EDITORIAL COMMENT

Learning From a Real-World Analysis of Implantable Cardioverter-Defibrillator Recipients

Comorbidities Matter*

Sumeet S. Chugh, MD, FACC, Kyndaron Reinier, PhD, Eric C. Stecker, MD, MPH
Portland, Oregon

With a 90% near-instantaneous mortality rate, sudden cardiac arrest may be the human disease condition with the most potential of benefiting from preventive interventions. The implantable cardioverter-defibrillator (ICD), one of the more remarkable therapeutic advances of the 20th century, is currently the most effective preventive intervention for sudden cardiac death (SCD). The majority of prospective secondary and primary prevention multicenter trials evaluating the ICD showed a significant beneficial effect on overall mortality, with several meta-analyses observing a clear net benefit compared with medical therapy (1–8).

Accordingly, guidelines have been written, indications have been established, and health care providers are already caring for a rapidly burgeoning population of ICD recipients, particularly for primary prevention indications (9). However, methodology for risk stratification has not developed at the same pace. In the randomized primary prevention ICD trials, the vast majority (60% to 80%) of ICD recipients did not require device therapies during an intermediate follow-up period of 3 to 5 years (1,7). Furthermore, recent population-based analyses indicate that only a minority of SCD cases have severely decreased left ventricular ejection fraction (LVEF); most have either normal LVEF or mildly to moderately decreased LVEF (10,11). Although the LVEF is a reasonable predictor of overall mortality, it is unlikely to be an efficient risk determinant, especially when used as the sole criterion for primary prevention ICD implantation (12). Clearly, methods of risk stratification need to be enhanced significantly, and this is an area of active investigation, but developments will take some time. In the meantime, much can be learned from ongoing evaluations of large groups of ICD recipients.

In this issue of the Journal, Lee et al. (13) have reported their observations from such a “real-world” evaluation of approximately 2,500 ICD recipients with a follow-up of at least 2 years, using a province-wide administrative database in Ontario, Canada. There are several interesting findings, the first being that comorbidities were significant determinants of mortality in ICD recipients. The risk conferred by comorbidities was incrementally related to number of comorbidities. Although not unexpected, because elevated sudden arrhythmic death risk, particularly in an aging populace, is likely to coexist with other morbidities, there has been a lack of such data among ICD recipients. Among other populations, comorbidities such as peripheral vascular disease, chronic obstructive pulmonary disease, and renal disease are established predictors of overall mortality, and ICD recipients are no exception (14). Although the distinction between less versus more advanced diabetes mellitus is often not made, the effect of this condition on both arrhythmic and nonarrhythmic mortality is a recurring theme (15). These findings underscore the need for a heightened awareness of the likely possibility of managing these conditions in ICD patients. However, they should not be construed as direct evidence that these specific comorbidities should influence our criteria for ICD implantation. Most of the analysis focuses on the ICD group alone. Since detailed comparisons were not made and the control group is not convincingly derived from a similar population, this study should not be used to evaluate the decision for ICD implantation. From an administrative database, without availability of ICD events and therapies, we cannot be sure about the specific contributions of comorbidities to arrhythmic versus nonarrhythmic mortality. Despite the improvement in response times, community-based studies of primary cardiac arrest have reported a decline in subjects presenting with ventricular fibrillation (VF) and a rise in the prevalence of pulseless electrical activity (16). Could older ICD recipients and those with more comorbidities be more likely to present with pulseless electrical activity, an arrhythmia that would be unresponsive to ICD therapy? The present analysis is not able to provide answers to such questions. However, because we are still hoping to maximize our ability to identify the patient with the highest risk of ICD-treatable ventricular arrhythmia, these findings could drive the design of future analyses that also reflect actual clinical practice.

Lee et al. (13) also report that heart failure burden was a prominent determinant of mortality. In patients with chronic heart failure and depressed LV systolic function,
risk of sudden death is related to severity of heart failure (17). These observations are also supported by greater benefit of the ICD with more advanced heart failure in the CIDS (Canadian Implantable Defibrillator Study) and DEFINITE (Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation) trials (3,4). However, because there is a 50-50 relationship between sudden death and pump failure mortality (18), there is likely to be a turning point in heart failure severity where mortality from pump failure overtakes the likelihood of ICD-treatable arrhythmic mortality. The randomized trials do not always report a consistent relationship between heart failure New York Heart Association (NYHA) functional class and ICD benefit (no relationship observed in MADIT-II [Multicenter Automatic Defibrillator Implantation Trial-II] [7], but in the SCD-HeFT [Sudden Cardiac Death in Heart Failure Trial] NYHA functional class II did better than III [1]); this inconsistency is likely related both to the differential proportions of various NYHA classes between trials as well as the vulnerability of the NYHA classification in clinical practice. A recent analysis from the MADIT-II pointed out the logical link between longevity conferred by the ICD and the burden of heart failure (19). The ICD recipients live longer, but that also gives them time to develop more heart failure. Here the message from this real world analysis is in agreement with the randomized clinical trials: Implantation of the ICD in a patient should be the marker for a renewed focus on prevention and management of heart failure in that patient.

This analysis found that older age was also a determinant of mortality even in patients in the 65- to 74-year age category. These findings are at variance with the randomized ICD trials. In particular, CIDS reported a significantly greater benefit of the ICD in patients aged over 70 years (3). The fact remains that although the risk of SCD increases with age (20), there have been no randomized trials of ICD implantation conducted specifically in the elderly. Another finding in the present analysis was a trend toward overall improved survival in ICD recipients, but this did not reach statistical significance. There were differences in the ICD and control groups that may have contributed toward negating the mortality benefit of the ICD. The ICD recipients were older, and were more likely to have a history of prior myocardial infarction, peripheral vascular disease, and renal disease—all conditions that can have independent effects on survival.

The analysis was not able to make a distinction between primary versus secondary indications for ICD implantation. Based on the timing of case ascertainment and the fact that 83% of the patients in the study had prior diagnosis of cardiac arrest, ventricular tachycardia (VT) or VF, the vast majority of patients are likely to have been implanted based on a history of prior cardiac arrest or of low EF with inducible VT. Therefore, these findings are unlikely to reflect outcomes in primary prevention ICD recipients as currently identified. The authors have compared their results to SCD-HeFT (1) but comparisons to the CIDS, CASH (Cardiac Arrest Study Hamburg), and AVID (Antiarrhythmics Versus Implantable Defibrillators) secondary prevention trials would be more relevant (3,5,8). The crude mortality rate (7.8% at 1 year and 14% at 2 years) compares well with these 3 trials. However, the significantly lower ICD mortality benefit (2% at 2 years) among patients with prior VT and cardiac arrest in the present analysis may have been confounded by the likely low specificity and positive predictive value of international classification of disease codes for diagnoses such as sudden cardiac arrest and ventricular arrhythmia (20). The randomized trials did not evaluate the mortality burden of individual noncardiac comorbidities.

As acknowledged by the authors, retrospective analyses based on administrative data sources can have significant limitations, including undercoding as well as inadequate specificity. In addition, no information is available regarding mode of death and clinical variables of importance such as the use of beta-blockers and angiotensin-converting enzyme inhibitors—factors that can independently contribute toward decreasing both arrhythmic and nonarrhythmic mortality (21,22).

The authors are to be commended for this real-world analysis in a large number of ICD recipients and control subjects that may well set the stage for subsequent such analyses reflecting actual clinical practice. Their findings emphasize the need for a strong consideration of noncardiac comorbidities in the care of a burgeoning and likely aging ICD population. An ICD implantation in a patient should prompt specific attention toward prevention and management of heart failure in that patient. Most importantly, the findings of this analysis provide much food for thought with regard to the design and conduct of future real-world studies, including the evaluation of whether comorbidities need to be incorporated in the decision for ICD implantation, the need for comparisons between primary versus secondary prevention, the availability of specific detail regarding clinical variables and mode of death, and the effects of age on survival after ICD implantation.

**REFERENCES**


