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Predicting appropriate shocks in patients with heart failure: Patient level meta-analysis from SCD-HeFT and MADIT II

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Abstract

Background—No precise tools exist to predict appropriate shocks in patients with a primary prevention ICD. We sought to identify characteristics predictive of appropriate shocks in patients with a primary prevention implantable cardioverter defibrillator (ICD).

Methods—Using patient-level data from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), we identified patients with any appropriate shock. Clinical and demographic variables were included in a logistic regression model to predict appropriate shocks.

Results—There were 1,463 patients randomized to an ICD, and 285 (19%) had 1 appropriate shock over a median follow-up of 2.59 years. Compared with patients without appropriate ICD shocks, patients who received any appropriate shock tended to have more severe heart failure. In a multiple logistic regression model, predictors of appropriate shocks included NYHA class (NYHA II vs I: OR 1.65, 95% CI 1.07-2.55; NYHA III vs I: OR 1.74, 95% CI 1.10-2.76), lower LVEF (per 1% change) (OR 1.04, 95% CI 1.02-1.06), absence of beta blocker therapy (OR 1.61, 95% CI 1.23-2.12), and single chamber ICD (OR 1.67, 95% CI 1.13-2.45).

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Conclusion—In this meta-analysis of patient level data from MADIT-II and SCD-HeFT, higher NYHA class, lower LVEF, no beta blocker therapy, and single chamber ICD (versus dual chamber) were significant predictors of appropriate shocks.

Keywords

implantable cardioverter defibrillator; primary prevention; meta-analysis

Background

The implantable cardioverter defibrillator (ICD) is one of the most effective interventions for the prevention of sudden cardiac death in patients with heart failure and reduced left ventricular ejection fraction (LVEF) with significant mortality benefits demonstrated beyond those of evidence-based medical therapy¹⁻³. However, this mortality benefit comes at a price: ICD shocks can cause significant negative psychological and quality of life effects even if the intervention is life-saving^{4,5}. Therefore, the careful and appropriate selection of patients for a primary prevention ICD is critical, and yet, the criteria available for this selection – primarily guidelines from professional societies – are relatively broad. It is well-known that only some patients with a primary prevention ICD receive appropriate ICD shocks. How to identify these patients accurately before the ICD is implanted remains a challenge.

We conducted the present analysis to determine the risk of appropriate ICD shocks and to identify factors predictive of an appropriate ICD shock in a population of patients that was shown to benefit from a primary prevention ICD in randomized controlled trials.

Methods

Data sources

We considered patients enrolled in prospective randomized controlled trials of primary prevention ICDs compared with no ICD for inclusion in this analysis. After considering a variety of major primary prevention ICD trials that showed survival benefit from an ICD, sufficient and relevant data for our analysis were only available from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II)³ and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)¹. Patients from the CABG-Patch trial were not included because they underwent coronary artery bypass grafting and the trial showed no benefit from an ICD⁶. Insufficient data were available from the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial⁷, Multicenter Unsustained Tachycardia Trial (MUSTT)², and MADIT I⁸ for inclusion in our analysis. Finally, data from the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT)⁹ were not included since no benefit from an ICD was demonstrated in this trial.

Patient population and definitions

Details of MADIT II and SCD-HeFT have been published previously^{1,3}. In general, patients were eligible for these studies if they were adults with reduced LVEF of $\geq 30\%$ (MADIT II) or $\geq 35\%$ (SCD-HeFT). There are some important differences between these two

randomized trials, but most notably, all patients enrolled in MADIT II had a history of prior myocardial infarction, whereas no such inclusion criterion existed for SCD-HeFT. In addition, while both trials excluded patients with symptoms consistent with New York Heart Association (NYHA) Class IV, SCD-HeFT also excluded patients with NYHA Class I symptoms. Both of the included studies collected data prospectively on patients randomized to a primary prevention ICD versus at least one control group including optimal medical therapy. For the current analysis, the following inclusion criteria were applied to the total populations (MADIT II n=1232, SCD-HeFT n=2521): LVEF known and $\geq 35\%$, NYHA class I-III, and no history of MI or most recent MI more than 40 days prior to enrollment. This resulted in inclusion of 1103 subjects from MADIT II and 1622 from SCD-HeFT. Next, we limited our cohort to those subjects randomized to receive an ICD. Thus, the final analysis population included 1,463 patients with 666 from MADIT II and 797 from SCD-HeFT.

In SCD-HeFT, an appropriate shock was defined as an ICD shock for rapid, life-threatening ventricular tachycardia or ventricular fibrillation as adjudicated by two independent reviewers. An “ICD shock” event was designated as one that triggers at least one ICD shock¹⁰. In MADIT II, shock events were adjudicated by two investigators and were deemed appropriate if delivered for ventricular tachycardia or ventricular fibrillation. An episode could include more than one shock since the episode was considered terminated once the device re-detected sinus rhythm¹¹.

Baseline descriptive statistics of the patient cohort are presented as means $\pm$ standard deviations for continuous variables and counts with percentages for categorical variables. Differences between patients with and without any appropriate shocks were evaluated using the χ^2 or Fisher's exact test for categorical variables and the Student's *t*-test for continuous variables.

Selection of predictors

First, all variables listed in Table 1 were included in a multiple logistic regression model. Next, a backwards stepwise procedure was applied that would retain variables to minimize the Akaike Information Criterion (AIC) that considers the trade-off between model goodness-of-fit and model complexity. After this initial selection process, additional variables considered critical to clinical interpretation of the prediction model were added including age, sex, race, diabetes, and kidney disease since these variables were available in both trial datasets¹²⁻¹⁵. Finally, we gave special consideration to ischemic versus nonischemic heart disease, which has not been predictive of appropriate shocks in most¹⁶⁻²¹ of the investigations in which it has been examined. This variable was found not to be predictive in our model, and when it was forced in, the AUC did not improve. Furthermore, there were insufficient data to investigate ischemic and nonischemic patients separately.

Results were considered statistically significant when two-sided p-values were less than 0.05. All analyses were performed with the statistical software R version 3.2.3.

Validation of the prediction model

After the selection of predictors, we developed our prediction model by first randomly splitting the dataset into halves: training and validation sets. The multiple logistic regression model was re-fit in the training set, and then actual values of the endpoint (indicator of whether the patient had an appropriate shock) from the validation set was compared against the corresponding predicted values. As a result, we obtained the receiver operating characteristics curves (ROC). To validate the performance characteristic of the prediction model, we repeated this process 100 times, and the median and interquartile ranges of the areas under the curve (AUC) were reported.

Review by the institutional review board determined that this research was exempt.

Results

Study population

Our cohort consisted of the 1,463 subjects randomized to primary prevention ICD from MADIT II and SCD-HeFT that met our inclusion criteria. These patients had a median follow-up of 2.59 years (interquartile range: 1.42 – 3.74). Of these patients, 1,178 (80.5%) subjects did not receive shocks or had only inappropriate shocks and 285 (19.5%) received at least one appropriate shock during follow-up (Table 1). Compared with subjects who did not receive any shocks or had only inappropriate shocks, those subjects receiving any appropriate shocks tended to have NYHA class II or III (versus NYHA class I), no beta blocker therapy, single chamber ICD (versus dual chamber), and, on average, had lower LVEF and longer QRS duration. Rates of other comorbidities including hypertension, diabetes, smoking and chronic kidney disease were similar between groups as was the use of guideline-directed medical therapy for heart failure.

Outcomes

The following variables were identified as significantly associated with appropriate ICD shock (Table 2): NYHA class (Odds Ratio (OR) for NYHA II vs I: 1.65, 95% CI 1.07-2.55; OR NYHA III vs I: 1.74, 95% CI 1.10-2.76, $p=0.04$), lower LVEF per 1% change (OR 1.04, 95% CI 1.02-1.06, $p<0.01$), absence of beta blocker therapy (OR 1.61, 95% CI 1.23-2.12, $p<0.01$), and single chamber ICD (OR 1.67, 95% CI 1.13-2.45, $p=0.01$).

Additional variables were included in the multivariable logistic regression model based on clinical expertise and previous analyses demonstrating association with appropriate ICD shocks rather than statistically significant prediction of appropriate shocks from the model: age (OR 1.01, 95% CI 0.99-1.02, $p=0.23$), female sex (OR 0.95, 95% CI 0.67-1.34, $p=0.76$), race ($p=0.28$; OR Black vs White 1.14, 95% CI 0.78-1.68, OR Other vs White 0.60, 95% CI 0.28-1.30), history of diabetes (OR 0.90, 95% CI 0.67-1.21, $p=0.49$), eGFR (OR 1, 95% CI 1.00-1.01, $p=0.55$), and QRS duration (OR 1.00, 95% CI 1.0-1.01, $p=0.11$). When history of coronary artery disease was evaluated, it was neither independently predictive of appropriate shocks nor did it improve the performance of the model.

In total, 10 variables were included in the multiple logistic regression model. With this model, the area under the ROC curve (in short, area under the curve or AUC) was 0.63 indicating fair predictive ability. After randomly dividing the dataset into training and validation sets 100 times, the median AUC was 0.60 (interquartile range: 0.58-0.61) (Figure 1). Notably, the *post hoc* addition of the clinically important variables (age, sex, race, history of diabetes, renal dysfunction, and QRS duration) did not change the model's AUC.

Development of nomogram

A nomogram for appropriate shock after implantation of a primary prevention ICD was developed with point scales for each of the variables included in the multiple logistic regression model (Supplement).

Discussion

In this patient-level analysis of data from two landmark randomized clinical trials of primary prevention ICDs, we examined rate and predictors of appropriate ICD shocks. Three main findings of this analysis are noteworthy. First, of the 1,463 subjects randomized to a primary prevention ICD, about one in five had at least one appropriate shock over 2.5 years of follow-up. Stated differently, 80% of the patients received no appropriate shocks during follow-up, indicating that a subset of patients may not derive benefit from an ICD. However, our analysis did not investigate which subgroups of patients were least likely to receive an appropriate shock, which is a clinically relevant and important question. Rather, our goal was to improve the ability to identify those patients most likely to benefit from an ICD.

We found that patients receiving an appropriate ICD shock tended to be older and sicker than patients without an appropriate shock. If tools existed to discriminate between patients at high and low risk of shocks, issues including risks of ICD implantation, implications of inappropriate shocks, and cost could be more thoroughly discussed with patients prior to implantation with informed estimates of risks and benefits. Indeed, questions still remain about how to proceed in patients without a pacing indication who reach end of battery life for a primary prevention ICD that has never delivered an appropriate shock especially when the LVEF improves to > 35%²²⁻²⁴.

Second, in our multiple logistic regression model, we identified significant independent predictors of appropriate ICD shocks during follow-up. These predictors included: a higher NYHA class, a lower LVEF, no treatment with a beta blocker therapy, and receipt of a single chamber ICD. Some variables that were expected to be significant predictors of appropriate ICD shocks were not and included sex, diabetes, and renal dysfunction, so these variables were “forced” into the model. It is possible that these factors have no real predictive value; however, a lack of significance as independent predictors in our model may be explained in other ways. For example, there were relatively few women enrolled in SCD-HeFT and MADIT II such that only 119 and 190 women were included in our analysis, respectively, and with fewer numbers, the event rate was quite low in this subgroup. The same is true in regard to ischemic versus nonischemic cardiomyopathy; while this factor was not predictive of appropriate shocks in our dataset, the numbers were small making it difficult to see a difference. In addition, it is likely that the severity of diabetes and renal dysfunction as they

are encountered in clinical practice is greater than it is in these two randomized trials. For example, mean creatinine in SCD-HeFT was 1.1 mg/dL, whereas patients with significant renal dysfunction commonly receive a primary prevention ICD in clinical practice ²⁵. This greater severity of disease may make this factor more powerfully predictive ²⁶.

With or without these additional variables, the model performance was fair with an AUC of 0.63 (and median AUC of 0.60, with interquartile range: 0.58-0.61 in our validation studies). A perfect model (AUC =1.0) can discriminate perfectly between those that will and will not have the outcome of interest (appropriate shock). A model that performs no better than chance has an AUC of 0.50.

Previous investigators have examined predictors of appropriate ICD shocks in primary prevention patients, and the summary findings from these various investigations are not entirely consistent with each other or with our findings. In a meta-analysis of 9 studies of patients with primary prevention ICDs for ischemic cardiomyopathy, clinical predictors of appropriate ICD shocks or antitachycardia pacing were examined, and factors associated with increased risk included: male sex, advanced NYHA class, hypertension, renal disease, lack of beta blocker use, and history of nonsustained ventricular tachycardia ²⁷. Our analysis included patient-level data for patients with ischemic and non-ischemic cardiomyopathy and did not include antitachycardia pacing as therapy; nonetheless, for those variables available in both analyses (male sex, hypertension, renal disease, NYHA class, and beta blocker use), there was overlap in some, but not all, factors predictive of appropriate therapy overall including NYHA class and beta blocker use. Other investigations not included in this meta-analysis have corroborated those findings ^{19, 28, 29}. In some cohorts, QRS duration ³⁰ has been predictive of appropriate shocks. Lastly, most of the patients in our analysis received a single-chamber ICD (79%), and this characteristic was predictive of appropriate shocks. This is in contrast to other randomized data demonstrating that patients with a dual chamber device may be more likely to receive an appropriate shock ³¹. This may be due to the disproportionate representation of single chamber ICDs in SCD-HeFT that followed patients for an average of 45.5 months compared with MADIT II in which there was a mix of single and dual chamber devices with an average follow-up of only 20 months.

Other factors that may be associated with appropriate shocks not available for our analysis include: atrial fibrillation ^{32, 33}, history of smoking ³⁴, history of nonsustained ventricular tachycardia ¹², measures of cardiac remodeling ^{12, 35}, and depression ³⁶. Notably, the factors found to be predictive of appropriate shocks in our study are all modifiable to at least some degree.

Even when compared with investigations from high quality randomized studies, our analysis includes a larger population and greater generalizability since it includes patient-level data from two distinct, high-quality randomized controlled trials of patients with ischemic and nonischemic cardiomyopathy.

Third, the fair performance of our model despite nearly a dozen important clinical characteristics highlights the complexity of predicting which patients are most at risk for sudden cardiac death, and this is further complicated by the fact that appropriate shocks are

not a perfect surrogate for mortality risk¹⁹. In addition, it is likely that some of the most powerful predictors of appropriate ICD therapy cannot be easily measured at a single point in time. Indeed, a previous study of the MADIT II population found that worsening of clinical status as measured by interim hospitalizations for heart failure or coronary events led to increasing risk of sudden cardiac death³⁵. Emerging tools like late gadolinium enhancement on cardiac magnetic resonance imaging³⁷ and biomarkers^{19, 38} are showing promise for risk stratification in the heart failure population, and these were either not readily available or appreciated at the time of the randomized clinical trials discussed here.

Thus, our findings add to a growing literature suggesting that there is sufficient conflicting evidence to justify a large prospective cohort study of patients with a primary prevention ICD that incorporates promising contemporary tools, like cardiac MRI, to determine who is at the highest risk for an appropriate ICD shock. Such an investigation would lead to a more precise quantification of risk in patients eligible for a primary prevention ICD and, therefore, assist providers in shared-decision making conversations with patients regarding an initial ICD implantation as well as considerations for replacements as time and comorbidities accumulate.

Limitations

Our analysis was limited by the variables available in both included studies, and this leaves out some factors that may be important including beta blocker dose among other things. Additionally, these factors were measured at enrollment only, and we could not account for the development of comorbidities (e.g., diabetes) or worsening of existing comorbidities during follow up. Second, we used the same cohort for developing and validating our predictive model; having 2 different cohorts for developing and validating the model would have likely improved the generalizability of our findings. Third, since MADIT II and SCD-HeFT were conducted in the early to mid-2000s, there have been meaningful changes in standard heart failure therapies (e.g., widespread use of aldosterone antagonists) as well as ICD technologies and management strategies including, but not limited to, the more widespread adoption of cardiac resynchronization therapy (CRT)-D, remote monitoring, and modern programming (e.g., delayed detection), all of which have been demonstrated to reduce ICD shocks³⁹⁻⁴². Indeed, recent evidence suggests the rate of appropriate shocks in a primary prevention population may be as low as 1.1% at 1 year and 2.6% at 30 months.⁴³ This further supports the call for a large, prospective cohort study to identify patients with the highest (or lowest) risk of future life threatening arrhythmias in the setting of heart failure and reduced ejection fraction. In addition, the effectiveness of ventricular arrhythmia ablation for the reduction of ventricular arrhythmia burden especially in patients with ischemic heart disease has improved substantially over the same period. These changes likely reduce overall risk of appropriate shocks and, when compared with our population, may change which patient characteristics are most predictive of an appropriate shock. Last, the length of follow-up in our population was relatively short, and it is possible that longer follow-up would allow for the accumulation of more shock events and more ability to identify important predictive characteristics.

Conclusion

Using patient-level data from two of the largest randomized clinical trials of primary prevention ICDs, we developed a model to predict which patients are most at risk for an appropriate ICD shock. Our model included age, sex, race, NYHA class, LVEF, diabetes, use of beta blockers, eGFR, QRS duration, and single chamber ICD type, which allowed for fair ability to predict appropriate shocks. Of these variables, the following were significant independent predictors of appropriate ICD shocks: a higher NYHA class, a lower LVEF, lack of use of beta blocker therapy and single-chamber ICD. These findings add to an existing literature based on various data sources that attempt to predict appropriate shocks with conflicting results. There are no precise tools to quantify risk of appropriate ICD shocks. As such, a compelling need remains for a large, prospective clinical trial applying modern ICD technology and programming and contemporary risk stratification tools to more precisely identify patients at risk for appropriate shocks. Until such time, the existing evidence must be applied in an individualized way. Moreover, regardless of the precision of a predictive tool or the strength of evidence behind a recommendation, shared decision making is always needed to incorporate individual preferences into the decision to proceed with implantation of an ICD or not.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

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Figure 1. Receiver operator curves

The dataset was randomly split into halves: training and validation sets. The logistic regression model was re-fit in each of the training sets, and then actual values from the validation sets were compared against the corresponding predicted values with the receiver operating characteristics curves (ROC) and the area under the curve (AUC). This process was repeated 100 times to obtain the median and interquartile ranges of the derived AUCs.

Table 1
Baseline characteristics of pooled subjects by presence or absence of any appropriate shock during follow-up

Characteristic	No ICD shocks or inappropriate shocks (N=1,178)	Any appropriate ICD shocks (N=285)	P-Value
Age	61.37 (11.66)	61.89 (10.96)	0.47
Sex, Female	234 (19.86)	54 (18.95)	0.80
Race			0.18
White	971 (82.43)	231 (81.05)	
Black	153 (12.99)	46 (16.14)	
Other	54 (4.58)	8 (2.81)	
NYHA			<0.01
Class I	215 (18.34)	30 (10.56)	
Class II	629 (53.67)	160 (56.34)	
Class III	328 (27.99)	94 (33.10)	
LVEF	23.79 (6.25)	21.98 (6.26)	<0.01
eGFR	69.54 (22.64)	69.18 (22.60)	0.81
Ischemic cardiomyopathy	869 (73.77)	196 (68.77)	0.10
Prior CABG	495 (42.02)	111 (38.95)	0.35
Prior MI	821 (69.69)	182 (63.86)	0.06
Prior PCI	385 (32.88)	81 (28.42)	0.16
Hypertension	631 (53.70)	149 (52.28)	0.69
Diabetes	373 (31.66)	81 (28.42)	0.32
Current or former smoker	882 (75.00)	222 (77.89)	0.32
Antiarrhythmic drug therapy	15 (1.27)	2 (0.70)	0.55
Amiodarone	42 (3.57)	6 (2.11)	0.27
Beta blocker	812 (68.93)	163 (57.19)	< 0.01
ACE inhibitor	1018 (86.42)	249 (87.37)	0.77
Chronic kidney disease	407 (34.76)	102 (35.92)	0.73
QRS duration	120.44 (32.60)	124.91 (32.68)	0.04
Single-chamber ICD	917 (79.33)	245 (85.96)	0.01

Continuous variables reported as means (SD); categorical variables reported as number (%).

Table 2
Independent factors included in a multivariable logistic regression model to predict appropriate ICD shocks

		95% CI		
Factor	OR	Lower	Upper	P-value
Age	1.01	0.99	1.02	0.23
Female	0.95	0.67	1.34	0.76
Race				0.28
Black (vs White)	1.14	0.78	1.68	0.280.49
Other (vs White)	0.60	0.28	1.30	0.20
Diabetes	0.90	0.67	1.21	0.49
eGFR	1.00	1.00	1.01	0.55
NYHA Class				0.04
II (vs I)	1.65	1.07	2.55	0.02
III (vs I)	1.74	1.10	2.76	0.02
Ejection Fraction *	1.04	1.02	1.06	<0.01
Absence of Beta Blockers	1.61	1.23	2.12	<0.01
QRS duration, per mm	1.00	1.00	1.01	0.11
Single-Chamber ICD	1.67	1.13	2.45	0.01

*
per 1% change