

Evolving Indications for Implantable Cardioverter-Defibrillators

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Implantable cardioverter-defibrillators are pacemaker-like devices that sense and treat ventricular tachycardia and ventricular fibrillation, and are generally used in an aging population. They have been proven in large randomized clinical trials to prevent death in patients who have already survived a life-threatening episode of ventricular arrhythmias. Recent studies have expanded their indications to the prevention of arrhythmic death in patients who have risk factors for this disorder. How widely they will be used, and at what cost, is unknown.

Key words: implanted defibrillator, arrhythmia, sudden death, anti-arrhythmic therapy, heart disease.

Tens of thousands of patients die of sudden cardiac death (SCD) each year in Canada. The current standard of care for patients at high risk of sudden death includes the use of amiodarone or an implantable cardioverter-defibrillator (ICD). Current ICDs can be implanted in the pectoral region using transvenous leads. They are highly programmable devices with sophisticated diagnostic algorithms and treatment capabilities. ICD use grew 20–30% annually through the 1990s, due to a combination of improved device technology, randomized clinical trials that showed a mortality benefit, and the intuitive appeal of an “electrical life insurance policy”.¹ Recently, ICDs have been tested in various clinical settings in several large randomized clinical trials. The clinical trials of ICDs for the prevention of SCD are grouped according to whether the target population is composed of survivors of sustained ventricular tachyarrhythmias (secondary prevention), or those who are at high risk of SCD without a previous sustained ventricular tachyarrhythmia (primary prevention).

Secondary Prevention of Sudden Cardiac Death

Three large randomized trials compared the efficacy of ICDs versus antiarrhythmic

mic drug therapy: the Antiarrhythmic Versus Defibrillator (AVID) trial,² the Canadian Implantable Defibrillator Study (CIDS)³ and the Cardiac Arrest Study Hamburg (CASH).⁴

AVID assessed the relative benefit of antiarrhythmic drugs versus ICDs on the survival of patients who had been resuscitated from ventricular fibrillation, had ventricular tachycardia (VT) with syncope, or who had hemodynamically significant sustained VT with a left ventricular ejection fraction (LVEF) $\leq$ 40%. The primary endpoint was total mortality using an intention to treat analysis. A total of 1,016 patients were randomized to therapy with an ICD or antiarrhythmic drugs. Of the 509 patients randomized to drug therapy, 496 received amiodarone. Over a mean follow-up of 18.2 ± 12.2 months, the crude death rates were $15.8 \pm 3.2\%$ in the ICD group and $24 \pm 3.7\%$ in the antiarrhythmic drug group. Although the ICD group had a 7–9% absolute greater survival throughout the study, use of the ICD prolonged life by only 2.7 months over the first three years.

CIDS enrolled a generally similar population of 659 patients who were eligible for randomization to either amiodarone or an ICD.³ The primary endpoint was total mortality. There was a non-significant trend toward a reduc-

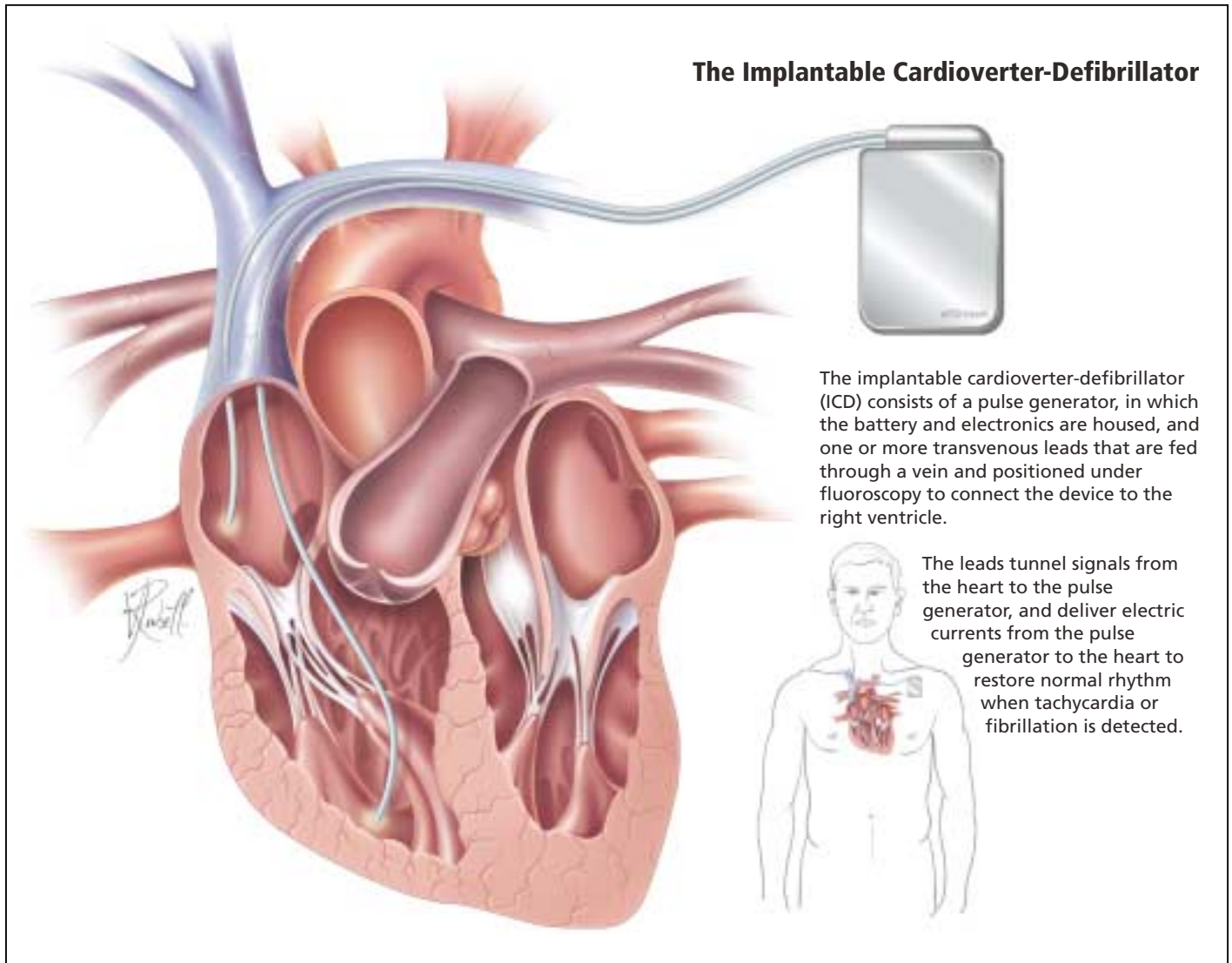
tion in total mortality in the ICD group (8.3%/year) compared with the amiodarone group (10.2%/year). This was almost entirely due to a non-significant reduction in the risk of arrhythmic death with the ICD. The ICD group had a 2–7% absolute greater survival than the antiarrhythmic drug group throughout the study.

CASH randomized survivors of cardiac arrest to antiarrhythmic drug therapy or ICD.⁴ This study used a more restrictive enrollment criterion than those used in either AVID or CIDS. A total of 288 patients were recruited to three main arms of the study: 99 to the ICD group; 92 to the amiodarone group; and 97 to the metoprolol group. For the final analysis, the amiodarone and metoprolol groups were combined into one antiarrhythmic drug group. Over a mean follow-up of 57 ± 34 months, the crude death rate in the antiarrhythmic drug group (44.4%) was non-significantly greater than in the ICD group (36.4%; $p=0.08$).

The data from AVID, CIDS and CASH were pooled and analysed in a meta-analysis.⁵ The risk reduction for total mortality with the ICD over amiodarone was 28% (95% CI, 13–40%; $p=0.0006$). For arrhythmic death, the relative risk reduction was 50% (95% CI, 33–63%; $p<0.0001$). Over a follow-up period of six years, the mean survival was extended by 4.4 months with the ICD.

Primary Prevention of Sudden Cardiac Death

Given the dismal prognosis following out-of-hospital SCD, we need to be able to identify patients at high risk of SCD in order to prevent it. The risk stratification methods that have been used for patient selection in randomized clinical trials include invasive electrophysiological testing, signal averaged electrocardiograms, heart



rate variability, non-sustained ventricular tachycardia and a low LVEF. Some of these tests were used in patient selection for trials of the primary prevention of SCD. There are five primary prevention trials of the ICD that have been completed: the Multicenter UnSustained Tachycardia Trial (MUSTT),⁶ the Multicenter Automatic Defibrillator Implantation Trial (MADIT),⁷ CABG-Patch, AMIOVIRT and MADIT II.

MUSTT and MADIT were based on studies showing that patients with poor LVEF, non-sustained VT and inducible sustained VT during electrophysiological study have a high risk of SCD. MUSTT was designed as a randomized trial of electrophysiologically guided antiarrhythmic drug therapy versus no

therapy in a high-risk population of patients with coronary artery disease, a LVEF $\leq 40\%$, asymptomatic non-sustained VT and inducible sustained VT during an electrophysiological study.⁶ Patients in the treatment arm received antiarrhythmic drug therapy, and those who did not respond acutely could receive an ICD. The likelihood of either cardiac arrest or death (not total mortality) in five years was 32% for the untreated group and 25% for the treated group (27% relative risk reduction; 95% CI 1–47%). There was a remarkable 76% relative risk reduction for death in patients who received an ICD ($p < 0.001$). The patients with ICDs accounted for the entire benefit seen in the treatment group randomized to receive antiarrhythmic drugs.

In MADIT, patients were randomized to receive an ICD at the discretion of their attending physicians in addition to a background of conventional antiarrhythmic therapy, or conventional medical therapy alone.⁷ Patients were enrolled if they had a prior myocardial infarction, a documented episode of asymptomatic, non-sustained VT, an LVEF $< 35\%$ and ventricular tachyarrhythmia induced during an electrophysiological study.

A total of 196 patients were enrolled in MADIT with a median LVEF of 26%. Over a 27-month mean follow-up, there were 15 deaths in the ICD group compared with 39 deaths in the no-ICD group, for a relative risk reduction of 54% ($p = 0.009$) with an ICD. MADIT provided the first randomized evidence

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that an ICD could reduce mortality in a high-risk population.

The results of the CABG-Patch trial conflict with those of MUSTT and MADIT. CABG-Patch enrolled 900 patients with coronary artery disease undergoing elective bypass surgery (CABG) who had a mean LVEF < 36% and an abnormal signal averaged electrocardiogram.⁸ Patients were randomized to subsequently receive either an ICD or no specific antiar-

rhythmic therapy. The mean age of patients was 63 years, almost 25% were in NYHA class III–IV heart failure and 55% had three-vessel coronary artery disease. The CABG-Patch trial was terminated prematurely when it was determined that any benefit of the prophylactic ICD would unlikely be found. Why were the results of MADIT and the CABG-Patch trial so different? At baseline, the groups appear similar, with comparable mean

age, gender, severity of heart failure and poor LVEF. It is very possible that the universal revascularization in CABG-Patch served to prevent the arrhythmia.⁹

AMIOVIRT was a randomized trial of amiodarone versus an ICD in patients who had a non-ischemic dilated cardiomyopathy with an LVEF < 35%, asymptomatic non-sustained VT and NYHA class I–III heart failure. The mean LVEF was 22–23%.¹⁰ After a mean fol-

Summary of Trials of the Implantable Cardioverter-Defibrillator (ICD)

Trial	Control Group	Inclusion Criteria	Result
Secondary Prevention			
AVID	Amiodarone or sotalolol	Cardiac arrest survivor or syncopal VT or symptomatic sustained VT with LVEF ≤ 40%	Significant reduction in total mortality with ICD
CIDS	Amiodarone	Cardiac arrest survivor or syncopal VT or symptomatic sustained VT with LVEF < 35% or syncope with inducible VT at EP study	Trend toward reduction in total mortality with ICD
CASH	Amiodarone, metoprolol, or propafenone (terminated early)	Cardiac arrest survivor	Trend toward reduction in total mortality with ICD compared with metoprolol/amiodarone
Primary Prevention			
*MUSTT	None	CAD and LVEF < 40% and NSVT and inducible VT at EP study; ICD used only if one or more AAD failed to suppress inducible VT	Significant reduction in primary endpoint (cardiac arrest or death) with EP guided therapy (benefit restricted to subgroup that received ICD)
MADIT	"Conventional" AAD therapy	Old MI and LVEF < 36% and NSVT and inducible VT at EP study (not suppressible with procainamide)	Significant reduction in total mortality with ICD
CABG-Patch	None	Coronary artery bypass surgery and LVEF < 36% and a positive signal averaged ECG	No difference in total mortality
AMIOVIRT	Amiodarone	NIDCM and LVEF < 35% and asymptomatic NSVT	No reduction in total mortality with ICD (not yet published)
MADIT II	"Conventional" therapy	CAD and LVEF < 30%	30% reduction in total mortality with ICD

AAD: antiarrhythmic drug; CAD: coronary artery disease; ECG: electrocardiogram; EP study: electrophysiological study; ICD: implantable cardioverter-defibrillator; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NIDCM: non-ischemic cardiomyopathy; NSVT: nonsustained ventricular tachycardia; VT: ventricular tachycardia.

*MUSTT was not strictly a trial of the ICD. It was actually a randomized trial of EP study guided therapy versus no antiarrhythmic drug therapy, with the ICD used as one option in the EP study guided therapy group.

low-up of 21 months, there was no statistically significant mortality difference between the two groups.

MADIT II posed a simple question: should patients with a depressed ejection fraction (< 30%) at least one month after a myocardial infarction and at least three months after coronary artery revascularization receive an ICD?¹¹ The study showed a 30% relative reduction in overall mortality with the use of an ICD. The latest post hoc analyses presented at the North American Society for Pacing and Electrophysiology meeting in May 2003 could not identify any subgroups that did not benefit. This finding may lead to a great expansion of the population that might benefit from ICD therapy, and the potential medical and financial implications of this study continue to reverberate in the arrhythmia community. ♦

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