Death Without Prior Appropriate Implantable Cardioverter-Defibrillator Therapy: A Competing Risk Study

Michael T. Koller, MD, MSc*; Beat Scher, MD*; Marcel Wolbers, PhD; Christian Sticherling, MD; Heiner C. Bucher, MD, MPH; Stefan Osswald, MD

Background—Implantable cardioverter-defibrillators (ICDs) improve survival in selected patients with left ventricular systolic dysfunction in randomized trials. Competing death without prior appropriate ICD therapy might preclude benefit from ICD implantation in a less selected routine-care population.

Methods and Results—We selected all patients with ischemic or dilated cardiomyopathy with an ICD implanted for primary or secondary prevention from a single-center prospective registry between 1994 and 2006. The end point was time to first appropriate ICD therapy/confirmed ventricular fibrillation or death without prior appropriate ICD therapy. In 442 patients, 73 deaths occurred during a median follow-up of 3.6 years (maximum, 12.7 years). The cumulative incidence of first appropriate ICD therapy until year 7 was 52%, whereas 11% died without prior ICD therapy. The cumulative incidence of appropriate ICD therapy for ventricular fibrillation was 13%, whereas 23% died without prior therapy for ventricular fibrillation. Appropriate ICD therapy was twice as likely in secondary prevention compared with primary prevention, whereas death rates before ICD therapy were similar in both groups. Diuretic use for heart failure compared with nonuse predicted a 4-fold-increased risk of death prior to ICD therapy, although the incidence of appropriate ICD therapy was similar in both groups.

Conclusion—In a contemporary ICD population, the risk of death without prior appropriate ICD therapy is substantial, especially in patients with advanced heart failure. (Circulation. 2008;117:1918-1926.)

Key Words: defibrillation ■ heart arrest ■ heart failure ■ prognosis ■ tachyarrhythmias

Evidence from randomized controlled trials indicates that implantable cardioverter-defibrillators (ICDs) reduce mortality from sudden cardiac death (SCD) by 30% to 54% compared with medical therapy alone.1-3 This lifesaving benefit is achieved by effective prevention of SCD resulting from ventricular tachyarrhythmia in both primary and secondary prevention and in ischemic and nonischemic cardiomyopathy.2 As a consequence, the number of ICD implantations has increased steadily in recent years. With the growing use of ICDs and expanding costs, guidelines have claimed refined methods for risk stratification to delineate subjects with most pronounced survival benefit.2,3

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Therefore, ICD implantation policy in routine care often is based on inclusion criteria used in randomized ICD trials. Although application of such inclusion criteria is straightforward in routine care, much less attention is paid to potential stringent patient exclusion criteria used to define a trial efficacy population. Because of a potential lack of generalization, it is of interest to develop risk stratification models that directly translate to routine care.

Two subsets of patients in an ICD population will never benefit from implantation: patients who die without or prior to first appropriate ICD therapy and patients who are alive but will never sustain a ventricular arrhythmia.4 Patients who qualify for ICD implantation often represent a multimorbid population of advanced age and of increased risk of death resulting from congestive heart failure or other causes. In routine care, it is of particular interest to know whether death without prior appropriate ICD therapy occurs in a relevant proportion of patients and how such patients could be identified prospectively. In contrast, in ICD recipients free of sustained ventricular arrhythmia, the probability of future...
ICD need is of interest when device replacement for dysfunction or battery depletion has to be considered.

Benefit from ICD implantation is therefore determined by 2 “competing” and mutually exclusive processes: appropriate ICD therapy and death without prior ICD therapy. Statistical methods to properly analyze competing causes of failure are available and have been a mainstay in heart valve diseases for some 30 years. Although appropriate use of competing risks analysis has been advocated in structural valve deterioration, the competing risk approach has not been translated yet to ICD research.

We used competing risk methodology to estimate the probability of appropriate ICD therapy or death without prior appropriate ICD therapy over a time period of 7 years (cumulative incidence function [CIF] approach). Furthermore, we aimed to identify predictors of appropriate ICD therapy and of death without prior ICD therapy.

**Methods**

**Study Population**

We used data from the ICD registry of the Department of Cardiology, University Hospital Basel, Switzerland. The registry is a prospective cohort of all 522 patients implanted with an ICD since 1994. We selected 442 of 522 available patients with either ischemic (coronary artery disease) or dilated cardiomyopathy who received an ICD for primary or secondary prevention. Patients with hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, idiopathic ventricular tachycardia (VT), or other rare conditions at risk of SCD were not considered. The administrative censoring date was the end of November 2006 for all patients alive until that date.

Electrophysiologists made the decision to implant an ICD. The secondary prevention group consisted of patients with aborted SCD, sustained or clinically critical VT, or syncope with inducible VT. The implantation policy of ICD primary prevention evolved over time, similar to that for the patient populations enrolled in recent trials.

Baseline examinations were carried out at the time of ICD implantation and consisted of patient demographics, the type of cardiomyopathy, the index arrhythmia or clinical event leading to device implantation, and medication use. Left ventricular ejection fraction (LVEF) was estimated by echocardiography with the disk summation method (modified Simpson’s rule).

**Follow-Up Assessment and Event Ascertainment**

Follow-up visits were performed at 1 and 3 months after ICD implantation and every 6 months thereafter. Devices were implanted according to standard practice. At each patient visit, a trained nurse and a cardiologist performed device interrogation and specific tests (determination of sensing, pacing thresholds, and lead impedance) in a standard fashion.

A trained electrophysiologist classified all stored intracardiac electrograms of ventricular tachyarrhythmia responsible for ICD therapy, together with the event date, and distinguished appropriate from inappropriate ICD therapy. ICD therapies were considered inappropriate when triggered by supraventricular arrhythmias, sinus tachycardia, noise, or T-wave sensing. All visits were registered prospectively and checked regularly for data consistency.

Appropriate ICD therapies were classified as follows. VT was terminated by antitachycardia pacing or cardioversion with a detection rate determined at the discretion of the managing cardiologist. Ventricular fibrillation (VF) was characterized by fibrillatory R waves and terminated by defibrillation. ICD therapy that failed to save the patient’s life at the time of the arrhythmia was classified as death, not as appropriate ICD therapy. Of note, this definition of appropriate ICD therapy involves an electrophysiologist’s judgment of every event and hence does not correspond to the clinical device setting, for which the “VF zone” is usually programmed at detection rates >220 bpm.

We recorded the date and reason for device exchange if applicable. Patients with device exchanges were not removed from analysis. In the case of a patient’s death, the date of death was recorded, and the classification of the terminal event was made according to attending cardiologists who used information from discharge letters or charts. For patients who died out of hospital, local cardiologists and primary care physicians were asked to classify the terminal event. Moreover, postmortem device interrogation was performed on a regular basis.

**End Points**

The primary end point in this analysis was time from ICD implantation until the first occurrence of any appropriate ICD therapy (for VT or VF) or death (ie, death without prior appropriate ICD therapy, called “prior death” here). In competing risk terms, any appropriate ICD therapy corresponds to the event of interest. The competing risk event is prior death.

The secondary end point was time from ICD implantation until the occurrence of ICD therapy for VF or death. Thus, all ICD therapies for VT before VF were disregarded. The occurrence of ICD therapy for VF (the event of interest) was assumed to be a surrogate for SCD. This represents a conservative approach; some of the VTs captured in the primary outcome definition may degenerate into VF if untreated.

We always coded the more serious event in the case of tied observations (ie, observations of events that occurred on the same day). If, for example, ventricular arrhythmia and death were tied on the same day, it was counted as death.

**Statistical Methods**

We used CIs to display the proportion of patients with the event of interest or the competing event as time progressed. To analyze the effect of baseline predictors on the CIF, we used the Fine and Gray regression model for the subdistribution hazard. The following predefined covariates were included in the model: age, LVEF, secondary prevention versus primary prevention, treatment of heart failure at implantation (β-blocker, angiotensin-converting enzyme inhibitor or angiotensin II blocker, amiodarone, and diuretic use), and the calendar year of ICD implantation.

The Fine and Gray model allows direct assessment of baseline covariates on the CIF (ie, patients with a lower subdistribution hazard also have a lower CIF). We prefer this model over a Cox model of the (cause-specific) hazard, which is difficult to interpret when the overall effects of covariates on the CIF are of interest. In the Fine and Gray model, we assumed distinct censoring distributions for patients with primary and secondary prevention because ICD implantation for primary prevention was introduced only about 1998 and thus these patients had less follow-up. In addition, we modeled the effect of the same covariates on overall survival (ie, any death) with a Cox model.

We assessed potential nonlinear effects of continuous covariates by using natural cubic spline transformations. To examine the assumption of proportional subdistribution hazards, we visually inspected Schoenfeld-type residuals and studied whether adding interaction terms between the logarithm of time and clinical covariates improved the model fit.

Finally, we estimated the conditional probability of appropriate ICD therapy within subsequent 2-year time intervals over the entire follow-up in subjects alive and free of ICD therapy at the beginning of each interval. We used bootstrap resampling to compute corresponding 95% confidence intervals (CIs).

We used R version 2.3.1 and its competing risk library cmprsk for all analyses. All reported CIs are at the 95% confidence level; tests are 2 sided at the 5% significance level.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.
Seventy-three deaths occurred in 442 patients followed up over a median of 3.6 years (95% CI, 3.3 to 4.3; maximum follow-up, 12.7 years). The median age at baseline was 63.4 years; 89% of the patients were male; and 76% had coronary artery disease. The median LVEF was 30%, and 59% of all patients received an ICD for secondary prevention (Table 1). Twenty-seven percent (118 of 442) required at least 1 device exchange, most often for battery depletion. All patients could be followed up until end of November 2006.

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (quartiles), y</td>
<td>63.4 (54.7, 70.6)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>395 (89)</td>
</tr>
<tr>
<td>Cardiomyopathy, n (%)</td>
<td>337 (76)</td>
</tr>
<tr>
<td>CAD</td>
<td>105 (24)</td>
</tr>
<tr>
<td>Primary prevention, n (%)</td>
<td>182 (41)</td>
</tr>
<tr>
<td>Secondary prevention, n (%)</td>
<td>68 (15)</td>
</tr>
<tr>
<td>VT</td>
<td>130 (29)</td>
</tr>
<tr>
<td>Syncope with inducible VT</td>
<td>62 (14)</td>
</tr>
<tr>
<td>LVEF, median (quartiles), %</td>
<td>30 (25, 36)</td>
</tr>
<tr>
<td>ICD type, n (%)</td>
<td>269 (61)</td>
</tr>
<tr>
<td>Single chamber (VVI)</td>
<td>91 (21)</td>
</tr>
<tr>
<td>Dual chamber (VDD)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>CRT</td>
<td>69 (16)</td>
</tr>
<tr>
<td>ICD manufacturers, n (%)</td>
<td>217 (49)</td>
</tr>
<tr>
<td>Medtronic</td>
<td>112 (25)</td>
</tr>
<tr>
<td>St Jude Medical</td>
<td>94 (21)</td>
</tr>
<tr>
<td>Intermedics</td>
<td>19 (4)</td>
</tr>
<tr>
<td>Therapy at implantation, n (%)</td>
<td>376 (85)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>408 (92)</td>
</tr>
<tr>
<td>Diuretic treatment</td>
<td>289 (65)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>127 (29)</td>
</tr>
</tbody>
</table>

**CAD** indicates coronary artery disease; **DCM**, dilated cardiomyopathy; **CRT**, cardiac resynchronization therapy; **ACE**, angiotensin-converting enzyme; and **AT II**, angiotensin II receptor blocker. n = 442.

### Table 2. Summary of Tachyarrhythmia Events and Death

<table>
<thead>
<tr>
<th>Arrhythmias, n (%)</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any first appropriate ICD therapy (VT or VF)</td>
<td>180 (41)</td>
</tr>
<tr>
<td>VT occurrences in patients with VT</td>
<td>157 (36)</td>
</tr>
<tr>
<td>VT</td>
<td>23 (5)</td>
</tr>
<tr>
<td>VT only*</td>
<td>44 (10)</td>
</tr>
<tr>
<td>Median (quartiles)</td>
<td>7 (2–25)</td>
</tr>
<tr>
<td>Range</td>
<td>1–414</td>
</tr>
<tr>
<td>VF occurrences in patients with VF (n=44)</td>
<td>29 (7)</td>
</tr>
<tr>
<td>Median (quartiles)</td>
<td>2 (1–12)</td>
</tr>
<tr>
<td>Range</td>
<td>1–44</td>
</tr>
<tr>
<td>Device exchange</td>
<td>94 (21)</td>
</tr>
<tr>
<td>Patients with &gt;1 exchange, n (%)</td>
<td>24 (5)</td>
</tr>
<tr>
<td>Time to first exchange in patients with exchange, median (quartiles), y</td>
<td>3.5 (2.6–4.5)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>73 (16.5)</td>
</tr>
<tr>
<td>Death, all</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Causes of death (n=73)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Electrical storm or EMD</td>
<td>34 (46)</td>
</tr>
<tr>
<td>Unknown, ICD failure possible</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Myocardial infarction§</td>
<td>32 (44)</td>
</tr>
<tr>
<td>Noncardiac</td>
<td>16 (55)</td>
</tr>
<tr>
<td>Death without prior appropriate ICD therapy</td>
<td>10 (34)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Death without prior appropriate ICD therapy for VF</td>
<td>11 (69)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>9 (56)</td>
</tr>
</tbody>
</table>

**EMD** indicates electromechanical dissociation.  
*Disregarding 21 (44–23) prior VT occurrences.  
†Disregarding 17 (174–157) prior VF occurrences.  
‡Of 34 deaths, 29 resulting from heart failure occurred in patients treated with diuretics.  
§Cancer, suicide, cerebrovascular, pulmonary embolism, after transplantation, and unknown causes.

### Results

Seventy-three deaths occurred in 442 patients followed up over a median of 3.6 years (95% CI, 3.3 to 4.3; maximum follow-up, 12.7 years). The median age at baseline was 63.4 years; 89% of the patients were male; and 76% had coronary artery disease. The median LVEF was 30%, and 59% of all patients received an ICD for secondary prevention (Table 1). Twenty-seven percent (118 of 442) required at least 1 device exchange, most often for battery depletion. All patients could be followed up until end of November 2006.

#### Cumulative Incidence of Appropriate ICD Therapy and Prior Death

We recorded a total of 180 first appropriate ICD therapies during follow-up, 157 appropriate ICD therapies for VT and 23 appropriate therapies for VF, and 29 deaths without any prior appropriate ICD therapy (Table 2). The estimated proportion of patients free of appropriate ICD therapy and death was 41% at 5 years and 36% at 7 years.

The cumulative incidence of any appropriate ICD therapy (the first of VT or VF) by year 7 was 52% (95% CI, 46 to 59), whereas 11% (95% CI, 7 to 16) of the patients died without any prior appropriate ICD therapy (Figure 1A). The dominating event was VT with a cumulative incidence of 47% (95% CI, 40 to 53); VF accumulated to 6% (95% CI, 3 to 8) by year 7.
appropriate ICD therapy for VF (Figure 1B). Assuming that VF is a surrogate for SCD indicates that an estimated 13% (95% CI, 9 to 17) of patient lives could be saved through appropriate ICD therapy by year 7. Of the 44 patients with VF, 16 subsequently died; the median survival after VF occurrence was 7.8 years (lower CI, 5.6; upper CI not reached). Of these 16 deaths, 12 were of cardiac causes, 9 of those due to heart failure (Table 2).

Competing Risk Regression Analysis of Appropriate ICD Therapy and Prior Death

In multivariate competing risk analysis, patients receiving an ICD for secondary compared with primary prevention were more likely to experience an appropriate ICD therapy (for VT or VF) (hazard ratio [HR], 1.87; 95% CI, 1.25 to 2.78; \(P=0.002\)) but were similarly likely to die without prior appropriate ICD therapy (HR, 1.14; 95% CI, 0.42 to 3.10; \(P=0.8\); Table 3). In contrast, patients who used diuretics for heart failure were not more likely to receive appropriate ICD therapy compared with nonusers (HR, 1.0; 95% CI, 0.73 to 1.36; \(P=1.0\)), but the former were much more likely to die without prior appropriate ICD therapy (HR, 4.33; 95% CI, 1.41 to 13.32; \(P=0.01\)) and showed a higher overall mortality (HR, 2.17; 95% CI, 1.16 to 4.05; \(P=0.02\)).

Older patients were more likely to experience appropriate ICD therapy (HR, 1.25 per 10-year increase; 95% CI, 1.09 to
Table 3. Multivariate Competing Risk Regression Analysis

<table>
<thead>
<tr>
<th></th>
<th>Any Appropriate ICD Therapy*</th>
<th>Prior Death*</th>
<th>All-Cause Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10-y increase)</td>
<td>1.25 (1.09–1.44)§</td>
<td>1.20 (0.77–1.86)</td>
<td>1.65 (1.24–2.19)§</td>
</tr>
<tr>
<td>LVEF (per 10% decrease)</td>
<td>1.19 (1.00–1.40)§</td>
<td>1.05 (0.76–1.46)</td>
<td>1.45 (1.10–1.92)§</td>
</tr>
<tr>
<td>Secondary vs primary prevention</td>
<td>1.87 (1.25–2.78)§</td>
<td>1.14 (0.42–3.10)</td>
<td>1.47 (0.77–2.80)</td>
</tr>
<tr>
<td>β-Blocker use</td>
<td>0.90 (0.61–1.31)</td>
<td>0.50 (0.21–1.16)</td>
<td>0.53 (0.30–0.94)§</td>
</tr>
<tr>
<td>ACE inhibitor/AT II use†</td>
<td>0.69 (0.42–1.16)</td>
<td>1.37 (0.20–9.25)</td>
<td>0.51 (0.22–1.18)</td>
</tr>
<tr>
<td>Diuretic use</td>
<td>1.0 (0.73–1.36)</td>
<td>4.33 (1.41–13.32)§</td>
<td>2.17 (1.16–4.05)§</td>
</tr>
<tr>
<td>Calendar year (per 5-y increase)‡</td>
<td>0.64 (0.48–0.83)§</td>
<td>1.36 (0.69–2.70)</td>
<td>2.23 (1.17–4.25)§</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; AT II angiotensin II receptor blocker.
*HR of the subdistribution hazard function.††HR of the subdistribution hazard function.†††Since 1994 until November 2006.
‡Since 1994 until November 2006.
§P<0.05.

1.44; P=0.002), as were those with lower LVEF (HR, 1.19 per 10% decrease in LVEF; 95% CI, 1.00 to 1.40; P=0.047). Increasing age but not decreasing LVEF showed a trend toward a higher incidence of death without prior appropriate ICD therapy. Furthermore, both predictors were significant predictors for overall mortality (Table 3). Patients using β-blockers compared with those not using β-blockers tended to be less likely to die without prior appropriate ICD therapy (HR, 0.50; 95% CI, 0.21 to 1.16; P=0.11) and had a lower overall mortality (HR, 0.53; 95% CI, 0.20 to 0.94; P=0.03). No evidence was found for differential predictor effects over time or for nonlinear effects of age or LVEF on the competing outcomes (data not shown).

The stratified cumulative incidence plots shown in Figure 2 illustrate the univariate effects of diuretic use versus nonuse (Figure 2A and 2B) and of secondary versus primary prevention (Figure 2C and 2D) on the cumulative incidences of appropriate ICD therapy or death without prior appropriate ICD therapy. Until year 7, 16% (95% CI, 10% to 22%) of patients treated with diuretics experienced death without prior appropriate ICD therapy compared with 4% (95% CI, 0% to 9%) of those without diuretics (Figure 2B). Similarly, at 7 years, 34% of patients with diuretic use for heart failure were alive and never used their device compared with 41% of patients without diuretic use.

Over the years since 1994, the cumulative incidence of any appropriate ICD therapy decreased significantly (HR, 0.64 per 5-year increase; 95% CI, 0.48 to 0.83; P=0.001; Table 3 and Figure 2E), and all-cause death increased (HR, 2.23; 95% CI, 1.17 to 4.25; P=0.01; Table 3).

Conditional Cumulative Incidence of Appropriate ICD Therapy
We estimated the conditional probability of appropriate ICD therapy within subsequent 2-year time intervals given that the subjects were alive and free of ICD therapy at the beginning of each interval (Figure 3). The conditional 2-year probability of any appropriate ICD therapy decreased from 38% (95% CI, 33 to 43) within the first interval to 6% (95% CI, 1 to 18) within the 6- to 8-year interval. Considering only VF as the event of interest, the conditional 2-year probability of appropriate ICD therapy steadily decreased from 8% (95% CI, 6 to 11) within the first interval to 4% (95% CI, 2 to 6) and 2% (95% CI, 0 to 7) within the second and third intervals, respectively. No first ICD therapies for VF occurred between 6 and 8 years in subjects alive and free of ICD therapy up to 6 years.

Discussion

Principal Findings
In this prospective cohort analysis of 422 patients with ischemic or dilated cardiomyopathy and ICD implantation for primary or secondary prevention, 52% of patients had appropriate ICD therapy during a 7-year observation period. Appropriate ICD therapy was dominated by termination of VT through antitachycardia pacing or cardioversion. VF might have ended in SCD in 13% of the population over 7 years, resulting in a median survival gain of 7.8 years after defibrillation. Nevertheless, depending on the type of tachyarrhythmia considered, 11% to 23% of the patients died without or before using their devices, and 36% of all patients stayed alive and never used the device during the 7 years. Moreover, the incidence of first appropriate ICD therapy strongly decreased during the last years.

Studying Competing Risks
We studied a routine-care population of a tertiary-care center and used a competing risk approach to study the processes of benefit and loss in ICD patients. To the best of our knowledge, this is the first application of competing risk methodology to an ICD population. In particular, the instantaneous event recording of stored electrograms makes the competing risk approach appealing. We prefer the competing risk approach over a simpler model for all-cause mortality as exemplified by Lee et al because, outside the randomized trial setting, an analysis of all-cause mortality cannot directly quantify the benefit of ICD therapy. As an example, a patient with a low LVEF might be saved from a devastating arrhythmia a few days after device implantation and gain a few years, although the low LVEF limits the life expectancy. In addition, estimates of benefit from ICD implantation should have a direct interpretation as probabilities over time in a real-world setting where competing deaths do occur. The
frequently used Kaplan-Meier analysis, in contrast to the CIF, artificially censors patients who die prior to appropriate ICD therapy. This leads to inflated probabilities of appropriate therapy because dead (and thus censored) subjects are treated as if they could experience the event of interest in the future.\textsuperscript{5,9,19} Similarly, competing events are not censored with the Fine and Gray model\textsuperscript{14,16} but are treated as distinct (competing) events. The only assumption about censoring that the competing risk approaches use is that administrative censoring or loss to follow-up is noninformative. Moreover, the Fine and Gray model is interpretation friendly in that it allows direct quantification of the effect of covariates on the CIF of competing events, in contrast to the more conventionally used (cause-specific) Cox models.\textsuperscript{15,20,21}

**Previous Studies**

According to trends from other published trials, we expected larger incidences of appropriate ICD therapy in patients with congestive heart failure.

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**Figure 2.** Stratified cumulative incidence functions of first appropriate ICD therapy (A, C, and E) or death prior to first appropriate ICD therapy (B, D, and F). CHF indicates congestive heart failure.
advanced heart failure.\textsuperscript{11,22} Severity of heart failure expressed as New York Heart Association (NYHA) class was inconsistently collected in our ICD cohort. However, evidence exists that (particularly loop) diuretics identify heart failure patients with a high risk for mortality.\textsuperscript{23–25} Therefore, we considered diuretic use for heart failure a surrogate for advanced heart failure. We found that appropriate ICD therapy was equally likely in patients using diuretics and in nonusers. However, the cumulative incidence of death without prior ICD therapy was 4-fold in diuretic users compared with nonusers in the first 7 years after ICD implantation. The effect on prior death was clearly larger than the effect on overall death (2-fold). In other words, both groups use the device equally often, but diuretic users are more likely to die with an unused device and nonusers are more likely to survive with an unused device.

The interaction of heart failure severity with ICD benefit has been examined in trials with divergent results. In the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE)\textsuperscript{22} trial and the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II),\textsuperscript{11} patients with worse NYHA class derived equal or greater benefits from ICD therapy. In the Sudden Cardiac Death/Heart Failure Trial (SCD-HeFT)\textsuperscript{13} trial, only patients in the prespecified NYHA class II, but not in the NYHA class III subgroup, had a statistically significant survival benefit from ICD implantation. Higher death rates prior to appropriate ICD therapy in patients with more severe heart failure and an increased heart failure risk after ICD therapy\textsuperscript{26,27} could be a plausible explanation for the limited benefit from ICD implantation for these patients. However, the incorporation of cardiac resynchronization therapy into ICD devices reduces death resulting from progressive heart failure in selected patients\textsuperscript{28} and might therefore have an impact on the incidence of death before and after ICD therapy. Of interest, overall mortality in the intervention group of SCD-HeFT\textsuperscript{11} was \(\approx 20\%\) at 4 years, similar to our population (Figure 1C). The incidence of appropriate ICD therapy for VT and VF was similar in MADIT II\textsuperscript{26} but was less frequent in SCD-HeFT, most likely because of the shock-only strategy in SCD-HeFT. Other cohort analyses found significant multivariate-adjusted associations between severity of heart failure and appropriate ICD therapy,\textsuperscript{29,30} but some did not.\textsuperscript{31} However, these cohort analyses either censored competing death or used a combined end point instead of differential models for the opposite benefit and loss of appropriate ICD therapy and prior death.

Appropriate ICD therapy was twice as likely in secondary compared with primary prevention. Decreasing LVEF also predicted appropriate ICD therapy, and neither of these 2 predictors was significantly associated with loss from death without prior appropriate ICD therapy. Moreover, our results
suggest that a similar (or higher) proportion of elderly patients receive appropriate ICD therapy (benefit) during follow-up compared with younger patients. In contrast, a recent pooled analysis of 3 clinical trials reports that the overall survival benefit of ICD implantation is lower in elderly patients, presumably a result of increasing nonarrhythmic death. This apparent discrepancy can be partially resolved by the finding from our study and those from others indicating that elderly patients and patients with a low LVEF had a significantly larger overall mortality. Moreover, in a larger study population, LVEF or age might become a significant predictor of death without prior ICD therapy.

The incidence of appropriate ICD therapy has decreased over time since the introduction of ICD implantation in 1994. In the same period, overall mortality increased significantly in our routine-care patients. Apparently, expanding indications with a generally more permissive use of ICD implantation seem to have resulted in a selection of patients who are less susceptible to benefit from ICD implantation.

Considerations for Device Replacement

The competing risk framework allows estimation of the actual probability of appropriate ICD therapy over time. In patients alive and free of appropriate ICD therapy in the first 6 years after ICD implantation, the probability of any first appropriate ICD therapy during years 6 to 8 was only 6%, and first VFs became unlikely (None were observed in our 35 patients at risk beyond year 6). Therefore, the effectiveness of device replacement in patients free of appropriate ICD therapy at the moment of device end of life may be low. However, because of the small number of individuals at risk toward the end of follow-up, probability estimates lack precision to guide and inform clinicians in the difficult decision of whether devices in such individuals should be replaced. Therefore, more data are needed before conclusive recommendations about device replacement in subjects free of appropriate ICD therapy can be formulated.

Study Limitations and Perspective

This study was conducted in a single center, and clinical practice for indication of ICD implantation and programming may be subject to variation in other centers. The detection of ventricular arrhythmia events depends on the ICD programming. Therefore, the reported cumulative incidences of appropriate ICD therapy and death without ICD therapy may depend in part on the device programming. For instance, the attitude toward the programming of dual-chamber devices has been influenced by the results of the Dual-Chamber and VVI Implantable Defibrillator (DAVID) trial, which showed that unnecessary stimulation of the right ventricle increases mortality. Since then, physicians have tried to avoid ventricular stimulation if possible.

Misclassification of appropriate ICD therapy as death without prior ICD therapy was kept to a minimum by postmortem device interrogation on a regular basis, but for out-of-hospital deaths, such misclassification cannot be excluded with full certainty. However, because of the tight 6-month follow-up schedule, potential misclassified deaths would pertain to patients with a limited survival benefit attributable to device implantation.

The ICD registry contains only a limited set of variables that have been consistently and routinely gathered. Information on NYHA class was not routinely collected, and natriuretic peptide levels have been available only since about 2002. However, the data set was complete for those variables used in our model, and follow-up information was complete for all individuals. Finally, our regression analysis lacked power, especially when looking at predictors for death without prior appropriate ICD therapy.

Finally, in future studies, the competing risk model should be transformed into a full prognostic model for the actual risk of appropriate ICD therapy and death without prior appropriate therapy.

Conclusions

Benefit from ICD implantation is determined by 2 mutually exclusive and competing processes: A patient either benefits from potentially lifesaving appropriate ICD therapy or is lost to death without or before appropriate ICD therapy. This work shows how the competing risk scenario can be built into risk stratification models for decisions on both device implantation and device replacement. Our analysis, based on routine-care data, revealed that the proportion of patients with appropriate ICD therapy was substantially larger in the secondary prevention setting. Despite the similar chance of appropriate ICD therapy, patients who use diuretics for heart failure are more likely to die with an unused device, whereas nonusers are more likely to survive with an unused device.

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Disclosures

Dr Osswald has served as a consultant and on the speakers’ bureau for and has received honoraria from Medtronic, Boston Scientific, and Biotronik. Dr Schaefer has received honoraria from Boston Scientific. Dr Sticherling has served as a consultant to Medtronic and has served on the speakers’ bureau for and received honoraria from Medtronic and Boston Scientific. The other authors report no conflicts.

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**CLINICAL PERSPECTIVE**

Implantable cardioverter-defibrillators (ICDs) improve survival in selected patients in randomized controlled trials. The contemporary ICD population, however, is older and has a higher comorbidity burden than the selected populations of randomized controlled trials. It is therefore of interest to study the extent to which patients die prior to appropriate ICD therapy for ventricular tachyarrhythmia in a “real-world” ICD population. Such “prior deaths” are referred to as competing risks and need to be taken into account when we build models to predict which patients will and which patients will not use their devices. The present study indicates that in our routine-care population, about half of the patients receive appropriate ICD therapy for ventricular tachycardia or ventricular fibrillation. Eleven percent died without ever using their devices. Focusing on ventricular fibrillation only shows that 13% experienced ventricular fibrillation and 23% died before experiencing ventricular fibrillation. In competing risk models, patients most likely to receive appropriate ICD therapy were those with a secondary prevention indication, higher age, or reduced ejection fraction. At the same time, patients who needed diuretic treatment for congestive heart failure had a 4-fold increased risk of dying before device use. Future risk stratification tools should aim to optimize device implantation and replacement, particularly in a routine-care population. Here, we demonstrate how the relevant risk of prior death may be integrated into such risk stratification tools.

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Michael T. Koller, Beat Schaer, Marcel Wolbers, Christian Sticherling, Heiner C. Bucher and Stefan Osswald

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