Prediction of sudden cardiac death in chronic heart failure patients with reduced ejection fraction by ADMIRE-HF risk score and early repolarization pattern

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Background. **AdreView myocardial imaging for risk evaluation in heart failure (ADMIRE-HF) risk score is a novel risk score to predict serious arrhythmic risk in chronic heart failure patients with reduced ejection fraction (HFrEF). Moreover, early repolarization pattern (ERP) has been shown to be associated with an increased risk of sudden cardiac death (SCD) in HFrEF patients. We sought to investigate the prognostic value of combining ADMIRE-HF risk score and ERP to predict SCD in HFrEF patients.**

Methods. **We studied 90 HFrEF outpatients with LVEF< 40% in our prospective cohort study. In cardiac MIBG imaging, the heart-to-mediastinum (H/M) ratio was measured on the delayed planar image. ADMIRE-HF risk score was derived from the sum of the point values of LVEF, H/M ratio, and systolic blood pressure. We also assessed ERP on the standard electrocardiogram.**

Results. **During a median follow-up of 7.5(4.5-12.0) years, 22 patients had SCD. At multivariate Cox analysis, ADMIRE-HF risk score and ERP were independently associated with SCD. Patients with both intermediate/high ADMIRE-HF score and ERP had a higher SCD risk than those with either and none of them.**

Conclusion. **The combination of ADMIRE-HF risk score and ERP would provide the incremental prognostic information for predicting SCD in HFrEF patients. (J Nucl Cardiol 2020;27:992–1001.)**

Key Words: Heart failure • RNA: planar • outcomes research • cardiac innervation

Abbreviations			
ADMIRE-HF	AdreView myocardial imaging for risk evaluation in heart failure	MIBG	Metaiodobenzylguanidine
HFrEF	Heart failure reduced ejection fraction	LVEF	Left ventricular ejection fraction
ERP	Early repolarization pattern	H/M	Heart to mediastinum
SCD	Sudden cardiac death	ICD	Implantable cardioverter defibrillator

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INTRODUCTION

Sudden cardiac death (SCD) remains a leading cause of mortality in chronic heart failure patients with reduced ejection fraction (HFrEF), despite sufficient medication.[1,2] The main cause of SCD is ventricular tachyarrhythmias. Therefore, identifying HFrEF patients at high risk of SCD is important.

Cardiac I-123-metaiodobenzylguanidine (MIBG) imaging provides prognostic information in patients with HFrEF.[3-13] AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) study provided a prospective validation of the independent prognostic value of MIBG scintigraphy in assessing patients with HFrEF.[8] Furthermore, ADMIRE-HF risk score is a novel index that combines clinical characteristics and MIBG imaging variables to provide individualized estimates of serious arrhythmic risk in patients with HFrEF.[14] However, there is no information available on the external validation of the ADMIRE-HF score for the prediction of SCD in HFrEF patients.

Early repolarization pattern (ERP) in the standard 12-lead electrocardiogram (ECG) is characterized by an elevation of the J point, which is due to QRS slurring or notching in at least two inferior or lateral leads.[15] Although ERP was considered benign for decades, previous clinical studies reported that patients with idiopathic ventricular fibrillation had a high prevalence of ERP.[16-18] Furthermore, in a case–control study, ERP was more common in patients with previous myocardial infarction who had ventricular arrhythmic events.[19] Pei et al. and we have recently shown that ERP in the inferior leads is associated with an increased risk of SCD in HFrEF patients.[20,21] However, no information is available on the long-term value of combining ADMIRE-HF risk score and ERP for predicting SCD in HFrEF patients.

The aim of this study was to perform the external validation of ADMIRE-HF risk score and compare the prognostic values of ADMIRE-HF risk score and ERP for predicting SCD in patients with HFrEF.

METHODS

We enrolled 111 consecutive HFrEF outpatients with radionuclide left ventricular ejection fraction (LVEF) $< 40\%$, from 1995 October to 2000 December. Heart failure was diagnosed from the clinical signs and symptoms according to the Framingham criteria.[22] Patients were required to be stable for at least 3 months on conventional therapy. Patients were excluded from the present study if they had significant renal dysfunction, insulin-dependent diabetes mellitus, or autonomic neuropathy. None of the patients had had an implantable cardioverter-defibrillator (ICD), biventricular pacemaker, or biventricular defibrillator (CRT-D) at enrollment. We also excluded 18 patients with bundle branch block and three patients with a pacemaker rhythm due to the inability to assess ERP.

The final study population included 90 HFrEF patients. The mean patient age was 65 ± 11 years. Of the 90 patients, 68 were men and 22 were women. Heart failure was due to ischemic heart disease in 50 patients and idiopathic dilated cardiomyopathy in 40 patients. The average New York Heart Association (NYHA) functional class was 2.0 ± 0.6 (class I, 11%; class II, 68%; class III, 21%). The LVEF was 31 ± 7%. 5 patients received ICD treatment during the follow-up period. Informed consent was obtained from each patient, and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. At entry, all patients underwent cardiac MIBG imaging, 12-lead electrocardiography, 24-hour Holter ECG monitoring, and echocardiography. In addition, a venous blood sample was drawn.

All patients were assessed while resting in the supine position by myocardial imaging with I-123 MIBG (FUJIFILM RI Pharma Co., Ltd, Tokyo, Japan) using a dual-head gamma camera (Prism 2000, Picker, Bedford, OH, USA) equipped with a low-energy, high-resolution, parallel-hole collimator. A 111 MBq dose of I-123 MIBG was injected intravenously with the patient at rest after an overnight fast. Initial and delayed images were obtained in the anterior chest view at 20 and 200 minutes after isotope injection, respectively. As previously described,[4] two independent observers, who were unaware of the clinical status of the patients, assessed the cardiac MIBG uptake. The MIBG heart to mediastinum (H/M) ratio was determined by dividing the counts/pixel in a visually drawn heart region of interest by the counts/pixel in a 7 × 7-pixel upper mediastinum region of interest. After considering the radioactive decay of I-123, the cardiac MIBG washout rate was calculated from the initial and delayed images. ADMIRE-HF score was derived from the sum of the point values of the following parameters as previously reported: LVEF ($< 25\%$, 5 points), MIBG H/M uptake ratio on the delayed image (< 1.6, 12 points), and systolic blood pressure (< 120 mmHg, 3 points; 120-139 mmHg, 0 points; > 140 mmHg, -3 points). The score had values ranging from -3 to 20. According to the previous study, study patients were classified into three groups; low (< 4), intermediate (4-15), and high (> 15) ADMIRE-HF risk score groups.[14]

We obtained a standard resting 12-lead ECG at enrollment. ERP was defined as J-point elevation ≥ 0.1 mV above the baseline in at least two inferior or lateral leads. The anterior precordial leads (V1-V3) were excluded to eliminate patients with potential Brugada syndrome. Two cardiologists (Y.F. and M.K.), who were blinded to the patient's clinical information, independently reviewed the 12-lead ECG of all subjects. The concordance rate was 90.2% for the diagnosis of ERP. If their opinions differed, a third cardiologist (T.Y.) blindly reviewed the ECG findings and confirmed the presence or absence of ERP. The RR interval, PR interval, QRS duration and QT interval were measured automatically. QT interval was

corrected for heart rate using Bazett's formula: QTc = QT/RR1/2 (ms), where QTc is the corrected QT interval. Patients also underwent 24-hour Holter ECG recording with a Marquette Electronics 8000 Holter monitoring system (Marquette Electronics, Milwaukee, WI, USA). The severity of ventricular arrhythmias was classified according to Lown's grade, the total number of ventricular premature contractions per day, and nonsustained ventricular tachycardia (defined as $\geq$ 5 consecutive premature ventricular beats lasting $<$ 30 seconds).

Blood sampling was done from an intravenous cannula after the patients had rested for $\geq$ 30 minutes in the supine position. The samples were used to assess plasma noradrenaline concentration, serum creatinine, sodium, potassium, and uric acid levels. The plasma noradrenaline concentration was determined using high-performance liquid chromatography at Shionogi Biomedical Laboratories (Osaka, Japan). Two-dimensional echocardiography was performed with a Toshiba SSH-380A recorder equipped with a 2.5 or 3.75 MHz transducer. The standard technique was employed to determine the size of the LV and left atrium. The LV dimension was measured at end-diastole (defined as the onset of the R-wave) just below the level of the mitral leaflets through the standard left parasternal window. The left atrial dimension was measured as the distance from the leading edge of the posterior left wall at end-diastole.

All study patients were followed up prospectively in our hospital at least once a month by clinicians who were blinded to the cardiac MIBG imaging results. The primary endpoint was SCD, defined as witnessed cardiac arrest or death within 1 hour of the onset of acute symptoms, unexpected or unwitnessed death in a patient who was known to have been well within the previous 24 hours. The secondary endpoint was defined as severe arrhythmic events (SAE) such as SCD, sustained VT and appropriate ICD therapy, which are following ADMIRE-HF study. Survival data were obtained by medical records in our hospital, direct contact with patient's primary physicians, or by telephone interview of patients or their family or mail by dedicated coordinators.

The data are presented as the mean ± standard deviation or median with first quartile to third quartile range. Continuous variables were compared using Student's t test or Mann–Whitney U test Wilcoxon rank sum test based on their distribution, and the differences in discrete variables were compared using a Fisher's exact test. In the univariate Cox proportional hazards regression model, the association of the baseline patient characteristics with SCD was assessed, and we used the multivariate Cox proportional hazards regression model to assess the prognostic value of ADMIRE-HF risk score and ERP, adjusting for the clinical variables (age, gender, NYHA functional class, and diabetes mellitus). Cardiac event-free rates were calculated using the Kaplan–Meier method, and differences between groups were detected using the log-rank test. All statistical analyses were performed using MedCalc, Version 16.1.2 (MedCalc Software bvba, Ostend, Belgium). p values $<$ 0.05 were considered significant.

RESULTS

During a median follow-up of 7.5 (4.5-12.0) years, 22 patients had SCD. The baseline characteristics of patients with and without SCD are listed in Table 1. There were no differences in age, gender, the proportion of patients with ischemic heart disease, NYHA functional class, heart rate, blood pressure, drug use, left ventricular end-diastolic dimension, left atrial dimension, serum creatinine, sodium, potassium, or uric acid levels between patients with and without SCD. The LVEF tended to be lower in patients with SCD. Patients with SCD had a significantly higher plasma concentration of noradrenaline.

As for MIBG parameters, patients with SCD had a significantly lower H/M ratio on the early and delayed images, and a greater washout rate than those without SCD (Table 2). ADMIRE-HF score was significantly higher in patients with than without SCD (12 [2-15] vs 3 [0-8.5], p = 0.0171) (Figure 1). On the other hand, 12 of 90 study patients had ERP. The ERP-positive rate was significantly higher in patients with than without SCD. The ERP-positive rate in both the inferior and lateral leads was significantly higher in patients with than without SCD, whereas no significant difference was observed in the ERP-positive rate in the inferior or lateral lead only between the two groups. No significant differences were found in the other parameters in 12-lead standard ECG and Holter ECG monitoring between the patients with and without SCD, except for Lown's grade and VPC / hour.

Kaplan-Meier analysis revealed that SCD was more frequently observed in higher ADMIRE-HF risk score group (high:50[5/10]% vs intermediate:33[10/30]% vs low:14[7/50]%, p = 0.0090; hazard ratio, high vs low 4.3 [95% CI 1.1 to 17.2], intermediate vs low 3.3 [95% CI 1.3 to 8.7]) (Figure 2). Moreover, patients with ERP had a higher risk of SCD than those without ERP (67[8/12] % vs 18[14/78] %, p = 0.0001, hazard ratio 4.9 [95% CI 1.3 to 19.5]) (Figure 3).

At univariate analysis, serum sodium and uric acid levels, plasma norepinephrine concentration, ADMIRE-HF risk score and ERP showed a significant association with SCD. Multivariate Cox analysis revealed that both ADMIRE-HF risk score and ERP were independently and significantly associated with SCD (Table 3). SCD was most frequently observed in patients with intermediate/high ADMIRE-HF score and ERP (80[4/5] %) (Figure 4). Moreover, patients with intermediate/high ADMIRE-HF risk score without ERP (31[11/35] %) and those with low ADMIRE-HF risk score and ERP (57[4/7] %) experienced SCD significantly more frequently than in those with low ADMIRE-HF risk score without

Table 1. Clinical characteristics in patients with and without sudden cardiac death

Variables	Sudden cardiac death		*p* value
	Yes (*n* = 22)	No (*n* = 68)	
Age (years)	67 (60–70)	65 (60–72)	0.9775
Men	77%	77%	1.0000
NYHA class	2 (2–3)	2 (2–2)	0.6325
Heart rate (beats/min)	72 ± 12	74 ± 12	0.4579
Systolic blood pressure (mmHg)	128 ± 13	129 ± 17	0.7881
Ischemic heart disease	47%	52%	0.7313
Hypertension	9%	15%	0.7229
Diabetes Mellitus	32%	24%	0.5743
Atrial fibrillation	40%	21%	0.1254
Medications			
ACE inhibitor/ARB	80%	82%	0.8067
Beta-blocker*	73%	72%	0.9442
Loop diuretics	86%	74%	0.2603
Aldosterone antagonist	60%	64%	0.7898
Amiodarone	9%	2%	0.1468
Radionuclide angiography			
LV ejection fraction (%)	28 (22–35)	32 (26–36)	0.0919
Echocardiography			
LVDd (mm)	62 (58–64)	62 (56–67)	0.7283
LAD (mm)	45 ± 7	42 ± 8	0.1146
Laboratory			
Creatinine (mg/dL)	0.83 (0.75–1.02)	0.87 (0.75–1.03)	0.7717
eGFR (mL/min/1.73m^2)	64 ± 19	62 ± 18	0.7533
Sodium (mEq/L)	139 (135–141)	140 (137–141)	0.2651
Potassium (mEq/L)	4.3 ± 0.6	4.2 ± 0.5	0.2196
Hemoglobin (g/dL)	13.6 ± 1.8	13.5 ± 1.4	0.8162
Uric acid (mg/dl)	7.5 (6.2–8.3)	6.7 (5.4–8.0)	0.1043
Norepinephrine(ng/ml)	557 (300–820)	330 (252–490)	0.0240

Data are shown as median with first to third quartile range or ratios (%) of patients
NYHA, New York Heart Association; *ACE*, angiotensin-converting enzyme; *ARB*, angiotensin II receptor blocker; *LV*, left ventricular; *LVDd*, left ventricular end-diastolic dimension; *LAD*, left atrial dimension
*Medication with beta-blocker (carvedilol) scored at the last follow-up

ERP (7[3/43] %). The adjusted hazard ratio for SCD prediction in patients with intermediate/high ADMIRE-HF score and ERP was 27.0 (95%CI 2.0 to 361.4), which was about 4-fold higher that the hazard ratio in those with either intermediate/high ADMIRE-HF score or ERP (6.5 [95%CI 2.8 to 15.3]).

During the follow-up period, three patients had sustained VT followed by ICD implantation, and one of two patients with the implantation of CRT-D had appropriate ICD therapy, so that 26 patients had SAE as secondary endpoint. ADMIRE-HF score (12 [2-15] vs 3 [0-8], $p = 0.0041$) and ERP-positive rate (31% vs 6%, $p = 0.0041$) were significantly higher in patients with than without SAE. Kaplan–Meier analysis revealed that SAE was more frequently observed in higher ADMIRE-HF risk score group (high:60[6/10]% vs intermediate:40[12/30]% vs low:16[8/50]%, p=0.0008; hazard ratio, high vs low 5.2 [95% CI 1.4 to 20.2], intermediate vs low 3.7 [95% CI 1.5 to 9.0]) (Figure 2). Moreover, patients with ERP had a higher risk of SAE than those without ERP (67[8/12] % vs 23[18/78] %, $p = 0.0002$, hazard ratio 4.2 [95% CI 1.1 to 15.4]) (Figure 3). At univariate analysis, LVEF, serum sodium and plasma norepinephrine concentration, ADMIRE-HF risk score and ERP showed a significant association with SCD. Multivariate Cox analysis revealed that ADMIRE-HF risk score and ERP were independently and significantly associated with SAE. Patients with intermediate/high

Table 2. MIBG and ECG findings in patients with and without sudden cardiac death

Variables	Sudden cardiac death		*p* value
	Yes (*n* = 22)	No (*n* = 68)	
MIBG imaging			
H/M(e)	1.72 ± 0.24	1.89 ± 0.25	0.0078
H/M(d)	1.57 ± 0.25	1.80 ± 0.30	0.0012
Washout rate	36.7 (26.3-45.5)	23.1 (16.2-33.5)	0.0027
Standard 12-lead ECG			
RR duration (ms)	855 ± 210	835 ± 147	0.6426
PR duration (ms)	164 ± 38	162 ± 25	0.8350
QRS duration (ms)	108 (104-117)	106 (97-115)	0.2751
QT interval (ms)	374 (361-418)	381 (353-399)	0.8293
QTc (ms)	418 (400-447)	422 (398-448)	0.9898
Positive ERP	36%	6%	0.0010
ERP location			
Both	18%	2%	0.0119
Inferior only	14%	2%	0.0917
Lateral only	5%	3%	0.5734
ERP type			
Notching	27%	4%	0.0059
Slurring	9%	2%	0.1468
24-Hour Holter ECG			
Lown's grade	4.5 (4.0-4.5)	4.0 (3.0-4.5)	0.0244
VPC/hour (*n*)	92 (8-166)	13 (1-76)	0.0159
NSVT(%)	23	16	0.5301

H/M(e) and H/M(d), heart-to-mediastinum MIBG uptake ratio on the early and delayed images, early repolarization pattern; *VPC*, ventricular premature contractions; *NSVT*, non-sustained ventricular tachycardia

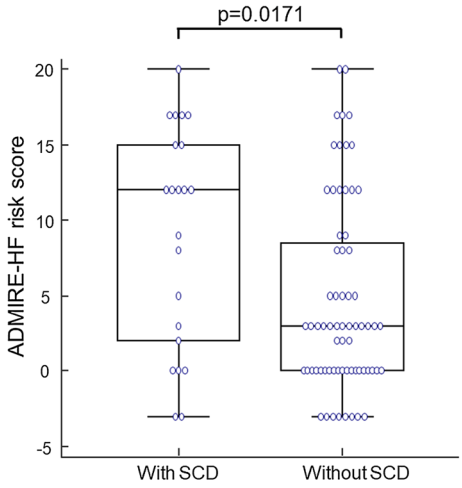

Figure 1. ADMIRE-HF risk score in HFrEF patients with and without sudden cardiac death (SCD).

ADMIRE-HF score and ERP (80[4/5]%) had a significantly higher risk of SAE than those with either (43[18/42]%) or none of them (9[4/43]%) (Figure 4).

DISCUSSION

The major finding of the present study was that we verified the prognostic value of ADMIRE-HF risk score for the prediction of SCD and the combination of ADMIRE-HF risk score and ERP identified a subset of HFrEF patients at high risk of SCD.

In HFrEF patients, sympathetic overactivity and parasympathetic withdrawal are associated with poor outcomes.[23] It is well known that increased sympathetic activity is associated with lethal arrhythmias and following SCD, and that increased parasympathetic activity can exert a protective effect.[24] The status of the cardiac autonomic nervous system can play a role in all three major pathways (trigger, substrate, and modulator) that are believed to contribute to the initiation and perpetuation of lethal arrhythmias.[25] ADMIRE-HF risk score includes a cardiac MIBG variable, which reflects cardiac sympathetic nerve activity. On the other hand, although the exact mechanism for the generation of ERP in patients with structural heart disease remains unknown, it has been reported that ERP in patients with coronary

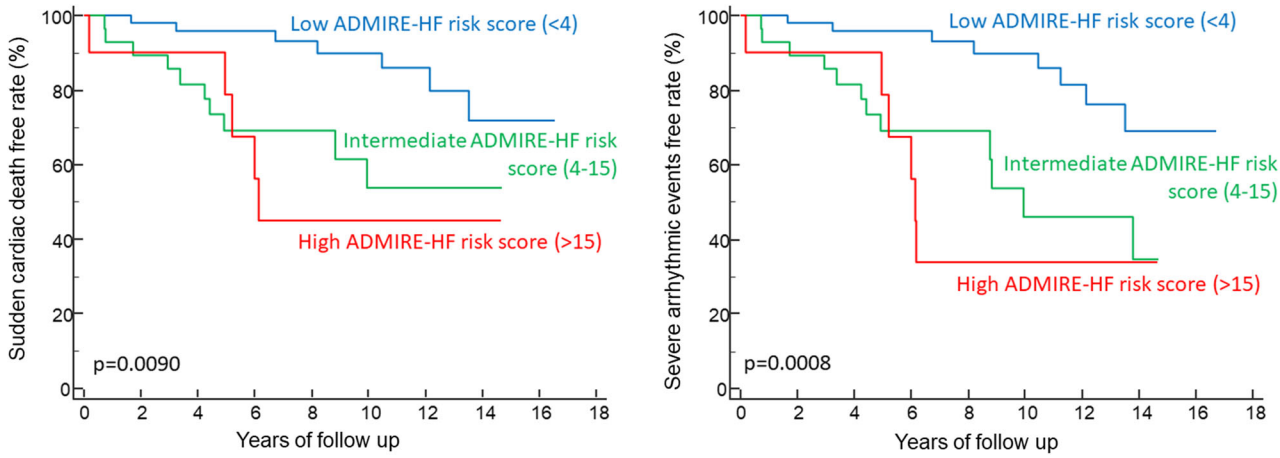

Figure 2. Sudden cardiac death (SCD)-free rate and severe arrhythmic event-free rate curves by Kaplan–Meier analysis in HFrEF patients with high-, intermediate- and low-ADMIRE-HF risk scores.

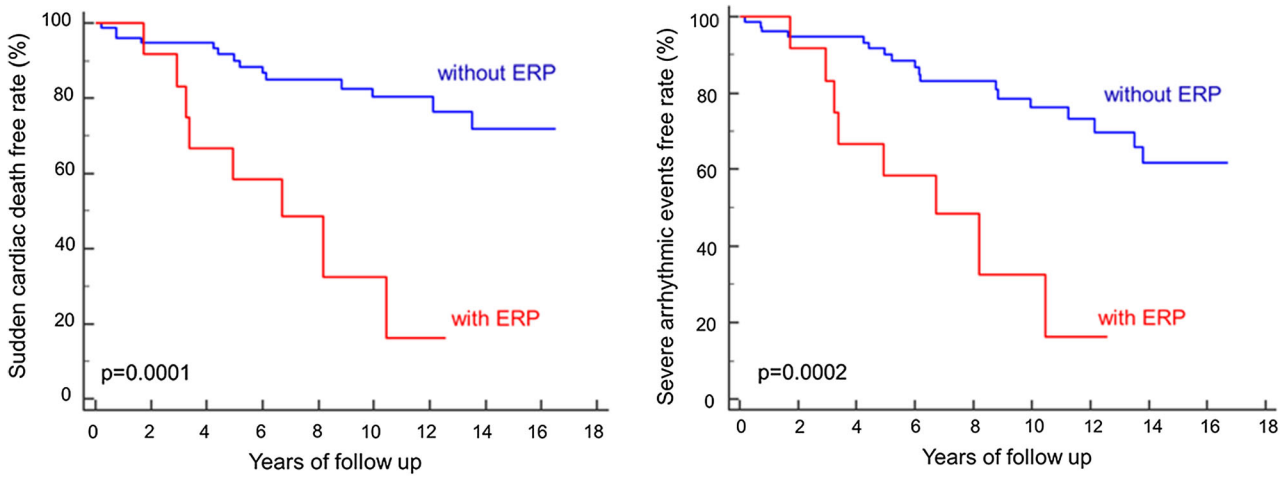

Figure 3. Sudden cardiac death (SCD)-free rate and severe arrhythmic event-free rate curves by Kaplan-–Meier analysis in HFrEF patients with or without early repolarization pattern (ERP).

artery disease may be related to the presence of myocardial scar,[26] which creates an arrhythmic substrate. This might account for our results that ADMIRE-HF risk score and ERP were independently associated with SCD in HFrEF patients.

ADMIRE-HF risk score has been shown to be a novel tool that effectively stratifies HFrEF patients according to their risk of serious arrhythmic events, and the risk is independent of other conventional risk factors.[14] In the sub-analysis of ADMIRE-HF study, which showed the utility of ADMIRE-HF risk score, the primary endpoint was a composite of SCD, resuscitated cardiac arrest, appropriate device therapy, and sustained ventricular tachycardia. Furthermore, no information is available on the external validation of the ADMIRE-HF score for predicting SCD in HFrEF patients. In the present study, ADMIRE-HF risk score was associated with SCD in HFrEF patients. Although there were differences in patients' characteristics between ADMIRE-HF study and the present study (e.g., less ischemic origin and greater LVEF, compared with ADMIRE-HF study), the present study confirmed that ADMIRE-HF risk score is useful for predicting SCD in patients with stable HFrEF.

The prevalence of ERP has been previously reported to be 1% to 13%.[16-18,27] ERP has been generally considered to be an innocuous finding in healthy subjects. Previous reports showed the

Table 3. Univariate and multivariate Cox proportional hazards analysis to identify patients with HFrEF at risk of sudden cardiac death

	Univariate variate analysis	
	***p* value**	**HR (95%CI)**
Age	0.2466	1.0257 (0.9826–1.0707)
Men	0.7110	0.8281 (0.3054–2.2458)
NYHA class	0.3745	1.4121 (0.6594–3.0241)
Heart rate	0.5083	0.9870 (0.9496–1.0260)
Systolic blood pressure	0.5981	0.9936 (0.9701–1.0176)
Ischemic heart disease	0.6691	0.8325 (0.3592–1.9297)
Diabetes mellitus	0.3328	1.5591 (0.6347–3.8299)
LV ejection fraction	0.0694	0.9486 (0.8960–1.0042)
LVDd	0.8624	1.0050 (0.9501–1.0630)
LAD	0.0950	1.0470 (0.9920–1.1049)
Creatinine	0.3212	2.1239 (0.4795–9.4081)
Sodium	0.0498	0.8679 (0.7534–0.9999)
Potassium	0.1002	2.0626 (0.8700–4.8899)
Hemoglobin	0.7459	0.9515 (0.7045–1.2852)
Uric acid	0.0357	1.2566 (1.0154–1.5552)
Norepinephrine	0.0017	1.0022 (1.0008–1.0036)
ADMIRE-HF risk score	0.0019	1.0955 (1.0343–1.1603)
ERP	0.0003	5.2207 (2.1335–12.7752)
Lown's grade	0.0596	1.5920 (0.9814–2.5825)
	Multivariate variate analysis*	
	***p* value**	**HR (95%CI)**
ADMIRE-HF risk score	0.0006	1.1111 (1.0464–1.1799)
ERP	< 0.0001	7.2128 (2.7958–18.6081)

*Adjusted for age, gender, NYHA class, ischemic heart disease, and diabetes mellitus

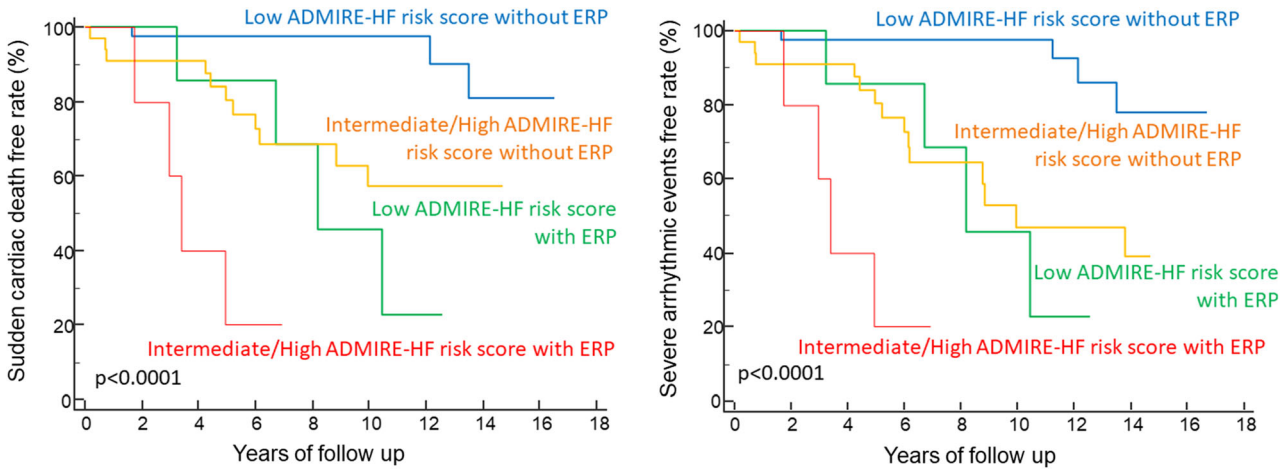

Figure 4. Sudden cardiac death (SCD)-free rate and severe arrhythmic event-free rate curves in HFrEF patients stratified by the ADMIRE-HF risk score and early repolarization pattern (ERP).

association between ERP and fatal ventricular tachyarrhythmia in patients without structural heart disease.[16,17] An experimental study showed that the presence of a prominent action potential notch in the epicardium but not in the endocardium provided a voltage gradient that manifests as a J-wave or elevated J-point in the ECG.[15] This voltage gradients can initiate arrhythmogenesis to increase the vulnerability to lethal ventricular tachyarrhythmias in healthy subjects. Although the precise mechanism for generation of ERP remains unknown in patients with HFrEF, ERP in HFrEF patients might differ from that in subjects without structural heart disease, as we previously reported.[21]

Recent clinical trials have shown that ICDs can reduce the risk of SCD in symptomatic HFrEF patients who have low LVEF.[28,29] Therefore, many guidelines recommend ICD implantation for the primary prevention of SCD based on LVEF.[30] However, the actual rate of appropriate shocks remains low in HFrEF patients with ICD implantation, according to the current guidelines.[31,32] Thus, alternative means are needed to refine the criteria for ICD implantation. In the present study, the combination of ADMIRE-HF risk score and ERP provided incremental prognostic information for the prediction of SCD in HFrEF patients. This result suggests that the combination of ADMIRE-HF risk score and ERP can identify a subset of HFrEF patients at high risk for SCD that could benefit more from ICD implantation. Furthermore, in the present study, it is notable that SCD occurred in only one patient in the group with low ADMIRE-HF risk score and without ERP during the initial 10 years of follow-up. This result also suggests that the combination of ADMIRE-HF risk score and ERP can identify patients with HFrEF who do not need ICD implantation.

Our study has several limitations. First, the small sample size is a major limitation. The results might have been influenced by fortuitous circumstances in this small number of patients. Second, no study patients received the current standard of care (i.e., there was insufficient use of beta-blockers, ICD, biventricular pacemakers, and biventricular defibrillators [CRT-D]) and the measurement of plasma brain natriuretic peptide level at entry because this study was started in the last century. The medications used during follow-up may have affected cardiac MIBG uptake, ERP, and the clinical outcomes. During the follow-up period, five patients received ICD/CRT-D treatment. Patients without SCD had a higher incidence of ICD/CRT-D therapy than those with SCD, although the difference was not statistically significant (7% vs 0%, $p = 0.32$). Even if the patients with ICD implantation during the follow-up period were excluded from analysis, the similar result was obtained. Third, there was a considerable overlap in ADMIRE-HF risk score between patients with and without SCD, which might reduce the usefulness of ADMIRE-HF risk score. Although the sensitivity (68[15/22]%) and positive predictive value (38[15/40]%) of high/intermediate ADMIRE-HF risk score for SCD prediction was not adequate, the negative predictive value was relatively high (86[43/50]%). This finding suggests that we might be able to identify patients at low risk of SCD if they have low ADMIRE-HF risk score. Fourth, we had no data from T-wave alternans testing, although we previously showed the comparison the prognostic value of heart rate variability with cardiac MIBG imaging.[7] Lastly, because we included only stable outpatients with mild-to-moderate HFrEF, patients in NYHA functional class IV were not included in this study. Therefore, our results should not be generalized to patients with severe HFrEF.

NEW KNOWLEDGE GAINED

The prognostic value of ADMIRE-HF risk score for the prediction of SCD was verified in HFrEF patients, and the combination of ADMIRE-HF risk score and ERP could identify the HFrEF patients with a higher risk of SCD.

CONCLUSION

The combination of ADMIRE-HF risk score and ERP provides incremental prognostic value for predicting SCD in patients with HFrEF.

Disclosure

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References

1. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Multicenter automatic defibrillator implantation trial II investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-883.
2. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Sudden cardiac death in heart failure trial (SCD-HeFT) investigators. Amiodarone or an implantable cardioverter-

defibrillator for congestive heart failure. N Engl J Med 2005;352:225-237.
3. Merlet P, Valette H, Dubois-Randé JL, Moyse D, Duboc D, Dove P, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. J Nucl Med 1992;33:471-7.
4. Ogita H, Shimonagata T, Fukunami M, Kumagai K, Yamada T, Asano Y, et al. Prognostic significance of cardiac I-123 metaiodobenzylguanidine imaging for mortality and morbidity in patients with chronic heart failure: A prospective study. Heart 2001;86:656-60.
5. Yamada T, Shimonagata T, Fukunami M, Kumagai K, Ogita H, Hirata A, et al. Comparison of the prognostic value of cardiac iodine-123 metaiodobenzylguanidine imaging and heart rate variability in patients with chronic heart failure: a prospective study. J Am Coll Cardiol 2003;41:231-8.
6. Kioka H, Yamada T, Mine T, Morita T, Tsukamoto Y, Tamaki S, et al. Prediction of sudden death in patients with mild-to-moderate chronic heart failure by using cardiac iodine-123 metaiodobenzylguanidine imaging. Heart 2007;93:1213-8.
7. Tamaki S, Yamada T, Okumura Y, Morita T, Sanada S, Tsukamoto Y, et al. Cardiac iodine-123 metaiodobenzylguanidine imaging predicts sudden cardiac death independently of left ventricular ejection fraction in patients with chronic heart failure and left ventricular systolic dysfunction. J Am Coll Cardiol 2009;53:426-35.
8. Jacobson AF, Senior R, Cerqueira, Wong ND, Thomas GS, Lopez VA, et al. ADMIRE-HF Investigators. Myocardial 123I-mIBG imaging and cardiac events in heart failure: results of the prospective ADMIRE-HF study. J Am Coll Cardiol 2010;55:2212-2221.
9. Kuramoto Y, Yamada T, Tamaki S, Okuyama Y, Morita T, Furukawa Y, et al. Usefulness of cardiac iodine-123 meta-iodobenzylguanidine imaging to improve prognostic power of Seattle heart failure model in patients with chronic heart failure. Am J Cardiol 2011;107:1185-90.
10. Nakata T, Nakajima K, Yamashina S, Yamada T, Momose M, Kasama S, et al. A pooled analysis of multicenter cohort studies of (123)I-mIBG imaging of sympathetic innervation for assessment of long-term prognosis in heart failure. JACC Cardiovasc Imaging 2013;6:772-84.
11. Kawai T, Yamada T, Tamaki S, Morita T, Furukawa Y, Iwasaki Y, et al. Usefulness of cardiac meta-iodobenzylguanidine imaging to identify patients with chronic heart failure and left ventricular ejection fraction <35% at low risk of sudden cardiac death. Am J Cardiol 2015;115:1549-54.
12. Hakui H, Yamada T, Tamaki S, Morita T, Furukawa Y, Iwasaki Y, et al. Usefulness of cardiac metaiodobenzylguanidine imaging to improve prognostic power of the model for end-stage liver disease scoring system in patients with mild-to-moderate chronic heart failure. Am J Cardiol 2016;117:1947-52.
13. Nakajima K, Scholte A, Nakata T, Dimitriu-Leen AC, Chikamori T, Vitola J, et al. Cardiac sympathetic nervous system imaging with 123I-meta-iodobenzylguanidine: Perspectives from Japan and Europe. J Nucl Cardiol 2017;24:952-60.
14. Al Badarin FJ, Wimmer AP, Kennedy KF, Jacobson AF, Bateman TM. The utility of ADMIRE-HF risk score in predicting serious arrhythmic events in heart failure patients: incremental prognostic benefit of cardiac 123I-mIBG scintigraphy. J Nucl Cardiol 2014;21:756-62.
15. Gussak I, Antzelevitch C. Early repolarization syndrome: clinical characteristics and possible cellular and ionic mechanisms. J Electrocardiol 2000;33:299-309.
16. Haïssaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med 2008;358:2016-2023.
17. Rosso R, Kogan E, Belhassen B, Rozovski U, Scheinman MM, Zeltser D, et al. J-point elevation in survivors of primary ventricular fibrillation and matched control subjects: incidence and clinical significance. J Am Coll Cardiol 2008;52:1231-8.
18. Tikkanen JT, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, et al. Long-term outcome associated with early repolarization on electrocardiography. N Engl J Med 2009;361:2529-37.
19. Patel RB, Ng J, Reddy V, Chokshi M, Parikh K, Subacius H, Alsheikh-Ali AA, et al. Early repolarization associated with ventricular arrhythmias in patients with chronic coronary artery disease. Circ Arrhythm Electrophysiol 2010;3:489-95.
20. Pei J, Li N, Gao Y, Wang Z, Li X, Zhang Y, et al. The J wave and fragmented QRS complexes in inferior leads associated with sudden cardiac death in patients with chronic heart failure. Europace 2012;14:1180-7.
21. Furukawa Y, Yamada T, Morita T, Iwasaki Y, Kawasaki M, Kikuchi A, et al. Early repolarization pattern associated with sudden cardiac death: long-term follow-up in patients with chronic heart failure. J Cardiovasc Electrophysiol 2013;24:632-9.
22. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: The Framingham study. N Engl J Med 1971;285:1441-6.
23. Floras JS. Clinical aspects of sympathetic activation and parasympathetic withdrawal in heart failure. J Am Coll Cardiol 1993;22:72A-84A.
24. Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post-myocardial infarction risk stratification. Circulation 1992;85(1 Suppl):I77-91
25. Borgquit R, Singh JP. An electrophysiological perspective on risk stratification in heart failure: can better understanding of the condition of the cardiac sympathetic nervous system help? J Nucl Med 2015;56:59S-64S.
26. Lee HY, Mun HS, Wi J, Uhm JS, Shim J, Kim JY, et al. Early repolarization and myocardial scar predict poorest prognosis in patients with coronary artery disease. Yonsei Med J 2014;55:928-36.
27. Klatsky AL, Oehm R, Cooper RA, Udaltsova N, Armstrong MA. The early repolarization normal variant electrocardiogram: correlates and consequences. Am J Med 2003;115:171-7.
28. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002 21;346:877-883.
29. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Sudden cardiac death in heart failure trial (SCD-HeFT) investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005 20;352:225-237.
30. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, et al. American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Heart Rhythm Society. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation 2013;127:e283-e352.

31. Moss AJ, Greenberg H, Case RB, Zareba W, Hall WJ, Brown MW, et al. Multicenter automatic defibrillator implantation trial-II (MADIT-II) research group. Long-term clinical course of patients after termination of ventricular tachyarrhythmia by an implanted defibrillator. Circulation 2004;110:3760-3765.
32. Zecchin M, Merlo M, Pivetta A, Barbati G, Lutman C, Gregori D, et al. How can optimization of medical treatment avoid unnecessary implantable cardioverter-defibrillator implantations in patients with idiopathic dilated cardiomyopathy presenting with ''SCD-HeFT criteria?''. Am J Cardiol 2012;109:729-35.