Clinical Investigation

Implantable Cardioverter-Defibrillator Placement for Primary Prevention in 2,346 Patients:

Predictors of One-Year Survival

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Guidelines suggest that patients who receive implantable cardioverter-defibrillators (ICDs) for primary prevention should be expected to live more than one year after placement. However, tools for validating this prognosis are not sufficiently predictive. We sought to identify definitive predictors of one-year survival after ICD placement.

By reviewing medical records and the Social Security Death Index, we analyzed baseline characteristics and survival outcomes of 3,164 patients who underwent ICD placement at our institution from January 2006 through March 2014.

Survival outcome could be confirmed for 2,346 patients (74%). Of these, 184 (7.8%) died within one year of ICD placement. We noted significant differences in numerous variables between those who lived and died. However, multivariable analysis revealed only 5 independent predictors of earlier death: worse New York Heart Association functional class (hazard ratio [HR]=1.87 per class [95% CI, 1.22–2.87]; P <0.01); lower serum sodium level (HR=0.93 per 1 mEq/L increase [95% CI, 0.88–0.99]; P=0.04); atrial fibrillation (HR=1.81 [95% CI, 1.03–3.21]; P=0.04); chronic lung disease (HR=2.05 [95% CI, 1.20–3.51]; P <0.01), and amiodarone use (HR=10.1 [95% CI, 4.51–22.5]; P <0.01). Using receiver operating characteristic curves, we developed a model with an area under the curve of 0.718 that predicted death at one year after ICD implantation.

Despite significant univariate differences between the ICD recipients who did and did not live beyond one year, we found only moderate predictors of survival. Better tools are needed to predict outcomes when considering ICD placement for primary prevention.
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Implantable cardioverter-defibrillators (ICDs) for primary prevention improve survival outcomes among appropriately selected patients who have impaired left ventricular ejection fraction (LVEF).[1,2] However, initial trial results indicate that several years of ICD therapy may be needed before its benefits are realized.[1,2] Therefore, consensus guidelines for ICD placement state that therapy is not indicated when there is no "reasonable expectation of survival with an acceptable functional status for at least one year," even if other criteria for ICD placement are met.[3] Individuals with advanced left ventricular dysfunction have multiple competing risks, including sudden cardiac death, nonarrhythmic cardiac death (progressive heart failure), and noncardiac comorbidities. The one-year survival threshold has a level of evidence class C, indicating that the recommendation is based only on expert consensus, case studies, or standard of care—not population-based evidence from randomized or nonrandomized studies.[3]

Considering the relatively scant data on selecting candidates for primary prevention, we evaluated predictors of survival beyond one year among ICD recipients at our large academic medical center.

Patients and Methods

We retrospectively reviewed the medical records of all patients who underwent de novo primary-prevention ICD placement at our institution from January 2006 through March 2014. The treating physician had made the decision to place an ICD, selected the device type (single-chamber, dual-chamber, or cardiac resynchronization

therapy defibrillator), and determined the implantation method. Procedural details and the patients' baseline clinical characteristics were ascertained from the medical records.

Our primary endpoint was all-cause death within one year after ICD placement. Vital status was determined by querying institutional medical records and the Social Security Death Index (SSDI). We excluded patients who could not be identified in the SSDI and for whom vital status could not be determined. The Emory University Institutional Review Board approved the study protocol.

Statistical Analysis

Continuous variables are presented as mean ± SD; categorical data, as frequencies. Comparisons across groups were performed by using the Student *t* test or Fisher exact test, as appropriate. A binomial logistic regression of variables with univariate *P* value ≤0.1 was used for multivariable logistic analysis. Model performance was evaluated by using receiver operating characteristic (ROC) curves to determine area under the curve (AUC) (c statistic). For all comparisons, a 2-tailed *P* value <0.05 was considered to be statistically significant. Analysis was performed with the use of MATLAB® software version 8.0 (The MathWorks, Inc.).

Results

Of 3,164 patients who underwent ICD placement for primary prevention during the study period, survival at one year after implantation was determined for 2,346 (74%), the cohort for this analysis (Table I). Of the 2,346 patients, 184 (7.8%) died within one year. There were numerous significant differences between the patients who died and those who survived, including older age at time of implantation (63.5 ± 16.3 vs 59.3 ± 14.3 yr; *P* <0.01), lower LVEF (0.22 ± 0.1 vs 0.25 ± 0.12; *P* <0.01), worse New York Heart Association (NYHA) functional class (2.76 ± 0.6 vs 2.48 ± 0.7; *P* <0.01) and more prevalent comorbidities, including atrial fibrillation (AF), coronary artery disease, chronic lung disease, diabetes mellitus, and poor renal function, including more need for chronic dialysis. Patients who died within one year also had significantly lower serum sodium levels (137 ± 4 vs 138.2 ± 3.1 mEq/L; *P* <0.01), although the absolute difference was small; and they were more likely to have taken amiodarone, diuretics, and long-acting nitrates at the time of ICD placement. Significant differences were apparent in more than half of the baseline variables during survival stratification.

However, in multivariable models, only 5 variables remained significant predictors of earlier death: worse NYHA class, lower serum sodium level, history of AF, chronic lung disease, and amiodarone use at the time of device implantation (Table II). From the multivariable model, we derived an ROC curve to predict death within one year (Fig. 1). The AUC of 0.718 suggests modest predictive capability.

On the basis of the ROC curve, a hypothetical ICD recipient who had NYHA class II symptoms, AF, and a serum sodium level of 140 mEq/L, but no chronic lung disease or amiodarone use, would have a predicted one-year death risk of 5.7%. From the ROC curve, if these variables were used as a threshold for predicting one-year death within our cohort, the sensitivity would be 77% and the specificity, 51%. For a different hypothetical patient—at greater risk of one-year death, with NYHA class III symptoms, AF, chronic lung disease, and a serum sodium level of 135 mEq/L, but not taking amiodarone—the predicted model-based one-year death risk would be 25% (sensitivity, 12%; and specificity, 98%).

Discussion

In our large cohort of ICD recipients, nearly 8% died within one year. Although numerous differences were identified between those who lived and died, only 5 variables remained significant predictors of earlier death: worse NYHA class, AF, lower serum sodium level, chronic lung disease, and use of amiodarone at the time of ICD placement. However, the model incorporating these 5 variables had only modest ability to predict one-year survival. These findings highlight the challenge of predicting medium- and long-term survival in primary-prevention ICD candidates.

Our one-year mortality rate of 7.8% is consistent with rates reported in previous studies. The one-year mortality rate was 8.8% in the National Cardiovascular Disease Registry (NCDR) of 172,985 ICD recipients[4]; 8% in the 655-patient Multicenter Automatic Defibrillator Implantation Trial-II[5]; and 5.2% in the 1,189-patient Prospective Observational Study of Implantable Cardioverter-Defibrillators.[6] These findings indicate that one of 10 to 20 recipients is unlikely to live long enough to benefit from ICD therapy. Therefore, investigators have tried to define predictors of survival to better identify who is most and least likely to benefit.

We identified 5 significant multivariable predictors of one-year survival. In a similarly designed study from the NCDR, 6 multivariable predictors were reported: older age, chronic lung disease, need for dialysis, NYHA class IV status, blood urea nitrogen levels ≥30 mg/dL, and systolic blood pressures <120 mmHg. The AUC for predicting one-year survival in that model was 0.7.[4] In a multicenter study that focused on clinical variables and a panel of novel biomarkers to predict one-year survival, 6 variables persisted in the multivariable model: age ≥75 years, NYHA class III/IV, the presence of AF and of diabetes mellitus, diuretic use, and estimated glomerular filtration rates <30 mL/min/1.73 m^2. The AUC was 0.77.[6] In 17,991 Medicare patients who underwent

TABLE I. Univariate Predictors of Survival Beyond One Year after ICD Placement

Variable	Died <1 Year (n=184)	Alive ≥1 Year (n=2,162)	*P* Value
Age (yr)	63.5 ± 16.3	59.3 ± 14.3	<0.01
Male	127 (69)	1,448 (67)	0.624
Left ventricular ejection fraction	0.22 ± 0.1	0.25 ± 0.12	<0.01
Prior heart-failure hospitalization	133 (72)	1,311 (61)	0.01
NYHA functional class	2.76 ± 0.6	2.48 ± 0.7	<0.01
I	2	163	—
II	54	829	—
III	114	1,128	—
IV	14	36	—
Atrial fibrillation or flutter	66 (36)	425 (20)	<0.01
Nonsustained ventricular tachycardia	55 (30)	424 (20)	<0.01
QRS interval (ms)	124.2 ± 28.2	121.9 ± 32.4	0.29
PR interval (ms)	180.4 ± 42.5	172.3 ± 40.2	0.05
Cardiac resynchronization therapy	64 (35)	676 (31)	0.34
Coronary artery disease	103 (56)	940 (43)	<0.01
Prior myocardial infarction	91 (49)	796 (37)	<0.01
Prior CABG	57 (31)	470 (22)	<0.01
Prior PCI	39 (21)	484 (22)	0.78
Lung disease	49 (27)	260 (12)	<0.01
Diabetes mellitus	83 (45)	723 (33)	<0.01
Hypertension	138 (75)	1,640 (76)	0.79
Dialysis	18 (10)	89 (4)	<0.01
Creatinine (mg/dL)	1.88 ± 2.3	1.36 ± 1.3	<0.01
Serum sodium (mEq/L)	137 ± 4	138.2 ± 3.1	<0.01
Medications			
Amiodarone	23 (13)	34 (2)	<0.01
Hydralazine	27 (15)	232 (11)	0.11
ACE inhibitors	129 (70)	1,578 (73)	0.39
Aspirin	122 (66)	1,536 (71)	0.31
β-blocker	151 (82)	1,910 (88)	0.06
Warfarin	54 (29)	558 (26)	0.25
Digoxin	52 (28)	486 (22)	0.07
Diuretic	144 (78)	1,513 (70)	<0.01
Nitrates (long-acting)	32 (17)	263 (12)	0.04
Clopidogrel	36 (20)	386 (18)	0.48
Statin	111 (60)	1,273 (59)	0.58

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association; PCI = percutaneous coronary intervention

Data are presented as mean ± SD or as number and percentage. $P < 0.05$ was considered statistically significant.

primary-prevention ICD placement, 7 variables were identified in a model designed to predict survival 1 to 4 years after implantation, including age ≥75 years, NYHA class, AF, chronic lung disease, chronic kidney disease, LVEF ≤0.20, and diabetes mellitus. In an independent validation cohort, the model had an AUC of 0.74.[7]

Despite slight differences between cohorts and models, our study and the others, together, reveal a set of risk factors apparently predictive of survival beyond one year after ICD placement. Chief among them are age, NYHA class, and the presence of AF, renal dysfunction, and chronic lung disease. However, models incorporating these clinical variables have AUCs of 0.7 to 0.77, suggesting modest predictive capability.

We did not find age to be significantly predictive, perhaps because our patients were slightly younger (59.3 ± 14.3 yr) than those in the NCDR cohort (67

TABLE II. Multivariable Logistic Regression for One-Year Survival

Variable	Hazard Ratio (95% CI)	*P* Value
NYHA functional class*	1.87 (1.22–2.87)	<0.01
Atrial fibrillation or flutter	1.81 (1.03–3.21)	0.04
Chronic lung disease	2.05 (1.20–3.51)	<0.01
Serum sodium level**	0.93 (0.88–0.99)	0.04
Amiodarone use	10.1 (4.51–22.5)	<0.01

NYHA = New York Heart Association

*Hazard ratio per rise of one class
**Hazard ratio per 1 mEq/L increase

P <0.05 was considered statistically significant.

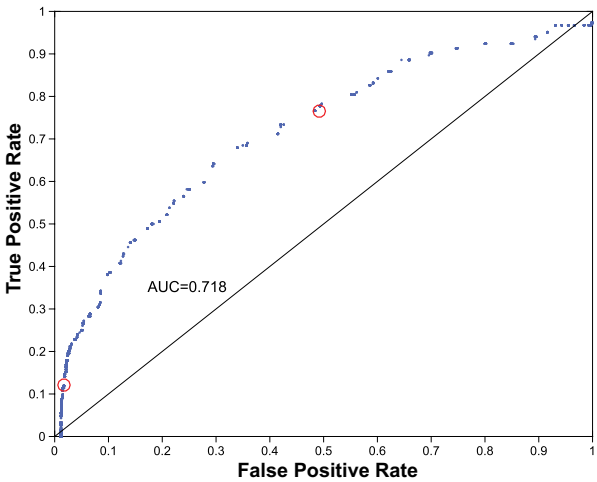

Fig. 1 *Receiver operating characteristic curve shows predicted one-year survival outcomes in implantable cardioverter-defibrillator recipients in accordance with 5 variables in the multivariable model. The first hypothetical patient discussed in the text is high on the curve, and the second is near the bottom (red circles).*

AUC = area under the curve

± 13 yr)[4] and the Medicare cohort (median, 72.5 yr).[7] Age between 30 and 65 years at time of implantation is suggested to have relatively little impact on one-year survival prospects, whereas age ≥75 years may be much more significant.[4]

We focused on one-year survival after ICD placement, which is the threshold in the guidelines for device therapy.[3] Our model identified statistically significant predictors; however, as with previous models, clinical application may be difficult because of only modest capability to determine which patients might or might not live beyond one year.[4,6,7] In practice, a guideline or recommendation without a validated, reproducible tool to implement it places clinicians in a difficult position. Although having a target for survival is important for patients undergoing primary-prevention ICD placement, the actual threshold and how best to gauge survival prospects remain unclear. Moreover, some patients who might benefit from this treatment will never undergo implantation because their prospects for survival are perceived to be poor. Even more broadly, in this time of quality metrics, pay-for-performance, and public reporting of outcomes, our data expose the challenges of predicting outcomes in potential ICD recipients and the difficulty of developing tools for evaluating medium- and long-term outcomes in patients who have cardiomyopathy.

Study Limitations

Our study has limitations. First, we confirmed one-year outcomes in only 74% of our cohort, and the missing data may have introduced bias into our findings. Second, we lack data on causes of death; this information would be useful in evaluating outcomes in ICD recipients who have multiple competing risks of death. Third, we were unable to report systematic data on the incidence of ICD therapies. Many individuals were referred to our institution specifically for device implantation and then were monitored locally by their referring physicians.

Our data are from one high-volume academic center with a limited number of physicians qualified to implant ICDs. The extent to which our data can be extrapolated to primary-prevention ICD placement in other circumstances is unclear; however, our findings are broadly consistent with those in similar cohorts, suggesting some generalizability. Last, we included only patients who were actually given an ICD, which implies that their referring physician and the one who implanted the ICD considered that the prospects for survival beyond one year were good. We cannot comment on outcomes of individuals who received no implant and whether any might have benefited from an ICD, had they received one.

Conclusion

As with previous studies, our multivariable model has only modest ability to predict one-year survival in primary-prevention ICD recipients. The need remains for better tools to predict medium- and long-term outcomes when considering ICD placement.

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