Are Implantable Cardioverter Defibrillator Shocks a Surrogate for Sudden Cardiac Death in Patients With Nonischemic Cardiomyopathy?

Kenneth A. Ellenbogen, MD; Joseph H. Levine, MD; Ronald D. Berger, MD; James P. Daubert, MD; Stephen L. Winters, MD; Eugene Greenstein, MD; Alaa Shalaby, MD; Andi Schaechter, RN; Haris Subacius, MA; Alan Kadish, MD; for the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators

Background—Ventricular tachyarrhythmias long enough to cause implantable cardioverter defibrillator (ICD) shocks are generally thought to progress to cardiac arrest. In previous ICD trials, shocks have been considered an appropriate surrogate for sudden cardiac death (SCD) because the number of shocks has been thought to be equivalent to the mortality excess in patients without ICDs. The practice of equating ICD shocks with mortality is controversial and has not been validated critically.

Methods and Results—The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial was a prospective, randomized, multicenter trial of ICD therapy in 458 patients with nonischemic cardiomyopathy. Patients were randomized to receive standard medical therapy (STD) or STD plus an ICD. Shock electrograms were reviewed, and the cause of death was evaluated by a separate blinded events committee. There were 15 SCD or cardiac arrests in the STD group and only 3 in the ICD arm. In contrast, of the 229 patients randomized to an ICD, 33 received 70 appropriate ICD shocks. Patients in the ICD arm were more likely to have an arrhythmic event (ICD shock plus SCD) than patients in the STD arm (hazard ratio 2.12, 95% CI 1.153 to 3.893, \( P = 0.013 \)). The number of arrhythmic events when one includes syncope as a potential arrhythmic event was similar in both groups (hazard ratio 1.20, 95% CI 0.774 to 1.865, \( P = 0.414 \)). Approximately the same number of total events was noted in each arm when we compared syncope plus SCD/cardiac arrest in the STD arm with SCD plus ICD shocks plus syncope in the ICD arm.

Conclusions—Appropriate ICD shocks occur more frequently than SCD in patients with nonischemic cardiomyopathy. This suggests that episodes of nonsustained ventricular tachycardia frequently terminate spontaneously in such patients.

Key Words: sudden death ■ arrhythmia ■ heart arrest ■ syncope ■ defibrillation

Patients with nonischemic dilated cardiomyopathy are at an increased risk for sudden cardiac death (SCD).1 A number of studies have shown syncope is an indicator of poor prognosis in this patient population.1–5 Specifically, patients who experience syncope have an increased risk of SCD.3–5 Several small studies examining the role of ICD therapy in these patients have shown an increased rate of appropriate ICD shocks.5–7 In some of these studies, appropriate ICD shocks have served as a surrogate for SCD. The underlying assumption in these studies is that episodes of ventricular tachycardia that are long enough to result in an ICD shock are likely to have caused SCD.

Editorial p 764
Clinical Perspective p 782

The DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) trial was a prospective, randomized trial of ICD therapy in patients with nonischemic cardiomyopathy.8 This trial demonstrated that ICD therapy produced a decrease in SCD and a trend toward a decrease in all-cause mortality.

We sought to determine whether ICD shocks in this patient population could serve as a surrogate for SCD. We reviewed the shock electrograms and the causes of death in this trial to
ICD Shocks in Nonischemic Cardiomyopathy

Methods
The DEFINITE trial is described in detail elsewhere. Briefly, DEFINITE was a randomized, prospective investigator-initiated study. Inclusion criteria were age between 21 and 80 years, nonischemic cardiomyopathy with a left ventricular ejection fraction ≤35%, history of symptomatic heart failure, and within the past 6 months, the presence of one of the following: nonsustained ventricular tachycardia on telemetry monitoring or Holter monitoring and/or an average of 10 premature ventricular contractions per hour on a 24-hour Holter monitor. Patients were excluded from enrollment if they had New York Heart Association class IV heart failure, were candidates for an ICD, or had a permanent pacemaker. Each patient was randomized to standard oral medical therapy for heart failure or standard oral medical therapy plus an ICD. The primary end point of the study was death due to any cause. A prespecified secondary end point was sudden death due to an arrhythmia. In this trial, at least 85% of patients received β-blockers, ACE inhibitors, and diuretics. The ICDs were programmed to VVI pacing at 40 bpm with a single tachycardia detection window programmed to a lower rate of 180 to 200 bpm. Antiarrhythmia pacing was not programmed unless monomorphic ventricular tachycardia was induced at a rate of 140 to 190 bpm. The cause of death was determined by an events committee whose members were unaware of the patients’ treatment assignments.

All shocks were reviewed by a separate committee. Shocks were classified by the committee as inappropriate or appropriate, and then appropriate shocks were further classified as monomorphic ventricular tachycardia, polymorphic ventricular tachycardia, or ventricular fibrillation. An episode was classified as monomorphic ventricular tachycardia when the electrogram had a uniform and constant morphology and amplitude, as polymorphic ventricular tachycardia when the electrogram showed a relatively constant amplitude but showed a shift in morphology or axis during the recording, and as ventricular fibrillation when a constant shift in axis and morphology of the electrogram was accompanied by marked and variable changes in electrogram amplitude (Figure 1).

Statistical Analysis
The baseline characteristics of the 2 groups were compared with the use of 2-sample t tests for continuous variables and χ² tests for categorical variables. The log-rank test was used to compare Kaplan-Meier survival curves in the 2 groups, and the Cox proportional-hazards model was used to adjust for covariates and to estimate the hazard ratio and corresponding 95% CIs in the ICD group compared with the STD group. All probability values were 2-tailed.

The primary end point in the present analysis was sudden arrhythmic death or being resuscitated from SCD in STD arm and appropriate shock or sudden arrhythmic death in the ICD arm. For the purposes of secondary analyses, combinations of all-cause mortality, indeterminate shocks, and syncope were also used as target events. Because the end points used in all analyses of the present study were composed of multiple events, only the earliest event was counted, and patients were censored after that point in this analysis. For example, consider the case in which the combined end point was defined as presence of syncope, shock, or sudden death. If a patient experienced all 3 in that chronological order, an occurrence of an event was recorded on the date of syncope, and the patient was no longer included in the analysis. Furthermore, all patients who crossed over from their original group, including 2 ICD patients who never received their implants, were censored from the analysis at the time of the crossover.

Results
Four-hundred fifty-eight patients with nonischemic dilated cardiomyopathy were enrolled. The baseline patient characteristics have been reported and are summarized in Table 1. Two-hundred twenty-nine patients were randomized to receive an ICD, and 227 received the device. Although the primary data analysis for DEFINITE was performed on the basis of an intention-to-treat analysis, because patients who did not receive an ICD could not experience ICD shocks, the 2 patients randomized to an ICD but who did not receive one were excluded from the shock analysis.

ICD Shocks
A total of 33 patients received 70 appropriate shocks, and 47 patients received 86 inappropriate shocks. Twelve patients received 18 shocks that the events committee could not reliably classify as appropriate or inappropriate. Of the 70 shocks classified as appropriate, 37 were for monomorphic ventricular tachycardia, 13 for polymorphic ventricular tachycardia, and 19 for ventricular fibrillation; 1 episode of ventricular tachycardia could not be clearly characterized as either monomorphic or polymorphic. The mean±SEM cycle length was 272±9 ms for monomorphic ventricular tachycardia, 211±11 ms for polymorphic ventricular tachycardia, and 183±14 ms for ventricular fibrillation (Figure 2). Of the 86 inappropriate shocks, 46 were due to atrial fibrillation and 31 to supraventricular tachycardia or sinus tachycardia; in 9 episodes, the investigators believed the shock was inappropriate, but a precise diagnosis could not be made.

Syncope
There were 34 episodes of syncope in the STD group and 39 in the ICD group. Twelve episodes of syncope in the ICD group were associated with an appropriate shock, and 27 episodes in the ICD group were not associated with an appropriate ICD shock. There was insufficient clinical information available to make a definitive diagnosis with regard to the potential cause of syncope or to allow specific causes of syncope to be included in the analyses.

Outcomes: Shock and Sudden Death
For statistical analyses of the primary and secondary end points, only the first event in each patient was used, because the first arrhythmic event could theoretically be fatal. There were no differences in demographic characteristics between the patients who did and did not receive appropriate ICD shocks. Patients who only received ICD shocks that could not be classified appropriately are excluded from this summary.

There were 15 fatal arrhythmic events, 13 SCDs, and 2 cardiac arrests in the STD group and 3 SCDs or cardiac arrests in the ICD group. Only 1 of the 3 SCDs in the ICD arm was not preceded by an appropriate shock. Twenty-six of the STD patients crossed over and received an ICD. These patients were censored from the analysis at the time of ICD implantation. The reasons for crossover were: syncpe (12 patients), New York Heart Association class

Ellenbogen et al
Figure 1. Intracardiac electrograms showing recordings of monomorphic ventricular tachycardia (top; MVT), polymorphic ventricular tachycardia (middle; PMVT), and ventricular fibrillation (bottom; VF).
III or IV heart failure and nonsustained ventricular tachycardia (6 patients), bradycardia requiring device implantation (3 patients), physician preference (3 patients), and resuscitated SCD (2 patients). There were no significant differences between the crossover patients and those maintained on medical therapy, except for a mean age that was 5 years younger in the patients who crossed over to ICD therapy ($P = 0.026$). Additionally, 2 ICD patients refused ICD implant, 1 patient had the device deactivated, and 1 patient had the device removed. As with the STD patients, these 4 patients were censored from the study from the time that they could no longer receive ICD therapy.

If each patient who received an appropriate ICD shock was considered to have a sustained ventricular arrhythmia, then there were 34 episodes (33 shocks and 1 death without prior shock) in the ICD group compared with 15 cardiac arrhythmic deaths in the STD group (hazard ratio [HR] 2.12, 95% CI 1.15 to 3.89, $P = 0.013$). Kaplan-Meier survival curves for freedom from an arrhythmic event are shown in Figure 3. Additionally, if the 12 patients who received shocks that could not be fully classified were also included, then there were 40 patients who experienced arrhythmic events in the ICD group and 15 in the STD group (HR 2.44, 95% CI 1.35 to 4.42, $P = 0.003$). The adjusted HR was 2.074 (95% CI 1.13 to 3.82, $P = 0.019$). No covariates were significant predictors of survival in the multivariate model.

A secondary analysis was also performed in which patients receiving STD therapy who crossed over to receive an ICD were not censored at the time of crossover but instead were followed up until an appropriate shock occurred or through the end of the trial. In this analysis, appropriate ICD shocks in the crossover group were also considered to be an arrhythmic event, a worst case assumption. When these assumptions were used to define events, the HR decreased to 1.89 (95% CI 1.07 to 3.34), but a significant difference between the ICD therapy group and the STD therapy group still existed ($P = 0.027$).

If one considers syncope as a potential arrhythmia and adds the number of syncopal events to the number of

![Scattergram - VT/VF Cycle Length](image)

**Figure 2.** Scattergram showing cycle lengths of all episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF).
arrhythmic events (eg, sudden death, cardiac arrest, or appropriate ICD shock) while censoring crossover patients at the time of ICD implantation, then similar numbers of patients in each group experienced an arrhythmic event (35 events in the STD group and 46 in the ICD group; HR 1.20, 95% CI 0.77 to 1.87, \(P=0.414\); see also Table 2). Kaplan-Meier survival curves for freedom from an arrhythmia event when syncope was added are shown in Figure 4. Note that in contrast to the survival curves that excluded syncopal episodes, the inclusion of syncopal episodes as potential arrhythmic events led to comparable numbers of events in the 2 groups.

If appropriate shocks in the crossover group are included in the analysis in addition to syncope (crossover cases in the STD arm are not censored), the difference in hazard rates between the 2 groups decreases even further. In this analysis, 6 additional events are counted in the STD group, and the HR approaches unity (HR 1.08; 95% CI 0.71 to 1.65, \(P=0.720\)). Adjustment for age, sex, New York Heart Association class, and left ventricular ejection fraction did not substantially alter any of these HRs.

Five of the 33 patients for whom appropriate therapy was delivered died during the trial. Only 1 of the 5 patients died within the first year of experiencing 2 appropriate shocks for ventricular fibrillation; however, the number of events was too small to determine whether the delivery of an appropriate shock affected survival.

**Discussion**

The major finding of the present study is that patients with nonischemic cardiomyopathy and implantation of an ICD for primary prevention experienced approximately twice as many shocks as the number of fatal events in the STD group. An increased number of syncopal events in the STD group balanced the excessive number of ICD shocks in the ICD group. The number of events in the STD group (eg, sudden cardiac arrest plus syncope) was almost identical to the number of events (eg, sudden cardiac arrest plus appropriate ICD shocks plus syncope) in the ICD group. This means that appropriate ICD shocks occur more frequently than SCD in patients with nonischemic cardiomyopathy, and many episodes of ventricular tachycardia must terminate spontaneously.

Syncope is an indicator of poor prognosis in patients with nonischemic dilated cardiomyopathy and is associated with an increased risk for SCD presumed to be due to ventricular tachyarrhythmias.\(^1\)\(^-\)\(^7\) The utility of electrophysiology studies to predict a subsequent ventricular arrhythmia in this patient population is poor.\(^8\)\(^-\)\(^10\) Analysis of stored electrograms from ICDs in small studies shows a significant number of patients receive ICD shocks for rapid ventricular tachyarrhythmias. It has been argued that the incidence of appropriate ICD therapy for ventricular tachycardia is a surrogate clinical end point for assessing the impact of ICD therapy on mortality.

**TABLE 2. Patients Experiencing Arrhythmic Events and Syncope**

<table>
<thead>
<tr>
<th></th>
<th>SCD/CA</th>
<th>Appropriate Shock</th>
<th>Syncope*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>STD</td>
<td>15 (6.6)</td>
<td>...</td>
<td>20 (8.7)</td>
<td>35 (15.3)</td>
</tr>
<tr>
<td>ICD</td>
<td>1 (0.4)</td>
<td>33 (14.4)</td>
<td>12 (5.2)</td>
<td>46 (20.1)</td>
</tr>
</tbody>
</table>

CA indicates cardiac arrest.

Values are \(n\) (%).

*In patients who did not also experience appropriate shocks.
We used the DEFINITE database to compare the rate of SCD in patients with STD therapy to the number of ICD shocks plus SCD in the ICD patient group. If ICD shocks are equivalent to SCD, these 2 numbers should be comparable.

These findings have particular relevance not only in terms of interpreting prior studies in which ICD shocks were used as a surrogate for mortality but also in terms of planning future studies and interpreting registry data. The Centers for Medicare and Medicaid Services have mandated a registry for all patients undergoing implantation of ICDs for primary prevention. Our findings clearly demonstrate that appropriate ICD shocks are not a reliable surrogate for SCD and overestimate the incidence of SCD in patients with nonischemic cardiomyopathy, because the ICD group experienced twice as many appropriate shocks as the number of fatal events in the control group. In other words, counting ICD shocks is not equivalent to counting lives saved by ICD therapy. It is important to realize that the number of appropriate ICD shocks will not equal the mortality benefit incurred by ICD implantation. These data suggest that ICD shocks overestimate the true efficacy of ICD therapy, because many episodes of tachycardia terminate spontaneously. The PAIN-FREE II trial also demonstrated that at least one third of very fast monomorphic ventricular tachycardia episodes terminated spontaneously. The PAIN-FREE II trial also demonstrated that at least one third of very fast monomorphic ventricular tachycardia episodes terminated spontaneously before antitachycardia pacing therapy. The present study data show that in patients with nonischemic cardiomyopathy, many episodes of polymorphic ventricular tachycardia and ventricular fibrillation also terminate spontaneously.

The excess number of syncopal episodes in the STD group balanced the increased number of ICD shocks and syncopal episodes associated with appropriate ICD shocks. The present study shows that most syncopal events in the ICD group were not associated with an ICD therapy and were probably multifactorial in etiology even in this group of patients. It is likely that most nonsustained arrhythmias that are sufficiently brief to go undetected by an ICD would be unlikely to lead to syncope. Conversely, many syncopal episodes were not associated with ICD discharges and thus were unlikely to represent a ventricular arrhythmia. These 2 observations further underline the limitations of the inclusion of syncope as a surrogate for ventricular arrhythmias in clinical trials of patients with cardiomyopathy.

The lack of superimposed myocardial ischemia in nonischemic cardiomyopathy patients may result in a higher likelihood of spontaneous termination of ventricular tachycardia. Transient ischemia enhances susceptibility to the initiation and maintenance of ventricular fibrillation through multiple mechanisms. Transient ischemia is associated with enhanced electrical instability due to abrupt changes in refractoriness, generation of delayed afterpotentials, increased sympathetically tone, phase 2 reentry, and microreentry near scar borders due to inhomogeneity of conduction and refractoriness. All of these factors favor destabilization of ventricular arrhythmias.

### Study Limitations
In the present study, we reviewed the ICD data logs but did not have information about the origin of syncopal spells not preceded by ICD shocks. Some patients may have experienced nonsustained polymorphic ventricular tachycardia not recorded by the ICD. Additionally, the cause of syncopal spells in the STD group is unknown because these patients did not have ambulatory ECG recorders, and additional clinical data to help make a definite diagnosis were not collected. Our numbers are too small to make any observations about the long-term prognosis of patients who received ICD shocks.

### Disclosures
Drs Kenneth Ellenbogen, Alan Kadish, Stephen Winters, James Daubert, and Ronald Berger are investigators for St Jude Medical. Drs Kadish, Winters, Daubert, and Ellenbogen have spoken or consulted for St Jude Medical.

### References


**CLINICAL PERSPECTIVE**

It is generally assumed that ventricular tachyarrhythmias that last long enough to cause an implantable cardioverter defibrillator (ICD) to deliver therapy, such as shocks, would progress to ventricular fibrillation and cardiac arrest in the absence of the ICD. Equating ICD therapy with mortality is controversial and has not been validated critically. DEFINITE was a multicenter, prospective, randomized trial that compared no specific arrhythmic therapy with ICD therapy in patients with a history of congestive heart failure and a nonischemic cardiomyopathy. All patients were also receiving optimal medical therapy for heart failure. The results of the present study show that many patients experience ICD therapy during follow-up. The total number of episodes of syncope and sudden cardiac death in the medical arm was similar to the number of sudden deaths, syncope, and ICD shocks in the ICD arm. Approximately twice as many patients experienced appropriate ICD shocks compared with the number of patients who experienced sudden cardiac death, which indicates that a simple counting of ICD therapies overestimates the benefit of ICDs. ICD therapy is not a reliable surrogate for sudden cardiac death in this patient population, because many ventricular arrhythmias would likely have terminated spontaneously in the absence of the ICD.
Are Implantable Cardioverter Defibrillator Shocks a Surrogate for Sudden Cardiac Death in Patients With Nonischemic Cardiomyopathy?


_Circulation_. 2006;113:776-782; originally published online February 6, 2006; doi: 10.1161/CIRCULATIONAHA.105.561571

_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/113/6/776

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/