)
Age (yrs)	60
Male (%)	77
Diabetes (%)	30
Ejection fraction (%)	25
Ischemic etiology (%)	52
Nonischemic etiology (%)	48
NYHA class II (%)	70
NYHA class III (%)	30
QRS duration (msec)	112
History of atrial fibrillation (%)	15
History of NSVT (%)	23
Hypertension (%)	56
Hyperlipidemia (%)	53

NSVT, nonsustained ventricular tachycardia;
NYHA, New York Heart Association

All patients were on OMT prior to randomization, and the drug regimens remained consistent throughout the study period (Table 2). Of note, beta-blocker usage actually increased from 69% at baseline to 78% at last follow-up (Table 2).

Drug	Baseline	Last follow-up
ACE inhibitor (%)	85	72
ACE inhibitor or ARB (%)	96	87
Beta-blocker (%)	69	78

Spironolactone (%)	19	31
Loop diuretics (%)	82	80
Aspirin (%)	56	55
Statin (%)	38	47

ACE, angiotensin converting enzyme;
ARB, angiotensin receptor blocker

The median follow-up period was 45.5 months. At the end of the study, a total of 666 deaths had occurred; 182 (22%) in the ICD group, 240 (28%) in the amiodarone group, and 244 (29%) in the placebo group. At 3 years, mortality rates were lower in the ICD patients when compared with amiodarone or placebo (17.1% vs 24% vs 22.3%). On the other hand, the use of amiodarone was not associated with any improvement in mortality compared with placebo by intention-to-treat analysis. At 5 years, patients treated with an ICD continued to have lower mortality rates than patients treated with amiodarone or placebo (28.9% vs 34.1% vs 35.8%) (Figure). Overall, ICD use was associated with a highly significant 23% reduction in all-cause mortality compared with placebo (P = .007). The mortality rate for placebo-controlled patients was 7.2% per year over 5 years.

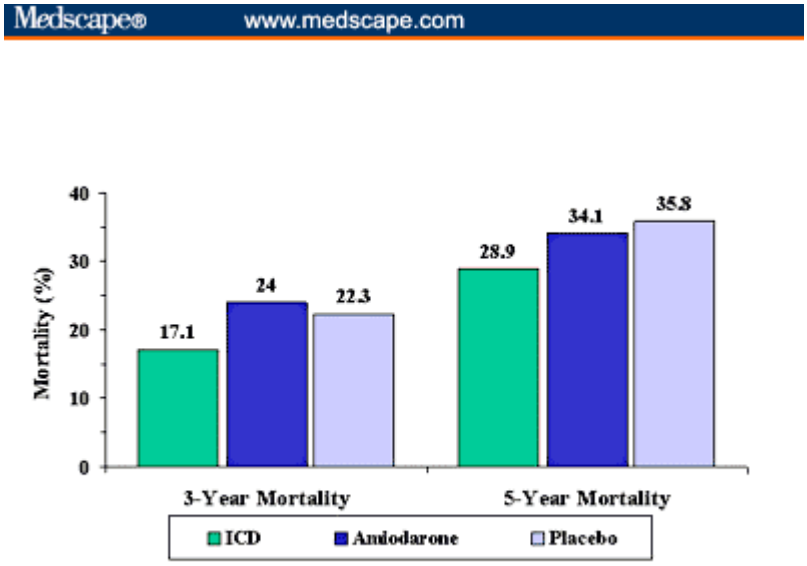

Figure. SCD-HeFT: 3- and 5-year mortality rates.

When analyzing the results based on disease etiology, both ischemic and nonischemic patients achieved similar degrees of benefit from ICD therapy. Trends in the subgroup data also suggested that patients with NYHA class II heart failure derived more benefit from ICD use than class III patients.

The investigators drew the following conclusions from the SCD-HeFT study:

1. In NYHA class II or III heart failure patients with EF ≤ 35% on OMT, the mortality rate for placebo-controlled patients was 7.2% per year over 5 years.
2. Implantation of a simple-shock only ICD decreased mortality by 23%.
3. Amiodarone, when used as a primary preventive agent, did not improve survival in these patients.

The present study shows us once again the dismal prognosis of patients with reduced left ventricular function and/or symptomatic heart failure. The failure of amiodarone to improve survival of these patients is also discouraging, whereas the use of a simple shock-only device confirmed the profound effect on survival reported in all the previous ICD trials, with the important addendum that the benefit is also conferred in patients with nonischemic cardiomyopathy. It is important to note, however, that the initial data presentation was preliminary, and it will be very interesting to follow the interpretation of these therapeutic alternatives through subsequent subgroup analysis.

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3. Moss AJ, Zareba W, Hall WJ, et al, for the Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation on a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346:877-883.

Table 2. SCD-HeFT: Medications at Baseline and Follow-up Conclusions Comment References