Implantable Cardioverter-Defibrillator
Lifesaver or a Device Looking for a Disease?

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Please implant a defibrillator in my patient, read the letter from the referring physician. "He was resuscitated from a cardiac arrest resulting from ventricular fibrillation. He had no myocardial infarction, and he has no evidence of acute ischemia, although he has extensive inoperable coronary artery disease."

The implantable cardioverter-defibrillator (ICD) is one of the most revolutionary therapies developed in the past two decades to treat patients with life-threatening ventricular arrhythmias. The device, created in the late 1970s to deliver a shock to terminate ventricular fibrillation (VF), has evolved into a sophisticated piece of equipment capable of VVI pacing for bradycardias and delivering programmed tiered therapy for ventricular tachyarrhythmias. In response to the patient’s rhythm disturbance, the ICD automatically escalates the intensity of treatment from competitive pacing to synchronous cardioversion and then to defibrillation. It matches the treatment to the arrhythmia sensed while storing ventricular electrograms documenting the arrhythmia and cataloging facts about device operation. This information can be collected noninvasively by interrogating the pulse generator. Biphasic and sequential shocks have lessened defibrillation energy, and the entire ICD system can now be implanted with surgery that is little more extensive than that required for a simple bradycardia pacemaker, reducing operative mortality to <1%. New leads with lower defibrillation thresholds and advances in capacitor design will shrink the ICD size from the current 80 cc to 60 cc in the near future. Ultimately, the ICD will incorporate a DDDR pacemaker with features that will help treat patients with reduced ventricular function and improve ventricular tachycardia (VT) differentiation by recognizing atrial activity and incorporating this information into tachycardia-detection algorithms.

This is wonderfully advanced technology, representing the height of device creativity. But in 1972, when the ICD was little more than just a concept, Lown and Axelrod wrote that the implantable defibrillator was "...an imperfect solution in search of a plausible and practical application." Certainly most cardiologists today would disagree with that disparaging appraisal and would comply with the above request from the referring physician who "knows" that the ICD is the treatment of choice for his or her patient. The physician reasons that any therapy that can reduce sudden cardiac death mortality to <2% per year in high-risk patients, particularly in light of disappointing drug data from the Cardiac Arrhythmia Suppression Trial (CAST) and other studies, has found its niche in our therapeutic thesaurus. After all, the ICD has been called the gold standard of treatment for these patients.2,3

But is that really true? Can it really be equated with a gold standard? Given without question that the ICD can terminate VT/VF, should it be implanted in the referred patient? Does it reduce overall or total mortality compared with the best medical therapy? Indeed, is that the correct question to ask? Or should we accept the fact that the ICD successfully terminates VT/VF, and should we be implanting the ICD in all patients who survive a cardiac arrest? Or are there subgroups in whom we can eliminate competing causes of death so that their risk of dying is from VT/VF alone, and should only they receive the ICD? Are patients with reduced ventricular function more likely to suffer a nonrhythmic death and therefore not profit from implantation of an ICD? Are patients with cardiac arrest resulting from VF more likely to have a cardiac arrest recurrence, and with that the possible need for an implantable defibrillator, than the patient with stable but recurrent episodes of VT? But might the patient with chronic stable VT benefit from the antitachycardia pacing capabilities of the ICD? For this patient, would the ICD improve the quality of life over drug treatment and perhaps reduce the cost of medical care if repeated hospitalizations and emergency department visits to treat recurrences of the VT could be avoided? Attempts to answer these and related vexing issues about the use of the ICD based on reports in the literature often fall short of completely satisfying, careful scientific scrutiny.

A search of the published literature reveals that no controlled, randomized trials comparing the ICD with other forms of treatment for patients with VT/VF have been reported. Do we need such data? After all, most of the published reports indicate that patients who have an ICD implanted experience a sudden death rate of <2% per year, as noted above, and 6% at 5 years.4 That is pretty good, considering that historical controls chart a mortality of 25% to 40% at 1 to 2 years for this group of patients5,6 and that therapy with amiodarone results in a sudden death rate of about 9%, 15%, and 21% at 1, 3, and 5 years, respectively.7,8 What more is there to know?

To establish the value of a therapy, unless its application so obviously and dramatically alters the natural history of a disease, we must compare it against something. Initial ICD studies used a surrogate end point for death,9-11 ie, each "appropriate" shock from the device indicated a

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patient death. Even with early studies, acceptance of this approach was illogical, considering the possibilities of delivering shocks for supraventricular tachycardias, non-sustained VT, well-tolerated sustained VT, and device malfunction. Next, investigators matched populations treated with the device against those without the ICD using historical controls and found, not surprisingly, benefit in favor of the device. Interestingly, several of these studies also showed a reduction in nonsudden cardiac death, painting an illusory picture that the ICD might be useful to treat heart failure or even myocardial ischemia. Naturally, that is quite unlikely, and very probably different populations were examined. Historical controls are only valid when they are identical to the test population, and that can be true only if the natural history of the disease is unchanged, the distribution of the disease remains constant (eg, same number of VT versus VF patients), no new therapies alter outcome (eg, use of angiotensin-converting enzyme inhibitors), and patients can be matched for identical clinical characteristics. These goals were rarely achieved in the reported studies. Carefully matched concurrent controls are less biased, but two such reports have shown conflicting results—a reduction and no reduction in total mortality.

Why compare total mortality? Why not just tabulate arrhythmic or sudden cardiac death mortality? After all, that is what the ICD is supposed to reduce. Total mortality must be used because accurately determining the cause of death can be very difficult, even with stored electrogram recordings, and total mortality is a more reliable measure of the effectiveness of an intervention. Complex clinical circumstances can obfuscate causality. Consider the patient resuscitated from VF who secondarily develops heart failure during the recovery period and dies in the hospital after many weeks and multiple complications. The arrhythmia in reality triggered the ineluctable path to death but might not be so linked in many studies. In addition, deaths must be classified according to an intention-to-treat analysis. For example, if during testing to receive an ICD a patient was found to have an elevated defibrillation threshold that precluded device implantation, his subsequent death from cardiogenic shock or “arrhythmia storm” due to the multiple inductions of VF and defibrillations must be assigned to the ICD. Most of the reported studies would not list the ICD as a cause of this death if the device was not actually implanted. Thus, the bottom line of a study is how many patients are alive or dead based on their actual or intended mode of therapy; cause of death is secondary.

The ethics of performing a randomized trial of the ICD have been challenged, much as the ethics of executing the CAST were questioned. This is an important issue and one that the organizers at the National Heart, Lung, and Blood Institute (NHLBI) and the participating investigators have wrestled with at length during the planning stages of the present study. Some would respond that it is unethical not to do such a study. The typical patient who is offered to dispute the ethical propriety is not the one presented in the first paragraph but rather a much younger version who has excellent left ventricular function with minimal coronary disease and has been resuscitated from VF. In that patient, recurrent VF looms front and center as the major risk of death, without competing abnormal hemodynamics, and we know that the ICD is the best therapeutic choice.

But do we really? Despite recent reports of superb implantation and short-term follow-up results of the ICD, it is important not to lose sight of device complications that can cause discomfort, disability, and, on occasion, even death. Citing better survival data for sudden or even total mortality in groups treated with devices compared with drugs can be challenged, as noted above, because the populations in the two treatment arms may not be the same.

Until we directly randomize the ICD against the best medical management, we will not know which therapy is best in general or for a specific patient group, eg, those with good left ventricular function and device resuscitated from cardiac arrest, VF, or hypertensive VT. In one of them, preliminary results on 229 patients show that there is no difference in total mortality between patients receiving amiodarone or β-adrenoceptor blockers in patients resuscitated from cardiac arrest, VF, or hypertensive VT. In the other study, recruitment continues after randomization of about 300 patients, presumably because the Data Safety Monitoring Board has found no reason to stop the study, ie, no differences exist in the two therapeutic arms. Amiodarone has been discontinued in 7% of patients, whereas the ICD has been removed without reimplantation in 2%. Eighteen percent of the ICD patients have received amiodarone, whereas 3.5% of amiodarone patients have received an ICD (Stuart Connolly, MD, personal communication).

To answer some of the questions raised above, a prospective, randomized, multicenter trial interpreted on an intention-to-treat basis has been designed. The Antiarrhythmics Versus Implantable Defibrillators (AVID) study, supported by the NHLBI, randomizes to the best drug treatment or an ICD patients resuscitated from VF, sustained VT with syncope, or sustained VT with serious hemodynamic consequences including chest pain, systolic blood pressure <80 mm Hg, or near-syncope and an ejection fraction ≤0.40. The primary end point is total mortality, with secondary end points of quality of life, cost, surgical morbidity and mortality, adverse drug experiences, and ICD system failure. Other patients whose arrhythmia is judged to be less serious, including those with sustained VT with a systolic blood pressure <80 mm Hg but an ejection fraction >0.40, stable sustained VT, out-of-hospital VT or VF due to a transient or correctable cause, or out-of-hospital unexplained syncope with structural heart disease and VT with symptoms induced at electrophysiological study, will be entered in a registry to judge the adequacy of the population sampling from which the randomized patients are drawn. These patients will be followed up through the National Death Index to allow mortality assessment so that AVID results can be put into proper perspective.

Patients who meet the entry criteria will then be randomized to drug or device. The ICD will be implanted via a nonthoracotomy approach when possible, unless the patient is also undergoing coronary artery bypass surgery. The choice of which ICD to use will be left to the investigator, but the ICD will be a state-of-the-art device with tiered therapy and bradycardia and antitachycardia
pacing options. AVID will not attempt to compare one ICD with another. Drug patients will be randomized to receive amiodarone or sotalol, the former empirically and the latter guided by ambulatory recordings or electrophysiological study. Patients who cannot receive sotalol because of reduced left ventricular function or because of an adverse response will receive empiric amiodarone. Only if both drugs are ineffective or are not tolerated will class I agents be used. Ample data support the selection of amiodarone and sotalol for these patients.7,8,25,26 Assuming a crossover rate from drug to ICD of 20%, a treatment effect from the ICD of 30%, and an event rate of 40% in the drug-treated group at a mean follow-up of 3.5 years, the power of the study would be approximately 70% for a two-sided P = .05.

AVID seeks an answer to the fundamental question of whether drugs are better than devices in a high-risk population. In reality, many patients receive an ICD plus an antiarrhythmic agent. One could envision AVID II, which could test whether an ICD plus an antiarrhythmic drug is better than an ICD alone.

AVID began with a pilot phase June 1, 1993, with 25 centers attempting to randomize 200 patients in 12 months. Recruitment of 1000 patients for the main trial begins March 1, 1995, and will conclude February 28, 1997, with completion of the follow-up period on August 31, 1998. Patients from the pilot phase could be added to those in the main trial if there are no major protocol changes. If the ICD is the overwhelming winner regarding survival, as the referring physician believes, the study could be terminated before the end of the recruitment of all the patients in the main study. The goal is to be able to tell this physician confidently that his patient should receive implantation of the ICD or would be better treated with amiodarone or sotalol and to support the decision with believable data. It is toward this level of certainty that we are striving. Until that time, physicians will continue to have to make therapeutic decisions based on the available published data.

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References


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