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Prediction of Nonarrhythmic Mortality in Primary Prevention Implantable Cardioverter-Defibrillator Patients With Ischemic and Nonischemic Cardiomyopathy

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ABSTRACT

OBJECTIVES The objective of this study was to investigate the feasibility of identifying heart failure patients who are less likely to benefit from implantable cardioverter-defibrillator (ICD) therapy among those eligible for primary prevention ICDs.

BACKGROUND The cost-effectiveness of ICDs in primary prevention may be improved dramatically.

METHODS Using a cause-of-death analysis approach, we evaluated the discriminative and predictive values of a risk score with regard to overall mortality and specific causes of death by examining 2,485 patients enrolled in the French Primary Prevention ICD program (2002 to 2012). The risk score included points for New York Heart Association functional class III or greater, age >70 years, QRS duration >120 ms, atrial fibrillation, and glomerular filtration rate <60 ml/min. Sensitivity analyses were performed for ischemic and nonischemic cardiomyopathy, as well as for patients undergoing cardiac resynchronization therapy.

RESULTS After a mean follow-up of 3.0 ± 2.1 years, the overall mortality rate was 5.9 per 100 patient-years (95% confidence interval: 5.4 to 6.5), which increased with the number of risk factors (0 to 5, respectively), as follows: 2.5, 2.9, 4.8, 9.0, 12.3, and 14.8 per 100 patient-years ($p < 0.001$). The higher mortality rate among patients with the highest scores resulted from an increase in nonarrhythmic mortality (from 2.1 to 14.8 per 100 patient-years, $p < 0.001$), whereas the occurrence of appropriate ICD therapies did not change significantly across the categories. The C statistic testing of the score was observed to be highly similar for patients with ischemic cardiomyopathy (0.685) and nonischemic cardiomyopathy (0.658) and those receiving cardiac resynchronization therapy (0.678).

CONCLUSIONS Our findings suggest the feasibility of and interest in identifying patients eligible for primary prevention ICD implantation who are at significant risk of nonarrhythmic death in the real-world setting. (J Am Coll Cardiol EP 2015;1-2:29–37) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CI = confidence interval

CRT = cardiac resynchronization therapy

CRT-D = cardiac resynchronization therapy plus defibrillator

GFR = glomerular filtration rate

ICD = implantable cardioverter-defibrillator

NYHA = New York Heart Association

SCD = sudden cardiac death

Implantable cardioverter-defibrillators (ICDs) have been demonstrated to be associated with a significant reduction in overall mortality (1-5); however, a substantial proportion of patients will not experience appropriate therapies after being implanted with an ICD (6), and this therapy has inherent risks that may affect morbidity and quality of life (7,8).

There is still room to improve patient selection and the risk-benefit ratio and cost-effectiveness of ICD therapy (9,10). A first approach comprises a better understanding of ventricular arrhythmia pathogenesis, as well as risk stratification to better identify patients at highest risk of sudden cardiac death (SCD) (11–14). However, most patients at risk for SCD also present with heart failure and other comorbidities and are therefore at a high risk of dying of other causes (15). Thus, identification of patients at high risk of nonarrhythmic death, which is rarely performed in daily clinical practice, may be of particular interest to improve patient selection. This is particularly valid in the real-world setting, where patients are more likely to have significant comorbidities (16).

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In this paper, we undertook a cause-of-death analysis in a large primary prevention ICD registry to investigate the extent to which a score derived from a randomized controlled trial in patients with coronary artery disease (17) may be valid and of potential interest in the real-world setting for patients with ischemic and nonischemic cardiomyopathy.

METHODS

THE DAI-PP STUDY. The DAI-PP study (Défibrillateur Automatique Implantable-Prévention Primaire; NCT01992458) enrolled all subjects with ischemic cardiomyopathy or dilated cardiomyopathy implanted with an ICD for primary prevention between 2002 and 2012 in 12 reference French centers. The study was funded by public sources, including the French Institute of Health and Medical Research (INSERM) and the French Society of Cardiology, and was coordinated by Clinique Pasteur, Toulouse and the Paris Cardiovascular Research Center, European Georges Pompidou Hospital, Paris, in France, and the Toulouse Association for the Study of Rhythm Disturbances. Many of the investigators were part of the European Network for the Treatment of Cardiac Arrhythmias Network, initiated in the 1990s. The study complied with the Declaration of Helsinki, and the data file of the DAI-PP study was declared to and authorized by the French data protection committee (Commission Nationale Informatique et Liberté).

To qualify for the study, patients had to be at least 18 years old at the time of ICD implantation. Overall, all patients with ischemic cardiomyopathy or nonischemic cardiomyopathy implanted with an ICD (single, double, or triple chamber) in the setting of primary prevention were considered and enrolled in the DAI-PP follow-up program. Primary prevention was defined when no prior history of sudden cardiac arrest or ventricular tachycardia/fibrillation was documented. Ischemic cardiomyopathy was defined as the presence of myocardial dysfunction resulting from previous myocardial infarction or history of coronary artery disease with or without revascularization (angioplasty or bypass surgery). Exclusion criteria included all patients who had an ICD implanted for secondary prevention purposes or for primary prevention without structural heart disease (including Brugada syndrome and long-QT syndrome) or structural heart disease other than ischemic or nonischemic cardiomyopathy (hypertrophy cardiomyopathy, noncompaction cardiomyopathy, and arrhythmogenic right ventricular dysplasia).

SAMPLE CHARACTERIZATION. All variables at the time of the procedure were defined and categorized according to the literature or common practice. In addition to New York Heart Association (NYHA) functional class, we collected information on the pathogenesis of the underlying heart disease (ischemic cardiomyopathy or dilated cardiomyopathy). Renal clearance (glomerular filtration rate [GFR]) was estimated with the Cockcroft-Gault formula and grouped into 2 categories (≥60 or <60 ml/min); QRS duration was categorized as <120 or ≥120 ms. Atrial fibrillation (AF) was defined as a history of AF (paroxysmal or

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persistent), documented on electrocardiogram or 24-h Holter monitoring. Comorbidities were collected systematically and included cancer, chronic obstructive pulmonary disease, chronic renal failure, chronic liver disease, history of transient ischemic neurological attack, and others (including diabetes mellitus). The type of ICD device implanted (biventricular, single chamber, or dual chamber; no indication on manufacturers) was recorded, and device programming was left to the discretion of the assisting physician. Medications prescribed at hospital discharge included beta-blockers, amiodarone, class Ic antiarrhythmic drugs, sotalol, digoxin, calcium blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, diuretic agents, antiplatelet agents, and vitamin K antagonists.

In accordance with the work of Goldenberg et al. (17), 5 clinical parameters, each assigned 1 point, were used to estimate the risk stratification score: age >70 years, NYHA functional class III or greater, GFR <60 ml/min, QRS duration >120 ms, and history of AF.

FOLLOW-UP AND OUTCOMES. Follow-up information was obtained retrospectively from appointments every 4 to 6 months for device evaluation, according to French guidelines (18). The different endpoints were occurrence of appropriate therapies, inappropriate therapies, and other complications, as well as overall and specific mortalities. Device interrogation printouts were checked by the local investigator for appropriate and inappropriate ICD therapy.

Appropriate ICD therapy was defined as an episode of ventricular tachycardia/ventricular fibrillation that resulted in a single or multiple shocks or anti-tachycardia pacing for arrhythmia termination. The date of the first appropriate ICD therapy was recorded, and the overall cumulated number of appropriate therapies was considered. Data regarding the occurrence of inappropriate shock(s), as well as the cause, were also collected. Adjudication as appropriate or inappropriate therapy was performed by the local electrophysiologist investigator. No central adjudication of therapies was performed, which we acknowledge may be a limitation because of the possible heterogeneity in the classification of arrhythmia episodes.

Vital status data were obtained from the hospital or the general practitioner and were systematically controlled through the National Institute of Statistics Economical Studies. Causes of death were obtained from the investigators or by the French Center on Medical Causes of Death (CépiDc-INSERM). The CépiDc-INSERM is an academic public institution focused on the analysis of circumstances and causes of death based on death certificate and medical records. Causes of deaths are classified according to the International Classification of Diseases-Tenth Revision. This information was reviewed by 2 investigators, and causes of death were adjudicated after consideration of all the available information and according to the following pre-specified groups: cardiovascular (including progressive heart failure death and stroke), noncardiovascular, ICD-unresponsive SCD (arrhythmic or not arrhythmic whenever the assessment was possible), and ICD-related death, as well as *unknown* when the quality of the information did not enable the investigators to appropriately identify the cause of death. ICD-unresponsive SCD was defined as sudden collapse in front of witnesses or that occurred in patients who 1) died suddenly and unexpectedly within 1 h of cardiac symptoms in the absence of progressive cardiac deterioration; 2) died unexpectedly in bed during sleep; or 3) died unexpectedly within 24 h after last being seen alive. Additionally, to be classified as SCD, extracardiac causes or prior terminal conditions, such as a malignancy that was not in remission or end-stage chronic obstructive lung disease, had to be excluded. Overall, cause-of-death assessment was possible for 372 patients (of 427 deceased; 87.2%). The accuracy of the score for identification of patients at risk of dying shortly (arbitrarily defined as within the first year after ICD implantation or before receiving any appropriate therapies) was also tested.

STATISTICAL ANALYSIS. Preparation of this report was in accordance with the "Strengthening the Reporting of Observational Studies in Epidemiology" statement for the reporting of observational studies (19).

The chi-square test was used for comparison of nominal variables, and the Student *t* test or 1-way analysis of variance was used for comparison of continuous variables. The Levene test was used to check the homogeneity of variance; when appropriate, nonparametric equivalents (Mann-Whitney test and Kruskal-Wallis test) were used. Results with $p < 0.05$ were regarded as significant. C statistics and the respective 95% confidence intervals (95% CIs) were used to estimate the discriminative capability of the Goldenberg score with regard to all of the assessed endpoints. Kaplan-Meier curves were plotted to illustrate survival according to the number of assigned risk factors.

Sensitivity analyses were performed regarding 3 specific populations: patients implanted with cardiac resynchronization therapy (CRT) devices, patients with nonischemic cardiomyopathy, and patients with ischemic cardiomyopathy patients.

Data were recorded on a pre-defined data introduction electronic sheet made available to all participating centers. After completion of follow-up, data from all centers were merged and analyzed at the Paris Cardiovascular Research Center (INSERM U970, Cardiovascular Epidemiology Unit) with SAS program version 9.3 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

POPULATION CHARACTERISTICS AND OUTCOMES. Of the 2,485 patients included in the analysis, 2,115 (85.1%) were men, and the average age was 62.5 ± 11.3 years. Most patients had ischemic cardiomyopathy (57.5%), and the average NYHA functional class was 2.4 ± 0.7. A CRT was used in 1,293 patients (52.0%), whereas 677 (27.2%) were implanted with a double-chamber ICD. More information on the general sample data can be found in **Table 1**.

During a total follow-up of 7,242 person-years (mean of 2.96 ± 2.07 years), 427 patients died (17.2%). Among these, 231 patients (54.1%) died of cardiovascular causes (mainly progressive heart failure), 96 (22.5%) of noncardiovascular causes, 37 of ICD-unresponsive SCD (8.7%), and 8 (1.9%) of ICD-related complications (mainly infection). It was not possible to determine the precise cause of death in 55 patients (12.9%).

Death in the first year after implantation occurred in 126 patients. If we exclude all patients who were alive at last contact but had less than 12 months of follow-up (which is the reason their outcome at the end of the first year was unknown), this corresponds to 6.0% of our sample. In addition, 315 patients died before receiving appropriate therapy; this represents a significant number of patients. After we ruled out those patients who were still alive and had not yet had appropriate therapy (but still had the potential to receive therapy in the future), this corresponded to 38.4% of the sample (Online Table 1).

Overall, 506 patients (21.3%) received at least 1 appropriate therapy, whereas 149 (6.3%) received at least 1 inappropriate shock (this was attributable to supraventricular tachycardia in 55.4% of cases, lead dysfunction in 26.6%, noise/interference in 9.4%, and T-wave oversensing in 8.6%).

TABLE 1 Sample Characterization

Age (yrs)	62.5 ± 11.3
Women	370 (14.9)
NYHA class	2.4 ± 0.7
Atrial fibrillation	528 (21.4)
Ischemic cardiomyopathy	1,430 (57.5)
Single-chamber ICD	493 (19.8)
Double-chamber ICD	677 (27.2)
CRT-D	1,293 (52.0)
Mean LVEF	27.1 ± 7.5
QRS width <120 ms	802 (32.6)
Age >70 yrs	748 (30.4)
GFR < 60 ml/min	934 (37.9)
NYHA ≥3	1,174 (47.7)
Comorbidities*	0.9 ± 0.7
ACEI or ARB	1,902 (80.2)
Beta-blocker	2,047 (86.3)
Amiodarone	507 (21.4)
Digoxin	131 (5.5)
Sotalol	6 (0.3)
Class Ic antiarrhythmic agent	1 (0)
Spironolactone	797 (33.6)
Furosemide	1,554 (65.5)
Antiplatelet agents	1,353 (57.0)
Vitamin K antagonists	852 (35.9)

Values are mean ± SD or n (%). *Number of comorbidities among the following: cancer, chronic kidney disease, chronic lung disease, hepatic failure, diabetes mellitus, and previous stroke.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CRT-D = cardiac resynchronization therapy with defibrillator; GFR = glomerular filtration rate; ICD = implantable cardioverter-defibrillator; LVEF = left ventricle ejection fraction; NYHA = New York Heart Association.

OUTCOMES ACCORDING TO NUMBER OF RISK FACTORS. Patients' characteristics according to the number of risk factors are presented in **Table 2**. Mortality increased progressively from lower-risk to higher-risk strata (from 2.5 to 14.8 per 100 patient-years; p for trend <0.001); however, appropriate therapies occurred with a similar incidence among patients with different numbers of risk factors (7.4 to 8.8 per 100 patient-years; p = 0.898) (**Figure 1**). In addition, no significant differences were observed in the occurrence of inappropriate shocks in the different strata (1.1 to 2.5 per 100 patient-years; p = 0.113) (**Table 2**). The risk score showed a discriminative ability for overall mortality (C statistic = 0.673; 95% CI: 0.644 to 0.701; p < 0.001) but was not a discriminator of appropriate therapies (C statistic = 0.488; 95% CI: 0.644 to 0.701; p = 0.411) (**Table 3**).

The survival outcome during follow-up in all risk strata is illustrated in **Figure 2**. Cardiovascular causes were the most frequent causes of death in this population (**Figure 2B**), increasing from 40.7% to 71.3% of all deaths along categories (p for trend < 0.001).

The mortality rate in the first year after the procedure increased progressively and markedly with the number of risk factors, from 1.1% to 16.7% (p < 0.001), and the score had a moderately high discriminative capacity for this endpoint (C statistic = 0.730; 95% CI: 0.687 to 0.773; p < 0.001)

TABLE 2 Sample Data Stratified by the Number of Risk Factors

Parameter	Number of Risk Factors						
	0 (n = 317)	1 (n = 605)	2 (n = 680)	3 (n = 506)	4 (n = 293)	5 (n = 84)	p Value
Age (yrs)	53.4 ± 9.8	57.5 ± 10.7	62.2 ± 10.0	67.0 ± 9.5	71.9 ± 6.5	74.9 ± 3.1	<0.001
Women	42 (13.2)	99 (16.4)	111 (16.3)	69 (13.6)	32 (11.0)	17 (20.2)	0.113
NYHA functional class	1.7 ± 0.4	2.0 ± 0.6	2.5 ± 0.7	2.7 ± 0.7	3.0 ± 0.4	3.2 ± 0.4	<0.001
Atrial fibrillation	0 (0)	45 (7.4)	101 (14.9)	151 (29.8)	150 (51.2)	84 (100)	<0.001
Ischemic cardiomyopathy	236 (75.9)	350 (58.2)	353 (52.4)	269 (53.6)	177 (61.2)	45 (53.6)	<0.001
Single-chamber ICD	158 (51.0)	173 (28.9)	92 (13.6)	52 (10.4)	15 (5.1)	3 (3.6)	<0.001
Double-chamber ICD	135 (43.5)	230 (38.5)	186 (27.5)	82 (16.3)	38 (13.0)	6 (7.2)	
CRT-D	17 (5.5)	195 (32.6)	399 (58.9)	368 (73.3)	240 (81.9)	74 (89.2)	
LVEF	29.6 ± 9.5	27.4 ± 7.6	26.6 ± 7.5	26.1 ± 7.1	26.4 ± 5.5	26.7 ± 5.2	<0.001
QRS width >120 ms	0 (0)	340 (56.2)	525 (77.2)	448 (88.5)	277 (94.5)	84 (100)	<0.001
Age >70 yrs	0 (0)	50 (8.3)	164 (24.1)	230 (45.5)	223 (76.1)	84 (100)	<0.001
GFR <60 ml/min	0 (0)	86 (14.2)	198 (29.1)	315 (62.3)	256 (87.4)	84 (100)	<0.001
Number of comorbidities	0.8 ± 0.6	0.9 ± 0.6	0.9 ± 0.7	1.0 ± 0.7	1.0 ± 0.7	1.0 ± 0.6	<0.001
Mean follow-up duration (months)	3.4 ± 2.1	3.0 ± 2.1	3.0 ± 2.0	2.7 ± 2.0	2.8 ± 2.1	2.3 ± 1.9	<0.001
Mortality	27 (8.7) 2.5 per 100 pt-yrs	52 (8.9) 2.9 per 100 pt-yrs	97 (14.7) 4.8 per 100 pt-yrs	122 (25.1) 9.0 per 100 pt-yrs	101 (35.3) 12.3 per 100 pt-yrs	28 (34.1) 14.8 per 100 pt-yrs	<0.001
Death in the first year after implantation	3 (1.1)	10 (2.0)	24 (4.2)	38 (9.0)	39 (15.5)	12 (16.7)	<0.001
Appropriate therapies	68 (22.2) 7.4 per 100 pt-yrs	124 (21.5) 8.0 per 100 pt-yrs	143 (22.0) 8.5 per 100 pt-yrs	100 (20.9) 8.8 per 100 pt-yrs	58 (20.5) 8.4 per 100 pt-yrs	13 (16.5) 8.1 per 100 pt-yrs	0.898
Death before an appropriate therapy	20 (22.7)	37 (23.0)	70 (32.9)	88 (46.8)	74 (56.1)	26 (66.7)	<0.001
Inappropriate shocks	21 (6.9) 2.0 per 100 pt-yrs	45 (7.8) 2.5 per 100 pt-yrs	46 (7.1) 2.3 per 100 pt-yrs	22 (4.6) 1.6 per 100 pt-yrs	13 (4.6) 1.6 per 100 pt-yrs	2 (2.6) 1.1 per 100 pt-yrs	0.116

Values are mean ± SD or n (%).
CRT-D = cardiac resynchronization therapy with defibrillator; GFR = glomerular filtration rate; ICD = implantable cardioverter-defibrillator; LVEF = left ventricle ejection fraction; NYHA = New York Heart Association; pt-yrs = patient-years.

(**Tables 2 and 3**). Similarly, mortality before receipt of an appropriate therapy also increased from 22.7% to 66.7% ($p < 0.001$), with a relatively similar discriminative capacity for predicting these events (C statistic = 0.660; 95% CI: 0.621 to 0.698; $p < 0.001$) compared with the overall group.

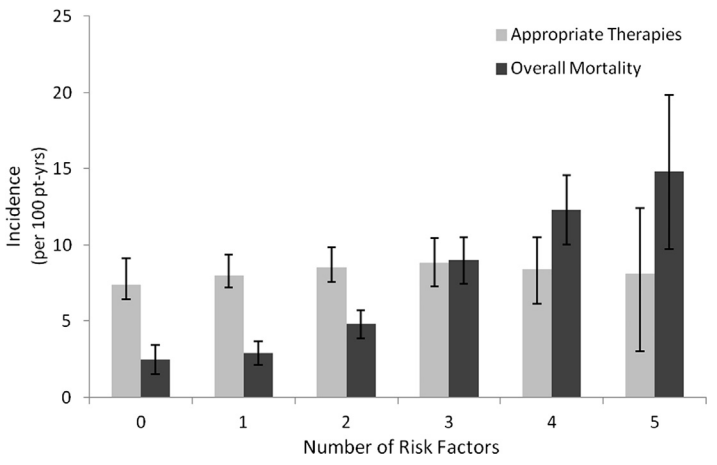
SENSITIVITY ANALYSES. When mortality in 3 specific subsets of patients was analyzed, a similar C statistic was found for patients with ischemic cardiomyopathy (C statistic = 0.685; 95% CI: 0.650 to 0.721; $p < 0.001$), patients with nonischemic cardiomyopathy (C statistic = 0.658; 95% CI: 0.611 to 0.705; $p < 0.001$), and those implanted with a CRT (C statistic = 0.678; 95% CI: 0.645 to 0.712; $p < 0.001$) (**Table 3**, Online Tables 2 and 3). With regard to appropriate therapies, the score was not a significant discriminator in any of the aforementioned groups. Data on the performance of the score according to the degree of QRS prolongation in patients in whom a CRT device with a defibrillator (CRT-D) had been implanted may be found in Online Table 5. Analysis of the variables composing the Goldenberg risk score in patients with CRT-Ds and non-CRT-Ds and their impact on mortality is shown in Online Table 4.

DISCUSSION

Our findings suggest that the use of a simple risk score is feasible and particularly efficient among heart failure patients eligible for an ICD for primary prevention to identify those most likely to not benefit from ICD implantation because of a high risk of competing nonarrhythmic mortality. In addition, the similar incidence of appropriate therapies observed among all risk strata demonstrates that those high-risk patients do not experience an incremental benefit from this therapy.

These results demonstrate the good discriminative ability of the score previously developed by Goldenberg and colleagues (20) when applied to real-world primary prevention ICD recipients with heart failure. More important, the cause-of-death analysis provides interesting first data on the relatively high specificity of such a score for nonsudden events (with a progressive and significant increase in the incidence of nonarrhythmic cardiovascular death and non-cardiovascular death across high-risk strata, whereas the difference in terms of arrhythmic events remained very low). Our data emphasize the extent to

FIGURE 1 Incidence (per 100 Patient-Years With 95% Confidence Interval) of Events Stratified by the Number of Risk Factors



pt-yrs = patient-years.

which the targeting of patients who are simultaneously at high risk of SCD and have a low risk of nonarrhythmic mortality, instead of patients with a high risk of SCD independent of their risk of nonarrhythmic mortality, could be an efficient way to eventually improve the cost-effectiveness of primary prevention ICD implantation. The fact that patients deemed to be at high risk according to this risk classification die of non-SCD has been suggested previously (11,17). Unlike in our study, in which all patients were treated with an ICD, in the long-term follow-up (median follow-up of 7.6 years) of the original MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) cohort, no benefit was found among high-risk patients (those with ≥3 risk factors) implanted with an ICD compared with their non-ICD-treated counterparts (11).

In the original derivation paper by Goldenberg et al. (17), low-risk patients (those with a score of zero) experienced no benefit from ICD therapy. This may be explained by the shorter follow-up duration (median of 1.5 years), which did not allow time for patients to experience appropriate ICD interventions. Also, unlike in our study, Barsheshet et al. (11) assessed the proportion of patients who moved to higher-risk categories because of the development of pre-specified risk factors during the MADIT-II in-trial period. This risk factor adjustment and the longer follow-up may explain why, in their long-term analysis, low-risk patients (those with a score of zero) derived the most pronounced benefit from ICD therapy (11).

In this contemporary cohort of primary prevention ICD patients, the incidence of ICD-unresponsive SCD was low (0.5 per 100 patient-years), which illustrates the efficacy of ICD therapy to prevent SCD in those high-risk patients (a sudden death rate of 10% during an average follow-up of 20 months was observed in the control group in the MADIT-II trial [21]). Consequently, most patients die of non-SCD (cardiovascular non-SCD or noncardiovascular death). Even though the incidence of SCD appeared to be numerically higher (2 to 3 times higher) in some of the high-risk groups, this difference did not reach statistical significance. This can be explained primarily by the small incidence of that specific type of event. Several thousand patients would be needed to produce a study with enough power to answer that question.

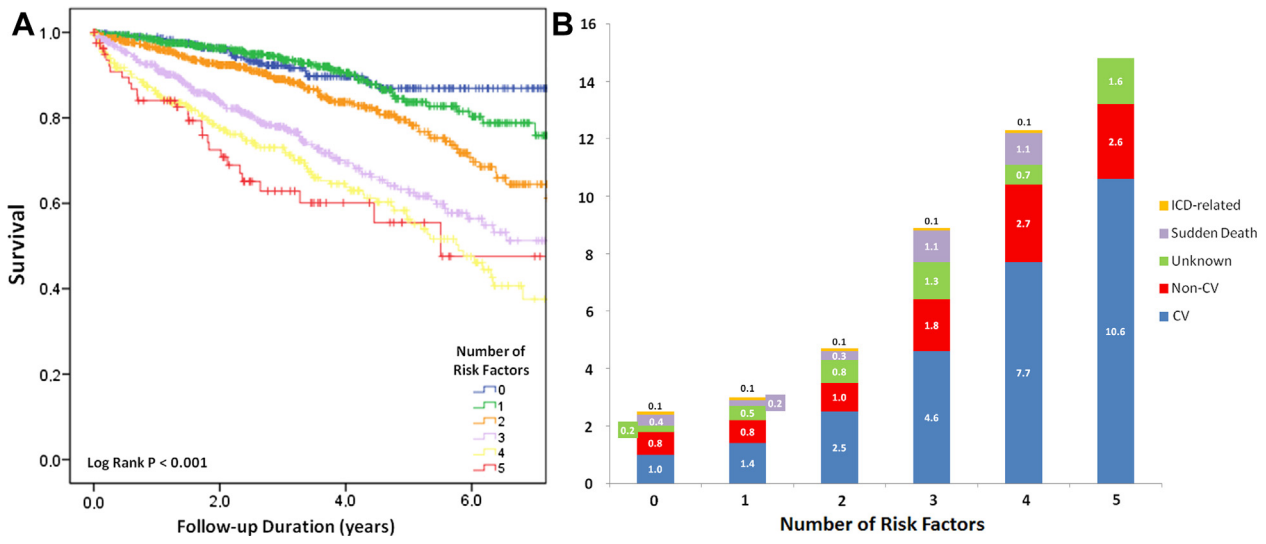
Almost one-half of our contemporary ICD patients die either before appropriate ICD therapy or within the first year after implantation (22). Our results add further insight to this matter: Patients in high-risk strata not only have higher mortality but also tend to die sooner after implantation and before receiving an appropriate ICD intervention. This reinforces the idea that in such circumstances, the use of ICDs does not significantly change the natural course of the underlying heart condition, which suggests the need for treatment optimization of the associated cardiac and systemic comorbidities.

TABLE 3 Assessment of the Discriminative Capability of the Goldenberg Risk Score in the Global Sample and Sensitivity Analysis for Specific Subsets

	Global Sample		Ischemic Cardiomyopathy		Nonischemic Cardiomyopathy		CRT	
Endpoint	C Statistic (95% CI)	p Value	C Statistic (95% CI)	p Value	C Statistic (95% CI)	p Value	C Statistic (95% CI)	p Value
Mortality	0.673 (0.644–0.701)	<0.001	0.685 (0.650–0.721)	<0.001	0.658 (0.611–0.705)	<0.001	0.678 (0.645–0.712)	<0.001
Appropriate therapies	0.488 (0.460–0.516)	0.411	0.486 (0.449–0.524)	0.480	0.488 (0.444–0.531)	0.586	0.500 (0.461–0.539)	0.982
Death in first year after implantation	0.730 (0.687–0.773)	<0.001	0.730 (0.677–0.782)	<0.001	0.728 (0.652–0.804)	<0.001	0.685 (0.633–0.736)	<0.001
Death before receiving an appropriate therapy	0.660 (0.621–0.698)	<0.001	0.661 (0.613–0.709)	<0.001	0.666 (0.601–0.731)	<0.001	0.659 (0.609–0.708)	<0.001

CI = confidence interval; CRT = cardiac resynchronization therapy with defibrillator.

FIGURE 2 **Impact of Number of Risk Factors on Mortality and Incidence of Specific Causes of Death**



(A) Kaplan-Meier curves illustrating the impact of the number of risk factors on overall mortality during follow-up of the cohort. **(B)** Incidence (per 100 patient-years) of specific mortality causes among the different risk strata. CV = cardiovascular; ICD = implantable cardioverter-defibrillator.

This score has been derived from a MADIT-II dataset, which comprised only patients with ischemic cardiomyopathy. To the best of our knowledge, our results represent the first validation through a large cohort of primary prevention patients, comprising both patients with nonischemic cardiomyopathy and patients with CRT. This is of importance because more and more patients are currently being implanted with CRT-D devices and nonischemic cardiomyopathy, representing 42% of all ICD implants in the National ICD Registry Report (23). Schaer et al. (24) recently provided interesting preliminary data about the use of this score in patients with various nonischemic heart conditions. Although the heterogeneity of the studied population and the lack of cause-specific sensitivity analysis call for a cautious interpretation of the data, the authors' findings suggest that such a score may be also be valid in other heart conditions besides ischemic cardiomyopathy, and even in secondary prevention (24).

Life expectancy is already considered for treatment decisions in the current recommendations for ICD therapy (25,26). The proposed cutoff of more than 1 year of life expectancy is somewhat subjective and may be more objectively and effectively replaced by a frailty index. When the different strata of the score used by Goldenberg et al. (17) were analyzed, we observed that even in the highest-risk category, mortality at the end of the first year did not exceed 15 deaths per 100 patient-years, which emphasizes that there is still room to improve this classification in its actual state as a mean of excluding patients from this therapy. On the other hand, the fact that almost two-thirds of the patients in the highest-risk category died before receiving an appropriate therapy indicates a degree of futility or harm in some higher-risk patients. They may end up not experiencing any appropriate ICD therapeutic benefit but still be exposed to the risk of possible complications. This narrow risk-benefit balance in high-risk categories would be an important issue to discuss with patients before referring them to ICD therapy.

A different approach for the assessment of competing mortality risks can be the analysis of medical comorbidity. A recent combined analysis of 4 major randomized controlled trials of primary prevention ICDs (MADIT-I, MADIT-II, DEFINITE [Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation], and SCD-HeFT [Sudden Cardiac Death in Heart Failure]) suggested that the benefit of ICD therapy (ICD vs. optimized medical therapy) could be attenuated by the number of coexisting comorbidities (smoking, ischemic heart disease, chronic kidney disease, diabetes, pulmonary disease, AF, and peripheral vascular disease). During a median follow-up of 2.6 years, patients with less comorbidity (<2 of the abovementioned conditions) experienced higher survival benefit from ICD therapy (27).

STUDY LIMITATIONS. First, because of the lack of data regarding diabetes mellitus and smoking habits, we were not able to assess and compare the Goldenberg score with other existing risk classifications; however, results in the literature show either similar results or a slightly better performance of the "SHOCKED" predictors (75 years of age or older, heart failure [NYHA functional class III], out of rhythm because of AF, chronic obstructive pulmonary disease, chronic kidney disease, left ventricular ejection fraction ≤20%, and diabetes mellitus; C statistic = 0.74 in its validation cohort) (28). Second, because this registry was started before the publication by Goldenberg et al. (17), we did not have data on blood urea nitrogen for most of our patients; this was replaced by the estimated GFR. Third, patients were categorized as having either ischemic or nonischemic cardiomyopathy. We have no information regarding the number of patients with ischemic cardiomyopathy and evidence of previous myocardial infarction. Also, we cannot know for sure how many patients presented with mixed cardiomyopathy (i.e., a combination of ischemic and nonischemic contributors). Fourth, the cause of death could not be determined in 12.8% of deaths. The complexity of clarifying the nature of "terminal" events associated with SCD is well known and may not be identified in the case of an ICD recipient who dies suddenly. The similar proportions of deaths of undetermined causes across the different categories of risk make a differential bias unlikely. Fifth, changes in clinical status that lead to migration among the different risk categories might have occurred during follow-up. The reassignment of these patients to the appropriate risk category at yearly intervals could have improved the performance of the score. Unfortunately, because of the lack of serial creatinine measurements, and therefore GFR, we could not perform this reclassification. Last, ICD programming was not uniform, and therefore, it is likely that the incidence of appropriate therapies may be an overestimation of the true incidence of sustained ventricular arrhythmias because of the short detection times that were frequently used in the first years of this registry. It has been shown that "unnecessary therapies" are associated with increased mortality (29), and therefore, we can hypothesize that less aggressive ICD programming could have led to a lower mortality in this cohort.

CONCLUSIONS

Our findings demonstrated the potential utility of a simple risk score for the global primary prevention ICD population, namely, in patients with nonischemic cardiomyopathy and those implanted with a CRT. This may provide important information when discussing the expected device benefits with patients eligible for a primary prevention indication.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE 1: A simple, 5-variable risk score allowed the detection of patients less likely to benefit from ICD therapy because of competing nonarrhythmic risks.

COMPETENCY IN PATIENT CARE 2: Overall mortality increases with the number of risk factors, although the incidence of appropriate therapies is similar in all risk groups.

COMPETENCY IN MEDICAL KNOWLEDGE: The Goldenberg risk score can be applied to all patients with ischemic and nonischemic cardiomyopathy who are candidates for a primary prevention ICD (with or without cardiac resynchronization therapy) and may improve patient selection for this therapy.

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KEY WORDS arrhythmia, competing risk, shock, sudden cardiac death, ventricular tachycardia

APPENDIX For a list of the investigators and institutions participated in the conception of the registry, and in the organization, collection, storage, and analysis of the data, as well as supplemental tables, please see the online version of this article.