The Role of Implantable Cardiac Devices in the Prevention of Sudden Cardiac Death

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The implantable cardioverter defibrillator (ICD) plays an important role in primary and secondary preventions of sudden cardiac death. Several trials conducted in the past few years have shown the superiority of ICDs over drug therapy. Cardiac resynchronization therapy (CRT) is also emerging as an adjunctive treatment for heart failure, with some survival benefits as well. This article reviews the major recent clinical trials of ICD and CRT devices and summarizes their importance in contemporary cardiology.

Key words: *cardioverter defibrillator, cardiac resynchronization, older adults, sudden cardiac death, cardiology*

Introduction

Sudden cardiac death (SCD) causes up to 450,000 deaths per year in the U.S., of which most are due to coronary artery disease and up to two-thirds may be due to malignant ventricular tachyarrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF).[1,2] For persons who are resuscitated from cardiac arrest and receive no antiarrhythmic therapy, the mortality rate at 2 years is approximately 45%.[3]

Sudden cardiac death is defined as death due to a cardiovascular cause in a person with or without known pre-existing heart disease, in whom the mode and time of death are unexpected,[4] usually within an hour time frame from change in clinical status to loss of consciousness. The term *sudden cardiac death* should be used for individuals who are not resuscitated, and the term *sudden cardiac arrest* should be used for those who are resuscitated and/or have a restoration of circulation.[1]

Implantable cardioverter defibrillators (ICDs) are pacemakers that can sense and treat malignant arrhythmias such as VT and VF. They consist of a generator and leads that are implanted in the heart. The generators are usually implanted in the pectoral region, and the leads are transvenously placed into the cardiac chambers—typically the right ventricle (and right atrium for other pacing or sensing reasons). The devices use various identifiers such as heart rate to differentiate between ventricular and supraventricular arrhythmias. Implantable cardioverter defibrillators deliver electrical therapy—either rapid antitachycardia pacing or shocks—and do not carry the long-term side effects or most proarrhythmic concerns of antiarrhythmic drug therapy. The clinical trials of ICDs include primary prevention trials (for individuals who are at high risk of SCD and may benefit from a prophylactic implantation) and secondary prevention trials (for individuals who have been resuscitated from cardiac arrest).

Recent studies have also examined the benefit of cardiac resynchronization therapy (CRT) or biventricular pacing in the treatment of heart failure, as well as for sudden death. This particular mode of pacing is often used for individuals with heart failure who receive ICDs. Cardiac resynchronization therapy devices have a generator as well as leads that go into the right heart, but they also have a lead in the coronary sinus to pace the left ventricle. With this, synchronous systolic function between the right and left ventricles can be achieved. Cardiac resynchronization therapy devices can function as biventricular pacing devices or with defibrillator capabilities.

Secondary Prevention Trials of ICDs

The first ICD randomized trials were for the secondary prevention of ventricular tachyarrhythmias. These consisted of a study by Wever *et al.* in 1995,[5] by Antiarrhythmic Versus Implantable Defibrillators Investigators in 1997,[6] the Cardiac Arrest Study Hamburg (CASH) in 2000,[7] and the Canadian Implantable Defibrillator Study (CIDS), also in 2000.[8] These studies all looked at individuals who had survived a cardiac arrest due to VT or VF and were then treated with antiarrhythmics (mostly amiodarone) or an ICD. All four showed a reduction in all-cause mortality among those treated with an ICD (although the mortality reductions seen in CIDS and CASH were not statistically significant). A substudy of CIDS revealed that age >70 years, left ventricular ejection fraction (LVEF) ≤35%, and New York Heart Association (NYHA) functional class III or IV were the main risk factors for death and that individuals who had at least two of the three had a 50% relative risk reduction when treated with an ICD.[9] Hence, individuals who have survived a cardiac arrest or symp-

Table 1: Major ICD Trials of Sudden Cardiac Death

Secondary Prevention Trials	Year	Benefit with ICD?
Wever *et al.*[5]	1995	Yes
AVID[6]	1997	Yes
CASH[7]	2000	Yes
CIDS[8]	2000	Yes
Primary Prevention Trials	**Year**	**Benefit with ICD?**
MADIT[10]	1996	Yes
CABG-Patch[13]	1997	No
MUSTT[11]	1999	Yes
MADIT II[12]	2002	Yes
CAT[15]	2002	No
AMIOVIRT[16]	2003	No
DEFINITE[17]	2004	Yes
DINAMIT[14]	2004	No
COMPANION[20]	2004	Yes
SCD-HeFT[18]	2005	Yes

AMIOVIRT = Amiodarone versus ICD Trial; AVID = Anti-arrhythmic Versus Implantable Defibrillators; CABG-Patch = Coronary Artery Bypass Graft Patch; CASH = Cardiac Arrest Study Hamburg; CAT = Cardiomyopathy Trial; CIDS = Canadian Implantable Defibrillator Study; COMPANION = Comparisons of Medical Therapy, Pacing, and Defibrillation in Heart Failure Trial; DEFINITE = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT = Defibrillator in Acute Myocardial Infarction Trial; ICD = implantable cardioverter defibrillator; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MUSTT = Multicenter Unsustained Tachycardia Trial; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial.

tomatic sustained VT and have no clearly reversible cause should receive strong consideration for ICD implantation.

Primary Prevention Trials of ICDs

The ICD may also have a prophylactic role among high-risk individuals with a low LVEF, nonsustained ventricular tachycardia (NSVT), and/or inducible VT at electrophysiologic study (EPS).[3] The first primary prevention study, the Multicenter Automatic Defibrillator Implantation Trial (MADIT) in 1996, examined persons with an LVEF ≤35%, NYHA classes I–III, NSVT, and inducible/nonsuppressible VT/VF at EPS who were treated with conventional treatment or ICDs. The ICD treatment group had only a 17% cardiac death rate at 3 years compared with 46% for the conventional treatment group.[10] The Multicenter Unsustained Tachycardia Trial (MUSTT) in 1999 also found that ICD benefited individuals with coronary artery disease, LVEF <40%, and NSVT or sustained VT at EPS. The relative risk reduction was of 76%.[11]

In 2002, the landmark MADIT II trial was published. It had a simple design and impressive results and has been very influential in shaping the current indication for primary prevention ICDs. In this trial, 1,232 individuals with a prior myocardial infarction (MI) and an LVEF <30% were enrolled and randomized to standard treatment or ICD. Over the 20-month follow-up, the mortality rate in the ICD group was 14.2% compared with 19.8% in the standard treatment group.[12]

There have also been two major primary prevention trials that have indicated a neutral effect for ICDs: the Coronary Artery Bypass Graft Patch study (CABG-Patch) in 1997[13] and the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) in 2004.[14] The CABG-Patch trial randomized 900 individuals with an LVEF <36% and an abnormal signal averaged electrocardiogram to standard treatment versus ICD. No significant difference in overall mortality was found. This may be explained by the improvement with revascularization, the fact that 88 persons were not randomized due to their unstable nature during the CABG, and also concerns that signal averaged electrocardiography may not be a good predictor of SCD. The DINAMIT trial enrolled 674 persons within 6–40 days after an MI with an LVEF <35% and evidence of impaired cardiac autonomic function (using heart rate variability or increased heart rates on Holter monitoring). Over a 30-month follow-up there was no difference in overall mortality between the ICD group and the medical treatment group. This may be explained by deaths from recurrent infarctions and heart failure in the early time period after an MI. Hence, these two trials have played a role in the rationale to wait for a few weeks after an MI or revascularization while taking optimal medications prior to deciding on device implantation.[3]

The trials reviewed above mainly studied individuals with coronary artery disease; however, primary prevention studies have also included high-risk individuals with nonischemic cardiomyopathy. These include the Cardiomyopathy Trial (CAT) in 2002,[15] the Amiodarone versus ICD Trial (AMIOVIRT) in 2003,[16] the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) in 2004,[17] and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) in 2005.[18] Neither CAT nor AMIOVIRT showed a reduction in mortality with ICD treatment, which may be explained by the small number of participants (~100 enrolled in each study) in both studies and the very low mortality in the control group. The DEFINITE trial, which included 458 participants, did show a 34% relative risk reduction over 29-month follow-up, but results were not

Table 2: Characteristics of Candidates for Primary Prevention ICD

Coronary artery disease on optimal medications with an LVEF ≤35% at least 1 month post-MI or 3 months postrevascularization
Nonischemic cardiomyopathy with an LVEF ≤35% on optimal medications for at least 9 months
Channelopathies or cardiomyopathies at high risk for life-threatening ventricular arrhythmias

ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

statistically significant. The SCD-HeFT trial randomized 2,521 persons (1,210 of which were nonischemic) with LVEF ≤35% and NYHA II or III to ICD, amiodarone, or placebo. The ICD group had a 23% decrease in mortality and, interestingly, there was no survival advantage with amiodarone when compared with placebo. Hence, the use of ICDs for primary prevention in high-risk patients with nonischemic cardiomyopathy is not as robust as in patients with coronary artery disease. Table 1 lists the trials discussed above, and Table 2 provides a summary of persons eligible for a primary prevention ICD.

Cardiac Resynchronization Therapy

Among persons with NYHA II or III congestive heart failure, SCD may account for up to 64% of deaths. However, among persons with NYHA IV, SCD may only account for 33% of deaths.[19] This accounts for some of the reluctance to include individuals with NYHA IV in primary prevention ICD trials. The Comparisons of Medical Therapy, Pacing, and Defibrillation in Heart Failure Trial (COMPANION) in 2004[20] included those with advanced congestive heart failure with NYHA III or IV (ischemic or nonischemic) and a QRS >120 ms (believed to be an electrocardiogram marker of ventricular dyssynchrony) who were randomized to optimal medical treatment, biventricular pacing, or biventricular pacing with ICD. The results showed a 24% (nonsignificant) reduction in all-cause mortality with biventricular pacing and a 36% reduction with biventricular pacing with ICD. Cardiac Resynchronization in Heart Failure (CARE-HF) in 2005 showed a mortality benefit among individuals with NYHA III or IV and a QRS >120 ms who received a CRT device when compared with medical treatment.[21] A meta-analysis including these two studies as well as others found a reduction in all-cause mortality, reduced hospitalizations, and improvement of at least one NYHA class among those who received CRT when compared with standard medical treatment.[22] Table 3 lists the characteristics of persons who are considered for CRT.

Table 3: Characteristics of Candidates for CRT

CHF with NYHA class III or IV on optimal treatment
Left ventricular ejection fraction ≤35%
Presence of cardiac dyssynchrony (QRS ≥120 ms)

CHF = congestive heart failure; CRT = cardiac resynchronization therapy; NYHA = New York Heart Association.

Complications

A recent meta-analysis of ICD trials looked at the complication rates in published studies.[23] Deaths associated with implantation can be as high as 1.2%, mechanical complications 5%, device malfunctions or lead problems/infections 1–2%, and inappropriate discharge 5–20%. This is balanced by about 5–12% receiving appropriate shocks per year. Complications rates, much like any other procedures, tend to be lower at higher-volume centres.

Older Adults and ICDs

The older adult population is growing; it is estimated that those over age 65 years will make up almost 20% (71 million) of the U.S. population by 2030.[24] Most of the clinical trials mentioned previously had participants with a mean age in the range of 60–69 years. Concerns of multiple comorbidities and frailty among older adults—especially if defined as over 75 years—the complication rates of device implantation, and a higher proportion of non-SCD deaths have to be taken into account in this population.[24] Interestingly, an analysis of the MUSTT study showed a higher arrhythmic death rate among older adults (over age 70 years) and, hence, a greater impact with ICDs.[25] Thus, there are now no clear age limits for device implantation. Older adults with risk factors for SCD who have a reasonable quality of life and no other major comorbidities to limit their life expectancy should be considered for device implantation.

Conclusion

The roles of ICDs are continuously growing in the management of arrhythmias, SCD, and heart failure. Ongoing and future developments will continue to provide more information on choosing the right device for each patient.

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Key Points

- Role of devices is continually expanding in cardiology.
- Patients at risk for ventricular arrhythmias and SCD should be considered for an ICD.
- Patients with severe CHF on optimal medical treatment may benefit from CRT.
- For patients with minimal comorbidities, there are no age limits for device implantation.
- Patients with devices need to be followed up regularly by an MD/device clinic.

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