Implantable Cardioverter-Defibrillators for Primary Prevention of Sudden Death in Heart Failure
Are There Enough Bangs for the Bucks?

Lynne Warner Stevenson, MD

The demonstrated efficacy of implantable cardioverter-defibrillators (ICDs) for reducing sudden death in heart failure trial populations presents a critical challenge to those responsible for the allocation of healthcare resources.\(^1-^3\) The current cost, multiplied by the prevalence of heart failure deemed high-risk, threatens to make this one enterprise the highest priced intervention for the Medicare population. The elegant cost-effectiveness analysis contributed by Dr Mark and colleagues from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) in this issue of Circulation provides an exemplary insight into this challenge.\(^4\) These investigators’ favorable conclusions are consistent with those from a meta-analysis by Sanders et al\(^5\) and with the slightly more conservative implications from the recent cost-effectiveness analysis of the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II by Zwaniger et al.\(^6\)

Article p 135

This editorial will offer an alternative conclusion based on both back-of-the-envelope estimations and scrutiny of model assumptions regarding different phases of survival for heart failure populations. ICDs for primary prevention of sudden death in the heart failure population may be less cost-effective than other recommended heart failure therapies, which are prescribed to modify disease progression and symptoms, decreasing costly hospitalizations as well as mortality.

The Back of the Envelope

Formal cost-effectiveness analysis is complex, but it may be illustrative to begin from simple considerations. A reasonable threshold for cost-effective intervention is often assigned as $40 000 per life-year saved, in line with the present article\(^4\) suggesting a cost of $38 389 per life-year saved and $41 530 per quality-adjusted life-year saved. This is approximately equal to the cost of the defibrillator device and implantation, as currently assessed for reimbursement. (The costs would be lower for the simpler device used in SCD-HeFT, which is not available now, and for outpatient implantation, which was common in SCD-HeFT but not the current standard.) This oversimplification does not encumber the ICD with any additional costs for care required as a result of the device or during the extra life-years enjoyed.

If the cost of each implantation procedure alone is comparable to the cost per life-year saved overall, then some combination of the following outcomes would need to be true, on average:

1. Each device fires and saves its recipient on average approximately 1 life-year;
2. Half of the devices fire and save their recipients an average of 2 years;
3. One fifth of the devices fire and save their recipients an average 5 years; or
4. One tenth of the devices fire and save their recipients an average 10 years.

The first 2 outcomes do not apply, as appropriate device firings occur in fewer than 25% of patients.\(^2\) There is no reason to believe that this device as used in SCD-HeFT saved lives without shocks, as there was no antitachycardia pacing programmed. The third outcome appears the most relevant. For patients receiving ICDs, the annual rate of ICD shock was 7.1% and of appropriate shock for rapid ventricular tachycardia or ventricular fibrillation was 5.1%, with a total of 21% patients receiving appropriate shocks (SCD-HeFT) over the 5 years. To save life-years for $40 000 each therefore, an ICD device would have to confer an average of 5 years of additional life after these potentially life-saving shocks.

Not all appropriate and successful shocks are life-saving. It is generally recognized that rapid ventricular tachycardia may convert spontaneously or persist with adequate circulation long enough for patients to seek medical attention. In nonischemic cardiomyopathy, the number of lives saved may be estimated as half of the number of appropriate shocks, as described by Ellenbogen et al in the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial.\(^7\) From the number of appropriate shocks in SCD-HeFT, a conservative estimate of patients whose lives were saved might be half of the 21%, or 10.5%. Even this exceeds the 7.2% survival benefit actually shown for ICDs compared with placebo by the end of the 5-year study, during which some patients whose lives had been saved by their ICD subsequently died.

The key question is how many life-years are saved after appropriate shocks? On a recent preliminary analysis of the SCD-HeFT subpopulation receiving appropriate shocks, 11%...
died within 24 hours. Those who survived 1 day after the shock then had a median survival time of approximately 1 year. Previous analyses from MADIT-II have also shown that patients who survive a shock for life-threatening tachyarrhythmia have a higher mortality rate than patients without shocks, due largely to death from heart failure. The mortality rate was particularly high for patients surviving a shock for ventricular fibrillation, with over 50% mortality at 2 years. The current data would indicate that approximately 10% of patients receiving ICDs for primary prevention received appropriate shocks, after which they survived more than 1 year. This rudimentary calculation suggests that the cost per life-year saved would be closer to $400,000 than $40,000.

Assumptions Regarding Late Survival

How do the cost-effectiveness models for life-years saved by ICDs arrive at conclusions that differ from those above? The current analysis provides the most complete information to date from which to appreciate the costs. The rigor and transparency of the assumptions and sensitivity analyses provide an excellent framework on which to assemble the current data. Perhaps the greatest challenge was to extrapolate the effect of the ICD beyond the time boundaries of the trial, which was done using multiple thoughtful approaches. The other major cost-effectiveness models by Sanders et al and Zwanziger et al faced similar challenges. The conclusions reached by each were similar, namely that the effect of the ICD to prolong life needed to extend beyond 7 to 8 years in order for the initial cost to be sufficiently defrayed over the lifespan of benefit. These conclusions are entirely consistent with the back-of-the-envelope considerations.

Multiple Slopes for Heart Failure Survival

The current model described 2 differing periods of ICD impact, the first 1.5 years with no benefit and the subsequent 3.5 years during which benefit appeared constant. It is likely, however, that there are several other relevant slopes that represent different populations, with the summed slope dependent on the relative proportions of each. Chronological age was used as a major determinant for extrapolated outcomes beyond 5 years in this analysis. Although heart failure outcomes are worse in older populations, the duration and stage of heart failure may well trump the contribution of age during the relatively short period for these analyses. New York Heart Association class II and class III heart failure have markedly different survival slopes. These differences were highly relevant in SCD-HeFT for benefit, all of which accrued from the class II curves. Furthermore, the farther the curves extend after baseline characterization, the more patients will have transitioned from the class II curve to the class III curve, which has not been a feature in any of the models thus far.

The survival curve with the ICD is dominated by the patients for whom the ICD does not fire. The difference between the survival curves with ICD and without ICD is determined only by the small proportion of patients who have life-threatening arrhythmias for which the ICD should fire successfully. Both SCD-HeFT and MADIT-II data indicate that the survival curve for ICD patients after shocks diverges immediately and sharply downward from the survival curve of patients without shocks. It is most likely that the first occurrence of ventricular tachycardia in a patient with symptoms of heart failure despite optimal medical therapy, including β-blockers, may be a marker for accelerating disease progression, but there remains some concern that the device firings themselves, even if inappropriate, may have adverse effects on survival.

Adjusting for Quality

Although all 3 models included consideration of quality in relation to extended life-years, the current model provides the most detailed analysis based on the time trade-off analysis repeated up to 2.5 years. This measure provides an exact translation of the patient preference for quality versus length of survival and does not require us to impute relationships between preference and symptom class. The value of the added years is strongly dependent on the adjustment factor used, which was 0.85 on average in this study, lower in the MADIT-II analysis. As for the straight survival slopes, the assumption that this remains constant after 2.5 years is at odds with the natural history of heart failure symptoms, which are not alleviated by an ICD. Transition from class II to class III symptoms has been associated with an average decline of the time trade-off utility from 0.89 to 0.65 (a value of 1 indicating a level of quality at which patients would not trade any survival time for better health). The diminution in quality would be expected to intensify further during the later years, particularly as the end is usually caused now by bradycardias in the setting of circulatory exhaustion rather than by sudden tachyarrhythmias. Thus, adjustment for quality during the later years after ICD implantation would further decrease the calculated years gained.

Cost-Effectiveness of Other Therapies

The appropriate threshold for cost-effectiveness is a philosophical and societal decision. There is a distinction, however, between high costs for saving lives of normal life expectancy, such as with seatbelts, and saving life-years, invoked for treatments of chronic illness with limited survival. This distinction is particularly vivid when the treatment does not improve the quality of the years saved.

In developing countries, the cost-effectiveness of the combination of angiotensin-converting enzyme inhibitors and metoprolol has been estimated to be $275 per quality-adjusted life-year saved. These medications delay disease progression, thus not only deferring mortality but also decreasing the number of costly hospitalizations. It is difficult to find a good bargain for a therapy that improves only survival. For instance, the most expensive β-blocker did not decrease hospitalizations compared with the generic β-blocker, so the small resulting benefit in survival would be at a cost of approximately $40,000 per life-year saved, depending on the specific prescription programs contracted. Implantation of an ICD has consistently been associated with increased hospitalizations, only some of which can be attributed to the small increase in years alive at risk. On the other hand, devices such as the resynchronization pacemaker that improve survival and
improve symptoms sufficiently to decrease hospitalizations could easily come in under the $40,000 threshold per adjusted life-year when high-responder populations are chosen.

It is curious that devices need only to be proven cost-effective, whereas interventions requiring dedicated personnel to manage care have traditionally been required to be cost-saving. Meta-analyses of heart failure management programs delivered by specialized multidisciplinary teams (as opposed to impersonal call centers) show consistent decreases in hospitalizations and improvements in quality of life and are cost-neutral or cost-saving. It may be necessary to introduce these programs into device clinics for optimal implementation of medical therapies known to be effective to decrease the heart failure disease progression that currently limits the duration of ICD benefit.

What Do We Need to Know Next?
The model presented by Mark et al has advanced our understanding of the factors determining ICD benefit. The most important factors currently are the rate of appropriate device firing in clinical subsets and the duration of survival afterward. It is particularly important that these factors be determined in the actual population receiving ICDs, who are older and present more comorbidities than represented in the trial populations. Fortunately, these key factors can be ascertained and tracked in a large contemporary national cohort without the need for new randomized trials. Since the initiation in April, 2006, of the American College of Cardiology National Cardiovascular Data Registry (ACC-NCDR) registry for implantable defibrillators, over 11,000 patients have been enrolled, more than 10 times the ICD patients from SCD-HeFT or MADIT-II. Although currently these data include only the initial implantation, these patients are clinically well characterized at the time of implantation, and a high priority is to institute longitudinal follow-up of device firings and survival in specified subgroups. This information is vital to direct the most effective deployment of this potentially life-saving therapy. It should still be possible to identify the right patients at the right time for ICD implantation to deliver enough bangs for the bucks.

Sources of Funding
Dr Stevenson has received research support from Medtronic, Inc.

Disclosures
Dr Stevenson has received honoraria from and has served as a consultant on the advisory board of Medtronic, Inc.

References

Key Words: Editorials ▪ cardiomyopathy ▪ death, sudden ▪ defibrillation ▪ heart failure ▪ defibrillators, implantable
Implantable Cardioverter-Defibrillators for Primary Prevention of Sudden Death in Heart Failure: Are There Enough Bangs for the Bucks?

Lynne Warner Stevenson

Circulation. 2006;114:101-103
doi: 10.1161/CIRCULATIONAHA.106.637405
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/114/2/101

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/