Mortality Benefits and the Implantable Cardioverter-Defibrillator

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Abstract The automatic implantable cardioverter-defibrillator (ICD) is highly effective in reducing sudden death rates in patients with life-threatening ventricular tachyarrhythmias. However, the magnitude of the ability of the ICD to improve overall survival is less certain. Data supporting the contention that the ICD prolongs survival are reviewed. It is evident that the mortality benefit consequent to the marked reduction in sudden death varies widely across subpopulations in a predictable manner. This observation reflects the powerful influence of other clinical factors that constrain survival in typical ICD patients. The implications for future studies on the ICD are discussed. (Circulation. 1994;89:1851-1858.)

Key Words • implantable cardioverter-defibrillators • survival • mortality

The automatic implantable cardioverter-defibrillator (ICD) was originally conceived by Mirowski and coworkers1 as a device for detecting and terminating potentially lethal ventricular tachyarrhythmias. Since the initial published report of successful resuscitation from ventricular tachycardia and fibrillation in humans 13 years ago, more than 30 000 devices have been implanted, and there have been dramatic advances in ICD technology. Newer devices are fully programmable and capable of antitachycardia pacing, synchronized cardioversion, defibrillation, back-up ventricular demand pacing, and retrieval of stored intracardiac electrograms. There is universal agreement that the device has demonstrated the ability to meet the goal set forth by its inventors, namely, to abort sudden cardiac death caused by ventricular tachyarrhythmias. In high-risk patients who have survived cardiac arrest or have drug-refractory hemodynamically significant ventricular tachyarrhythmias, the ICD is highly effective in reducing sudden death rates, in most studies to 1% and 5% at 1 and 3 years, respectively.2-8

However, while acknowledging this dramatic reduction in sudden death rates, some reports suggest that treatment with the ICD is not paralleled by a proportionate reduction in overall mortality.2-8 Skeptics have seriously questioned the magnitude of the ability of the ICD to improve survival,10-12 giving rise to a controversy described as the implantable defibrillator “backlash.”13 They argue that regardless of the ability of the device to terminate potentially fatal ventricular tachyarrhythmias (which is not in question), it has not been convincingly shown to prolong life compared with alternate therapies, and the cost and morbidity of the technology remain unjustified. In this article, early studies with the ICD and the origins of the survival benefit controversy are reviewed. It is evident that the mortality benefit consequent to the marked reduction in sudden death varies widely across subpopulations in a predictable manner. This observation reflects the powerful influence of other clinical factors that constrain survival in the typical ICD patient. Failure to anticipate the partial effects of these factors has led to unrealistic expectations regarding the survival benefits conferred by the ICD. Data supporting the contention that the ICD significantly prolongs survival in certain subsets of patients with malignant ventricular tachyarrhythmias are presented. Finally, the implications of these observations for future studies on the ICD are discussed.

Early Studies With the ICD and the Origins of the Survival Benefit Controversy

Much of this controversy stems from the fact that early randomized controlled trials comparing the ICD with other therapies were not done, largely because of the mistaken perception that the benefits of this technology were so striking that withholding it from patients in a study would be unethical. However, several such trials are now either being planned or actively enrolling patients, and a careful review of the accrued experience leading to this controversy is timely. In a landmark early report, Mirowski et al8 documented a 1-year sudden death rate of 8.5% in 52 survivors of repeated cardiac arrest treated with the ICD. This appeared to represent a dramatic reduction in expected sudden death rates compared with the 30% and 45% recurrent cardiac arrest rates at 1 and 2 years of follow-up, respectively, reported in studies from the 1970s.14-18 These early studies best approximated the natural history of cardiac arrest survivors, as the majority of patients were untreated by contemporary standards. In addition, Mirowski et al8 introduced the concept of “potential” sudden cardiac deaths aborted by the ICD as confirmation of the efficacy of the device. This concept is based on the premise that each “clinically appropriate” discharge (that is, shocks preceded by presyncope or syncope, presumptively denoting hemodynamically unstable tachyarrhythmias) delivered by the ICD would represent sudden cardiac death for the patient had the device not been implanted. Thus, the difference between the number of patients who received appropriate shocks and those who died suddenly within a given time.
interval represents the reduction in sudden death mortality conferred by the device. Applying this logic, Mirowski et al\(^2\) estimated an 82% reduction in sudden death mortality at 1 year with the ICD. Subsequently, numerous investigators similarly reported an 85% to 90% reduction in estimated 1-year sudden death rates.\(^3\)\(^4\)\(^5\)\(^6\) However, this method has important limitations that may result in inaccurate estimates of sudden death rates. The assumption that an appropriate shock always represents rescue from a life-threatening event is erroneous. It is now well recognized that some recurrences of ventricular tachycardia that may trigger the ICD are self-terminating\(^9\)\(^10\) or hemodynamically tolerated.\(^21\) Supraventricular tachyarrhythmias, mimicking ventricular tachyarrhythmias, also may trigger ICD shocks. Thus, expected sudden death rates based on shock delivery may overestimate the reduction in sudden death rate by the ICD.\(^7\)\(^12\)\(^22\) Alternately, as many as 49% to 68% of episodes of ventricular tachycardia may be preceded by minimal or no symptoms\(^23\)\(^24\) or occur during sleep, in which case a properly delivered shock would be labeled as “inappropriate” and the expected sudden death rate would be underestimated. Additionally, sole reliance on shock delivery as an efficacy end point would fail to account for successful termination of ventricular tachycardia by antitachycardia pacing available in third-generation ICDs and thereby underestimate the clinical benefit of the device.\(^24\)

Despite controversy regarding the magnitude of the reduction in sudden cardiac death rates, the efficacy of the ICD in terminating ventricular tachyarrhythmias is unquestioned. A more vexing problem, unanticipated by early investigators, is defining the survival benefit conferred by the ICD. Mirowski et al\(^2\) reported a substantial overall mortality at 1 year of 22.9%. This appeared inconsistent with the marked reduction in sudden death rate attributed to the ICD. Subsequently, others have shown that despite the near elimination of sudden cardiac death from ventricular tachyarrhythmias by the ICD across heterogeneous populations, total cardiac mortality remains substantial at approximately 15% to 20% at 2 years.\(^5\)\(^9\)

### Survival Constraints and Measuring Bias: The Case for Limited Mortality Benefits

These observations point out the difficulties in assessing the impact of new therapies without the advantage of well-designed prospective randomized trials. Recent studies suggest that the recurrence rate in cardiac arrest victims is declining,\(^25\) presumably as a result of aggressive treatment of ischemic heart disease and left ventricular dysfunction. This may confound the comparison of contemporary treatment strategies to prevent sudden death and prolong survival (such as the ICD) with historical control populations. Additionally, a reasonable estimate of a proportionate reduction in overall mortality resulting from a reduction in sudden cardiac death must be established. It is suggested that ICD survival benefits fall short of expectations because the 85% to 90% reduction in sudden death rates has not yielded a similar reduction in overall mortality. However, this statement fails to consider three important facts: (1) sudden death comprises a fraction of total cardiac deaths in any population of patients with malignant ventricular tachyarrhythmias; (2) a significant percentage (perhaps 20% or more) of sudden deaths in patients with advanced heart failure (particularly nonischemic dilated cardiomyopathy) are due to brad arrhythmias or electromechanical dissociation\(^26\)\(^27\) and therefore are not prevented by the antitachycardia/defibrillation capabilities of the conventional ICD; and (3) implantation of the ICD is associated with a small but significant risk of perioperative nonsudden death, ranging from 1.5% to 5.4%.\(^4\)\(^5\)\(^7\)\(^8\)\(^28\) Allowing for heterogeneity among populations, roughly one half to two thirds of all postarrest cardiac deaths are sudden and the remainder are nonsudden.\(^21\)\(^29\)\(^30\) Thus, based on the reasonable assumptions that sudden deaths constitute one half of postarrest cardiac deaths and that 80% of sudden deaths are due to ventricular tachycardia or fibrillation, simple algebra reveals that a 90% reduction in sudden tachyarrhythmic deaths can only yield a 36% maximum reduction in total cardiac mortality. If ICD implantation is associated with a 1% to 3% increase in mortality, then the total cardiac mortality reduction would diminish to the 33% range. This estimate would vary directly with the proportion of sudden tachyarrhythmic deaths in any population. Deaths by noncardiac causes would further diminish the overall mortality benefit (although this effect would be similarly distributed across treatment populations).

Although it seems counterintuitive that a reduction in sudden death rate might not result in a parallel reduction in overall mortality (controlling for noncardiac deaths and the increase in nonsudden deaths attributable to implantation of the device), this possibility exists when actuarial methods are used to estimate survival. The majority of patients who are successfully rescued from a malignant tachyarrhythmia by the ICD eventually die as the result of progressive myocardial dysfunction, often preceded by additional successful shocks. These deaths would then be classified as nonsudden, and if they occurred within the bounds of the time interval used in the survival analysis, the nonsudden death rate would appear to increase and the overall mortality would remain unchanged despite the successful resuscitation(s) from sudden death by the ICD. This phenomenon has been termed “conversion” of the mode of death and is offered by some authors as a partial explanation for the failure of the ICD to reduce overall mortality to the extent initially envisioned.\(^7\)\(^12\) The impact of this possibility on survival analyses in ICD series is not known and raises important questions. What duration of life extension after successful rescue by the ICD is meaningful? Most would agree that incessant ventricular tachycardia or fibrillation in a patient with severe myocardial power failure represents a terminal event, and “successful” rescue by the ICD merely “saves” the patient to die of heart failure shortly thereafter. These have been termed “not-so-sudden” deaths\(^31\) and “arrhythmia-related nonsudden deaths.”\(^3\) These investigators and others\(^22\) have argued that such deaths would clearly reduce the clinically meaningful impact of successful arrhythmia termination and by extension, the mortality benefit conferred by the ICD. In contrast, two recent studies involving a large number of ICD patients\(^32\)\(^33\) failed to observe a significant number of arrhythmia-related deaths other than surgical mortality, suggesting that the clinical impact of reclassification of mode of death may be overstated. The
limitation of the “conversion” concept (as originally described) is that it implicitly considers the patient at the time when recurrent ventricular arrhythmias presage imminent death as a result of end-stage heart failure. Measured at only this point in time, the survival benefit of the ICD would appear to be marginal. In fact, the majority of patients will live long enough by virtue of the marked reduction in sudden death attributable to the ICD to experience “conversion” of their mode of death. This “unnatural history” is a reflection of advances in prevention of sudden death outstripping treatment of heart failure and altering the mode of death.

It is obvious that the mortality benefit of the ICD, despite near elimination of sudden tachyarrhythmic death, is limited by the extent of left ventricular dysfunction and ischemia, which interact with recurrent tachyarrhythmias as the major independent determinants of long-term cardiac survival. Heart failure and ventricular tachyarrhythmias are “fellow travelers,” and the vast majority of patients who receive ICDs have at least a moderate degree of left ventricular systolic dysfunction. Several studies attempted to demonstrate the survival benefit of the ICD across strata of left ventricular ejection fraction using actuarial statistics derived from estimated sudden death rates in the manner described above.3,4 Although these studies uniformly demonstrated that the ICD is effective at terminating ventricular tachyarrhythmias in the presence of severely depressed left ventricular function, the concept of “potential” cardiac deaths salvaged by the device does not adequately address the difficult problem of diminishing survival returns in a patient population with poor residual myocardial function.

Thus, many patients who are at high risk for recurrent life-threatening ventricular tachyarrhythmias and receive ICDs are at similarly high risk for nonarrhythmic cardiac death caused by progressive myocardial dysfunction. Generally, clinical predictors of arrhythmic death and death caused by progressive heart failure in patients with ischemic heart disease overlap extensively and may be better viewed as nonspecific predictors of overall cardiac mortality.30,34-37 Although some studies have found that certain clinical variables such as poor left ventricular function38-40 and persistent inducibility at electrophysiology study41 predict earlier and more frequent ICD discharges, others have not.42,43 This inability to predict accurately the likelihood of arrhythmia recurrences and device utilization in individual patients is elemental to understanding the difficulties in demonstrating ICD survival benefits in diverse groups of patients.

Consideration of Evidence for Prolongation of Survival

In the absence of randomized studies, the influence of the ICD on survival can be partially characterized by two types of studies: direct mortality comparisons between patients who received ICDs and a carefully defined control population who did not or inferred mortality benefit based on prolongation of life after appropriate ICD discharge. Serious and potentially misleading pitfalls associated with these methodologies have been outlined in this article. Three published studies compared survival between ICD recipients and a control population. Fogoros et al3 analyzed mortality in a population of 78 patients with symptomatic drug-refractory ventricular tachyarrhythmias. Twenty-one of 50 patients whose presenting arrhythmias produced loss of consciousness (syncope or cardiac arrest) received an ICD and amiodarone, and 29 received amiodarone alone (because of temporary unavailability of the ICD). The remaining 28 patients had presenting arrhythmias that did not produce loss of consciousness and received amiodarone alone. There were no significant differences between the groups in age, sex, mean ejection fraction, inducibility at baseline electrophysiology study, or actuarial risk of arrhythmia recurrence during follow-up. The cycle length of induced tachycardias was significantly shorter in patients who presented with loss of consciousness compared with those who did not. In patients whose presenting arrhythmias caused loss of consciousness, a significant survival advantage was conferred by the ICD compared with amiodarone therapy alone. After 2 years of follow-up, the sudden death and total mortality rates were 0% and 5%, respectively, in the ICD patients versus 24% and 37%, respectively, in the non-ICD patients. The 2-year sudden death and total mortality rates in the subgroup that presented without loss of consciousness and received amiodarone alone were 4% and 19%, respectively. Importantly, there were differences in nonsudden death rates between groups (lowest in the ICD patients), raising the possibility of treatment selection bias.

Newman et al44 used a retrospective case-control method to examine this issue in a population of patients with sustained ventricular tachycardia or aborted sudden cardiac death. Each patient who received an ICD (n=60) was matched to two historical control patients (n=120) from the same institution according to five clinical variables: age, left ventricular ejection fraction, type of underlying heart disease, presenting arrhythmia, and amiodarone treatment history. Survival estimates for the ICD patients were calculated from the time of device implantation and included surgical mortality; for the control patients, survival estimates were calculated from the time an ICD would have been implanted (ie, clinical recurrence of arrhythmia despite amiodarone or discontinuation of amiodarone because of toxicity). Actuarial survival curves showed a significant difference between the ICD patients and non-ICD matched control patients when followed to 60 months (89% versus 72%, 65% versus 49% at 1 and 3 years, respectively). Total sudden deaths were reduced 50% (10% versus 5%, P<.01) and the 3-year mortality was reduced 31% with the ICD (51% to 35%, P<.01). However, the survival advantage conferred by the ICD appeared to dissipate over time; the survival curves converged by 40 months. This suggests that as sudden tachyarrhythmic deaths are eliminated by the ICD, total cardiac mortality is progressively determined by the nonsudden cardiac death rate, which would be predicted to be similar for the two groups on the basis of the matched baseline clinical variables and assuming that therapies for nonsudden death were longitudinally similar. Similar to Fogoros et al,3 the nonsudden death rate was significantly lower in the ICD group despite matching of relevant baseline variables and may have biased survival in favor of the ICD patients.
A recent study\(^{40}\) retrospectively compared long-term outcomes with the ICD versus drug therapy guided by programmed stimulation in 331 survivors of out-of-hospital cardiac arrest. An ICD was implanted in 150 patients, and 181 patients were treated with electrophysiologically guided antiarrhythmic drug therapy. The patients who received ICDs had significantly lower mean ejection fractions (35% versus 45%) and lower rates of surgical revascularization (22% versus 37%) than patients who received drug therapy. Absence of an ICD was a significant multivariate predictor of cardiac mortality (relative risk of dying, 2.70; \(P=.017\)) and a marginally significant predictor of total (all cause) mortality (relative risk of dying, 2.27; \(P=.06\)). Among patients with ejection fraction \(\geq 40\%\), implantation of an ICD was associated with a survival advantage at 5 years (96% versus 82%) but not at 1 and 3 years compared with patients whose inducible arrhythmias were drug suppressible. Among patients with ejection fraction \(< 40\%\), treatment with an ICD was associated with a survival advantage at 1 year (94% versus 86%) and 5 (64% versus 43%) years compared with patients whose arrhythmias were drug suppressible. Regardless of ejection fraction, patients with persistently inducible arrhythmias who did not receive an ICD had worse survival rates than patients with drug-suppressible arrhythmias or those who received an ICD. Thus, in patients with relatively well-preserved left ventricular function (ie, ejection fraction \(\geq 40\%\)), a lengthy cardiac survival would be expected in the absence of sudden arrhythmic death. The similar survival at 1 and 3 years for patients treated with an ICD compared with those with drug-suppressible arrhythmias suggests that both treatment strategies effectively reduced sudden death and that the mortality outcome was driven by other factors, chiefly nonsudden cardiac death. However, the late survival advantage (at 5 years) conferred by the ICD raises several intriguing possibilities. The increased mortality in the drug-suppressible patients might represent late drug failures, proarrrhythmia, or a change in the cardiac substrate that rendered the drug ineffective. Thus, an extended period of follow-up in patients with relatively well-preserved left ventricular function might be necessary before the survival benefit of the ICD is seen when compared with drug suppression of induced tachyarrhythmias. In patients with impaired left ventricular function (ie, ejection fraction \(< 40\%\)), an early and late (1 and 5 years) survival advantage was conferred by the ICD. This presumably reflects the higher sudden death rate caused by arrhythmia recurrence despite initial drug suppressibility in such patients.\(^{36}\)

Four studies analyzed prolongation of life after a successful rescue by the ICD as a surrogate for measuring survival benefit, and two compared survival outcomes in patients with similar degrees of left ventricular function who did or did not receive an appropriate ICD discharge. Such analyses rely on the delivery of an “appropriate” shock as the reference point for measuring subsequent events. This approach has serious (but not insuperable) limitations, as mentioned previously, and may significantly overestimate (or underestimate) the actual incidence of life-threatening arrhythmia recurrences. Fogoros et al\(^{46}\) analyzed survival in 119 patients with drug-refractory ventricular tachycardia or fibrillation who received ICDs. Forty patients had a left ventricular ejection fraction \(< 30\%\) and 79 had ejection fraction \(\geq 30\%\). Seven of 40 patients with ejection fraction \(< 30\%\) who died and had at least one appropriate shock survived a mean of 11±14 months after the initial shock compared with 3 of 79 patients with ejection fraction \(\geq 30\%\) who died a mean of 42±9 months after their first appropriate shock (\(P<.02\)). As expected, survival after presumed successful arrhythmia termination was longer in patients with high ejection fractions and very limited in some patients with low ejection fractions. Similarly, cumulative survival measured from time of ICD implantation was greater in patients with ejection fraction \(\geq 30\%\) versus those with ejection fraction \(< 30\%\) (survival at 36 months, 96% versus 67%, respectively; \(P<.01\)). The difference in cumulative survival was accounted for by higher rates of death caused by progressive heart failure in the group with lower mean ejection fraction. A more useful comparison would have been the duration of survival after implantation in those patients who died without activation of their device and duration of survival in similar patients who had at least one successful rescue, in which the increment of time between the first rescue and death would represent the survival benefit of the ICD.

This type of data was provided by Myerburg et al\(^{9}\) who followed 60 patients treated with ICDs for recurrent cardiac arrest or failed drug treatment of ventricular tachyarrhythmias. Thirteen deaths occurred during a mean follow-up of 25 months, of which 12 occurred during the posthospital period and were subjected to analysis. The mean time to death among all deaths was 14.8±13.1 months, among deaths with any prior shocks was 14.1±13.9 months, and among deaths with no prior shocks was 16.7±11.5 months (no significant differences). However, among patients who had any shock during follow-up and subsequently died, the mean time to the first valid shock was 2.3±2.0 months, and the mean time to death indexed from the first shock was 14.2±13.9 months, yielding a mean survival increment of 11.8 months. This difference between estimated survival (assuming death at the time of the first shock) and actual survival, measured from the time of ICD implantation, was significant (\(P<.05\)). The delivery of an appropriate shock before death did not bear any relation to the classification of the terminal event as sudden or nonsudden. All four patients whose deaths were classified as sudden experienced ICD discharges before death, and only one was a true arrhythmic sudden death; the other three occurred in the setting of an acute myocardial infarction or acutely decompenated heart failure. Five of eight patients who died nonsuddenly had ICD discharges before death (one patient was censored from analysis). These findings suggest that successful rescue by the ICD from an early arrhythmic death conferred a survival benefit that enabled these patients to live, on average, as long as patients who did not receive a shock (and presumably did not have recurrent ventricular tachycardia or fibrillation) before death. The only clinical variable that was significantly different between the survivors and nonsurvivors in this study was baseline left ventricular ejection fraction, which was lower in the nonsurvivor group (mean ejection fraction, 35% versus 25%, respectively) and independent of whether or not they received any shocks before death.
Bocker et al.\textsuperscript{33} analyzed survival in 107 consecutive patients treated with third-generation ICDs. This study capitalized on the ability of these ICDs to retrieve stored intracardiac electrograms and/or tachycardia cycle lengths (RR interval memory) before device therapy and thus has the merit of documenting arrhythmias before shock delivery. Furthermore, by restricting analysis to fast ventricular tachycardias (>240 beats per minute), the estimation of mortality benefit was made more rigorous. The mortality benefit was estimated from the difference between total arrhythmia-related death (sudden death plus nonsudden arrhythmia-related death) and the rate of occurrence of fast ventricular tachycardia (>240 beats per minute), assuming that most of these events would have been fatal without termination by the ICD. Actuarial survival rate free of events at 6, 12, and 18 months was 100% for sudden death and 97% for nonsudden arrhythmia-related death. Actuarial survival rate free of fast ventricular tachycardia at 6, 12, and 18 months was 83%, 74%, and 69%, respectively. Thus, the estimated survival benefit (difference between total arrhythmia-related deaths and fast ventricular tachycardia) was 14%, 23%, and 28% at 6, 12, and 18 months, respectively. Importantly, the total cardiac death rate was unusually low for an ICD population (5% at 6, 12, and 18 months), possibly reflecting the relatively preserved left ventricular systolic function (mean ejection fraction, 40%).

Levine et al.\textsuperscript{48} reported on survival after first appropriate shock in 218 patients who received an ICD for cardiac arrest or failed drug treatment of recurrent sustained ventricular tachycardia. Of the 197 patients who survived hospitalization, 105 (53.3%) had an appropriate shock within 9.1±11.1 months of follow-up. The mean survival after ICD discharge was 23.8±18 months. There was no difference in mean survival among patients who had appropriate shocks versus those who did not (32.8±19.5 versus 28±19.9 months, respectively), suggesting, as in the Myerburg study,\textsuperscript{9} that a prolongation of life probably attributable to the ICD enabled patients who received shocks to live as long as patients who did not receive shocks before death. Heart failure functional class was the best multivariate predictor of survival after spontaneous shock. Importantly, the wide range of survival times after first appropriate ICD discharge implies that some patients experienced very limited benefit (<1 month). This was most evident in the subgroup with functional class IV heart failure whose mean survival was 0.92±2.3 months, regardless of whether they had a spontaneous shock.

A similar conclusion was reached by Mehta et al.\textsuperscript{45} In their study, 112 patients who received ICDs for drug-refractory ventricular tachycardia or fibrillation were subdivided into two subgroups based on ejection fraction (≥30% or <30%) and followed for a median of 36 months. With the exception of baseline ejection fraction, there were no significant differences between the two subgroups such as age, sex, type of underlying cardiac disease, clinical arrhythmia, or induced arrhythmia. Sudden death mortality at 4 years was 5% and 9% (P>.05) in patients with ejection fractions ≥30% and <30%, respectively. However, after 2 years of follow-up, total cardiac mortality was significantly higher in the group with ejection fractions <30% versus ≥30% (40% versus 12%, P=.05), and this difference persisted at 4 years (43% versus 15%, P<.01). Importantly, there was no significant difference in total cardiac mortality among those patients who had at least one appropriate ICD discharge and those who did not within either ejection fraction subgroup. These findings suggest that successful termination of recurrent ventricular tachyarhythms by the ICD conferred the same survival outcome as patients with a similar degree of left ventricular dysfunction but no recurrent tachyarrrhythmias causing ICD discharge. Consistent with the work outlined previously, total cardiac mortality remained substantial and significantly higher in the subgroup with severely depressed ejection fraction (<30%) regardless of whether there was an appropriate ICD discharge.

Virtually identical conclusions were reached by Grimm et al.\textsuperscript{46} in a retrospective analysis of 241 consecutive ICD patients. Survival among patients who had spontaneous shocks versus those who did not was not significantly different. The only significant multivariate predictor of overall survival was ejection fraction <30%. Importantly, the occurrence of spontaneous shocks increased longitudinally throughout follow-up (15%, 51%, and 76% at 1, 3, and 5 years), confirming earlier observations.\textsuperscript{13,43}

**Predicting Survival Benefits in Prospective ICD Patients**

Despite the methodological limitations outlined previously, these studies provide strong circumstantial evidence that the ICD prolongs survival in certain subsets of patients with lethal ventricular arrhythmias. When viewed in aggregate, a conceptual framework for anticipating ICD mortality benefits begins to emerge. This can be illustrated with hypothetical mortality curves derived from the available data. In patients with preserved left ventricular function (left ventricular ejection fraction >40% to 45%) and none or mild symptoms of congestive heart failure (New York Heart Association [NYHA] class I-II), the relative survival benefit of the ICD compared with drug therapy is likely to be late and may not be demonstrated for years after follow-up (Figure, panel A). This reflects the early efficacy of drug therapy and the low incidence of nonsudden death in such patients and is consistent with data reported by Powell et al.\textsuperscript{40} The late advantage of the ICD may be multifactorial and reflect drug failure, proarrhythmia, or a changing cardiac substrate with altered drug efficacy. In patients with moderately depressed left ventricular function (left ventricular ejection fraction 30% to 40%) and at least moderate symptoms of congestive heart failure (NYHA class II-III), the relative survival benefit of the ICD is likely to be early but may not be sustained. This is compatible with the lower likelihood of arrhythmia suppression, unreliability of programmed stimulation in certain clinical subsets (ie, idiopathic dilated cardiomyopathy), reduced drug treatment options for hemodynamic considerations, and early drug breakthrough despite initial suppressibility in patients with moderate heart failure.\textsuperscript{36,40,47} However, despite the near elimination of sudden death caused by ventricular tachyarrrhythmias, the total cardiac death rate will remain significant because of progressive nonsudden cardiac death. Thus, the long-term effect of the ICD on overall survival will dissipate as nonsudden death su-
death rates are likely to be prohibitive, and conversion of the mode of death from sudden to nonsudden is likely to be early. Additionally, a significant sudden death rate would persist despite the ICD because of the increased incidence of sudden bradyarrhythmias or electromechanical dissociation in these patients, as outlined earlier. This scenario is consistent with survival data reported by several investigators.\textsuperscript{6,9,38,45,48} Although the majority of deaths in these patients are due to progressive heart failure, Kim et al\textsuperscript{48} made the important observation that surgical mortality and arrhythmia-related nonsudden death (ie, death within 24 hours after successful device resuscitation from intractable ventricular tachyarrhythmias) account for a significant proportion of deaths in patients with severely depressed ejection fraction (defined as <30%). Thus, when total arrhythmia-related deaths (sudden death, surgical death, and arrhythmia-related nonsudden death) are considered, the survival benefit in ICD patients with severely depressed ejection fraction is further reduced. However, it would be expected that the use of transvenous nonthoracotomy endocardial lead systems combined with biphasic pulse generators will reduce surgical mortality in all patients, especially those with severely depressed left ventricular function. Despite these sobering observations, the near elimination of sudden tachyarrhythmic death may be meaningful in this high-risk population if medical advances improve survival in severe heart failure or if the patient is a candidate for cardiac transplantation.

**Implications for Future Studies**

The evidence for mortality benefit in patients treated with ICDs versus drug therapy has been reviewed. The benefit is predictably limited in certain subsets of patients and more dramatic in others. Failure to consider the important lessons of this early nonrandomized experience could result in major errors in the design of future randomized trials. These trials should address one fundamental question: Which patients are most likely to derive a significant survival benefit from the ICD? There are two requisite conditions. First, there must be at least one life-threatening arrhythmia recurrence that is successfully terminated by the device. The ability to predict ICD discharges in the individual patient is limited, although it seems obvious that the frequency and density of spontaneous shocks may vary widely across populations. The incidence of appropriate shocks increases progressively over time.\textsuperscript{13,43,46} Thus, ceteris paribus, the survival benefit consequent to successful arrhythmia termination is a time-dependent, cumulative statistic. Since it is not known whether there is a safe outer time limit after device implantation beyond which a life-threatening arrhythmia is unlikely to occur, premature termination of follow-up may significantly underestimate survival benefits. Second, the life expectancy independent of recurrent arrhythmic events must be reasonable. As outlined above, the reduction in total cardiac mortality resulting from a reduction in sudden death will increase as the nonsudden death rate decreases. In patients with significant left ventricular dysfunction and/or ischemic heart disease, the ICD should be viewed as one component of combination therapy (allied with revascularization and aggressive pharmacological treatment of ischemia and...
heart failure) directed at decreasing total mortality. Inclusion of patients at high risk for nonsudden cardiac death (i.e., advanced congestive heart failure, incompletely treated ischemic heart disease, etc) will reduce the survival benefits of the ICD (or any other therapy specifically directed at sudden arrhythmic death). Patients with a low risk of nonsudden cardiac death in whom sudden arrhythmic death is the major long-term threat to survival would be expected to derive the greatest long-term survival benefit from the ICD. Paradoxically, some of these patients would be drug responsive at electrophysiological testing and therefore be expected to have a good overall prognosis even without implantation of the ICD. However, a single unprotected arrhythmia recurrence can be catastrophic and significantly shorten an otherwise lengthy expected survival. If the arrhythmia recurrence rate were low, an extended follow-up (5 to 10 years) would be necessary to demonstrate this benefit. Furthermore, the elimination of arrhythmic drug therapy might reduce deaths caused by late proarrhythmia.

What implications do these observations extend to future studies with the ICD? First, and most important, reasonable expectations for total mortality reductions must be established. These must take into consideration the fact that sudden tachyarrhythmic death constitutes a fraction of total cardiac death, and this fraction may vary dramatically across populations, directly modifying benefits in whom sudden arrhythmic death is the major long-term threat to survival would be expected to derive the greatest long-term survival benefit from the ICD. Paradoxically, some of these patients would be drug responsive at electrophysiological testing and therefore be expected to have a good overall prognosis even without implantation of the ICD. However, a single unprotected arrhythmia recurrence can be catastrophic and significantly shorten an otherwise lengthy expected survival. If the arrhythmia recurrence rate were low, an extended follow-up (5 to 10 years) would be necessary to demonstrate this benefit. Furthermore, the elimination of antiarrhythmic drug therapy might reduce deaths caused by late proarrhythmia.

What implications do these observations extend to future studies with the ICD? First, and most important, reasonable expectations for total mortality reductions must be established. These must take into consideration the fact that sudden tachyarrhythmic death constitutes a fraction of total cardiac death, and this fraction may vary dramatically across populations, directly modifying the mortality benefit accruing from the successful termination of ventricular tachyarrhythmias. The ICD is an unequalled therapy for reducing sudden cardiac death in all populations but may yield limited total mortality benefits in selected subpopulations. Because the total mortality reduction conferred by the ICD may realistically be in the range of 33%, the possibility of a type II error (failure to detect a true difference) is substantial. Sufficient power for detecting a true but moderate difference in mortality must be ensured by a large sample size. In patients with life-threatening ventricular arrhythmias, for example, it is highly unlikely that a significant difference in total mortality would be detected between amiodarone and ICD therapy with a sample size of less than 1000 patients and an extended follow-up period.

Additionally, prolongation of life after successful resuscitation by the ICD should be more fully explored as a measure of clinical benefit. The rapid evolution of intracardiac electrogram storage, noncommitted therapy options, incorporation of hemodynamic sensors into detection algorithms, and other advances in “smart” technology should reduce the controversy regarding the appropriateness of delivered shocks and permit the objective use of some spontaneous shocks as surrogate mortality end points. Identification of patient subgroups with limited survival after successful arrhythmia termination would have important meaning, particularly regarding the application of the ICD as a bridge to cardiac transplantation. Sufficient duration of follow-up must be allowed to explore the possibility that mortality benefits in certain subgroups, such as patients with drug-suppressible arrhythmias, well-preserved left ventricular function, and an otherwise lengthy expected survival, may be relatively late compared with early benefits in patients with reduced left ventricular function. Recent work indicates that left ventricular ejection fraction and the results of electrophysiological testing are time-dependent variables that have different predictive influences on early- and late-phase recurrence after cardiac arrest.49 Ventricular function appears to be a more powerful predictor of early recurrences, whereas the outcome of electrophysiological testing is a more powerful predictor of late recurrences (>6 months) after cardiac arrest. This underscores the importance of patient classification on the basis of electrophysiological testing and ventricular function to stratify ICD population benefits and to provide a reproducible framework for making rational comparisons with alternate therapies.

Conclusions

The ICD has irrevocably altered the landscape for treating patients with malignant ventricular tachyarrhythmias. There is universal agreement that these devices markedly reduce the risk for sudden death in diverse populations. However, this is accompanied by wide variations in overall mortality benefit caused by the influence of other powerful factors that affect survival in the defibrillator population as well as survival measurement bias. Consideration of these factors results in more realistic expectations for survival benefits conferred by the ICD. Future studies with the ICD must recognize these considerations to permit a rational, complete, and unbiased assessment of clinical benefit.

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