Development and validation of a risk score to predict early mortality in recipients of implantable cardioverter-defibrillators

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BACKGROUND Current guidelines do not recommend implantable cardioverter-defibrillator (ICD) implantation in patients with a life expectancy of <1 year. Better methods are needed for identifying patients at high risk for early mortality despite ICD therapy.

OBJECTIVE To develop and validate a risk prediction score to identify patients at high risk for death within 1 year despite ICD therapy.

DESIGN Detailed clinical data were collected on a large observational cohort of ICD patients from 3 tertiary care centers. One-third of the patients were randomly selected to form the prediction group (PG) from which a risk score was developed using logistic regression. This score was then applied to the remaining two-thirds of the cohort (validation group [VG]) to assess the risk score's predictive accuracy.

RESULTS The total cohort included 2717 ICD patients (mean age = 64.6 ± 14.5, male = 77.2%, primary prevention = 74.7%). A simple risk score incorporating peripheral arterial disease, age ≥ 70 years, creatinine ≥ 2.0 mg/dL, and ejection fraction ≤20% (PACE) accurately predicted 1-year mortality in the VG. Patients with a risk score of ≥3 had a >4-fold excess 1-year mortality compared with patients with a risk score of <3 (16.5% vs 3.5%; $P < .0001$).

LIMITATION Risk reduction provided by ICD therapy in this cohort is not known given the lack of a control group.

CONCLUSIONS A simple risk score accurately predicts 1-year mortality in ICD patients, as patients with a PACE risk score of ≥3 are at high risk despite ICD therapy.

KEYWORDS Implantable cardioverter-defibrillators; Outcomes research

ABBREVIATIONS **ICD** = implantable cardioverter-defibrillator; **LVEF** = left ventricular ejection fraction; **NYHA** = New York Heart Association; **PAD** = peripheral arterial disease; **PG** = prediction group; **VG** = validation group

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Introduction

Prevention of sudden cardiac death with implantable cardioverter-defibrillator (ICD) implantation improves survival in well-selected patients.[1–5] However, the majority of patients who receive an ICD never receive appropriate therapies from their device and remain at risk for complications, including inappropriate shocks and infections.[6,7] Furthermore, patients with advanced comorbidities who receive ICDs may die of causes other than ventricular arrhythmia such as strokes, acute coronary syndromes, malignancy, or progressive heart failure.[8,9] Importantly, the guidelines for ICD implantation do not recommend device therapy for patients with life expectancies of <1 year.[10]

While advanced age alone has not been endorsed as an exclusion criterion for implantation, accumulated comorbidities (particularly renal insufficiency) are known to attenuate the benefits of ICDs.[11–14] In this context, the design of pivotal clinical trials in ICD therapy has been criticized as leaving important questions about patient selection unaddressed.[6,15] Specifically, prospective identification of patients at high risk for mortality despite ICD implantation remains an important unmet need.

This multicenter observational cohort study aimed to develop a simple scoring system using easily obtained demographic and clinical characteristics to predict poor patient outcomes despite ICD implantation.

Methods

Patient population

Consecutive patients receiving ICDs with either Medtronic Sprint Fidelis or Sprint Quattro leads at Beth Israel Deaconess Medical Center (Boston, MA), Mayo Clinic (Rochester, MN), and Minneapolis Heart Institute (Minneapolis, MN) from November 2001 to December 2008 were eligible for inclusion. All record review and associated research

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activities were conducted with institutional review board approval from each participating institution.

Data collection

Detailed demographic and clinical data were collected by manual electronic medical record review. Vital status was determined with the use of the Social Security Death Index by investigators at each center. The presence or absence of specific clinical variables such as atrial fibrillation, diabetes, and congestive heart failure at the time of ICD implant were determined by review of physician notes, procedure records, and discharge summaries. Measured or assigned variables such as left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) heart failure class, and creatinine were taken at the time of implant or the closest available value. Peripheral arterial disease (PAD) was considered present if a patient had an intervention on the carotid arteries or lower extremities, thoracic or abdominal aorta, or had clinical claudication.

Data analysis

One-third of the patients were randomly selected by the use of random integer assignment to form the prediction group (PG), and the remainder formed the validation group (VG). The PG was used to develop a risk score for the prediction of the primary endpoint, all-cause 1-year mortality. This score was then applied to the remaining two-thirds of the cohort (VG) to assess the risk score's predictive accuracy.

To develop the risk score, clinical variables associated with mortality were identified with a $\chi 2$ test for categorical variables and a Student's t test for continuous variables. Variables with a univariate correlation with a P value of $<.10$ were then evaluated in a stepwise logistic regression model that identified the factors included in the risk score, with a cutoff P value of .05 for retention in the model. Survival for risk score groups was compared with Kaplan–Meier curves and the log-rank statistic. All statistics were performed with SAS 9.2 (SAS Institute, Cary, NC).

Results

Patient characteristics

The total cohort included 2717 ICD recipients. The demographic and clinical characteristics for the PG, VG, and overall cohort are shown in Table 1. The PG and VG were well matched, with no statistically significant differences in major characteristics. The mean age overall was 64.6 ± 14.5 years. Patients were predominantly male (77.2%) and white (91.1%). Indication for device implantation was most commonly primary prevention (74.7%), with the most common substrates of ischemic heart disease (58.1%), dilated cardiomyopathy (24.5%), hypertrophic cardiomyopathy (5.5%), and ion channel abnormalities (1.3%). Cardiac resynchronization therapy (CRT)-ICD devices were implanted in 31% of patients. The mean LVEF was 31.3% ± 14.6%, and mean creatinine was 1.25 ± 0.61. One-quarter (25.6%) of all patients had NYHA Class III or IV heart failure.

Clinical follow-up and mortality statistics for the PG, VG, and entire cohort are shown in Table 2. At a mean follow-up of 3.1 ± 1.82 years, 421 of the 2717 (15.5%) patients died, with similar mortality in the PG and the VG.

Each of the clinical and demographic variables was evaluated for associations with mortality as described above. Hazard ratios before (Table 3) and after (Table 4) adjustment for the 4 clinical variables with the largest univariate correlates are shown. The variables that remained after adjustment were peripheral arterial disease, age ≥ 70, cre-

Table 1 Variables of study population

Variable	PG (n = 905)	VG (n = 1812)	Entire cohort (n = 2717)	*P* value*
Age	65.6 ± 14.5	64.3 ± 14.6	64.5 ± 14.5	.200
Male (%)	78.3	76.7	77.2	.3231
Primary prevention (%)	75.8	74.2	74.7	.5747
White (%)	91.9	90.7	91.1	.2977
CHF (%)	67.9	64.6	67.7	.0881
ICM (%)	58.9	57.7	58.1	.5606
DCM (%)	25.3	24.1	24.5	.4979
HCM (%)	4.3	6.1	5.5	.0507
Channelopathy (%)	1.3	1.2	1.3	.8048
LVEF (mean)	31.1	31.4	31.3 ± 14.6	.5538
LVEF < 20 (%)	28.3	26.5	27.1	.3205
Creatinine (mean)	1.26	1.24	1.25 ± 0.61	.4988
Cr > 2.0 (%)	6.5	5.7	6.0	.3863
PAD (%)	8.9	9.4	9.2	.6511
AF (%)	39.2	36.0	37.1	.0989
CHF III or IV (%)	26.6	25.3	25.8	.4657
Diabetes (%)	35.8	32.4	33.5	.0763
COPD (%)	16.0	12.1	13.4	.0052

AF = atrial fibrillation; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; Cr = creatinine; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; ICM = ischemic cardiomyopathy; LVEF = left ventricular ejection fraction; PAD = peripheral arterial disease; PG = prediction group; VG = validation group.

*P value for comparison between PG and VG.