

# Predictors of appropriate therapy in patients with implantable cardioverter-defibrillator for primary prevention of sudden cardiac death

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## Abstract

The purpose of this study was to evaluate predictors of appropriate therapy in patients with implantable cardioverter-defibrillators (ICD) for primary prevention of sudden cardiac death. A retrospective cohort of 321 patients with systolic heart failure undergoing ICD placement for primary prevention of sudden cardiac death was queried with a mean follow-up period of 2.6 years. Appropriate ICD therapy was defined as therapy delivered for termination of a ventricular tachyarrhythmia. Appropriate ICD therapy was delivered in 142 (44%) of the patients. In a multivariate model, body mass index  $\geq 28.8$  kg/m<sup>2</sup>, chronic kidney disease, left ventricular ejection fraction  $\leq 20\%$  and metabolic syndrome were found to be independent predictors of appropriate ICD therapy. Appropriate ICD therapy was associated with higher cardiovascular mortality. These findings show the importance of identification of risk factors, especially metabolic syndrome, in patients following ICD implantation as aggressive treatment of these co-morbidities may decrease appropriate ICD therapy and cardiovascular mortality.

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## Introduction

Several randomized controlled trials have demonstrated a survival benefit with an implantable cardioverter-defibrillator (ICD) among patients who are at high risk for sudden cardiac death in primary prevention settings.<sup>1,4</sup> It is of major importance to identify patients who will benefit from ICD implantation and generator replacement after battery depletion. From multivariate risk profiles, approximately 50-60% of patients will receive an ICD therapy within 9 $\pm$ 11 months after implantation, including an average of 2.3 shocks/patient/year.<sup>5-8</sup> ICD therapy decreases quality of life and increases health care utilization.<sup>9</sup> Therefore it is important for clinicians to identify the predictors of ICD therapy in order to prevent ICD shocks which may improve quality of life and reduce healthcare costs. Although randomized studies provide the best evidence, longitudinal studies provide complementary data. The purpose of this study was to identify predictors for appropriate ICD therapy using demographic and clinical characteristics in patients who have received ICD for primary prevention of sudden cardiac death.

As there is little information available regarding the impact of metabolic syndrome (MetS) on sudden death in a heart failure population, we also sought to determine if individual components of metabolic syndrome itself are associated with appropriate ICD therapy.

## Materials and Methods

A retrospective cohort of 321 patients with systolic heart failure undergoing ICD placement for primary prevention of sudden cardiac death was queried from April 2004 to September 2008, at the Regions Hospital of University of Minnesota Medical School. All patients had ICD placement based on the American Heart Association recommendations for primary prevention of sudden cardiac

death. All patients received standard heart failure treatment including beta-blocker, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, lipid-lowering drugs, aspirin and diuretics based on the discretion of the treating physician.

Clinical data collected at the time of ICD placement included: age, gender, smoking history, hypertension, hypercholesterolemia, and diabetes mellitus. Fasting lipid profile was assessed for all patients as was information on statin use. Left ventricular function was determined by transthoracic echocardiogram prior to the implantation. The clinical identification of patients with MetS was based on the modified criteria proposed by the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII).<sup>10</sup> Patients were considered to have MetS when 3 of the 5 following criteria were present: i) body mass index (BMI)  $\geq 28.8$  kg/m<sup>2</sup>; ii) elevated fasting glucose  $\geq 110$  mg/dL or drug treatment for elevated blood sugar; iii) fasting triglycerides  $\geq 150$  mg/dL; iv) reduced high-density lipoprotein cholesterol  $< 40$  mg/dL for men and  $< 50$  mg/dL for women; v) blood pressure  $\geq 130/85$  mmHg or drug treatment for elevated blood pressure. BMI was used instead of waist circumference as waist circumference was not routinely documented in the medical record. MetS status was evaluated at the time of ICD placement.

Chronic kidney disease (CKD) was defined according to the National Kidney Foundation Classification based on glomerular filtration rate (GFR): stage 1 (normal GFR  $\geq 90$  mL/min per 1.73 m<sup>2</sup>) and persistent albuminuria; stage 2 (GFR 60 to 89 mL/min per 1.73 m<sup>2</sup>) and persistent albuminuria; stage 3 (GFR 30 to 59 mL/min per 1.73 m<sup>2</sup>); stage 4 (GFR 15 to 29 mL/min per 1.73 m<sup>2</sup>); and stage 5 (GFR  $< 15$  mL/min per 1.73 m<sup>2</sup>).<sup>13</sup> The GFR was estimated using the Modification of Diet in Renal Disease (MDRD) study equation.<sup>13</sup>

## Follow-up

The mean follow-up period was 2.6 years. Follow-up consisted of reviewing the clinical visits, emergency department visits, urgent

care visits and hospital records. Outcomes measured were appropriate ICD therapy and cardiovascular mortality. Among patients who had more than one ICD therapy, only one was recorded for analysis. Stored data were analyzed to classify the arrhythmias responsible for precipitating ICD therapy according to the following definitions.<sup>14</sup> Ventricular fibrillation or flutter was defined as ventricular tachyarrhythmias with a cycle length of 240 ms or less. Ventricular tachycardia was defined as ventricular tachyarrhythmias with a cycle length of more than 240 ms.

An appropriate ICD therapy was defined as antitachycardia pacing for termination of ventricular tachycardia and/or ICD shock for termination of ventricular tachycardia or ventricular fibrillation.

Cardiovascular death included all patients who died of cardiovascular causes (myocardial infarction, heart failure and cerebrovascular accidents) as determined by review of medical records and the social security death index.

### Statistical analysis

All statistical analyses were performed using STATA 10.0 software (StataCorp, Texas, USA). Continuous variables were expressed as mean  $\pm$  standard deviation and were compared by using 2-sample t tests for independent samples. Differences in proportion were compared using  $\chi^2$  test or Fisher's exact test, as appropriate. Univariate analysis was carried out with Cox's regression and hazards ratio (HR) was calculated. Multivariate analysis was performed with logistic regression to assess the factors independently associated with adverse outcomes. A probability value  $P \leq 0.05$  was considered statistically significant.

## Results

A total of 321 patients with systolic heart failure (mean age  $72 \pm 11$  years, 65% male) underwent ICD placement for primary prevention of sudden cardiac death. Of 321 patients, 90% had ischemic cardiomyopathy. The average ejection fraction was  $26.5 \pm 11.3\%$ . Thirty-nine percent of patients had diabetes mellitus, 69% had hypertension, and 29% had chronic kidney disease.

Forty-one percent of the patients were identified as having MetS. The average age of patients with MetS was  $70 \pm 8$  years and  $71 \pm 6$  years for those without MetS ( $P > 0.05$ ). Ninety-one percent of patients with MetS and 89% of patients with non-MetS had ischemic cardiomyopathy ( $P > 0.05$ ). Baseline characteristics are shown in Table 1. Both groups had a higher prevalence of male patients ( $P = ns$ ). The mean ejection fraction was  $23.4 \pm 7.4\%$  with MetS and  $28.9 \pm 9.3\%$  without MetS ( $P = 0.04$ ).

**Table 1. Baseline patient's characteristics.**

	All (321)	MetS (n=131)	Non-MetS (n=190)	P ns
Age (years)	$72 \pm 11$	$70 \pm 8$	$71 \pm 6$	
Male (%)	65	66	64	ns
Ejection fraction (%)	$26.5 \pm 11.3$	$23.4 \pm 7.4$	$28.9 \pm 9.3$	0.04
BMI $\geq 28.8$ kg/m <sup>2</sup> (%)	56	73	44	0.001
Ischemic cardiomyopathy (%)	90	91	89	ns
NYHA heart failure class (%)				
II	16	15	17	ns
III	73	77	70	0.04
IV	11	10	12	ns
DM-2 (%)	39	49	32	0.01
HTN (%)	69	76	64	0.03
CKD (%)	18	23	14	0.002
COPD (%)	24	22	25	ns
Fasting glucose (mg/dL)	$142 \pm 39$	$172 \pm 29$	$121 \pm 21$	0.02
HDL (mg/dL)	$39 \pm 10$	$32 \pm 7$	$44 \pm 7$	0.001
Triglycerides (mg/dL)	$144 \pm 27$	$169 \pm 21$	$125 \pm 11$	0.01
Systolic blood pressure (mmHg)	$132 \pm 31$	$149 \pm 24$	$127 \pm 21$	0.03
Diastolic blood pressure (mmHg)	$89 \pm 19$	$93 \pm 17$	$86.5 \pm 9$	0.07
QRS duration (ms)	$121.2 \pm 26.8$	$119 \pm 18.7$	$122.1 \pm 24.9$	ns
Medications (%)				
Aspirin	81	83	79	ns
Beta blocker	88	91	87	ns
ACEI	71	64	75	0.04
ARB	21	28	16	0.02
Diuretics	28	39	21	0.01
Statin	61	62	60	ns

ACEI: angiotensin converting enzymes inhibitors; ARB: angiotensin receptor blockers; BMI: body mass index; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; HTN: hypertension; HDL: high density lipoprotein; MS: millisecond; NYHA: New York Heart Association; ns: not significant ( $P > 0.05$ ).

**Table 2. Univariate predictor of appropriate ICD therapy.**

	Hazard ratio	P
Age >70 years	1.29 (1.09-1.71)	0.02
Male	0.92 (0.61-1.42)	0.62
Diabetes mellitus	2.13 (1.21-3.43)	0.01
HTN	1.87 (0.56-1.87)	0.54
LVEF $\leq 20\%$	4.66 (2.31-9.34)	<0.001
NYHA heart failure class $\geq$ III	1.41 (1.11-3.01)	0.04
Fasting blood sugar $\geq 110$ mg/dL	0.93 (0.46-1.64)	0.08
HDL <40	2.03 (1.32-3.42)	0.002
TG $\geq 150$	1.82 (1.63-2.51)	0.04
BMI $\geq 28.8$ kg/m <sup>2</sup>	2.56 (1.26-5.85)	0.001
CKD	2.06 (1.34-4.36)	0.003
COPD	0.91 (0.41-1.98)	0.76
Beta blocker therapy	1.21 (0.85-2.46)	0.23

BMI: body mass index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; HDL: high density lipoprotein; HTN: hypertension; TG: triglycerides.

The prevalence of diabetes (49% *vs.* 32%,  $P = 0.01$ ) and chronic kidney disease (23% *vs.* 14%,  $P = 0.002$ ) were higher in patients with MetS as compared to those without MetS.

Appropriate ICD therapy was delivered in 142 (44%) patients. Of those, 46 (14%) experienced shocks and 96 (30%) had antitachycardia pacing with no shocks.

Cox's regression analysis was performed to obtain unadjusted hazards ratio (HR) for following variables to identify the predictors of appropriate ICD therapy: age >70 years, body mass index  $\geq 28.8$  Kg/m<sup>2</sup>, New York Heart Association heart failure class  $\geq$  III, diabetes mellitus, HDL <40, left ventricular ejection fraction  $\leq 20\%$ , and chronic kidney disease.

Table 2 shows the predictors of appropriate ICD therapy by Cox's regression analysis. After including these variables in a multivariate model, body mass index  $\geq 28.8$  kg/m<sup>2</sup> (adjusted HR=1.96, 95% CI 1.12-2.91, P=0.01), left ventricular ejection fraction  $\leq 20\%$  (adjusted HR 3.95, 95% CI 2.69-8.11, P<0.001) and chronic kidney disease (adjusted HR 1.28, 95% CI 1.09-2.13, P=0.02) were found to be independent predictors of appropriate ICD therapy. In the subgroup of patients who had ICD shocks for ventricular fibrillation (VF), body mass index  $\geq 28.8$  kg/m<sup>2</sup> and left ventricular ejection fraction  $\leq 20\%$  were found to be predictors of VF in both univariate and multivariate analyses, left ventricular ejection fraction  $\leq 20\%$  was found to be the only predictor for ventricular fibrillation (adjusted HR 2.7, 95% CI 1.37-5.31, P=0.004). QRS duration was not a predictor of appropriate ICD therapy in our study population.

Although all components of MetS other than body mass index  $\geq 28.8$  kg/m<sup>2</sup> were not independent predictors of appropriate ICD therapy, further multivariate analysis was carried out to evaluate whether MetS itself was an independent predictor of appropriate ICD therapy (Table 3). In the multivariate analysis, after adjusting for age, sex, medications, left ventricular ejection fraction and co-morbidities, MetS was found to be a significant predictor of appropriate ICD therapy (OR 2.01, 95% CI, 1.12-3.88, P=0.03).

During our follow-up period, 29 (9%) patients died of cardiovascular causes including 19 (6%) patients who had undergone appropriate ICD therapy and 10 (3%) patients who had had no ICD therapy.

In multivariate analysis, after adjusting for age, sex, medications and comorbidities, left ventricular ejection fraction  $\leq 20\%$  was associated with an increased hazard risk cardiovascular mortality (adjusted HR 2.66, 95% CI 1.56-6.07, P=0.001). In Kaplan-Meier analysis, patients who had appropriate ICD therapy were found to have a higher incidence of cardiovascular mortality (HR= 2.26, 95% CI 1.08-4.67, P=0.03) than patients without any ICD therapy (Figure 1).

## Discussion

In the present study, we examined predictors of appropriate ICD therapy in 321 patients who received ICD for primary prevention of sudden cardiac death. We identified body mass index  $\geq 28.8$  kg/m<sup>2</sup>, left ventricular ejection fraction  $\leq 20\%$  and chronic kidney disease as the independent predictors of appropriate ICD therapy. MetS was also found to be independently associated with a higher incidence of appropriate ICD therapy. We did not find an independent

**Table 3. Multivariate logistic regression analysis showing independent predictors of implantable cardioverter-defibrillators therapy.**

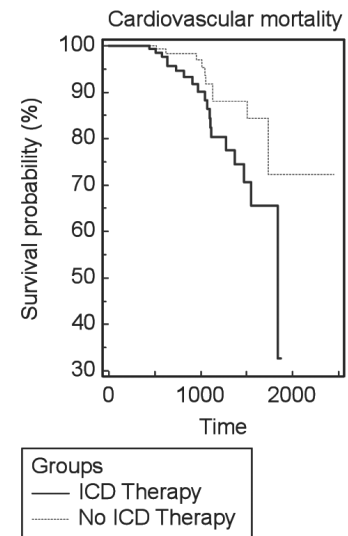
Predictor	HR (95% CI)	P
LVEF $\leq 20\%$	3.95 (2.69-8.11)	<0.001
BMI $\geq 28.8$ kg/m <sup>2</sup>	1.96 (1.12-2.91)	0.01
CKD	1.28 (1.09-2.13)	0.02
MetS	2.01 (1.12-3.88)	0.03

BMI: body mass index; CI: confidence interval; HR: hazard ratio; MetS: metabolic syndrome.

association between all individual components of MetS with appropriate ICD therapy in multivariate analysis. The results suggest that patients with MetS are at an increased risk of ventricular arrhythmia and appropriate ICD therapy to patients without MetS.

There is substantial evidence that MetS contributes to the development of heart failure, but no data exists on the impact of MetS in patients with heart failure who have received an ICD. In the present study, we examined the prevalence and outcomes of the MetS in the heart failure population who received ICD for primary prevention of sudden cardiac death. The prevalence of MetS was 41%, which exceeds that reported in the general population, but is lower than reported in heart failure populations.<sup>15,16</sup> The prevalence of MetS in our study is lower than two previous studies. The prevalence of MetS in a heart failure population has been reported to be 68.3% and 78% in prior studies.<sup>16,17</sup> In our study, we found that patients who had at least one episode of appropriate ICD therapy are at higher risk of subsequent cardiovascular mortality than those without any ICD therapy. This indicates that patients who are at higher risk for having appropriate ICD therapy are also at higher risk for cardiovascular mortality. This finding is in accordance with the findings of previous studies where cardiovascular mortality was found to be higher with MetS.<sup>18-21</sup> In a meta-analysis of 21 prospective cohort studies, patients with MetS had increased cardiovascular mortality with relative risk of 1.74 (95% CI 1.29-2.35).<sup>22</sup> Another meta-analysis including 37 studies and 172,573 individuals showed that MetS was associated with a relative risk of 1.78 for cardiovascular events and death (95% CI, 1.58-2.0).<sup>23</sup> MetS has also been found to be associated with an increased risk of stroke (RR 1.76; 95% CI 1.37-2.25).<sup>22</sup> Appropriate ICD discharge was found to be higher in MetS, which suggests that patients with MetS are at higher risk for arrhythmic events and sudden cardiac death. These findings provide new evidence that MetS is associated with an increased risk of cardiovascular events.<sup>23</sup>

Our data suggests that patients with chronic kidney disease are more prone to develop ventricular arrhythmias and receive appropriate ICD therapy. In a historic cohort study, patients



**Figure 1. Kaplan-Meier graph of cardiovascular mortality in patients with implantable cardioverter-defibrillators therapy as compared to patients without any implantable cardioverter-defibrillators therapy.**

with chronic kidney disease were more likely to have experienced an acute myocardial infarction, angina, heart failure, stroke, and/or cardiovascular death versus those with preserved kidney function. In multivariate analysis, chronic kidney disease was the most significant independent risk factor for a cardiovascular event (HR 2.5, CI 95% 1.3-4.8).<sup>24</sup> These patients might benefit more from the ICD placement for primary prevention of sudden cardiac death than patients with normal kidney function. The increased frequency of ventricular arrhythmias and appropriate ICD therapy in patients with chronic kidney disease documented in our study is in keeping with other reports in the literature.<sup>25,26</sup>

Left ventricular ejection fraction was a significant risk factor for both appropriate ICD therapy, ventricular fibrillation and cardiovascular mortality. This finding was in accordance with previous findings in clinical trials where left ventricular ejection fraction over 20% was found to reduce sudden cardiac death risk.<sup>27</sup> In our study, we did not find an association of

QRS duration with appropriate ICD therapy and cardiovascular mortality. This finding is consistent with the findings of Buxton *et al.*<sup>28</sup> where QRS duration was not a predictor of ventricular tachycardia or ventricular fibrillation resulting in ICD therapies.

### Limitations

Our data were derived from a single large center registry. This observational study was non-randomized and data were analyzed retrospectively. Thus unidentified confounders may exist which could impact the results of this study.

### Conclusions

MetS, chronic kidney disease, left ventricular ejection fraction  $\leq 20\%$  and body mass index  $\geq 28.8$  kg/m<sup>2</sup> are significantly associated with appropriate ICD therapy in patients who received ICD implantation for primary prevention of sudden cardiac death. To our knowledge, this is the first study to show that MetS predicts an increased incidence of appropriate ICD therapy and cardiovascular mortality in a systolic heart failure cohort that underwent ICD implantation for primary prevention of sudden cardiac death. Although individual components of MetS were not found to be independent predictor, MetS itself was found to be independent predictor of appropriate ICD therapy. The findings of this study highlight the importance of identifying patients with MetS as aggressive treatment of these co-morbidities may decrease appropriate ICD therapy which in turn may decrease hospitalizations and healthcare costs.

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