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Unresolved Issues in Implantable Cardioverter-Defibrillator Therapy

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Over the last 15 years, a series of well-designed randomized clinical trials has clearly demonstrated that implantable cardioverter-defibrillator (ICD) therapy reduces mortality in select high-risk populations [1,2]. The initial key studies were secondary prevention trials that showed that ICD therapy was superior to antiarrhythmic drug therapy in patients who had survived an episode of sustained ventricular tachycardia or cardiac arrest. Such patients were known to have a high risk for recurrence, and ICD therapy reduced total mortality by 25% to 37%. Subsequently, primary prevention trials that included patients who had ischemic or nonischemic cardiomyopathies showed that ICD implantation lowered mortality by a similar percentage in high-risk patients who did not have a prior history of a sustained arrhythmia. In early 2005, the Centers for Medical and Medicaid Services issued guidelines for ICD implantation [3] that included secondary and primary indications. Well over 140,000 ICDs are now being implanted each year in the United States alone. Despite the widespread acceptance of ICD therapy, many questions related to its optimal use remain (Box 1). This article discusses several key issues now confronting clinicians.

Epidemiology

Although multiple investigators have estimated that there are about 350,000 sudden cardiac deaths in the United States each year, this number may not accurately describe the population that could benefit from ICD therapy because not all these deaths are out-of-hospital deaths that might be prevented by an ICD. According to 1999 data from the Centers for Disease Control and Prevention [4], only about 64% of all cardiac deaths occur out-of-hospital or in a hospital emergency department (Fig. 1). Slightly more than one third of cardiac deaths occur among hospitalized patients. Presumably, many of the patients who died during a hospital stay were being effectively monitored and their deaths were not sudden or unexpected. More recently, the American Heart Association (AHA) estimated that the true incidence of out-of-hospital cardiac arrest is about 0.55/1000 population or 165,000 events annually in the United States [5]. The same AHA statistical report also estimated that about two thirds of unexpected sudden cardiac deaths occur in subjects who do not have prior recognized heart disease. This latter group of victims is an unlikely potential target for an expensive and invasive therapy like an ICD.

Studies have also shown that the age of sudden death victims is increasing and that the proportion of out-of-hospital cardiac arrest victims who have ventricular fibrillation documented by emergency medical teams has decreased significantly [5,6]. Asystole and pulseless electrical activity are now the initial rhythms most commonly recorded. Elderly patients account for a large fraction of the cardiac deaths that occur outside the hospital. In the 1999 data cited previously, over 40% of all emergency room or out-of-hospital cardiac deaths occurred in individuals older than 75 years, with 24% of those older than 85 years (Fig. 2). Although these deaths may be classified as sudden, they may not be unexpected or preventable. These observations suggest that the strategies for increased ICD utilization that are targeted at

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Box 1. Key unresolved issues in implantable cardioverter-defibrillator therapy

How should the epidemiology of sudden cardiac death affect ICD utilization?
Will subgroup analysis of the randomized trials be helpful?
Is there any role for antiarrhythmic drug therapy?
How should comorbidities influence decisions about ICD utilization?
Should every resynchronization device be an ICD?
How should ICD lead and generator reliability influence therapy?

individuals identified as being at high or very high risk will have a relatively small impact from a public health perspective.

Subgroup analysis

Randomized trials are designed to test a hypothesis involving a single or a composite primary end point that applies to the entire study group. After the trial has been completed, however, it is common to examine subgroups to see whether results from the entire population hold for patients who have certain clinical characteristics. Subgroup analysis may be useful for formulating new hypotheses that can be tested in future trials, but the results of such analyses must be interpreted and applied to individual patients by clinicians with great caution. Attempts to guide therapy based on analysis of subgroups from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) [7] illustrate this problem. The main conclusion of the SCD-HeFT was that ICD therapy was superior to placebo and amiodarone for reducing total mortality in patients who had ischemic or nonischemic cardiomyopathies, class II or class III heart failure symptoms, and a left ventricular ejection fraction of 0.35 or less. Subgroup analysis, however, showed that the hazard ratio was not significantly reduced among women, in those who had an ejection fraction of 0.30 or higher, and in diabetics. Excluding individuals in these groups from ICD therapy would be difficult for clinicians in light of current published guidelines [3]. Subgroup analysis may also give discordant results when different trials are examined. For example, in SCD-HeFT, ICD therapy was beneficial in patients who had class II but not class III heart failure symptoms, whereas in the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation trial [8], most of the benefit with ICD therapy observed was in the class III subgroup. Women did not benefit in SCD-HeFT but did in the Multicenter Defibrillator Implantation Trial II (MADIT-II) [9]. Most studies are statistically designed to have adequate power to test the primary hypothesis only in the entire study group. Observations made in subgroups may be thought provoking but are rarely convincing enough to warrant clinical decisions contrary to the overall result.

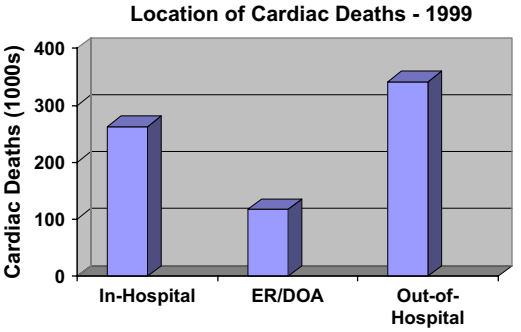

Fig. 1. Cardiac deaths in the United States during 1999 by location as compiled by the Centers for Disease Control and Prevention. ER/DOA, death in or on arrival to the emergency room. (*Data from* Center for Disease Control and Prevention. State-specific mortality from sudden cardiac death—United States, 1999. MMWR Morb Mortal Wkly Rep 2002;51(6);123–6.)

Antiarrhythmic drug therapy

Some argue that antiarrhythmic drug therapy should not be used in the era of ICD therapy. The major secondary and primary intervention trials compared ICD therapy to antiarrhythmic drug therapy or to no therapy. In the secondary prevention trials, patients in whom antiarrhythmic drugs were believed necessary to control frequent or recurrent arrhythmias were excluded. In clinical practice, however, antiarrhythmic drugs are frequently required. Several studies have now shown that the use of antiarrhythmic drugs decreases ICD shock frequency and may thus make long-term ICD therapy more acceptable [10–12]. An example can be seen in the Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients trial [10], in which therapy with sotalol and amiodarone plus a β-blocker produced significant reductions in ICD shocks. Similar data have been

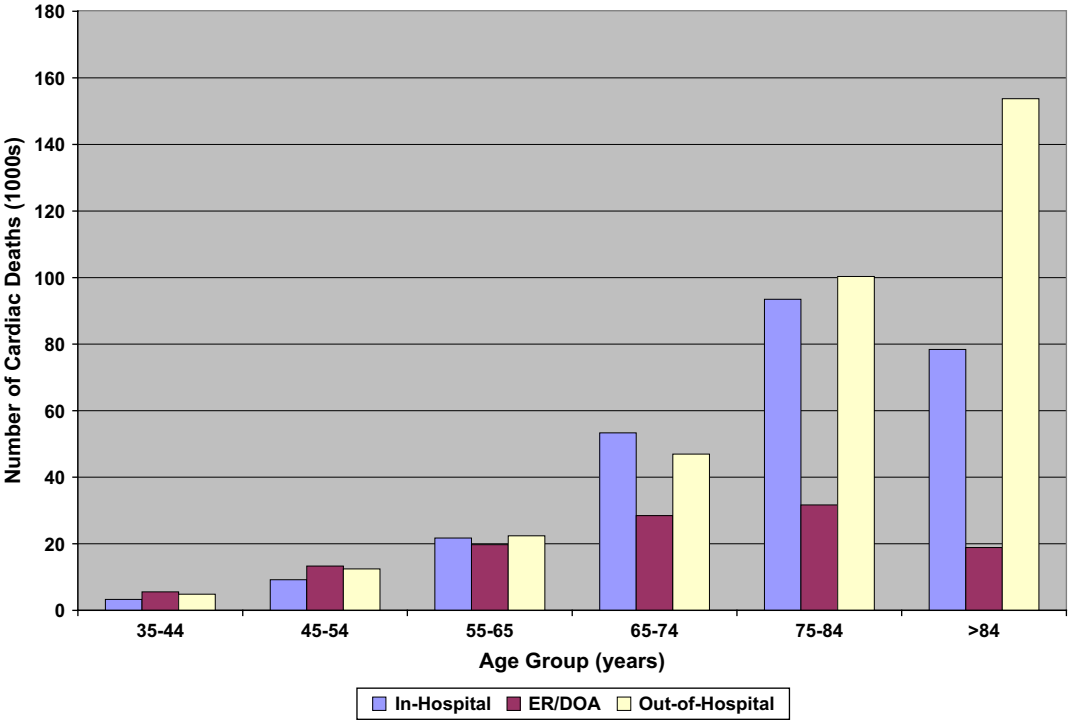

Fig. 2. Age distribution of cardiac deaths in the United States during 1999 as compiled by the Centers for Disease Control and Prevention. ER/DOA, death in or on arrival to the emergency room. (*Data from* Center for Disease Control and Prevention. State-specific mortality from sudden cardiac death—United States, 1999. MMWR Morb Mortal Wkly Rep 2002;51(6);123–6.)

reported for sotalol [11] and azimilide [12]. Thus, many patients, particularly those who receive an ICD for secondary prevention or who require ICD therapy for ventricular tachycardia or ventricular fibrillation after an implant for a primary prevention indication, would benefit from the careful prescription of an antiarrhythmic drug.

Comorbidities

Patients entered in clinical trials are not always representative of the patients encountered by clinicians, of whom many have multiple coexisting diseases [13]. The presence of coexisting disease is rarely mentioned in ICD clinical guidelines [14] beyond a general admonition not to implant unless the patient has a "reasonable expectation of survival with a good functional status for more than 1 year." Some studies specifically exclude patients who have certain high-risk characteristics. For example, the MADIT-II [9] excluded all patients who had moderately severe renal insufficiency. Studies are also often affected by "pre-enrollment" bias because investigators select patients who they think will be "good" and reliable candidates for the study. These patients tend to be healthier and less complicated than many patients seen in everyday clinical practice who might be difficult to follow according to a strict trial protocol.

Advanced age is perhaps the most important factor that is not taken into consideration by published guidelines. In the published primary and secondary ICD prevention trials, the mean age for enrollees was between 58 and 64 years [1,2,14]. Although they were not specifically excluded, relatively few patients older than 80 years were enrolled. In contrast, recent data from the ICD Registry compiled by the National Cardiovascular Data Registry show that 15% of all ICD recipients are older than 80 years, and an additional 16% are between 75 and 79 years old [15]. Other studies have shown that the ratio of sudden to non–sudden deaths declines steeply as the age range of subjects increases [16,17]. This finding limits any potential benefit of an ICD in this age range despite the fact that even very elderly patients would still be considered candidates by guideline criteria.

Other groups have begun to study the impact of comorbidities on the value of ICD therapy. Parkash and colleagues [18] reviewed survival data from a large ICD database from a single institution. These investigators devised a scoring system that included the following risk factors: age 80 years or older (2 points), ejection fraction less than 0.30, atrial fibrillation, creatinine greater than 1.8 mg/dL, and class III or IV heart failure symptoms. Patients who had risk scores of 1 or 2 had low mortality with ICD therapy but patients who had risk scores of 3 or greater had high 6-month and 1-year death rates. In a retrospective analysis of all ICD recipients in Ontario, Canada, Lee and colleagues [19] showed that age, heart failure, peripheral vascular disease, pulmonary disease, diabetes with complications, renal disease, and malignancy all independently had an adverse effect on survival in ICD recipients. In an analysis of the MADIT-II database, Goldenberg and colleagues [20] identified five risk factors for all-cause mortality: advanced heart failure symptoms, atrial fibrillation, QRS duration greater than 120 milliseconds, age greater than 70 years, and blood urea nitrogen level between 27 and 50 mg/dL (Table 1). A small group of patients who had more advanced renal disease was separately classified as ''very high risk.'' Patients who had no risk factors had no improvement in survival with ICD therapy. Patients who had three or more risk factors and the very high risk group also had no improvement in survival with an ICD. These findings resulted in what the investigators described as a U-shaped curve for ICD efficacy.

As cardiologists and electrophysiologists deal with increasingly elderly patients who have multiple concomitant diseases, they will need to realize that guidelines based on clinical trials should not be employed without first carefully considering all the factors that might influence the treatment decision in that individual patient. In many cases, comorbid conditions will limit any potential benefit from an ICD implant, and the risks and costs of the procedure may be avoided. This principle should also apply to decisions regarding elective ICD generator replacements for battery depletion because changes in the patients' condition may now make them unsuitable candidates for continued ICD therapy. As recently reported by Hauptman and colleagues [21], however, few physicians discuss these issues with their patients, even if they agree with the general principle.

Table 1
Risk factors for all-cause mortality in the Multicenter Defibrillator Implantation Trial II

Risk factor	HR (95% CI)	P
NYHA functional class >II	1.87 (1.23–2.86)	.004
Atrial fibrillation at baseline	1.87 (1.05–3.22)	.034
QRS >120 ms	1.65 (1.08–2.51)	.020
Age >70 y	1.57 (1.02–2.41)	.042
BUN 26–50 mg/dL	1.56 (1.00–2.42)	.048

Abbreviations: BUN, blood urea nitrogen; CI, confidence interval; HR, hazard ratio; NYHA, New York Heart Association.

From Goldenberg I, Vyas AK, Hall WJ, et al for the MADIT-II Investigators. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. J Am Coll Cardiol 2008;51:292; with permission.

Cardiac resynchronization therapy with or without an implantable defibrillator

Prior the release of large cardiac resynchronization therapy (CRT) trials, defibrillator therapy was contraindicated in patients who had class IV heart failure except as a bridge to transplant. This group of patients has such high morbidity and mortality from heart failure–related complications that defibrillators have not been shown to improve survival. In addition, these patients are prone to excess complications from defibrillator therapy, including inappropriate shocks and device infections [22].

The COMPANION trial compared treatment strategies for patients who had severe heart failure [23]. Patients were randomly assigned to receive medical therapy, a CRT device, or a CRT device with a defibrillator (CRT-D). The primary combined end point of time to hospitalization and mortality from any cause was substantially improved in the group receiving CRT-D. This end point was also statistically improved in patients receiving CRT alone. The secondary end point of time to death from any cause was not statistically different between the CRT group and the medication group, but there was a trend toward the CRT group having decreased time to death, and the CRT-D group had a clear decreased time to death. The patients in the CRT and CRT-D groups experienced improved quality of life over those on medication alone.

In a subgroup of patients who had ambulatory class IV symptoms, the CRT-D group had a significant reduction in time to sudden death [24]; however, the CRT and CRT-D groups experienced similar reduction in time to death or

hospitalization for any cause. Both groups also experienced similar reduction in time to death from any cause and heart failure hospitalization.

The Cardiac Resynchronization–Heart Failure (CARE-HF) study had even more dramatic findings [25]. This study evaluated patients who had class III or IV heart failure and either a QRS greater than 150 milliseconds or, if the QRS was between 120 and 149 milliseconds, echocardiographic evidence of dyssynchrony. The patients were randomized to receive medical therapy or CRT using a pacemaker with defibrillation capacity. There was a substantial decrease in total mortality in the patients who received CRT. The mortality was 55% in the medication group versus 39% for the CRT group over a mean of 29.4 months of follow-up. This benefit continued to be seen over long-term follow-up [26].

These findings altered the indications for defibrillator therapy. Patients who have end-stage heart failure have high mortality from causes other than ventricular arrhythmias, and these patients derive questionable benefit from defibrillators; however, if CRT can improve the morbidity and possibly the mortality in class IV congestive heart failure, then defibrillator therapy seems to be more reasonable. Current guidelines still define class IV heart failure as a contraindication for defibrillator therapy unless the patient is receiving a CRT device. Essentially, by guidelines, virtually any patient who is receiving a CRT device also qualifies for a defibrillator. But does that mean that every patient who receives a CRT device should get a defibrillator?

Although guidelines suggest that every patient who gets a CRT device also qualifies for a defibrillator, these studies raise several important issues. CRT alone may have antiarrhythmic properties. Defibrillators are substantially larger than biventricular pacemakers, and patients who have class IV heart failure are often elderly, thin, and relatively immune incompetent. They have higher risk for erosion and infection of the device. Patients who have defibrillators are also at risk for inappropriate shocks. In contrast, implantation of coronary sinus left ventricular leads in the CARE-HF study had a low risk for complications [27]. It is possible that the added complication rate of defibrillators offsets any incremental benefit over CRT alone.

The cost differential between CRT and CRT-D is also substantial. One study of the long-term cost-effectiveness of CRT versus CRT-D found that both were cost effective [28]; however, CRT-D was only moderately cost-effective compared with CRT plus medication and only in patients who had a life expectancy of at least several years.

At this point, it seems best to evaluate patients who have end-stage heart failure for CRT versus CRT-D devices on a case-by-case basis, taking into account clinical history and patient preferences. There are still not enough data to determine which groups of patients benefit the most from CRT and the incremental benefit incurred by the addition of a defibrillator. Until further data become available, these decisions will need to be made on an individual basis.

Device malfunctions

The number of patients who have ICDs has dramatically increased over the last several years. Concomitantly, the number of patients having a device that is recalled or that malfunctions has increased. The numbers of ICD recalls and malfunctions have proportionally increased more than would be expected compared with pacemaker malfunctions. One recent meta-analysis of device registries demonstrated a 20-fold higher incidence of ICD failure compared with pacemakers [29].

There are multiple reasons for this finding. ICD technology is much newer than pacemaker technology and far more complex. The expanding competitive market has also led to a ''short product life cycle'' in which new innovations are being developed and implemented at a rapid pace. Finally, there may be a lower threshold for ICD recalls than pacemaker recalls because an acute ICD malfunction has a greater potential to cause death.

Most device malfunctions are not due to recall-related failures. Most malfunctions are due to random component failures. Currently, there is no ICD ever marketed that has a malfunction rate lower than 0.1%. Recent data suggest that 2% of all implanted defibrillators are removed due to malfunction [30]. ICD leads have an even more striking failure rate. A long-term study of ICD leads showed a 20% failure rate at 10 years of follow-up [31]. This observation should be particularly concerning for younger patients who might have the potential for multiple lead failures during their lifetime.

Most devices that are recalled by the manufacturer never malfunction, but large numbers of patients are affected in a recall. In 2000, there were only two ICD advisories, but over 20,000 patients were affected [32]. Recalls present unique issues for

physicians and patients. Due to widespread media coverage of the more recent device recalls, patients are more aware of the potential for device recalls but often do not have a sophisticated understanding of what a recall means. Most recalls do not require the device to be explanted because the risk of malfunction may be small or substantially mitigated by programming changes or closer device follow-up; however, it is unsettling to many patients to have a "defective" device, and many of them will want a new one. The difficulty with this is that explanting and replacing a device has a significant complication rate. One study of patients who had device explants for recall-related issues showed a major complication rate of 6%, with a postoperative mortality rate of 0.4%. The control subjects, who did not have their recalled devices explanted, had an advisory-related complication rate of 0.1% [33].

Review of device registries over the last several years suggests that the numbers of ICD malfunctions and recalls is stabilizing somewhat after a marked increase in prior years [29]. Nonetheless, with the substantial increase in device implants, a single recall affects a large number of patients, and even if the number of malfunctions decline, it is still significant. It is important for implanting centers to have the resources available to evaluate patients who have recalled devices and to address their concerns appropriately.

Summary

ICD therapy is a powerful intervention with a clear ability to prolong life. Few other therapies are able to reduce mortality by 20% to 30% when added to standard treatment in well-managed patients. As discussed, however, the answers to questions regarding the optimal use of ICD are not contained in results of clinical trials. Careful clinical judgment is still required to use this powerful tool wisely.

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