ORIGINAL ARTICLE

Clinical risk profile score predicts all cause mortality but not implantable cardioverter defibrillator intervention rate in a large unselected cohort of patients with congestive heart failure

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Background: Primary prophylactic implantable cardioverter defibrillator (ICD) therapy is indicated for patients with reduced left ventricular ejection fraction (LVEF). We aimed to determine if preoperative clinical risk profiling can predict long-term benefit, and if clinical risk scores can be applied and improved in a patient cohort outside the clinical trial setting.

Methods: Using registry data, 789 patients with reduced LVEF who received ICDs for primary prevention during 2006–2011 were identified (age 64 ± 11 years, 82% men, 63% ischemic etiology, 52% cardiac resynchronization therapy with defibrillator). The patients were divided into three risk groups, based on the presence of baseline clinical risk factors (age >70 , QRS duration >120 ms, New York Heart Association class III–IV, atrial fibrillation history, or creatinine >106 $\mu\text{mol/L}$). Endpoints were all-cause mortality and survival free of adequate ICD therapy.

Results: Mean follow-up was 39 ± 18 months. Annual mortality was 7.6%, and increased with risk group ($p < .001$). Rates of appropriate antitachycardia pacing and shock therapy were not statistically different between the groups, and ranged from 11%–16% and 6%–14%, respectively. By combining the previous risk score with data on diabetes, a better independent prediction of mortality was achieved; mortality rates then ranged from 11% (low-risk) to 46% (high-risk) ($p < .0001$).

Conclusions: Implantable cardioverter defibrillator therapies occur across the spectrum of comorbidities in a population with systolic heart failure. However, all-cause mortality is considerably higher in the group of patients with accumulated risk factors, and using the proposed scoring system can be helpful for the evaluation and risk stratification of the patient prior to making a decision for a primary prophylactic ICD implantation.

KEYWORDS

heart failure, implanted cardioverter defibrillator, primary prevention, risk score, sudden cardiac death

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

1 | INTRODUCTION

Use of implantable cardioverter defibrillators (ICDs) is considered to be the most efficient mode of secondary prevention of sudden cardiac death (SCD) in patients who survive cardiac arrest caused by ventricular fibrillation (VF), as well as in primary prevention of SCD in patients considered to be at high risk (Bardy et al., 2005; Buxton et al., 1999; Epstein et al., 2013; Moss et al., 1996, 2002; Theuns, Smith, Hunink, Bardy, & Jordaens, 2010). While there is no controversy regarding the choice of treatment for those who survive cardiac arrest, the risk stratification and proper selection of candidates for primary prophylactic ICD implantation to prevent SCD is still debated (Goldberger et al., 2014). The impact of age and medical comorbidity on the effectiveness of ICDs for primary prevention is highly relevant with regard to evaluation of the cost-benefit of the treatment, and a substantial part of early mortality in ICD-treated patients can be attributed to nonarrhythmic causes (Chan et al., 2009; Packer et al., 2009).

Current guidelines define indications for ICD implantation for primary SCD based on the main results of the large randomized trials (Epstein et al., 2013), but subanalyses and large registry data suggest that the real net benefit of ICD therapy may be substantially lower or absent in patients with significant other comorbidities (Barsheshet et al., 2012; Bilchick, Stukenborg, Kamath, & Cheng, 2012; Goldenberg et al., 2008). Given that ICD treatment is expensive, and complications are common (Alter, Waldhans, Plachta, Moosdorf, & Grimm, 2005), it is important to identify risk factors that can help in pinpointing the patient subgroups expected to gain the most benefit from ICD therapy. Post hoc analyses of patients enrolled in the Multicenter Automatic Defibrillator Implantation II (MADIT II) study showed that in a cohort of patients with ischemic cardiomyopathy, presence of age >70 years, a history of atrial fibrillation (AF), renal failure, prolonged QRS duration (>120 ms), and advanced heart failure (New York Heart Association, NYHA III–IV class) were significantly associated with poor prognosis in a U-shaped relationship (Barsheshet et al., 2012; Goldenberg et al., 2008). Patients without risk factors and patients at very high risk received no benefit from ICD therapy, while medium-score patients treated with ICDs demonstrated a 49% relative reduction in the risk of death versus non-ICD-treated patients. These findings were also to a large extent reproduced in two American registry-based studies (Bilchick et al., 2012; Parkash, Stevenson, Epstein, & Maisel, 2006). However, in the long-term follow-up of MADIT II this pattern was partly altered, as the low-risk patients then began to show benefit from ICD therapy versus medical therapy, whereas the high-risk patients still had no significant effect on mortality (Barsheshet et al., 2012).

In our study on an unselected patient population outside the clinical trial setting we aimed to see if the preoperative clinical risk profile can correctly determine long-term survival and benefit of ICD treatment, and if the proposed clinical risk score from the MADIT II trial (Goldenberg et al., 2008) can be applied to a mixed population of ischemic and dilated cardiomyopathy with or without concomitant cardiac resynchronization therapy.

2 | METHODS

Patients were identified from the Swedish Pacemaker Registry that includes all patients implanted with pacemakers or implantable defibrillators in Sweden (F G. The Swedish Pacemaker Registry, 2013). All patients who received an ICD for primary prevention of SCD during 2006–2011 at four large tertiary-care Swedish hospitals were included. The individual medical records were reviewed manually for verification of the information obtained from the Swedish Pacemaker Implant Registry, assessment of the patients' clinical profiles at the time of ICD implantation, and outcome measures. Only patients with ischemic or dilated cardiomyopathy fulfilling indications for primary preventive ICD implantation according to ACC/AHA/ESC 2006 guidelines for the prevention of SCD were included in the analysis (European Heart Rhythm et al., 2006). Programming of the devices was at the discretion of the implanting physician. In Sweden there is a general consensus of opinion to adhere to the recommendation arising from the PainFREE II trial (Wathen et al., 2004), with relatively long detection intervals (typically ≥ 24 beats for the VT zone), a VF zone above 240–250 beats per minute and no active VT-detection or therapies below 185–188 beats per minute. This standard type of programming is used regardless of device manufacturer.

2.1 | Baseline status

Information regarding clinically relevant risk factors known at the time of ICD implantation was obtained during manual review of the medical records, and this included age, QRS morphology and duration, NYHA class, history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft (CABG) surgery, AF or stroke, smoking habits, diabetes and serum creatinine levels. All patients were assigned to one of the three risk factor groups proposed by Goldenberg et al. (2008) on the basis of data from the MADIT II trial, and the performance of the risk score in the prediction of endpoints was evaluated. In brief, the presence of AF, QRS width >120 ms, NYHA class III–IV symptoms, and age >70 years each counted as one risk factor. The original parameter blood urea nitrogen >26 mg/dl was replaced by the approximate equivalent serum creatinine >106 $\mu\text{mol/L}$, since urea nitrogen values were not available in our cohort. Patients with no risk factors were assigned to the "low risk" group, those with one or two risk factors to the "medium risk" group and those with 3–5 risk factors to the "high risk" group. Other independent clinical risk factors known at the time of ICD implantation were then evaluated in combination with the existing risk score.

2.2 | Study endpoints and follow-up

The primary outcome measure was all-cause mortality. The secondary endpoint was survival free of appropriate ICD therapy, defined as either appropriate antitachycardia pacing (ATP) or ICD shock discharge. Survival status at the end of follow-up (May 2013), that is, the primary endpoint, was determined by using database record linkage

with the Swedish Cause of Death Registry that contains information on the date and cause of death for all Swedish residents. For patients who died in-hospital ($n = 99$), the cause of death was adjudicated from the medical records, for all other patients the cause of death as stated in the Swedish Cause of Death Registry was used. Secondary endpoint follow-up information was based on the manual review of the medical records, looking for any documented arrhythmia episodes after implantation, using device interrogation reports and hospital admissions for clinical arrhythmias. With regard to arrhythmic events, the type of arrhythmia, delivered ICD therapies, and effect of therapy were documented, as well as all inappropriate ICD discharges and their causes. All arrhythmia endpoints were verified by a senior electrophysiologist, and cross-validated by another senior electrophysiologist if there was any doubt. If the same arrhythmia episode was treated with both ATP and shock therapy, it was classified as shock therapy. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the regional human research committee in Lund. The necessity of individual written informed consent was waived by the decision of the committee.

2.3 | Statistics

Continuous data are presented as mean $\pm$ standard deviation or median [IQ range], as appropriate. Nominal data are presented as percentage (number of cases). Fisher's exact test was used for comparison of categorical variables, t test was used for continuous variables with normal distribution and Mann-Whitney U test for continuous variables with non-normal distribution. A two-sided p -value $< .05$ was considered statistically significant. For survival analysis, Kaplan-Meier curves were used, with the log-rank test to test for differences between groups. Cox regression analysis was used for the evaluation of independent predictors of survival and event-free survival as defined in the results section. All variables with a p -value $< .20$ in univariate analysis were entered into a multivariate backwards stepwise regression analysis. All analyses were carried out with SPSS software (IBM, Version 21).

3 | RESULTS

3.1 | Clinical characteristics

From 2006 to 2011, a total of 865 consecutive patients received primary prophylactic ICD treatment in the participating centers and fulfilled study inclusion criteria. In 76 patients, partially missing data prevented allocation to a specific risk factor group. The remaining 789 cases were included in this study. Baseline clinical data are presented in Table 1, and the mean follow-up time was 39 ± 18 months. The average number of risk factors was 2.2 ± 1.3 ; in 7% of cases no risk factors (low-risk group) were identified, 54% had one or two risk factors (medium-risk group) and 39% had 3–5 risk factors (high-risk group) (Table 2). The patients in the high-risk factor group generally had more comorbidity in addition to the conditions included in the risk score, compared with those in the low- and intermediate-risk groups. They were to a larger extent male, had a higher rate of CRT-D (compared

with ICD only), more often had had previous coronary artery bypass (CABG) surgery, diabetes, hypertension and stroke, but fewer were active smokers.

3.2 | Appropriate ICD treatment, and mortality

Neither appropriate nor inappropriate therapy differed significantly between groups (Table 2). Eighty percent of those who died did so without ICD therapy or malignant arrhythmias detected on previous device interrogations, and these patients were evenly distributed in all three risk groups (Table 2). Of the 40 patients who died and who had received shocks at a prior event, the median time between first treatment and death was 13.4 months (range 1–58 months). The patients who received adequate therapy and survived to the end of the follow-up period had a lower number of risk factors compared with those who received therapy and later died (mean 2.1 vs 2.9, $p = .002$). Mode of death differed between groups; the most common cause of death being heart failure, 17% in the low-risk group and higher in the medium- and high-risk groups (44% and 47%, respectively). Death from arrhythmia (as classified in the National Cause of Death Registry) was uncommon but occurred in all groups, and the relative incidence ranged from 0.6% (medium- and high-risk groups) to 1.7% (low-risk group) ($p = .7$).

Overall, 18% (140) of the patients received appropriate ICD therapy. Annual mortality was 7.6%, and it increased significantly along with the increasing risk factor score ($p < .001$). In total, 197 patients (25%) died or had a heart transplant (see Table 3). Among the 77 patients who were not included in the risk factor analysis as a result of incomplete information concerning their risk profiles in medical records, total mortality (21%) did not differ from that in the studied cohort.

3.3 | Diabetes-adjusted risk score

Predictors of mortality are presented in Table 3, and Kaplan-Meier plots of risk groups are presented in Figure 1a, b. There was no significant difference in survival between the low- and medium-risk groups, but a significant increase in mortality in the high-risk group compared with the low- and medium-risk groups (HR 2.7, 95% CI 2.0–3.6, $p < .001$). The same pattern was seen for the secondary endpoint of survival and appropriate ICD therapy, but with a lower HR of 2.0 (95% CI 1.6–2.5, $p < .001$, Fig. 1b).

Since the existing MADIT II-based risk score did not discriminate between low- and medium-risk patients with regard to mortality in our cohort, and since diabetes was a strong independent predictor of both death and "death or appropriate ICD therapy," a new risk score was constructed, incorporating diabetes in addition to the other five risk factors. The maximum total score was then 6 points, and the cohort was divided into three risk categories: low-risk (0–1 risk factors), medium-risk (2–3 risk factors), and high-risk (4–6 risk factors). Twenty-four percent of the patients qualified for the low-risk group, 48% for the medium-risk, and 28% for the high-risk group. Multivariate analysis was repeated (Table 3, inscribed in gray at the bottom), and it showed a highly significant independent predictive value for all-cause mortality using the new risk groups: HR 2.1 (1.3–3.5) for the

TABLE 1 Baseline demographic and clinical data stratified in different risk groups

	Entire cohort (n = 789)	Low-risk group 8% (n = 59)	Medium-risk group 53% (n = 421)	High-risk group 39% (n = 309)	p-Value
Follow-up time	39 ± 18	36 ± 14	39 ± 19	40 ± 18	.22
Age at implantation	65 ± 11	59 ± 11	61 ± 11	71 ± 8	<.001
Female gender	17% (137)	27% (16)	21% (87)	11% (34)	<.001
Ischemic etiology	63% (494)	73% (43)	59% (243)	66% (204)	.03
NYHA					
Class I	6% (38)	20% (9)	7% (24)	2% (5)	<.001
Class II	33% (211)	80% (37)	44% (142)	12% (32)	
Class III	60% (385)	0	48% (156)	84% (229)	
Class IV	2% (10)	0	1% (4)	2% (6)	
Atrial fibrillation	38% (299)	0	23% (96)	66% (203)	<.001
Chronic obstructive lung disease	10% (81)	10% (6)	9% (37)	12% (38)	.3
QRS duration	134 (54)	101 (10)	130 (58)	148 (40)	<.001
ECG pattern (n = 775)					<.001
Narrow QRS complex	36% (283)	93% (54)	42% (174)	18% (55)	
LBBB	42% (322)	3% (2)	36% (148)	56% (172)	
RBBB	4% (34)	2% (1)	5% (19)	5% (14)	
Atypical conduction block	15% (112)	2% (1)	14% (57)	18% (54)	
Paced QRS complex	3% (24)	0	3% (13)	4% (11)	
Hypertension	48% (376)	48% (28)	43% (181)	54% (167)	.01
Previous stroke and TIA	11% (83)	7% (4)	8% (33)	15% (46)	.006
Diabetes	29% (228)	17% (10)	25% (106)	36% (112)	.001
Beta-blocker therapy	94% (717)	95% (54)	94% (376)	94% (287)	.98
CRT-D	52% (408)	7% (4)	44% (187)	70% (217)	<.001
CABG	30% (237)	20% (12)	23% (97)	42% (128)	<.001
Smoker (active)	15% (116)	19% (11)	18% (75)	10% (30)	.02
Number of risk factors	2.1 ± 1.3	0	1.5 ± 0.5	3.5 ± 0.7	<.001
LVEF	25 (10)	30 (10)	25 (10)	25 (10)	.002

CABG, coronary artery bypass grafting; CRT-D, cardiac resynchronization therapy with defibrillator; ECG, electrocardiogram; LBBB, left bundle branch block; NYHA, New York Heart Association classification of heart failure; RBBB, right bundle branch block; TIA, transient ischemic attack.

TABLE 2 Arrhythmic events and mortality stratified in risk groups

Total 789 patients	All patients n = 789	Low-risk group 7% (n = 59)	Medium-risk group 54% (n = 421)	High-risk group 39% (n = 309)	p-Value
Inappropriate shock n (%)	7% (153)	5% (3)	7% (31)	6% (19)	.71
ATP therapy n (%)	13% (105)	15% (9)	11% (48)	16% (48)	.24
Shock therapy n (%)	8% (63)	14% (8)	6% (27)	9% (28)	.11
Death or heart transplant n (%)	25% (197)	14% (8)	16% (69)	39% (120)	<.001
Death with prior ICD therapy	20% (40)	25% (2)	17% (12)	22% (26)	.74
Death without prior ICD therapy	80% (157)	75% (6)	83% (57)	78% (94)	.74
ICD therapy but still alive at end of follow-up	13% (100)	17% (10)	12% (52)	12% (38)	.59

ATP, antitachycardia pacing therapy; ICD, implantable cardioverter defibrillator.

medium-risk group ($p = .003$) and HR 4.0 (2.3–6.9) for the high-risk group ($p < .0001$)—see also Figure 2 illustrating Kaplan–Meier curve analysis of the modified risk score performance. The HR for “death or

appropriate therapy” was 1.6 (1.1–2.2) in the medium-risk group and 2.4 (1.7–3.4) in the high-risk group. The risks of ATP, and appropriate and inappropriate shocks did not differ between groups, but all-cause

TABLE 3 Univariate and independent predictors of total mortality

	Univariate Cox regression				Multivariate Cox regression			
	p-Value	HR	95% CI for HR		p-Value	HR	95% CI for HR	
Female gender	.69	0.9	0.6	1.4				
CRT-D	.001	1.6	1.2	2.2	.9	1.0	0.7	1.4
CABG	<.001	1.7	1.3	2.3	.02	1.4	1.1	2.0
Smoker	.03	0.6	0.4	0.9	.12	0.7	0.4	1.1
Chronic obstructive lung disease	<.001	2.1	1.5	3.1	.06	1.7	1.2	2.5
Diabetes	<.001	1.9	1.5	2.6	<.01	1.7	1.2	2.3
Hypertension	.02	1.4	1.1	1.9	.4	0.9	0.7	1.2
Stroke	.6	0.9	0.6	1.4	.14	0.7	0.4	1.1
LVEF	.02	0.98	0.96	0.996	.12	0.98	0.97	1.0
Original MADIT II risk factor score								
Risk factor group Low risk versus								
Medium risk	.7	1.1	0.6	2.4	.78	0.91	0.4	1.9
High risk	.002	3.0	1.5	6.2	.08	1.96	0.9	4.2
Modified risk factor score (diabetes included):								
Risk factor group with diabetes low risk versus								
Medium risk	.003	2.0	1.3	3.3	.005	2.1	1.3	3.5
High risk	<.001	4.8	3.0	7.6	<.001	4.0	2.3	6.9

Baseline variables were assessed for prediction of mortality, using Cox regression analysis. At the bottom (italics) are results after using the newly proposed risk groups. Numbers in bold type indicate variables with p-values <0.05 in the corrected multivariate regression model.

CABG, coronary artery bypass grafting; CRT-D, cardiac resynchronization therapy with defibrillator; LVEF, left ventricular ejection fraction; MADIT II, Multicenter Automatic Defibrillator Implantation Trial.

mortality was 11% in the low-risk group, 21% in the medium-risk group, and 46% in the high-risk group—a highly significant difference for all groups ($p < .0001$).

4 | DISCUSSION

4.1 | Main findings

This study on a large real-life cohort of 789 consecutive ICD recipients for primary prevention of sudden death due to heart failure shows that ventricular arrhythmias are common in all patient categories, and that appropriate ICD therapy is evenly distributed across groups of patients with different comorbidities. The previously proposed risk score by Goldenberg et al. seems to be applicable for teasing out the high-risk patients in this cohort of mixed ischemic and dilated cardiomyopathy, including a substantial number of CRT-D-treated patients. However, by adding diabetes as a comorbidity, the prognostic value of the risk score in this real-life cohort was substantially improved, making discrimination between both low-to-medium and medium-to-high risk populations possible with regard to both total mortality, and to survival free of ICD treatment.

4.2 | Mortality and correlation with risk factors

Our results are in agreement with those of previous studies regarding identification of predictors of mortality for ICD-treated patients (Barsheshet et al., 2012; Bilchick et al., 2012; Goldenberg et al., 2008; Parkash et al., 2006). Schaer, Kuhne, Blatter, Osswald, and Sticherling (2014) recently published results from a similar cohort of 1032 unselected patients treated with ICD (48% secondary prevention, 22% CRT-D), and presented data showing a good predictive value for cumulative survival, using the Goldenberg score. Similar to our study, no meaningful correlation was found between adequate ICD therapy and the number of risk factors, and patients with 0 or >2 risk factors had no different risk of a first ever ICD therapy. All-cause mortality increases with the number of comorbidities, and if diabetes is incorporated into the previously proposed risk score system from the MADIT II trial, the discriminatory value and clinical usefulness of the risk score is likely to increase. The previously used MADIT II risk score did not discriminate between low- and medium-risk patient groups as regards long-term survival or survival free from ICD therapy.

In the MADIT II risk score, a history of treated diabetes was associated with a hazard ratio of approximately 1.5 in the univariate

FIGURE 1 Kaplan-Meier curves stratified according to risk group: Low-risk group (green), medium-risk group (yellow), and high-risk group (red). (a) shows cumulative survival. Low- versus medium-risk group, $p = .68$; medium- versus high-risk group, $p < .0001$. (b) shows survival free of implantable cardioverter defibrillator (ICD) therapy. Low- versus medium-risk group, $p = .70$; medium- versus high-risk group, $p < .001$

analysis, but did not add incremental value to the final risk score with the five other variables included (Goldenberg et al., 2008). However, during long-term follow up, as shown by Cygankiewicz et al. (2009), addition of diabetes mellitus to the risk stratification scheme in the original MADIT II cohort proved it to be a significant risk factor in the

FIGURE 2 Kaplan-Meier curves for survival and survival free of implantable cardioverter defibrillator (ICD) therapy, using the diabetes-adjusted risk score. Low-risk group (green), medium-risk group (yellow), and high-risk group (red). (a) shows cumulative survival. Low- versus medium-risk group, $p < .0001$. (b) shows survival free of ICD therapy. $p < .0001$ for all groups

multivariable analysis. Our findings made in the unselected real-life cohort of patients treated within the same health care system support the observations made in the clinical trial settings. The MADIT-II risk score incorporating diabetes mellitus seems to identify three groups of patients with distinct differences in all-cause mortality during long-term follow-up, thus providing useful clinical information for tailoring

decisions on ICD therapy for individual patients. Using the composite risk score, it may be easier to provide the patients with adequate preoperative information regarding life expectancy, which could be helpful to the patient's decision on whether or not to accept primary prophylactic ICD therapy.

Multicenter Automatic Defibrillator Implantation-II risk score and its modification by Cygankiewicz et al. were based on the population with ischemic cardiomyopathy, while our cohort included both ischemic and nonischemic patients as well as both ICD and CRT-D recipients. However, testing the score performance in the subgroups has reproduced the findings made on the entire study cohort, thus, further supporting the score relevance for a broader population of patients with heart failure.

Patients with the high-risk profile had a poor prognosis, 39% mortality during 3.25 years of follow-up. Compared with the other risk groups they had a hazard ratio of 4.6 for death during follow-up, and the majority of the high-risk patients died from advanced heart failure. Therefore, correct preimplant identification of these high-risk patients may help them and their treating physicians to make an informed choice with regard to realistic assessment of prognosis and expected benefit of ICD therapy. It is possible that some patients with high risk would make an informed choice *not* to undergo device therapy, or opt for a CRT-pacemaker instead of a CRT-defibrillator, so that they do not feel denied of "a painless death" from cardiac arrest. This discussion may become especially important in view of recent findings from a study of post-mortem ICD interrogations that demonstrated a high risk of multiple ICD shocks at the end of life (Kinch Westerdahl, Sjöblom, Mattiasson, Rosenqvist, & Frykman, 2014).

4.3 | Other possible risk factors

One of the best-validated risk scores is the Seattle Heart Failure Model that consists of 20 clinical and laboratory parameters, and has been validated in a few cohorts with CRT-D-treated patients (Perrotta et al., 2012; Regoli et al., 2013; Smith et al., 2012). In a mixed population of 1139 device-treated heart failure patients (55% CRT-D and 45% CRT-P) the SHFM had a modest prediction value for all cause mortality (Regoli et al., 2013), somewhat underestimating mortality rates, but in another cohort of 413 CRT-D-treated patients the SHFM offered adequate discrimination of all-cause mortality (Smith et al., 2012). In clinical practice, however, the actual use of the SHFM is perceived to be limited by the extensive number of variables required, even though convenient on-line and app-versions are now available. Therefore, we believe that a less complicated score giving virtually the same clinical information is useful, such as the diabetes-adjusted MADIT II score.

Left ventricular ejection fraction (LVEF) is the primary selection criterion for prophylactic ICD therapy, but has a well-known limitation in specificity for lethal arrhythmias, and indeed lower EF did not predict outcome in our study; a similar finding as in the subanalysis of the MUSTT trial, where Buxton et al. (2007) concluded that the risk of SCD depends on many variables other than LVEF. However, in a large Medicare-based registry analysis carried out by Bilchick et al.

(2012), LVEF was incorporated into the final risk group "SHOCKED" (age, Heart failure class III–IV, Out of Rhythm (AF), Chronic obstructive pulmonary disease, Kidney disease, EF <20% and Diabetes), in which the highest risk quintile had a 58% 3-year mortality rate, suggesting very little benefit from ICD treatment. Although our analysis is similar in design to this Medicare-based study, adding LVEF and previous stroke to the risk score did not strengthen the prediction of mortality or "mortality or appropriate ICD therapy" in our cohort, even though these factors both showed a trend as regards independent prediction of mortality. This may, however, be a result of our cohort being smaller in size, and hence underpowered to detect significant correlations with some of the weaker covariates.

Our findings of association between the risk scores and mortality despite similar incidence of ICD therapies the different risk groups indicate that both risk scores reflect the burden of comorbidities, which is directly linked to the probability of death rather than the risk of ventricular arrhythmias. This explanation is supported by earlier studies of the cause of death in ICD recipients. Arrhythmia was the cause of death in only 16 of 125 ICD recipients who died and had their ICDs explanted and interrogated in our previous study (Kinch Westerdahl, Sjöblom, Mattiasson, Rosenqvist, & Frykman, 2014). In a separate analysis, we reviewed the cause of death in primary prevention ICD recipients included in the current study and found arrhythmic mechanism being reported in only 4% while the vast majority died from heart failure or noncardiac causes (Sjöblom et al., 2015). Eighty percent of deaths in our cohort occurred without prior ICD therapies.

The results of our study add to the existing evidence that a relatively simple risk score is useful for prediction of all-cause mortality, but not for prediction of adequate ICD therapy. This information can be useful for the clinician in the preoperative discussion with the would-be ICD-treated patients with heart failure. Clearly there is now enough prospectively collected evidence to support primary prophylactic ICD treatment in both the low-risk and medium-risk groups of patients, whereas the high-risk patients have a very high mortality in spite of their ICD treatment, as shown in this cohort and other. Due to the lack of control group no conclusions can be drawn as to whether the addition of an ICD affects mortality in the high-risk group, but it is clear that the overall benefit is less than that for the patients with fewer risk factors. Even so, our results indicate that a significant number of individuals in all risk groups will benefit from their ICDs, and a detailed individual discussion with the patient is warranted regarding prognosis and side effects of the treatment, to allow for an informed decision. For the time being, it is not advisable to defer an ICD implantation solely on the basis of comorbidities (given a predicted life expectancy of more than 1 year, a prerequisite for eligibility for an ICD according to current guidelines), but ideally prospective studies should be carried out to evaluate if the subset of high-risk patients do or do not have an added benefit of an ICD.

4.4 | Limitations

This study was retrospective by design, and accordingly the conclusions should be interpreted with caution. Since comparison is

made to the riskscore from the MADIT II study, a possible reason for the difference in results regarding the risk scores may be the fact that our material was based on a mix of patients with dilated cardiomyopathy and ischemic cardiomyopathy, whereas the MADIT II material consisted only of patients with ischemic cardiomyopathy. Programming of the devices was at the discretion of the implanting physician, which may have influenced the rate of appropriate therapies, primarily as a result of differences in the detection intervals programmed. Longer detection intervals may have allowed nonsustained VT episodes to stop spontaneously to a higher degree than shorter detection intervals, thus affecting the secondary combined endpoint in the study. However, in Sweden there is a general consensus of opinion to adhere to the recommendation arising from the PainFREE II trial as described above (Wathen et al., 2004), and variation in the programming is therefore likely to have been limited. Mode of death was adjudicated from hospital records, but in approximately half of the patients death occurred outside hospital and the cause had to be derived from the national Swedish Death Registry, with its inherent limitations. This means that actual cause of death may have been multifactorial or even wrong, compared to what was registered, and this must be taken into account when interpreting these data.

5 | CONCLUSIONS

Our observational data from a large real-life multicenter cohort support that ventricular arrhythmias occur across the spectrum of comorbidities in an unselected ICD-treated population with systolic heart failure. However, all-cause mortality is considerably higher in the group of patients with accumulated risk factors, and using a modified MADIT II-derived risk score (including diabetes) may be helpful for the evaluation and risk stratification of the patient prior to making a decision for a primary prophylactic ICD implantation.

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CONFLICT OF INTEREST

The authors report no relationships that could be construed as a conflict of interest.

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