Editorial Comment

Survival of Implantable Cardioverter-Defibrillator Recipients
Can the Iceberg Remain Submerged?

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Implantable cardioverter-defibrillator (ICD) devices are now being widely proposed as definitive antiarrhythmic therapy in patients with sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) and in survivors of cardiac arrest. This approach has been recommended as a first line of treatment in sudden death victims.1 Like other therapeutic cardiovascular procedures that have evolved in the last 15 years, application in early clinical trials was initially justified in patients without adequate therapeutic alternatives. Reliable device reversion of VT/VF coupled with a remarkably low incidence of recurrent sudden death in ICD recipients has advanced its therapeutic role and made competition with other antiarrhythmic therapies inevitable.

Now considered “established” clinical practice in gravy ill patients, ethical considerations and use patterns have made controlled trials a formidable challenge. Because of this handicap, several types of outcome analyses have been performed in device recipients. Earliest efforts used historical control data from drug-refractory patients for comparison. This was succeeded by attempts to use the patient as an internal control by analysis of ICD use for VT/VF reversion. Scientific acceptance of such data has been uneven. Temporal disparity in patient recruitment, inevitable in the former approach, could not eliminate the influence exerted by intervening therapeutic refinements. This factor alone makes noncomparable patient populations likely. Equation of device use with aborted sudden death, used in the latter approach, is undermined by available data on device discharge for events other than sustained VT/VF. Conversely, inclusion of only symptomatic discharges in an effort to rigorously screen out other arrhythmias excluded many VT events in which ICD discharge occurs before symptoms develop. Use of event counters with data logging in newer ICD devices is expected to elucidate this clinical scenario.2,3 A third approach used by us and others has been to compare outcome of device-implanted patients who experience VT recurrences on follow-up (ICD users) with those who do not (ICD nonusers).4-6 Comparable outcomes for the two groups have been reported4,6 but also disputed.5 It has been inferred by us that these comparable outcomes result from the near elimination of arrhythmic mortality in patients with recurrent VT/VF after ICD implant.

Presentation of survival analyses in reported ICD experiences has also raked up old controversies and unveiled new challenges. Concern is focused on end points used in such reports, their definitions (sudden, arrhythmic, or non-sudden cardiac), and emphasis (sudden, cardiac, or total mortality). The distillate of data included and/or excluded critically changes the flavor of the outcome. Subgroup analysis is even more vulnerable. It is in this milieu that the current report of Kim et al7 in this issue of Circulation should be viewed. Clinical results of antiarrhythmic therapy in the population in question have often been stratified by cardiac disease and left ventricular function.8 Several earlier studies of drug and device therapy have demonstrated significantly increased cardiac mortality rates in patients with left ventricular ejection fraction of less than 30%.8-10 For ICD patients, these now range from 14% to 43% at 3 years compared with 3–15% for patients with higher ejection fractions.3,9,10 These statistics include sudden death rates, which are uniformly relatively low even in patients with left ventricular ejection fractions of less than 30%. The implication that nonsudden cardiac death, most often related to progressive myocardial dysfunction, accounts for the majority of attrition has been widely accepted. Kim et al challenge this idea and suggest that perioperative mortality and “arrhythmia-related” cardiac death should selectively be included in arrhythmic death estimates of ICD outcome. In their series, these two components account for five of the 12 nonsudden cardiac deaths after ICD implant. This challenge reopens old controversies concerning perioperative and sudden death analyses and initiates some new debate on concordance between sudden death and tachyarrhythmic mortality.

Confidently splitting the etiology of mortality events has been historically difficult in patients with multisystem disorders. Whereas cardiac and noncardiac events are often but not always differentiated, stratification of sudden and nonsudden cardiac mortality has frequently been even more problematic. Interval-based definitions from onset of symptoms for sudden death vary from minutes to 24 hours, although 1 hour is now often accepted.11,12 Unwitnessed death is empirically included, even when noncardiac illnesses are in progress.

The opinions expressed in this editorial comment are not necessarily those of the editors or of the American Heart Association.

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Equation of sudden death with tachyarrhythmic death in principle can also be fallacious. Bradyrhythmic death, particularly in drug-treated patients, can account for up to 20% of recorded cardiac arrests.13 Nonrhythmic cardiac etiologies (e.g., massive infarction, myocardial rupture) or noncardiac mechanisms (e.g., pulmonary embolism) of sudden death operate in these same patients. Agonal ventricular tachyarrhythmias can often complicate these conditions based on tissue metabolic imbalances. ICD activation in this scenario, when detected, is incidental to the mechanism of sudden death and may have little possibility of averting cardiovascular collapse. Even the use of event counters with RR interval measurements and stored intracardiac electrograms in currently investigational devices may fail to resolve this dilemma. The limitations in the sole use of sudden death incidence for assessing recurrent VT/VF events are apparent. In this report, Kim et al use a combination of instantaneous demise and a 24-hour interval after a VT/VF episode to evaluate arrhythmic death. Allowing for the particular nature of this definition, only two of nine deaths after discharge in a relatively small population fall in this latter category. Addition of three perioperative deaths as “arrhythmia related” substantially bolsters this proportion. Clearly, the influence of a limited number of events in a small patient group may appear magnified and should be viewed with caution.

Nevertheless, the principle of total arrhythmia-related death rates in the report of Kim et al deserves careful consideration. They, like many others, have used stratification of mortality events along sudden and nonsudden time bases. Their concern that all perioperative mortality is often excluded from sudden death rates has merit. However, they do not stratify perioperative deaths along the same definitions as subsequent events and include it wholly in arrhythmic death incidence. Similarly, hospital admission for recurrent VT/VF followed by death in 24 hours is similarly considered. Both situations are viewed in light of a stated direct causal relation to the arrhythmia. This argument may not fully address the complex pathophysiological events that result in initiation of VT/VF.14 Some functional influences, such as ischemia, may initiate both mechanical and electrical phenomena. Certainly, experimental studies validate the occurrence of ventricular arrhythmias before any infarction is ever established. The occurrence of VT/VF along with terminal mechanical events may be indivisible and result in nonsudden death with arrhythmic involvement. Anatomic events such as plaque rupture may initiate the same sequence.15 The occurrence of arrhythmic involvement with nonsudden death in patients with extensive cardiac disease, as witnessed in the Kim study both perioperatively and up to 54 months after ICD implant, and a cause-and-effect relation must be viewed with great caution. Certainly, autopsy examination could shed light in some instances but may not be conclusive in others. Many other experiences suggest that progressive myocardial failure dominates this component of mortality. A concomitant increase in the frequency of ICD discharges and earlier device activation can accompany this deterioration.1416 Critical examination of the nature of nonsudden cardiac death will be valuable in extending our knowledge of mortality in ICD recipients.

A secondary theme in this report is the potentially limited benefit derived by patients with left ventricular ejection fractions of less than 30% with ICD therapy. Quantitation of survival benefit in prospective clinical trials has established a firm scientific rationale for the use of widely applied treatments. A much less complete data base exists for ICD therapy. Projected survival rates, even with their attendant limitations, suggest a dismal outcome for these VT/VF patients without ICD intervention.910 One-year projected survival rates range from 36% to 56%, and one report projected a 6% survival at 3 years. Although more frequent device use has been reported in patients with depressed left ventricular function, in our experience, the incidence of ICD use stratified by left ventricular ejection fraction (<30% and >30%) has been comparable after 4 years of follow-up. Cardiac survival for patients with low ejection fractions (≤30%) has been comparable in ICD users and nonusers. This again suggests that the expected negative impact of VT/VF recurrences is avoided by the use of ICD therapy. Finally, measurement of ICD benefit has been until now largely focused on survival data. Another benefit yet to be quantified is the avoidance of prolonged hospitalization, which accompanies recurrences of sustained VT/VF in this population. Prompt arrhythmia reversion by the ICD obviates this clinical and economic burden and merits study. The opportunity to avoid hospitalization may be most valuable to patients, such as those in this report, with limited survival expectations. Clearly, rational minimum limits to life expectancy also must be defined before the institution of ICD therapy. Existing data from cardiac transplant candidates may provide important insights in this issue.18

How can and should the issues raised be objectively addressed? The problem and its multiple facets argue for a controlled randomized clinical trial comparing ICD therapy with the best alternative therapy available for the largest proportion of VT/VF patients. Analogous to all other cardiovascular therapies, the primary end point of such a trial must be total mortality or total cardiovascular mortality. Secondary end points, such as the incidence of sudden death and VT/VF recurrences, should be examined. Prospective definitions of end points consistent with other antiarrhythmic trials should be considered.1920 An intention-to-treat analysis from the point of selection of ICD or alternative therapy is essential. Comparison with medically treated patients in reported clinical studies as discussed by Kim et al is fraught with a variety of perils that will be obviated by using the treatment-intent approach. For example, the medical in-hospital mortality of drug therapy selection empirically or otherwise is rarely available. In one report from our center, during in-hospital establishment of amiodarone therapy, recurrences occurred with a frequency up to 61% with a small but definite in-hospital mortality.21 Proarrhythmic or recurrent cardiac events cannot therefore be estimated. Finally, such an effort would, in subgroup analysis, define the best therapeutic alternative(s) in specific clinical populations and objectively estimate the benefit in various subgroups such as those analyzed in this report. It would respond to concerns of patients, their treating physicians, and investigators, resulting in firmly based therapeutic expectations from ICD therapy. Having once
hoisted this iceberg up from submersion in “established” clinical practice, its totality can then be fully grasped.

References


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