Life-Years Gained From Defibrillator Implantation
Markedly Nonlinear Increase During 3 Years of Follow-Up and Its Implications

Tushar V. Salukhe, BSc, MRCP; Konstantinos Dimopoulos, MD; Richard Sutton, DMedSci; Andrew J. Coats, MA, DM; Massimo Piepoli, MD, PhD; Darrel P. Francis, MA, MRCP

Background—Although treatment benefit in randomized controlled trials of defibrillators is often summarized by the numbers of lives saved (absolute risk difference), this may not be a good representation of what matters most to patients, namely, the amount of life they should expect to gain from implantation. The estimate of gain in life-years may depend on duration of follow-up. In this study, we examine this dependency.

Methods and Results—We estimated, from published data of 8 landmark defibrillator trials, the cumulative benefit in life-years gained at time points from 3 months to 3 years. Because the trial populations, clinical status, and prognosis varied widely between studies, we expressed for each study the benefit at each time point as the proportion of benefit at 3 years. The average dependency of the benefit on duration of follow-up was then calculated. We found that the number of life-years gained from 1 device implantation increases with length of follow-up considered. Importantly, this increase is markedly nonlinear. Within the 3-year span addressable, the benefit rises with the square of time (gain \( \propto t^{1.94} \), \( R^2 = 0.998 \), \( P < 0.001 \)).

Conclusions—Measurable benefit from a defibrillator to patients’ life spans (life-years gained) is dramatically dependent on the time window over which the benefit is assessed. Because the effort of implantation is front loaded, yet benefit grows with time, the choice of an early time point artificially reduces apparent benefit and artificially increases the apparent number needed to treat to prevent an event. These are useful considerations for the formulation of treatment policy (and even for planning of the follow-up phase of clinical trials). (Circulation. 2004;109:1848-1853.)

Key Words: survival ■ defibrillator ■ follow-up studies

Implantation of a defibrillator differs from administration of a drug in that the therapeutic benefit continues to evolve long after the administration. Costs of drug therapy are approximately linearly related to follow-up duration, whereas device therapy has very front-loaded costs. Therefore, although economic evaluation of drug therapy may be valid over any arbitrary time span, there is only 1 valid time span over which to evaluate the benefits of device implantation—the life span of the device, typically 5 to 7 years. This long-term information is not always available from defibrillator trial data.

A mortality statistic rarely addressed in trial publications but critically important from the patient’s perspective is how many more years of life they can expect if a device is implanted. Funders, too, are interested in the expected gain in life-years per device implanted. Expected gain in life span can be evaluated from trial data easily, as the area between the survival curves for the device and no-device groups, as shown in Figure 1.

Simple inspection of Figure 1 reveals that the observed number of life-years gained per device implanted increases as the duration of follow-up increases. In the present study, we set out to examine how the number of life-years gained per device implanted is related to the follow-up duration and to assess the implications for the design of device trials and the evaluation of their results.

Methods

Search Strategy
The trials included in the present analysis were located through the Medline database. Key words used for searching for studies included (automated) implantable cardioverter-defibrillator, (A)ICD, survival, mortality, and randomized controlled trial.

Inclusion Criteria
We identified the landmark trials that compared defibrillator implantation with medical therapy alone (or no therapy) and that reported survival presented in the form of Kaplan-Meier curves. The clinical status of patient populations studied differed between trials. In all
trials, patients included were at high risk of ventricular arrhythmias, and coronary artery disease was common in most trial patients. Table 1 summarizes the trials included in the present study.

Analysis

All the studies presented, in the public domain, Kaplan-Meier curves that showed the proportion of survivors in each arm against time. With calibrated enlargements of these Kaplan-Meier survival curves, at 3-month intervals from the beginning to the end of the study, the absolute difference in survival probability between the curves was measured at each time point. The segmental area between the 2 curves was calculated for each 3-month interval, and cumulative area between the curves for each time point was calculated as the cumulative sum of area segments. The cumulative area represents the life-years gained (survival benefit) from device therapy at any given time point in the study.

The shortest maximum follow-up period among the trials included in the present study was 3 years. Therefore, for the purpose of analysis, the cumulative area between curves (life-years gained) was expressed as a proportion of the absolute gain at 3 years. To assess the behavior of survival benefit of defibrillator therapy with duration of follow-up, the 3-year data were averaged across the 8 trials to obtain overall trends for life-years gained.

Results

Characteristics of Included Trials

Eight trials were identified with the stated criteria. Their characteristics are shown in Table 1. Seven were randomized, and in the eighth, patients were allocated by sensitivity to amiodarone. Different durations of survival follow-up were presented in the 8 trials, but all provided survival curves for at least 3 years.

### TABLE 1. Description of Trials Included in the Study

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Treatment Groups</th>
<th>Clinical Setting</th>
<th>N</th>
<th>Mean Follow-Up Period</th>
<th>Reported Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD vs medical therapy</td>
<td>RCT</td>
<td>ICD vs antiarrhythmic drug therapy</td>
<td>Patients who survived cardiac arrest after an old myocardial infarction</td>
<td>60</td>
<td>2.25 y</td>
<td>22% Reduction in mortality in ICD arm at 2.25 y (P&lt;0.0001)</td>
</tr>
<tr>
<td>MADIT</td>
<td>RCT</td>
<td>ICD vs antiarrhythmic drug therapy or no therapy</td>
<td>Patients with prior myocardial infarction, documented nonsustained VT, and nonsuppressible VT on EP study</td>
<td>196</td>
<td>2.25 y</td>
<td>22% Reduction in mortality in ICD arm at 2.25 y (P&lt;0.009)</td>
</tr>
<tr>
<td>AVID</td>
<td>RCT</td>
<td>ICD vs antiarrhythmic drug therapy</td>
<td>Patients resuscitated from VF or symptomatic sustained VT and LV ejection fraction &lt;40%</td>
<td>1013</td>
<td>3 y</td>
<td>31% Relative risk reduction in mortality in ICD arm at 3 y (P&lt;0.02)</td>
</tr>
<tr>
<td>MUSTT</td>
<td>RCT</td>
<td>ICD vs no therapy</td>
<td>Patients with coronary artery disease, LV ejection fraction &lt;40%, and EP-stimulated sustained VT</td>
<td>704</td>
<td>5 y</td>
<td>6% Reduction in overall mortality in ICD arm at 5 y (P&lt;0.001)</td>
</tr>
<tr>
<td>CIDS</td>
<td>RCT</td>
<td>ICD vs amiodarone</td>
<td>Postinfarct sudden death survivors; patients resuscitated from VF or VT or with unmonitored syncope</td>
<td>659</td>
<td>5 y</td>
<td>20% Relative risk reduction in mortality with ICD therapy at 5 y (P=NS)</td>
</tr>
<tr>
<td>CASH</td>
<td>RCT</td>
<td>ICD vs antiarrhythmic drug therapy</td>
<td>Patients resuscitated from cardiac arrest due to ventricular arrhythmia</td>
<td>1987</td>
<td>4.75 y</td>
<td>23% Reduction in mortality rate in ICD arm at 4.75 y (P=NS)</td>
</tr>
<tr>
<td>ICD vs amiodarone</td>
<td>RCT</td>
<td>ICD vs amiodarone</td>
<td>Patients with prior myocardial infarction and EP-stimulated sustained VT. Patients with amiodarone-resistant VT were assigned to ICD arm and the rest to the amiodarone arm.</td>
<td>84</td>
<td>5.25 y</td>
<td>29.5% Reduction in overall mortality at 5.25 y (P=0.03)</td>
</tr>
<tr>
<td>MADIT II</td>
<td>RCT</td>
<td>ICD vs no treatment</td>
<td>Patients with myocardial infarction and LV ejection fraction &lt;30%</td>
<td>1232</td>
<td>1.67 y</td>
<td>5.6% Reduction in overall mortality in ICD arm at 20 mo (P=0.01)</td>
</tr>
</tbody>
</table>

ICD indicates implantable cardioverter defibrillator; RCT, randomized controlled trial; VT, ventricular tachycardia; EP, electrophysiology; AVID, Antiarrhythmics Versus Implantable Defibrillators; VF, ventricular fibrillation; LV, left ventricular; and NRT, nonrandomized trial.
Life-Years Gained From Device Implantation From Individual Trials
Kaplan-Meier survival curves in the device and no-device arms of each of the trials are shown in Figure 2. Under each Kaplan-Meier curve is a graphical representation of cumulative life-years gained, calculated at 3-month intervals. Below this, the cumulative life-years gained are expressed as a proportion of the gain seen at 3 years. This approach makes it possible to visualize the comparative gain at different time points despite differences in absolute gain from individual trials.

Averaged Pattern of Benefit Across All Trials
With the gain observed at 0 years standardized at 0 and the gain observed by 3 years standardized at 100% for each trial, the average pattern of gain between 0 and 3 years was determined by averaging the graphs, as shown in Figure 3. This pattern was clearly not linear with time. The best-fit power-law relationship was gain = t^1.94, R^2=0.998, P<0.001.

Potential Impact of Reduced Duration of Observation on Number Needed to Treat
If fewer life-years are shown to be gained at earlier time points, the number of patients that must be treated to gain 1 life-year will be higher. Table 2 shows, for each trial, how the number needed to treat to gain 1 life-year declines dramatically as follow-up duration is lengthened from 1 to 3 years.

\[ y = 0.1315x^{1.9385} \]
\[ R^2 = 0.9984 \]
In Table 3, the averaged number needed to treat across trials is expressed as a multiple of its value at 3 years. This table clearly demonstrates how the number needed to treat is artificially inflated if analysis is conducted not at 3 years but at an earlier time point. If examined at 2 years, for example, the number needed to treat to gain 1 life-year would be 1.9 times higher than the number needed to treat when the data are examined at 3 years. More dramatically, at 1 year, the number needed to treat to save 1 life-year is 7.1 times higher than the number needed at 3 years.

**Discussion**

Benefit from defibrillator implantation (measured in life-years gained) rises with time, and much more than linearly. It appears to rise with the square of time over the time period addressed by the present study. This ballooning of benefit should be taken into account when studies are planned and in evaluating the clinical and economic merits of device implantation.

**TABLE 2. Individual Trial Data Demonstrating Impact of Follow-Up Time on Observed Benefit (Life-Years Gained per Device Implanted) and on Observed Number Needed to Treat to Gain 1 Life-Year**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Life-Years Gained per Device Implanted</th>
<th>Size of Number Needed to Treat to Gain 1 Life-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 Year</td>
<td>2 Years</td>
</tr>
<tr>
<td>Wever et al¹</td>
<td>0.10</td>
<td>0.30</td>
</tr>
<tr>
<td>MADIT²</td>
<td>0.11</td>
<td>0.30</td>
</tr>
<tr>
<td>AVID³</td>
<td>0.05</td>
<td>0.12</td>
</tr>
<tr>
<td>CIDS⁴</td>
<td>0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>MADIT II⁵</td>
<td>0.01</td>
<td>0.06</td>
</tr>
<tr>
<td>CASH⁶</td>
<td>0.01</td>
<td>0.09</td>
</tr>
<tr>
<td>Schlüpf⁷</td>
<td>0.07</td>
<td>0.23</td>
</tr>
<tr>
<td>MUSTT⁸</td>
<td>0.07</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Number of life-years gained is the most meaningful measure of benefit to a patient facing a grim prognosis. This is identical to the number of life-years gained per device implanted, which is arguably the most important measure in economic analyses. Numerically, it is identical to the area between the Kaplan-Meier survival curves (when survival is plotted on a scale from 0 to 1, and follow-up time is measured in years).

How have absolute risk difference and its reciprocal, number needed to treat to prevent 1 event, become so universally applied as a measure of effectiveness? Perhaps they have been adopted by default because of their utility in evaluating other therapies. Absolute risk difference (and number needed to treat to prevent an event) can validly describe the merits of a single therapy aimed at preventing a single event in the short term, for example, a course of antibiotics to prevent septicemia from leading to death, or thrombolysis for myocardial infarction to prevent death. But for evaluation of one-off therapies with front-loaded costs that provide continuing protection in the face of ongoing event risk, absolute risk difference and number needed to treat are the wrong measures because they cannot represent the dramatic growth of benefits with time.

Why does the number of life-years gained rise so markedly with time? The fundamental reason is that the vertical gap between 2 survival curves enlarges with time, whereas the horizontal duration of follow-up also lengthens with time. The number of life-years gained, being the area enclosed by the survival curves, therefore grows approximately with the square of follow-up duration for the 3 years after implantation.

Pooling study data as we have done allows us to observe patterns that are likely, in individual studies, to be overwhelmed by inevitable natural random variation. For example, in the Multicenter Automated Defibrillator Implantation Trial II (MADIT II),⁷ the Canadian Implantable Defibrillator Study (CIDS),⁵ and the Cardiac Arrest Study Hamburg (CASH),⁶ the survival curves appear to begin relatively parallel and then diverge later, whereas in Wever...
et al,1 Schlappfer et al,6 and the Multicenter Unsustained Tachycardia Trial (MUSTT),4 the curves appear to diverge earlier. In fact, there are no peculiarities of the former trials to explain the unique delayed survival benefit effect. It is far more plausible that there is an underlying trend for an approximately linear divergence in early survival (albeit with a different pair of slopes in each study because of different baseline risks), which is best seen when the different baseline risks are corrected for and random noise is averaged out by pooling data.

Clinical Implications

Trials of device therapy are often terminated and the results reported long before the full clinical benefit is observed.7,9 Typically, this occurs because the trial design commits the investigators to stopping the trial if and when statistical cutoffs are reached. At this predetermined trial stopping point, the true benefit, in numbers of life-years gained, may be grossly underestimated. A squared relationship implies that at 1 year, one can see only approximately 1/9 of the benefit that one would be able to see at 3 years. This large discrepancy is not widely addressed. The InSync ICD,10 CONTAK CD,11 and COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure) trials, for example, had mean follow-up periods of 1 year or less.

The second clinical implication is that we should be wary of a reported “number needed to treat to prevent an event” in device trials. Any published number needed to treat to prevent an event applies only to 1 follow-up duration (and declines with longer follow-up). But more importantly, the number needed to treat to gain 1 life-year, a more clinically and economically valid measure, declines very dramatically with time. As shown in Table 3, terminating a trial at 1 year instead of 3 years would artificially increase the number needed to treat by 7-fold. Thus, the MADIT II7 trial, which had a mean follow-up of 20 months, led to many making the inappropriate conclusion that 18 defibrillators would be required to save 20 months of life.

Study Limitations

In this study, survival was examined to 3 years, a period for which Kaplan-Meier survival data were available for all the studies. Although the survival curves appear to gradually diverge during this time, they may not do so in later years, and indeed, they must ultimately converge when all the patients die. Thus, from the present study, we cannot be certain what the relationship is beyond 3 years. Moreover “real-life” patients typically have more coexisting morbidity than is seen in patients recruited for randomized controlled trials. Some of this comorbidity will generate excess mortality that will not be reduced by the presence of a defibrillator, and therefore the survival benefit will be attenuated. Nevertheless, on the assumption that within the time period addressed in the present study, deaths due to comorbidity affect both randomized groups equally and approximately linearly, then the relationship of life-years gained (area between the curves) and follow-up duration would remain quadratic.

One of the trials included was not randomized.8 In that trial, patients with prior myocardial infarction and electrophysiologically stimulated sustained ventricular tachycardia were classified as amiodarone sensitive or amiodarone refractory based on repeat electrophysiology study after amiodarone therapy. Amiodarone-resistant patients were assigned a defibrillator, and those who were sensitive received amiodarone. This unique prospective observational trial was included because of its landmark status, extensive follow-up, and the fact that any bias within it would have reduced rather than enhanced the apparent benefit of defibrillators.

It is a potential weakness of the study that the survival proportions were obtained from the published data. However, all the trials chose to use Kaplan-Meier graphs (rather than equivalent numerical values at the multiple time points required for our analysis), and they will have ensured that the published graphs are accurate. Our measurement of survival difference from magnified, calibrated representations of the published survival proportions had in all cases a resolution of <0.01. The coefficient of variation of life-years gained was 2.4% (intraobserver) and 3.5% (interobserver). We approached all the trial groups to obtain raw data, but these data were not uniformly available. To avoid bias, we decided to use the published data, which are uniformly available for all these trials.

Conclusions

The expected benefit in life span (life-years gained) for a patient who has a defibrillator implanted is dramatically dependent on the time window over which the benefit is assessed. For the first 3 years, this benefit rises with the square of time. In clinical or economic evaluations of device implantation, it is important (1) to use life-years gained as the measured variable and (2) not to cut short the duration of follow-up to the (often early) date at which statistical significance becomes evident.

Acknowledgments

Dr. Salukhe is supported by the Robert Luff Fellowship and the British Heart Foundation, Dr Dimopoulos is supported by the European Society of Cardiology, and Dr. Francis was supported by the British Heart Foundation.

References


Life-Years Gained From Defibrillator Implantation: Markedly Nonlinear Increase During 3 Years of Follow-Up and Its Implications
Tushar V. Salukhe, Konstantinos Dimopoulos, Richard Sutton, Andrew J. Coats, Massimo Piepoli and Darrel P. Francis

_Circulation_. 2004;109:1848-1853; originally published online April 5, 2004;
doi: 10.1161/01.CIR.0000125522.10053.29

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 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/109/15/1848

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/