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Devices

Optimizing Patient Selection for Cardiac Resynchronization Therapy With or Without Defibrillator in a Multicenter Study of Japanese Patients

— Assessment of the MADIT-ICD Benefit Score —

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Background: Although the MADIT-ICD benefit score (MBS) helps select suitable implantable cardioverter defibrillator (ICD) candidates, optimal indicators for cardiac resynchronization therapy (CRT) remain uncertain. Evaluating the applicability of the MBS in Japanese CRT patients is imperative.

Methods and Results: This multicenter study assessed the cumulative incidence of ventricular tachycardia/fibrillation (VT/VF) and non-arrhythmic mortality (AM) in CRT patients grouped according to potential benefit (lowest, highest, and intermediate). Among 400 primary prevention patients (mean age 65 years, 76% male), VT/VF occurred in 4 (7%), 68 (24%), and 14 (23%) patients in the lowest-, intermediate-, and highest-benefit groups, respectively (P=0.027), over a median follow-up of 34 months. Non-arrhythmic death was observed in 15 (25%), 91 (33%), and 9 (15%) patients in the lowest-, intermediate-, and highest-benefit groups, respectively (P=0.025). Multivariate analysis identified VT/VF score ≥7 (hazard ratio [HR] 2.14; 95% confidence interval [CI] 1.09–4.19; P=0.027) as a significant VT/VF predictor. The presence of left bundle branch block (HR 0.51; 95% CI 0.29–0.92; P=0.025) was associated with a reduced risk of VT/VF events. Non-AM score ≥3 (HR 1.70; 95% CI 1.01–2.88; P=0.047), systolic blood pressure <100 mmHg (HR 1.84; 95% CI 1.25–2.70; P=0.002), and estimated glomerular filtration rate <30 mL/min/1.73 m^2 (HR 1.98; 95% CI 1.23–3.20; P=0.005) were significant predictors of non-arrhythmic death.

Conclusions: The MBS can identify suitable candidates for CRT-D among Japanese individuals.

Key Words: Cardiac resynchronization therapy; Heart failure; Implantable cardioverter defibrillator; MADIT-ICD benefit score; Patient selection

Implantable cardioverter defibrillators (ICDs) have demonstrated significant efficacy in reducing mortality in patients with heart failure with reduced ejection fraction (HFrEF) in multiple randomized trials.[1,2] However, the benefit of ICDs in non-ischemic cardiomyopathy has been brought into question, particularly in light of the DANISH study, which failed to show significant reduction in all-cause mortality.[3] This discrepancy may derive from the presence of competing risks for non-arrhythmic death, including heart failure (HF), myocardial infarction, stroke, and non-cardiovascular causes such as malignancy and infectious diseases.[4]

To address these challenges, the MADIT-ICD benefit score (MBS; **Figure 1**) has recently been developed as a tool to aid in the optimal selection of candidates for ICD therapy.[5] This scoring system integrates both the risk of ventricular tachycardia (VT) and ventricular fibrillation (VF) and the risk of non-arrhythmic mortality, stratifying patients into 3 subgroups based on the potential benefit of ICD therapy. However, although the utility of the MBS has been demonstrated in certain populations, its applicability to patients receiving cardiac resynchronization ther-

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A

MADIT-ICD benefit group	Lowest	Intermediate		Highest
VT/VF score	Low (<7)	Low (<7)	High (≥7)	High (≥7)
Non-arrhythmic mortality score	High (≥3)	Low (<3)	High (≥3)	Low (<3)

B

VT/VF score	
Variables	Points
LVEF ≤25%	+1
Atrial arrhythmia	
Heart rate >75bpm	
Systolic blood pressure <140mmHg	+2
Myocardial infarction	
Age <75 years	
Male	
Prior NSVT	

Non-arrhythmic mortality score	
Variables	Points
CRT	-1
NYHA class ≥II	+1
Diabetes	
BMI <23kg/m^2	+2
Atrial arrhythmia	
LVEF ≤25%	
Age ≥75 years	

Figure 1. (**A**) MADIT-ICD benefit score and groups. The MADIT-ICD benefit score comprises 2 components: the ventricular tachycardia (VT)/ventricular fibrillation (VF) score and the non-arrhythmic mortality score. Based on these scores, patients are categorized into 3 groups: lowest-benefit group (low VT/VF score and high non-arrhythmic mortality score); highest-benefit group (high VT/VF score and low non-arrhythmic mortality score); and intermediate-benefit group (either both scores high or both scores low). (**B**) MADIT-ICD VT/VF and non-arrhythmic mortality scores. The VT/VF score is calculated based on 8 risk factors and ranges from 0 to 13 points, with a score of >7 indicating a high risk of ventricular arrhythmias. The non-arrhythmic mortality score is determined by 7 risk factors and ranges from 1 to 10, with a score of ≥3 indicating a high risk of mortality from non-arrhythmic causes. CRT, cardiac resynchronization therapy; BMI, body mass index; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; SBP, systolic blood pressure.

apy (CRT), with or without defibrillator, remains uncertain. CRT has emerged as a valuable therapeutic option for patients with HFrEF, often leading to improvements in left ventricular function and reductions in the risk of sudden cardiac death.[6] Notably, the patient populations studied in the 4 MADIT trials (MADIT-II,[1] MADIT-CRT,[7] MADIT-RIT,[8] and MADIT-RISK[9]) comprised only 40% of individuals receiving CRT with defibrillator (CRT-D), with limited representation from Asian populations.

Given the variations in genetic predispositions, underlying disease characteristics, and treatment responses across different ethnic groups, there is an imperative to assess the relevance of MBS specifically in Japanese patients undergoing CRT. Previous studies have indicated that Asian populations have a lower prevalence of ischemic heart disease and sudden cardiac death compared with Western populations.[10] However, another study suggested that Asian populations with HF and mid-range QRS duration (QRSd) may derive greater benefit from CRT due to their smaller body size.[11] These findings underscore the potential for unique clinical profiles among Japanese and Asian populations, including differences in disease etiology, comorbidity patterns, and treatment responses, which could influence the efficacy of CRT and the necessity of defibrillator implantation. Therefore, the aims of this study were to evaluate the applicability of MBS in Japanese CRT patients and identify factors that may affect the effectiveness of defibrillator therapy in this population.

Methods

Study Population

This retrospective multicenter observational cohort study enrolled 505 consecutive patients who underwent CRT device implantation at Tohoku University Hospital (Sendai, Japan) and the National Cerebral and Cardiovascular Center (Osaka, Japan) between January 2012 and August 2020. CRT device implantation procedures followed the recommendations outlined in the 2019 guideline from the Japanese Circulation Society (JCS).[12]

The major eligibility criteria for CRT implantation, as per the Japanese guideline, included HF symptoms persisting despite optimal medical therapy, New York Heart Association (NYHA) functional class II–IV, left ventricular ejection fraction (LVEF) ≤35%, and QRSd ≥120 ms. Patients with a history of prior VT/VF, corresponding to secondary prevention, or those for whom MBS was unavailable were excluded from the study. Cases of CRT upgrades from pacemakers or ICDs were included in the analysis.

Baseline clinical data, including age, sex, physical measurements, vital signs, etiology of heart disease, history of prior VT/VF, CRT device model, comorbidities, prescribed medications, blood laboratory parameters, 12-lead

electrocardiogram findings, and echocardiographic parameters, were collected for all patients at the time of or before implantation. Heart rate data were collected from a 12-lead electrocardiogram taken at rest before device implantation. Following implantation, all patients received multidisciplinary care, including device optimal programming, guideline-directed medical therapy, rehabilitation, and telemonitoring.

This research was approved by the University of Tohoku Institutional Review Board (2022-1-916) and was conducted in accordance with the principles outlined in the Declaration of Helsinki.

MBS and Group Assignment

The MBS was calculated for each patient at the time of or before device implantation. This scoring system comprises 2 components: the VT/VF score and the non-arrhythmic mortality score (**Figure 1**).[5]

The VT/VF score is determined by 8 risk factors: LVEF ≤25% (+1 point), atrial arrhythmia (+1 point), heart rate >75 beats/min (+1 point), systolic blood pressure (SBP) <140 mmHg (+2 points), history of myocardial infarction (+2 points), age <75 years (+2 points), male sex (+2 points), and prior non-sustained VT (NSVT; +2 points). The score ranges from 0 to 13 points, with a score of ≥7 indicating a high risk of ventricular arrhythmias.

The non-arrhythmic mortality score is determined by 7 risk factors: the presence of CRT (−1 point), NYHA functional class ≥II (+1 point), diabetes (+1 point), body mass index (BMI) <23 kg/m^2 (+2 points), atrial arrhythmia (+2 points), LVEF ≤25% (+2 points), and age ≥75 years (+2 points). This score ranges from 1 to 10, with a score of ≥3 indicating a high risk of mortality from non-arrhythmic causes.

Based on these scores, patients are categorized into 3 groups: (1) a lowest-benefit group, comprising patients with a low VT/VF score and a high non-arrhythmic mortality score; (2) a highest-benefit group, comprising patients with a high VT/VF score and a low non-arrhythmic mortality score; and (3) an intermediate-benefit group, comprising patients with either both scores high or both scores low.

Endpoint Assessment

The primary endpoints of this study included the occurrence of ventricular arrhythmias and non-arrhythmic death during the follow-up period. Ventricular arrhythmias were identified as either the occurrence of sustained VT not requiring therapy or appropriate therapy for VT/VF. Stored intracardiac electrograms were reviewed by cardiac electrophysiology specialists to confirm the occurrence of ventricular arrhythmia and the appropriateness of therapy. Non-arrhythmic mortality data were extracted from electronic health records. Arrhythmic death was defined as death resulting from VT/VF that was either witnessed during monitoring or at the time of the initial

Table 1. Patient Characteristics Overall and According to MADIT-ICD Benefit Score

	Overall (n=400)	Benefit			P value
		Highest (n=61)	Intermediate (n=279)	Lowest (n=60)	
MADIT-ICD VT/VF score (points)	7.8±2.2	8.4±1.1	8.3±2.0	4.7±1.3	<0.001
Score ≥7 points	301 (75.3)	61 (100)	240 (86.0)	0 (0)	<0.001
MADIT-ICD non-arrhythmic mortality score (points)	4.1±2.0	1.6±0.8	4.5±1.9	4.6±1.3	<0.001
Score ≥3 points	300 (75.0)	0 (0)	240 (86.0)	60 (100)	<0.001
Age (years)	64.9±14.5	59.2±11.3	63.8±14.9	75.9±8.6	<0.001
Age ≥75 years	121 (30.3)	0 (0)	76 (27.2)	45 (75.0)	<0.001
Male sex	302 (75.5)	53 (86.9)	222 (79.6)	27 (45.0)	<0.001
Body height (cm)	162.6±8.6	164.0±7.7	163.6±8.1	156.2±9.3	<0.001
Body weight (kg)	58.9±12.4	67.0±10.7	59.8±12.3	53.7±11.4	<0.001
BMI (kg/m^2)	22.6±3.6	24.8±3.0	22.2±3.6	21.8±3.3	<0.001
BMI <23 kg/m^2	226 (56.5)	10 (16.4)	177 (63.4)	39 (65.0)	<0.001
SBP (mmHg)	110.7±19.3	112.9±18.0	108.0±19.1	121.4±18.1	<0.001
SBP <140 mmHg	375 (93.8)	60 (98.4)	264 (94.6)	51 (85.0)	0.005
SBP <100 mmHg	121 (30.3)	14 (23.0)	101 (36.2)	6 (10.0)	<0.001
Heart rate (beats/min)	66.8±14.2	68.7±13.7	66.7±14.7	65.5±12.5	0.446
Heart rate >75 beats/min	100 (25.0)	20 (32.8)	67 (24.0)	13 (21.7)	0.290
Hypertension	187 (46.8)	28 (45.9)	125 (44.8)	34 (56.7)	0.245
Diabetes	137 (34.3)	5 (8.2)	112 (40.1)	20 (33.3)	<0.001
Myocardial infarction	77 (19.3)	7 (11.5)	65 (23.3)	5 (8.3)	0.007
Stroke	47 (11.8)	7 (11.5)	38 (13.6)	2 (3.3)	0.080
NYHA functional class					0.013
I	7 (1.8)	2 (3.3)	4 (1.4)	1 (1.7)	
II	232 (58.0)	42 (68.9)	153 (54.8)	37 (61.7)	
III	132 (33.0)	17 (27.9)	93 (33.3)	22 (36.7)	
IV	29 (7.2)	0 (0)	19 (10.4)	0 (0)	

(**Table 1** continued the next page.)

	Overall (n=400)	Benefit			P value
		Highest (n=61)	Intermediate (n=279)	Lowest (n=60)	
Previous HF hospitalization	330 (82.7)	42 (68.9)	243 (87.4)	45 (75.0)	0.001
Ischemic etiology	93 (23.3)	6 (9.8)	74 (26.5)	13 (21.7)	0.019
CRT-D	311 (77.8)	54 (88.5)	231 (82.8)	26 (43.3)	<0.001
CRT-P	89 (22.2)	7 (11.5)	48 (17.2)	34 (56.7)	
Upgrade[A]	112 (28.0)	15 (24.6)	71 (25.4)	34 (56.7)	0.016
Atrial arrhythmia	194 (48.5)	14 (23.0)	159 (57.0)	21 (35.0)	<0.001
Prior NSVT	267 (66.8)	46 (75.4)	208 (74.6)	13 (21.7)	<0.001
QRSd (ms)	158.2±29.7	158.2±31.1	156.4±29.9	166.8±26.0	0.050
QRSd >150 ms	244 (61.0)	38 (62.3)	161 (57.7)	45 (76.3)	0.029
LBBB	118 (29.5)	23 (37.7)	71 (25.4)	24 (40.7)	0.021
RV pacing	95 (23.8)	10 (16.4)	60 (21.5)	25 (42.4)	0.001
LVEF (%)	26.1±9.3	28.7±10.0	24.8±8.9	29.1±9.6	<0.001
LVEF ≤25%	213 (53.3)	22 (36.1)	167 (59.9)	24 (40.0)	<0.001
LVDd (mm)	64.1±10.1	65.1±10.4	65.0±10.0	58.8±8.6	<0.001
LVDd ≥65 mm	184 (46.0)	26 (42.6)	143 (51.3)	15 (25.0)	0.001
LVDs (mm)	55.7±11.7	55.6±12.2	56.9±11.7	50.3±9.4	<0.001
LAD (mm)	46.4±8.4	44.4±8.3	47.5±8.4	43.5±7.5	<0.001
LAD >45 mm	195 (48.8)	23 (39.0)	149 (55.0)	23 (38.3)	0.012
BNP (pg/mL)	317.4 [159–573]	185.7 [86–373]	347.1 [180–590]	336.6 [166–640]	0.001
eGFR (mL/min/1.73 m^2)	53.5 [38–66]	61.3 [45–70]	53.8 [40–67]	42.0 [33–54]	<0.001
eGFR <30 mL/min/1.73 m^2	55 (13.8)	11 (18.3)	37 (13.3)	7 (11.5)	0.500
ACEi/ARB	321 (80.3)	58 (95.1)	215 (77.1)	48 (80.0)	0.006
β-blocker	327 (81.8)	52 (85.2)	230 (82.4)	45 (75.0)	0.298
MRA	238 (59.5)	37 (60.7)	175 (62.7)	26 (43.3)	0.021
Diuretics	311 (77.8)	43 (70.5)	224 (80.3)	44 (73.7)	0.168
Digoxin	56 (14.0)	3 (4.9)	47 (16.8)	6 (10.0)	0.033
Pimobendan	61 (15.2)	6 (9.8)	52 (18.6)	3 (5.0)	0.013
Amiodarone	85 (21.2)	12 (19.7)	69 (24.7)	4 (6.7)	0.008
Antiplatelet	141 (35.2)	14 (23.0)	100 (35.8)	27 (45.0)	0.037
Anticoagulation	224 (56.0)	29 (47.5)	170 (60.9)	25 (41.7)	0.028

Unless indicated otherwise, data are given as the mean±SD, median [interquartile range], or n (%). [A]Upgrade from a pacemakers or implantable cardioverter defibrillator (ICD). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; eGFR, estimated glomerular filtration rate; HF, heart failure; LAD, left atrial diameter; LBBB, left bundle branch block; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; QRSd, QRS duration; RV, right ventricle; SBP, systolic blood pressure; VF, ventricular fibrillation; VT, ventricular tachycardia.

medical contact. In cases where the cause of death was not documented, a telephone interview with primary physicians was conducted to ascertain the cause of death. Sudden unexpected death was classified as arrhythmic death. Non-arrhythmic mortality was defined as death occurring without any evidence of VT/VF and not meeting the criteria for arrhythmic death. Patients who underwent left ventricular assist device (LVAD) implantation due to end-stage HF were categorized as having non-arrhythmic mortality.

Statistical Analysis

Continuous variables are presented as mean±SD for normally distributed data and as the median with interquartile range (IQR) for non-normally distributed variables. Categorical variables are expressed as numbers and percentages. The significance of differences in normally and non-normally distributed variables were determined using Student's t-test and the Wilcoxon signed-rank test, respectively. Group comparisons were made using one-way analysis of variance, the Kruskal-Wallis test, and the Chi-squared test as appropriate.

Cause-specific cumulative incidence analysis was used to analyze event distribution related to ventricular arrhythmias and non-arrhythmic death during follow-up. This included calculation of unadjusted incidence estimates and 95% confidence intervals (CIs) for endpoint events. Incidence-time curves were constructed for ventricular arrhythmias, with group comparisons conducted using the Gray test. Fine–Gray proportional regression models, considering non-arrhythmic death as competing events, were used to calculate subdistribution hazard ratios (HRs) and their 95% CIs. For non-arrhythmic mortality, Kaplan-Meier analyses with the log-rank test and multivariable analyses using Cox proportional regression models were conducted to calculate HRs. Multivariable analyses used a stepwise selection method based on the Akaike information criterion. Statistical analyses were performed using EZR[13] on R commander version 1.61 (Saitama Medical Centre, Jichi Medical University), which provides a graph-

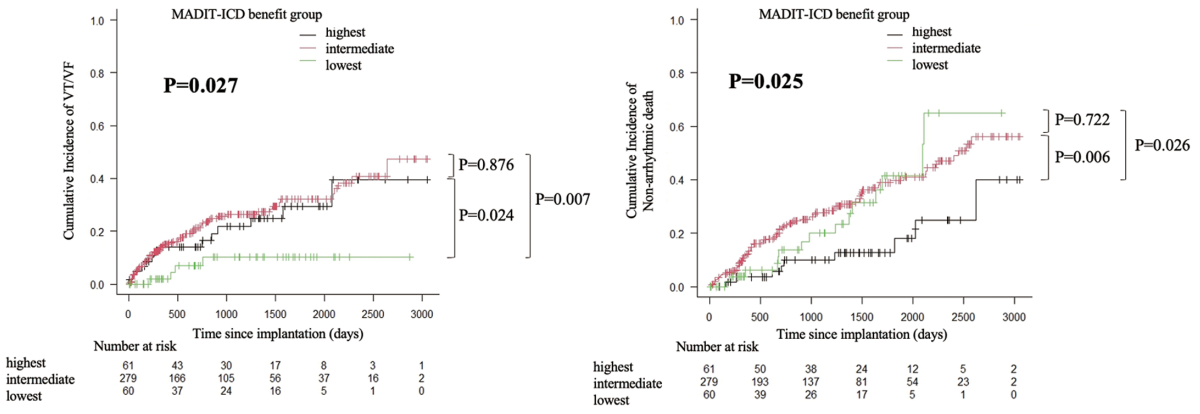

Figure 2. Cumulative incidence of (**A**) ventricular tachycardia (VT)/ventricular fibrillation (VF) and (**B**) non-arrhythmic death according to MADIT-ICD benefit group. (**A**) VT/VF occurred in 4 (6.7%), 68 (24.3%), and 14 (23.0%) patients in the lowest-, intermediate-, and highest-benefit groups, respectively (Gray test, P=0.027). Compared with patients in the lowest-benefit group, those in the highest and intermediate groups had hazard ratios (HRs) of 3.35 (95% confidence interval [CI] 1.10–10.2; P=0.033) and 3.56 (95% CI 1.30–9.79; P=0.013) for VT/VF, respectively. (**B**) Non-arrhythmic death was documented in 15 (25.0%), 91 (32.6%), and 9 (14.8%) patients in the lowest-, intermediate-, and highest-benefit groups, respectively (log-rank test, P=0.025). Compared to with patients in the lowest-benefit group, those in the highest-benefit group had an HR of 0.40 (95% CI 0.17–0.92; P=0.031) for non-arrhythmic death, whereas there was no significant difference in risk in the intermediate-benefit group (HR 1.10; 95% CI 0.64–1.91; P=0.723).

ical user interface for R (version 2.13.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

Of 505 consecutive patients implanted with a CRT device, 400 (79.2%) undergoing primary prevention were included in this study. The baseline characteristics of these patients are summarized in **Table 1**. Mean age was 64.9±14.5 years, and 302 (75.5%) were male. Mean LVEF was 26.1±9.3%, mean QRSd was 158.2±29.7 ms, and 118 (29.5%) had left bundle branch block (LBBB). Ischemic heart disease etiology was present in 93 (23.3%) patients, and mean BMI was 22.6±3.6 kg/m^2, reflecting unique Asian population features. Of these 400 patients, 311 (77.8%) received CRT-D and 89 (22.2%) received CRT with pacemaker (CRT-P) devices, with 112 (28.0%) having upgrades from pacemakers or ICDs.

Among the 400 patients, 60 (15.0%) were in the lowest MADIT-ICD benefit group, 279 (69.8%) were in the intermediate group, and 61 (15.2%) were in the highest group. Compared with the other 2 groups, the highest-benefit group tended to be younger, more often male, and had higher BMI, larger left ventricular end-diastolic diameter (LVDd), lower B-type natriuretic peptide (BNP) levels, better renal function, a lower incidence of diabetes, and fewer previous HF hospitalizations.

In this study, echocardiographic data of post-CRT implantation were available for 330 (82.5%) patients. Among these patients, 141 (42.7%) were classified as CRT responders, defined by a reduction in left ventricular end-systolic volume of ≥15%.

VT/VF Events

Over a median follow-up period of 33.6 months (IQR 12.7–55.4 months), VT/VF events were observed in 86 (21.5%) patients. The median cycle length of tachycardia of VT/VF events was 309 ms (range 280–375 ms). Appropriate therapies were administered in 57 (66.3%) patients through anti-tachycardia pacing (ATP), and in 19 (22.1%) through shock. In 10 (11.6%) patients, no treatment was provided because the heart rate was below the therapy zone. According to MADIT-ICD benefit group, VT/VF occurred in 4 (6.7%), 68 (24.3%), and 14 (23.0%) patients in the lowest-, intermediate-, and highest-benefit groups, respectively (Gray test, P=0.027). The cumulative incidence of VT/VF is shown in **Figure 2A**. Compared with the lowest-benefit group, patients in the highest- and intermediate-benefit groups had HRs of 3.35 (95% CI 1.10–10.2; P=0.033) and 3.56 (95% CI 1.30–9.79; P=0.013) for VT/VF, respectively. There was no significant difference in the incidence of VT/VF between the highest- and intermediate-benefit groups (HR 0.95; 95% CI 0.54–1.69; P=0.870).

Comparing patient backgrounds between patients with and without VT/VF revealed significant differences in some factors (**Supplementary Table 1**). Specifically, those with VT/VF had a higher VT/VF score, were younger age,

Table 2. Predictors of VT/VF Comprising the MADIT-ICD VT/VF Score

Predictors	Univariable		Multivariable	
	HR [95% CI]	P value	HR [95% CI]	P value
Age <75 years	1.72 [1.01–2.93]	0.046	1.70 [1.07–3.37]	0.029
Male sex	1.76 [0.98–3.17]	0.058	1.67 [0.92–3.05]	0.096
SBP <140 mmHg	3.19 [0.79–13.0]	0.100	3.13 [0.74–13.3]	0.120
Heart rate >75 beats/min	0.70 [0.41–1.16]	0.180	0.64 [0.37–1.11]	0.110
Myocardial infarction	1.50 [0.93–2.41]	0.098	1.67 [0.99–2.80]	0.051
Atrial arrhythmia	1.20 [0.79–1.83]	0.390	–	–
Prior NSVT	2.48 [1.43–4.28]	0.001	2.23 [1.29–3.85]	0.004
LVEF ≤25%	0.93 [0.61–1.42]	0.740	–	–

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

Table 3. Predictors of VT/VF in Addition to the MADIT-ICD VT/VF Score

Predictors	Univariable		Multivariable	
	HR [95% CI]	P value	HR [95% CI]	P value
MADIT-ICD VT/VF score ≥7	2.50 [1.30–4.83]	0.006	2.14 [1.09–4.19]	0.027
Diabetes	1.31 [0.85–2.00]	0.220	–	–
QRSd >150 ms	0.63 [0.41–0.96]	0.031	–	–
LBBB	0.47 [0.27–0.64]	0.011	0.51 [0.29–0.92]	0.025
LVDd ≥65 mm	1.43 [0.94–2.18]	0.096	–	–
LAD >45 mm	1.73 [1.11–2.68]	0.015	1.49 [0.96–2.30]	0.076
ACEi/ARB	0.94 [0.55–1.62]	0.830	–	–
β-blocker	1.92 [0.97–3.81]	0.061	1.72 [0.87–3.43]	0.120
MRA	1.45 [0.93–2.27]	0.099	–	–

Abbreviations as in Tables 1,2.

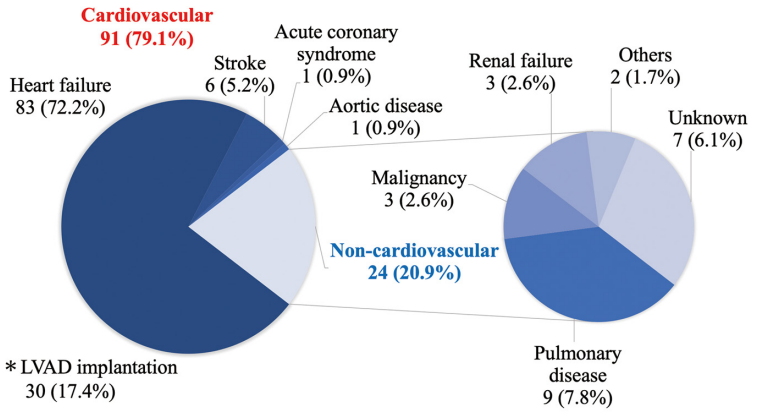

Figure 3. Causes of non-arrhythmic death. Of the 115 (28.8%) patients who died because of non-arrhythmic causes, heart failure was the cause in 83 (72.2%) patients, with 30 (17.4%) of them having undergone left ventricular assist device (LVAD) implantation. Non-cardiovascular deaths occurred in 24 (20.9%) patients.

were more likely to be male, and to have prior NSVT, QRSd >150 ms, LBBB, larger LVDd, and a larger left atrial diameter (LAD; **Supplementary Table 1**). In addition, the rate of β-blocker and amiodarone use was higher in the group with VT/VF (**Supplementary Table 1**), suggesting the results of interventions targeting patients with inherently high VT/VF risk.

To evaluate the factors comprising the VT/VF score in this cohort, multivariable Fine-Gray proportional regression analysis revealed age <75 years (HR 1.70; 95% CI 1.07–3.37; P=0.029) and prior NSVT (HR 2.23; 95% CI 1.29–3.85; P=0.004) as significant factors (**Table 2**). In addition, to assess the validity of the VT/VF score, multivariable analysis was conducted including the above significant factors and optimal pharmacotherapy. This analysis identified 2 significant predictors of VT/VF: a VT/VF score ≥7 (HR 2.14; 95% CI 1.09–4.19; P=0.027) and the presence of LBBB (HR 0.51; 95% CI 0.29–0.92; P=0.025; **Table 3**).

Non-Arrhythmic Death

During the follow-up period non-arrhythmic death occurred

Table 4. Predictors of Non-Arrhythmic Death Comprising the MADIT-ICD Non-Arrhythmic Mortality Score

Predictors	Univariable		Multivariable	
	HR [95% CI]	P value	HR [95% CI]	P value
Age ≥75 years	1.29 [0.88–1.82]	0.191	1.38 [0.93–2.04]	0.114
Body mass index <23 kg/m^2	1.50 [1.02–2.20]	0.040	1.45 [0.97–2.14]	0.058
Diabetes	1.16 [0.80–1.70]	0.430	–	–
Atrial arrhythmia	1.32 [0.91–1.90]	0.141	–	–
LVEF ≤25%	1.48 [1.01–2.16]	0.041	1.47 [1.01–2.16]	0.047
NYHA Class ≥II	–	–	–	–

Abbreviations as in Tables 1,2.

Table 5. Predictors of Non-Arrhythmic Death in Addition to the MADIT-ICD Non-Arrhythmic Mortality Score

Predictors	Univariable		Multivariable	
	HR [95% CI]	P value	HR [95% CI]	P value
MADIT-ICD non-arrhythmic mortality score ≥3	2.15 [1.30–3.56]	0.003	1.70 [1.01–2.88]	0.047
Systolic blood pressure <100 mmHg	2.03 [1.41–2.94]	<0.001	1.84 [1.25–2.70]	0.002
Previous HF hospitalization	3.51 [1.63–7.54]	0.001	2.20 [0.97–4.92]	0.058
QRSd >150 ms	0.66 [0.46–0.95]	0.026	–	–
LBBB	0.57 [0.35–0.92]	0.021	0.62 [0.38–1.00]	0.051
LVDd ≥65 mm	1.08 [0.75–1.56]	0.676	–	–
LAD >45 mm	1.25 [0.86–1.82]	0.237	–	–
eGFR <30 mL/min/1.73 m^2	2.07 [1.31–3.27]	0.002	1.98 [1.23–3.20]	0.005
ACEi/ARB	0.59 [0.39–0.91]	0.015	–	–
β-blocker	1.07 [0.64–1.76]	0.807	–	–
MRA	1.68 [1.12–2.51]	0.011	–	–

Abbreviations as in Tables 1,2.

in 115 (28.8%) patients. Among these patients, heart failure was the most common cause of cardiovascular death, occurring in 83 patients (72.2%), with 30 of these patients (26.1%) having undergone LVAD implantation. Defining CRT responders as those with a reduction in left ventricular end-systolic volume of ≥15%, 13 of 83 (15.7%) heart failure deaths occurred in CRT responders, whereas 51 (61.4%) deaths were among CRT non-responders (P<0.001). In addition, 21 of 30 (70%) patients who underwent LVAD implantation were CRT non-responders. Other causes of death were stroke in 6 patients, acute coronary syndrome in 1 patient, and aortic disease in 1 patient. Conversely, non-cardiovascular death occurred in 24 (20.9%) patients (**Figure 3**).

According to MADIT-ICD benefit group, non-arrhythmic death was documented in 15 (25.0%), 91 (32.6%), and 9 (14.8%) patients in the lowest-, intermediate-, and highest-benefit groups, respectively (log-rank test, P=0.025). The cumulative incidence of non-arrhythmic death is shown in **Figure 2B**. Compared with the lowest-benefit group, those in the highest-benefit group had an HR of 0.40 (95% CI 0.17–0.92; P=0.031) for non-arrhythmic mortality, whereas there was no significant difference in risk in the intermediate-benefit group (HR 1.10; 95% CI 0.64–1.91; P=0.723).

Comparing patient backgrounds between 2 groups based on the presence or absence of non-arrhythmic death revealed significant differences in several factors (**Supplementary Table 2**). Specifically, those with non-arrhythmic death had a higher non-arrhythmic mortality score, lower body weight, lower BMI, lower SBP, more severe NYHA functional class, more previous HF hospitalizations, QRSd >150 ms, LBBB, larger LAD, higher BNP levels, and lower renal function. In addition, the use of diuretics, inotropes, amiodarone, and anticoagulants was higher in the group with non-arrhythmic death, indicating the presence of risk factors for advanced HF.

To assess the factors comprising the non-arrhythmic mortality score in this cohort, multivariable Cox proportional regression analysis identified LVEF ≤25% (HR 1.47; 95% CI 1.01–2.16; P=0.047) as a significant factor (**Table 4**). Subsequently, we evaluated the validity of the non-arrhythmic mortality score, including the above significant factor and optimal medical therapy. Multivariable analysis revealed 3 significant predictors of non-arrhythmic death: a non-arrhythmic mortality score ≥3 (HR 1.70; 95% CI 1.01–2.88; P=0.047), SBP <100 mmHg (HR 1.84; 95% CI 1.25–2.70; P=0.002), and estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (HR 1.98; 95% CI 1.23–3.20; P=0.005; **Table 5**).

Discussion

The present study has 2 important clinical implications. First, the MBS effectively identifies Japanese CRT patients at risk for both ventricular arrhythmias and non-arrhythmic death, serving as a valuable tool in determining the necessity of defibrillator. Second, in conjunction with the MBS, the presence of LBBB emerged as an independent predictor of reduced ventricular arrhythmia risk, whereas low SBP and severe renal impairment were independently associated with increased non-arrhythmic death among

Japanese CRT patients.

Remaining Questions on CRT-D vs. CRT-P Selection

The optimal selection between CRT with or without a defibrillator, often referred to as "CRT-D or CRT-P" has been a longstanding topic of discussion within the HF management landscape. According to recent guidelines, it is strongly recommended that patients with symptomatic HF and an LVEF ≤35% undergo ICD implantation for primary prevention. Moreover, those with symptomatic HF and specific electrocardiographic criteria, such as LVEF ≤35% and prolonged QRSd, are considered candidates for CRT.[12,14,15]

Despite these well-defined recommendations, there remains a degree of uncertainty surrounding the comparative efficacy of CRT-D vs. CRT-P. This uncertainty is exemplified by the recent introduction of shared decision-making principles in the 2021 European Society of Cardiology guidelines, highlighting the need for individualized treatment approaches tailored to each patient's unique clinical profile.[14]

In 2022, the RESET-CRT trial, derived from the German National Registry, sought to address this uncertainty by investigating whether CRT-P was non-inferior to CRT-D in patients with HFrEF who were candidates for CRT.[16] That open-label randomized controlled trial aimed to demonstrate non-inferiority in terms of all-cause mortality between CRT-P and CRT-D recipients, excluding patients requiring defibrillators for secondary prevention. Throughout a median follow-up of 2.4 years, no significant differences in the cumulative incidence of all-cause death were observed between the 2 groups after adjusting for age.[16] Furthermore, a comprehensive meta-analysis incorporating data from 5 randomized controlled trials compared patients assigned to CRT to those in a control group, revealing a significant reduction in all-cause mortality and death or HF hospitalization among CRT recipients.[17] Subgroup analyses within this meta-analysis did not demonstrate any significant interaction between CRT-D and CRT-P recipients concerning all-cause mortality. In addition, a recent meta-analysis of 26 observational studies, encompassing over 100,000 CRT patients, reported a noteworthy reduction in all-cause mortality with CRT-D vs. CRT-P.[18] However, this reduction was not consistently observed across all patient subgroups, prompting further investigation into potential predictors of treatment response and outcomes.

Assessment of the MBS for Risk Stratification in CRT Patients

Only 40% of CRT patients were included in the cohort for which the MBS was designed,[5] and its applicability to CRT patients has been insufficiently validated. A single-center retrospective study from Belgium reported on the validity of the MBS in CRT patients.[19] Consistent with our findings, that study observed significant stratification of the cumulative incidence of ventricular arrhythmia and non-arrhythmic mortality based on the MBS. However, in our study, Japanese patients had a lower BMI and a lower prevalence of hypertension and ischemic etiology compared with the study cohort in Belgium, suggesting unique clinical features among Asian and Japanese patients. Despite differences in patient baseline characteristics, the applicability of the MBS remained consistent.

We investigated which factors comprising the MBS were significantly weighted in CRT patients. Younger (<75 years) age and prior NSVT emerged as significant predictors of ventricular arrhythmia. This finding aligns with a meta-analysis suggesting the benefit of defibrillators in CRT patients younger than 75 years,[18] consistent with our study results. The presence of NSVT is crucial for determining a Class 1 indication for ICD in patients with symptomatic HFrEF according to the 2019 guideline from the JCS.[12] The CHART-2 study demonstrated that Japanese HFrEF patients with NSVT had a higher incidence of fatal arrhythmic events than those without NSVT.[20]

Conversely, LVEF ≤25% was identified as a significant predictor of non-arrhythmic death. Although LVEF ≤25% is a common predictor for ventricular arrhythmia and non-arrhythmic death according to the MBS, it was not significantly associated with ventricular arrhythmia (HR 0.93; 95% CI 0.61–1.42) in our study. This suggests that lower LVEF may be more strongly linked to HF and non-cardiovascular death than to ventricular arrhythmia among CRT patients.

Increased heart rate has long been reported as a risk factor for sudden death. The association between increased heart rate and heart failure severity has been demonstrated in the BEAUTIFUL and SHIFT trials.[21,22] However, our study focused on CRT patients who were fully paced by devices, differing from the original MADIT-ICD benefit score study.[5] Consequently, heart rate >75 beats/min may not have been an independent risk factor in this context.

The rate of ischemic etiology in the present study was 23.3%, which is lower than the 38.9% reported in previous European studies.[19] This indicates that the majority of Japanese CRT patients have a non-ischemic etiology. We conducted a subgroup analysis based on ischemic and non-ischemic etiologies.

Among patients with ischemic etiology, VT/VF occurred in 1 (7.7%), 19 (26%), and 2 (33%) patients in the lowest-, intermediate-, and highest-benefit groups, respectively (P=0.447). In contrast, among patients with non-ischemic etiology, VT/VF occurred in 3 (6.4%), 49 (24%), and 12 (22%) patients in the lowest-, intermediate-, and highest-benefit groups, respectively (P=0.062). Regarding non-arrhythmic death, among patients with ischemic etiology, it was observed in 3 (23%), 22 (30%), and 1 (17%) patient in the lowest-, intermediate-, and highest-benefit groups, respectively (P=0.439). Among patients with non-ischemic etiology, non-arrhythmic death was observed in 12 (26%), 69 (34%), and 8 (15%) patients in the lowest-, intermediate-, and highest-benefit groups, respectively (P=0.047). As a result, the MADIT-ICD benefit score showed trends indicating its usefulness for risk stratification of non-arrhythmic death among patients with non-ischemic etiology. In the future, increasing the number of patients with ischemic etiology in larger cohorts could help address this issue.

Effectiveness of CRT in Patients With LBBB

Our study found that LBBB was independently associated with a nearly halved risk of ventricular arrhythmia among CRT patients. Numerous prior studies have indicated that patients exhibiting LBBB may experience greater degrees of reverse remodeling and a reduction in ventricular arrhythmias with CRT than individuals with alternative QRS morphologies.[7,23,24] For instance, in the REVERSE trial, CRT patients with reverse remodeling had a significantly lower incidence of VT/VF than those without reverse remodeling (5.6% vs. 16.3% at 2 years; HR 0.31;

P=0.001).[23] Dupont et al. also reported that QRS morphology was a more critical baseline electrocardiographic determinant of CRT response than QRSd.[24] Therefore, the presence of LBBB serves as an independent predictor of reverse remodeling and a reduction in ventricular arrhythmia among CRT patients. In cases where LVEF is likely to recover to ≥35% by CRT for LBBB patients, CRT-D may not be necessary.

In the present study, the lower-than-expected responder rate (42.7%), compared to the generally reported 70%, may be due to the relatively low prevalence of LBBB (29.5%). Non-arrhythmic mortality was high in even the highest-benefit group, compared with that in the previous European study.[19] We hypothesize that the HF deaths in the non-responder group contributed to the high rate of non-arrhythmic deaths in this study.

LBBB was present in 37.7% of patients in the highest-benefit group, 25.4% of patients in the intermediate-benefit group, and 40.7% of patients in the lowest-benefit group (P=0.021), indicating a significant difference among the 3 groups. However, as indicated in **Table 3**, both the absence of LBBB and a high MADIT-ICD VT/VF score (≥7 points) were independent predictors of VT/VF. This suggests that the absence of LBBB, combined with a high MADIT-ICD VT/VF score, is associated with an increased risk of developing VT/VF, indicating a potentially greater benefit from an ICD.

Effects of CRT on Low SBP and Renal Impairment

Low SBP is a known predictor of adverse outcomes in HF patients. However, CRT has been shown to elevate SBP after implantation. Studies, including a MADIT-CRT trial substudy, indicate that CRT-D may offer incremental benefits, particularly in patients with lower baseline SBP values.[25–27] Notably, preserved SBP at 1-year after implantation has been associated with a lower risk of HF or death compared with low SBP groups.[28]

Renal impairment significantly affects mortality in CRT patients, with each 10-unit decrement in eGFR associated with a 19% increase in all-cause mortality. Studies suggest that patients with severe renal impairment, including those on dialysis, may not derive significant survival benefits from primary prevention with defibrillators.[29–31] Although not currently factored into risk assessment tools like the MBS, considering CRT-P in cases of severe renal dysfunction among CRT candidates warrants attention.

Additional Stratification of the Intermediate-Benefit Group

The intermediate-benefit group (n=279; 69.8%) was the largest group in this cohort. As shown in **Figure 1A**, this group was defined as either having both a high VT/VF score and a high non-arrhythmic mortality score (n=240; 86.0%) or both a low VT/VF score and a low non-arrhythmic mortality score (n=39; 14.0%). This indicates that the majority of the intermediate-benefit group had higher risks of both VT/VF and non-arrhythmic death. Therefore, the cumulative incidences of the intermediate-benefit group were similar to those of the highest-benefit group for VT/VF (P=0.876) and the lowest-benefit group for non-arrhythmic death (P=0.722), resulting in no significant differences.

The study found that CRT-D is preferable for the highest-benefit group due to the high incidence of VT/VF, whereas CRT-P is preferable for the lowest-benefit group because of the high incidence of non-arrhythmic death, thereby validating the MBS in Japanese CRT patients. However, the optimal choice between CRT-D and CRT-P for the intermediate-benefit group was not addressed in the previous study,[19] and has remained unresolved. To address this, we conducted an additional subgroup analysis of the intermediate-benefit group (n=279; 69.8%).

The additional subgroup analysis revealed that the absence of LBBB was a significant predictor of VT/VF in univariable analysis (HR 0.50; 95% CI 0.25–0.98; P=0.045), but not in multivariable analysis (HR 0.54; 95% CI 0.27–1.05; P=0.070) (**Supplementary Table 3A**). Conversely, SBP <100 mmHg and eGFR <30 mL/min/1.73 m^2 were independent predictors of non-arrhythmic death (HR 1.67 [95% CI 1.07–2.61; P=0.025] and 2.19 [95% CI 1.24–3.85; P=0.007], respectively; **Supplementary Table 3B**). Based on these results, CRT-D should be considered for intermediate-benefit group patients without LBBB, whereas CRT-P implantation is recommended for those with SBP <100 mmHg or eGFR <30 mL/min/1.73 m^2.

Study Limitations

Limitations of this study include its retrospective nature and the fact that it was conducted at 2 centers in Japan with a limited patient sample. In addition, the study may have included relatively slow VT events below the detection threshold, potentially leading to an underestimation of ventricular arrhythmia events. Patient activity levels affect HF severity; however, differences in activity measurements across device manufacturers limit uniform quantitative assessment. The cohort was predominantly non-ischemic, male, and with a minority having LBBB, affecting generalizability. Moreover, the intermediate MADIT-ICD benefit group constituted a heterogeneous population. Finally, data on newer medications, such as angiotensin receptor-neprilysin inhibitors and sodium-glucose cotransporter 2 inhibitors, which affect cardiovascular outcomes,[32,33] were not available for analysis due to enrollment before 2019.

Conclusions

The MBS can identify suitable candidates for CRT-D, specifically among Japanese individuals.

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IRB Information

This study was approved by the University of Tohoku Institutional Review Board (2022-1-916).

Data Availability

The deidentified participant data from this study will not be shared.

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Supplementary Files

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