Review

Implantable Cardioverter-Defibrillators

Indications and Unresolved Issues

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Since the implantable cardioverter-defibrillator was first used clinically in 1980, several large randomized controlled trials have shown that therapy with this device can be beneficial in various patient populations. Evidence suggests that this therapy is useful in the secondary prevention of sudden cardiac death among patients who have survived arrhythmic events. Several trials have also shown the usefulness of implantable cardioverter-defibrillator therapy in the primary prevention of sudden cardiac death in patients with coronary artery disease and nonischemic cardiomyopathy. Other data support the use of this device for various infiltrative and inherited conditions. When used with cardiac resynchronization therapy, implantable cardioverter-defibrillators have improved survival rates and quality of life in patients with severe heart failure. Further research is needed to examine the potential benefits of implantable cardioverter-defibrillators in elderly, female, and hemodialysis-dependent patients, and to determine the optimal waiting period for implantation after myocardial infarction, coronary revascularization, and initial heart-failure diagnosis. ***(Tex Heart Inst J 2012;39(3):335-41)***

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The concept of the implantable cardioverter-defibrillator (ICD) was introduced in the late 1960s, and the first clinical ICD placement was performed in 1980.[1] However, it was not until the late 1980s and early 1990s that the first randomized controlled trials (RCTs) were designed. The results of several large RCTs, published from the late 1990s to the mid-2000s, showed that ICD therapy is useful in both primary and secondary prevention of sudden cardiac death (SCD). Thus, ICD placement was established as an integral therapy in the treatment of patients at risk of SCD.[2-11] Despite rapid advances in the understanding of indications for ICD placement, additional research is needed to resolve several unanswered questions.

Trials for Secondary Prevention of Sudden Cardiac Death

The early trials of ICDs were conducted in the patient populations at highest risk for SCD. These secondary-prevention trials[4,6,7] enrolled patients who had survived an arrhythmic event, such as hemodynamically significant ventricular tachycardia (VT) or ventricular fibrillation (VF). These patients were at high risk for recurrent events and death. Patients with reversible risk factors, such as electrolyte abnormalities or acute myocardial infarction, were excluded.

The AVID (Antiarrhythmic Versus Implantable Defibrillator) trial[4] was conducted in the United States and, in 1997, became the first published study of the use of ICDs for secondary prevention (Table I). The 1,016 enrolled patients were survivors of VF or had experienced VT accompanied by either syncope or a left ventricular ejection fraction (LVEF) of 0.40 or less. The trial compared ICD therapy (n=507) with antiarrhythmic therapy, primarily amiodarone (n=509), over a 2-year period. The results showed a significant survival benefit of ICD use in comparison with antiarrhythmic therapy: the absolute reduction in death was 7%, and the relative risk reduction was 27%. Of note, the AVID registry included follow-up of 4,219 patients in parallel with the RCT.[12] The registry study included all patients who were screened for the AVID trial (whether or not they were actually included in the trial) and who had any ventricular arrhythmias or unexplained syncope that might indicate ICD placement or antiarrhythmic therapy. The AVID registry study showed that the risk of death from arrhythmia was high, even in those patients with asymptomatic VT or with VT or VF due to correctable transient causes who were previously thought to be at low risk for SCD. Accordingly, the registry study provided a firm basis for generalizing the

AVID trial's results to the larger population of patients who had ventricular arrhythmias like those of the patients in the trial.

The 2nd trial of ICD use for secondary prevention was CIDS (Canadian Implantable Defibrillator Study),[6] the results of which were published in 2000. The 659 patients included those with VF, out-of-hospital cardiac arrest due to VF or VT, VT with syncope, VT with symptoms and LVEFs of 0.35 or less, or unmonitored syncope with subsequent spontaneous or induced VT. This study was terminated early after the outcomes from AVID were published, and the results of CIDS did not reach statistical significance. However, there was a trend toward a survival benefit with ICD implantation in comparison with standard medical therapy: the absolute risk reduction was 2%, and the relative risk reduction was approximately 20%.

Another trial, CASH (Cardiac Arrest Study of Hamburg),[7] was conducted in Germany over a 9-year period, and the results were published in 2000. The patients were survivors of VF and VT. This relatively small study (288 patients) did not show a statistically significant benefit of ICD placement in comparison with standard medical therapy (P=0.08). However, the benefits were similar to those found in the other 2 trials: the absolute risk reduction was approximately 8%, and the relative risk reduction was approximately 23%.

All 3 of these secondary-prevention trials were conducted in very similar patient populations and produced similar results, confirming the superiority of ICD therapy over current medical therapy. Even though the results of the 2 smaller trials (CIDS and CASH) did not reach statistical significance, a meta-analysis of the 3 trials yielded a significant result.[13] By clearly showing that ICD use reduces mortality rates, these findings have established the secondary prevention of SCD as a Class I indication for ICD placement.

Trials for Primary Prevention of Sudden Cardiac Death

Once ICD therapy was confirmed to be safe and effective in the highest-risk members of the secondary-prevention patient population, attention shifted toward expanding the use of this therapy to other categories of patients. Patients with substantial structural heart disease but no arrhythmic events were the next logical group for study.

Intensive research conducted during the past 20 years[2,3,5,8-11,14,15] has clarified the usefulness of ICD therapy in appropriate candidates for primary prevention of SCD (Table II). Studies were initially performed in groups of patients with coronary artery disease (CAD), but investigation eventually expanded to include other patient populations.

Coronary Artery Disease. One of the first RCTs of ICDs for the primary prevention of SCD was MADIT (Multicenter Automatic Defibrillator Implantation Trial), which was reported in 1996.[2] This trial compared ICDs (n=95) with antiarrhythmic drugs, primarily amiodarone (n=101). The patients were those with CAD, prior myocardial infarction, LVEF no greater than 0.35, nonsustained VT on ambulatory monitoring, VT inducible by programmed stimulation, and failure of intravenous procainamide to prevent inducibility. At 2 years of follow-up, these high-risk patients appeared to benefit significantly from ICD therapy, with an absolute risk reduction of 19% and a relative risk reduction of 59% (P=0.009). There was no evidence that amiodarone, β-blockers, or any other antiarrhythmic therapy had a significant influence on the observed hazard ratio. Another study, MUSTT (Multicenter Unsustained Tachycardia Trial),[5] examined whether the inducibility of VT in patients with a history of CAD also indicated SCD risk. Patients with a history of myocardial infarction, LVEFs of 0.40 or less,

TABLE I. Secondary-Prevention ICD Clinical Trials

Trial	No. Pts.	Treatments	Enrollment Criteria	Follow-Up (yr)	ARR (%)	RRR (%)
AVID[4] (1997)	1,016	ICD vs medical therapy (primarily amiodarone)	VF, VT with LVEF ≤0.40, or VT with syncope	2	7	27
CIDS[6] (2000)	659	ICD vs amiodarone	VF, out-of-hospital cardiac arrest due to VF or VT, VT with syncope, VT with symptoms and LVEF ≤0.35, or unmonitored syncope with subsequent spontaneous or induced VT	2	2	20
CASH[7] (2000)	288	ICD vs medical therapy with amiodarone, propafenone, or metoprolol	VT or VF	9	8	23

ARR = absolute risk reduction; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; Pts = patients; RRR = relative risk reduction; VF = ventricular fibrillation; VT = ventricular tachycardia

TABLE II. Primary-Prevention ICD Clinical Trials

Trial	No. Pts.	Treatments	Enrollment Criteria	Follow-Up (yr)	ARR (%)	RRR (%)
MADIT[2] (1996)	196	ICD vs AAD (amiodarone)	Prior MI, LVEF ≤0.35, NSVT on ambulatory monitoring, inducible VT, and failure of VT suppression from intravenous procainamide	2	19	59
MUSTT[5] (1999)	704	EP-guided arm: ICD vs AAD	Prior MI, LVEF ≤0.40, NSVT, and failure to suppress VT inducibility	5	31	58
CABG-Patch[3] (1997)	900	ICD vs conventional therapy	CAD, undergoing nonemergent CABG, LVEF <0.36, and abnormal signal-averaged ECG	2	N/A	N/A
MADIT II[8] (2002)	1,232	ICD vs conventional therapy	Prior MI and LVEF ≤0.30	2	6	31
DINAMIT[9] (2004)	674	ICD vs conventional therapy	MI within past 40 d, CAD, LVEF ≤0.35, depressed HRV, and average 24-hr heart rate ≥80 beats/min	2.5	N/A	N/A
DEFINITE[10] (2004)	458	ICD vs conventional therapy	Nonischemic cardiomyopathy, CHF, LVEF <0.36, and >10 PVC/hr or NSVT	2.5	6	44
SCD-HeFT[11] (2005)	2,521	ICD vs amiodarone vs conventional therapy	Ischemic and nonischemic cardiomyopathy, LVEF ≤0.35, and NYHA class II or III symptoms	5	7	23
COMPANION[14] (2004)	1,520	Optimal medical therapy vs CRT alone vs CRT-D	Ischemic and nonischemic cardiomyopathy, LVEF ≤0.35, QRS duration ≥120 ms, and NYHA class III or IV symptoms	1	12	40
MADIT-CRT[15] (2009)	1,820	CRT-D vs ICD	LVEF ≤0.30, QRS duration ≥130 ms, and NYHA class I or II symptoms	2.4	8	34

AAD = antiarrhythmic drugs; ARR = absolute risk reduction; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHF = congestive heart failure; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy with defibrillation; ECG = electrocardiogram; EP = electrophysiologic; HRV = heart-rate variability; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; N/A = not applicable; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; Pts = patients; PVC = premature ventricular complexes; RRR = relative risk reduction; VT = ventricular tachycardia

nonsustained VT, and inducible VT despite antiarrhythmic drug use were randomly assigned to receive an ICD, electrophysiologically guided antiarrhythmic therapy, or no antiarrhythmic therapy. After 5 years of treatment, the ICD recipients had a 31% absolute risk reduction and a 58% relative risk reduction. Electrophysiologically guided antiarrhythmic therapy did not reduce the rate of cardiac arrest, death from arrhythmia, or the overall mortality rate in comparison with no antiarrhythmic therapy.

Another trial, CABG-Patch (Coronary Artery Bypass Graft Patch),[3] evaluated the benefit of ICDs in CAD patients who underwent nonemergent coronary artery bypass surgery and who had LVEFs less than 0.36 and abnormal signal-averaged electrocardiograms. At 2-year follow-up, there was no evidence that prophylactic ICD implantation in patients undergoing elective surgical revascularization conferred a survival benefit in comparison with standard medical therapy.

A subsequent trial, MADIT II,[8] evaluated ICDs in a lower-risk patient population than those studied in MADIT I and MUSTT. The MADIT II study consisted of CAD patients with prior myocardial infarction and LVEFs no greater than 0.30. Unlike the patients in MADIT I and MUSTT, these patients underwent no electrophysiologic testing. The study examined mortality rates in 742 patients with ICDs and 490 patients on conventional medical therapy. The results (published in 2002 after a 2-year follow-up) showed that ICD use yielded a 6% absolute risk reduction and a 31% relative risk reduction in comparison with conventional therapy.

In contrast with the above-mentioned trials, DINAMIT (Defibrillator in Acute Myocardial Infarction Trial)[9] examined the potential benefit of ICDs early after myocardial infarction in CAD patients with LVEFs of 0.35 or less. In this randomized, open-label comparison, 332 patients were given ICD therapy 6 to 40 days after a myocardial infarction, and 342 patients did not receive ICD therapy during that period. In addition to reduced LVEFs (≤0.35), the patients had impaired cardiac autonomic function that manifested itself as depressed heart-rate variability or an elevated average 24-hour heart rate on Holter monitoring. At 2.5-

year follow-up, there was no survival benefit from early ICD implantation, which was associated with lower arrhythmic mortality rates but with an unexplained increase in nonarrhythmic death, in comparison with the outcomes after conventional therapy. As a result of this trial, it is now recommended that ICD placement be delayed for at least 40 days in patients with acute myocardial infarction.

Nonischemic Cardiomyopathy. The DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) trial,[10] published in 2004, was one of the first major RCTs to investigate ICD therapy in patients with nonischemic cardiomyopathy. These patients had a history of heart failure, LVEFs less than 0.36, and evidence of arrhythmia with more than 10 premature ventricular complexes per hour or nonsustained VT. The trial compared ICD therapy with conventional therapy: 229 patients were randomly assigned to receive standard medical therapy, and another 229 were given standard medical therapy plus a single-chamber ICD. The trial's results, although not statistically significant, showed a strong trend toward ICD benefit: the overall mortality rate was 7.9% in the ICD group and 14.1% in the standard-therapy group (P=0.08).

The SCD-HeFT (Sudden Cardiac Death-Heart Failure Trial)[11] was the largest primary-prevention clinical trial of ICDs. The investigators enrolled 2,521 patients with nonischemic or ischemic cardiomyopathy, LVEFs of 0.35 or less, and New York Heart Association (NYHA) functional class II or III congestive heart failure. The study had an ICD arm, a drug arm with amiodarone therapy, and a control arm with standard medical therapy for heart failure. All patients were monitored for about 5 years. This trial's results (published in 2005) showed no difference between the control and amiodarone groups, whereas the survival benefit of ICD therapy became apparent after the first 2 years and was even greater at 5 years. Overall, the absolute risk reduction was 7% and the relative risk reduction was 23% from ICD therapy when compared with the control group. The SCD-HeFT was a significant trial, because it expanded ICD indications to a broad range of heart-failure patients. In addition, it simplified patient selection for ICD therapy to patients with LVEFs of 0.35 or less and symptoms of mild-to-moderate heart failure.

A meta-analysis of all primary-prevention ICD trials associated ICD placement with an overall 29% relative reduction in all-cause death. This association was driven by a 65% relative reduction in arrhythmic deaths in patients who received an ICD.[16]

ICD Use for Primary Prevention of SCD in Less Common Cardiac Diseases

The substantial benefit of ICD use in both secondary and primary prevention of SCD led to intense interest in extending that benefit to patients with uncommon conditions, such as infiltrative and inherited diseases, that are associated with high risks of ventricular arrhythmia and SCD. However, the rarity of these diseases precludes large-scale RCTs. Support for the use of ICDs for at-risk patients has been derived from retrospective analyses of observational data from registries, small case series, and expert recommendations. Most of these conditions are Class IIa indications for ICD placement.

Infiltrative Conditions. Among infiltrative diseases, cardiac sarcoidosis is generally accepted as an indication for ICD placement when the condition is accompanied by sustained or even nonsustained VT, regardless of the patient's LVEF. Sarcoidosis is considered to be a Class IIa indication for ICD placement. For other infiltrative conditions, such as amyloidosis, the indications are less well defined.[17]

Inherited Conditions. Inherited cardiac diseases comprise a heterogeneous group of conditions whose primary expression can be either structural or arrhythmic. Structural disorders include hypertrophic cardiomyopathy and arrhythmogenic right ventricular dysplasia. Genetically based primary arrhythmia disorders include Brugada syndrome, long QT syndrome, and catecholaminergic polymorphic VT.

In patients with hypertrophic cardiomyopathy, the major risk factors for SCD include LV wall thickness of 30 mm or more, unexplained syncope, a family history of SCD, nonsustained VT, a high LV outflow gradient, and a blunted blood-pressure response to exercise.[18-20] Patients with at least one of these major risk factors have a Class IIa indication for ICD placement. Among patients with arrhythmogenic right ventricular dysplasia, ICD therapy is recommended for those with symptomatic ventricular arrhythmias.

Patients with congenital long QT syndrome usually benefit from an ICD if they experience syncope, VT, or both while on β-blocker therapy. Similarly, ICDs are recommended for patients with catecholaminergic polymorphic VT who have had syncope or documented sustained VT while taking β-blockers.

Brugada syndrome was initially described in the 1990s and is categorized into types I, II, and III according to the electrocardiographic patterns associated with them. Therapy with an ICD is usually recommended for primary prevention in patients with type I Brugada syndrome and suspected VT or syncope.[21]

Use of ICDs with Cardiac Resynchronization Therapy

The COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial is the only one thus far in which ICD therapy has been evaluated in patients with NYHA class IV heart failure.[14] Prior primary- and secondary-prevention trials excluded these patients because their chief mechanism of death was thought to be pump failure rather than an ar-

rhythmia. Unlike other cardiac resynchronization therapy (CRT) trials, COMPANION evaluated not only functional endpoints such as 6-minute walk distance and quality of life, but also survival benefit. In COMPANION, patients with low LVEFs, QRS duration of at least 120 ms, and NYHA class III or IV heart failure were randomly assigned to CRT alone, CRT with defibrillation (CRT-D), or no device therapy, so that the efficacy of CRT and CRT-D could be evaluated in the treatment of heart-failure symptoms and in preventing death. During an average follow-up period of 2.4 years, heart-failure hospitalization and all-cause mortality rates were lower in both the CRT (24%, $P=0.059$) and CRT-D (36%, $P=0.003$) groups than in the group that received no device therapy. In addition, CRT was associated with a significant reduction in LV volumes and improvement in LVEF. The benefit did not differ significantly between patients with ischemic or nonischemic cardiomyopathy. The difference between the CRT and CRT-D groups was not statistically significant. The COMPANION trial results suggest that CRT-D is indicated in patients with NYHA class III–IV heart failure and wide QRS interval, because the therapy improved heart-failure symptoms and reduced the mortality rate.

Most recently, the MADIT-CRT trial—the results of which were published in 2009—evaluated the use of CRT-D in patients with mild heart-failure symptoms.[15] The investigators enrolled 1,820 patients with ischemic or nonischemic cardiomyopathy, LVEFs of 0.30 or less, QRS duration of at least 130 ms, and NYHA class I or II ischemic or class II nonischemic heart failure. Patients were randomly assigned in a 3:2 ratio to CRT-D or ICD placement. Death or nonfatal heart-failure–related events occurred in 17.2% of CRT-D patients versus 25.3% of ICD patients, for a relative risk reduction of 34%. However, there was no difference in survival rate, indicating that the difference in the frequency of the primary endpoint was driven by a decrease in nonfatal heart-failure events in the CRT-D patients. Nonetheless, because CRT-D significantly reduced the incidence of the primary endpoint in this trial, CRT-D is now recommended for patients in NYHA functional classes I and II. A further subgroup analysis of the MADIT-CRT trial data suggested that patients with a QRS duration of 150 ms or longer were more likely to benefit from CRT-D than from an ICD alone.

Limitations of Clinical Trials of ICDs

Although the aforementioned clinical trials have increased our understanding of various indications for ICD placement, several questions remain to be answered. For example, patients older than 80 years of age were excluded from these trials. Retrospective studies, such as that conducted by Groeneveld and colleagues,[22] have associated ICD therapy (as compared with standard medical therapy) with a significant decrease in mortality rates in elderly, primary-prevention patients hospitalized for congestive heart failure (hazard ratio=0.62; 95% confidence interval, 0.58–0.67). In contrast, in a recent meta-analysis of major clinical trials of ICDs versus standard medical therapy for the primary prevention of SCD in patients with severe LV dysfunction, the survival benefit after ICD placement was not statistically significant in elderly patients.[23] However, no prospective study has examined the effects of ICD therapy or CRT-D in such patients. Given the increasing age of the overall patient population, it is important to understand the effectiveness and limitations of ICD therapy and CRT-D in the elderly.

Similarly, patients with renal disease that required hemodialysis were mostly excluded from these trials. These patients have a high prevalence of CAD and other forms of cardiac disease that increase their risk of ventricular arrhythmias. However, data suggest that these patients are more likely to die from noncardiac causes than from cardiac causes, so the benefits of ICD therapy for such patients might be limited.[24,25] Including hemodialysis-dependent patients in future ICD trials might better delineate any expected benefits from device-based therapy.

Likewise, ICD placement in patients with less severe chronic kidney disease warrants further critical evaluation. In an interesting study, Amin and colleagues[26] used a complex prediction model to determine that the benefit of ICDs in patients with renal insufficiency is limited to patients younger than 80 years for stage 3 renal insufficiency, younger than 75 years for stage 4, and younger than 65 years for stage 5. In view of the controversy about the potential overestimation of ICD benefits and concern about cost-effectiveness, it is worth evaluating the benefits of ICDs in the chronic kidney disease population in well-designed, large-scale, prospective RCTs.[25]

Another group in which ICD therapy and CRT-D have not been adequately evaluated is female patients. This is mainly because low numbers of women were enrolled in prior clinical trials. Although the same guidelines are used for both sexes, the effectiveness of ICD and CRT-D may not be the same; in fact, a meta-analysis of major clinical trials showed that ICD therapy for the primary prevention of SCD does not reduce all-cause death in women.[27] A similar observation resulted from the COMPANION trial: the female patients did not receive a statistically significant benefit from CRT-D in comparison with optimal medical therapy. In contrast, CRT-D therapy was associated with greater benefit in women than in men in the MADIT-CRT study.

Finally, concerns have recently been raised in regard to the inappropriate use of ICD therapy.[28] In most such cases, ICD placement was deemed "non-evidence-based" because of its timing. The American College of

Cardiology/American Heart Association and the Heart Rhythm Society guidelines[29] recommend against placing an ICD within 3 months of the initial diagnosis of heart failure, within 40 days of myocardial infarction, or within 3 months of coronary revascularization. However, most of the support for these recommendations is derived from the enrollment criteria of major ICD trials: the existing scientific data do not make clear what the optimal waiting period is after such events. Further studies are needed to risk-stratify patients and identify the highest-risk population that could benefit from earlier ICD placement or use of an external wearable defibrillator before the end of the mandatory waiting period specified in the current guidelines. It is hoped that ways will be found to identify those patients who will gain the most from ICD therapy and to avoid exposing other patients to unnecessary procedural risks. In the DINAMIT trial, in-hospital device-related complications occurred in 7.5% of patients who received an ICD, including lead dislodgment, pneumothorax, and inappropriate shocks. No deaths during device implantation were reported.[9] Given that this group of patients derived no survival benefit from the ICD, the rate of complications is unacceptably high. On the other hand, results did show a statistically significant decrease in the rate of arrhythmic death: in the ICD group, 12 patients died of arrhythmia, compared with 29 in the control group (annual rates, 1.5% and 3.5%, respectively).

Further studies are needed to identify patients at the highest risk of SCD after acute myocardial infarction so that they can be considered for an external wearable defibrillator.

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