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JACC: CLINICAL ELECTROPHYSIOLOGY
VOL. 2, NO. 1, 2016

ISSN 2405-500X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacep.2015.09.009

Long-Term Prognostic Role of the Diagnostic Criteria for Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the long-term prognostic role of the 2010 task force criteria (TFC)-based scoring in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D).

BACKGROUND Categories of the 2010 TFC include the risk factors for cardiovascular mortality and sudden cardiac death in patients with ARVC/D.

METHODS Ninety patients with ARVC/D who met the definitive diagnosis of the 2010 TFC were retrospectively studied. ARVC/D risk score was calculated as the sum of major (2 points) and minor (1 point) criteria in all 6 subdivided categories of the TFC and was divided into tertile groups of scores; group A (4 to 6 points), group B (7 to 9 points), and group C (10 to 12 points). The primary endpoints were major adverse cardiovascular events: cardiovascular death, heart failure hospitalization, and sustained ventricular tachycardia or ventricular fibrillation.

RESULTS During the follow-up period of 10.2 ± 7.1 years, 19 patients died because of cardiovascular causes, 28 patients were admitted because of worsened heart failure, and 47 patients experienced sustained ventricular tachycardia or ventricular fibrillation. Patients in groups B and C were at increased risk for major adverse cardiovascular events compared with those in group A (hazard ratio [HR]: 4.80; 95% confidence interval [CI]: 1.87 to 12.33; $p = 0.001$; and HR: 6.15; 95% CI: 2.20 to 17.21; $p = 0.001$, respectively). Patients in groups B and C were at increased risk for sustained ventricular tachycardia or ventricular fibrillation compared with those in group A (HR: 6.64; 95% CI: 2.00 to 22.03; $p = 0.002$; and HR: 9.18; 95% CI: 2.60 to 32.40; $p = 0.001$, respectively).

CONCLUSIONS Our study suggests that risk scoring based on the 2010 TFC is useful to predict major adverse cardiovascular events in patients with ARVC/D. (J Am Coll Cardiol EP 2016;2:107–15) © 2016 by the American College of Cardiology Foundation.

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a cardiomyopathy characterized by ventricular arrhythmias and fibrofatty replacement of the right ventricular (RV) myocardium (1,2). ARVC/D slowly progresses to more diffuse RV and left ventricular (LV) dysfunction (2,3). In the early (concealed) phase, structural change is absent or minor, but patients may be at risk for sudden cardiac death (SCD) caused by sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) in younger patients and athletes (1–5). Life-threatening ventricular arrhythmia and SCD can constitute the initial presentation of ARVC/D (2,3). In the overt (electric) phase, patients have symptomatic ventricular arrhythmia with manifested structural abnormalities of the right and/or left ventricle (2).

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From the Department of Cardiology, Tokyo Women's Medical University, Tokyo, Japan. Dr. Shiga has received research funding from Daiichi-Sankyo and Eisai and lecture fees from Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Eisai, Sanofi, and Toa Eiyo. Dr. Hagiwara has received research funding from Boehringer Ingelheim, Bayer Healthcare, Bristol-Myers Squibb, Daiichi-Sankyo, Sanofi, and Pfizer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received September 1, 2015; accepted September 10, 2015.

ABBREVIATIONS AND ACRONYMS

ARVC/D = arrhythmogenic right ventricular cardiomyopathy/dysplasia

CI = confidence interval

ECG = electrocardiography

HF = heart failure

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

LV = left ventricular

MACE = major adverse cardiovascular event(s)

RV = right ventricular

SAECG = signal-averaged electrocardiography

SCD = sudden cardiac death

TFC = task force criteria

VF = ventricular fibrillation

VT = ventricular tachycardia

In the later phase, patients experience progressed right or biventricular heart failure (HF) with or without the presence of ventricular arrhythmia (2).

Thus, there is no single diagnostic tool for ARVC/D, and the clinical diagnosis of ARVC/D is often complex and difficult. The 1994 task force criteria (TFC) first provided the clinical diagnosis of ARVC/D on the basis of several categories, such as structure, function, histology, electrocardiography (ECG), arrhythmia, and family history (6). These criteria were modified in 2010 to improve diagnostic sensitivity by advances in the diagnostic modalities and the genetic knowledge of ARVC/D (7).

SEE PAGE 116

Several electrocardiographic and electrophysiological abnormalities and structural features of both ventricles have been reported as clinical markers of a worse prognosis in patients with ARVC/D, but the predictive value of each factor itself is not high (8). The categories of TFC also include risk factors of cardiovascular mortality and SCD in patients with ARVC/D (7,8). We hypothesized that risk scoring on the basis of the 2010 TFC for the diagnosis of ARVC/D has a role in predicting ARVC/D-specific outcomes: cardiovascular death, worsening HF, and sustained VT or VF. The aim of this study was to evaluate the long-term prognostic role of 2010 TFC-based scoring in patients with ARVC/D.

METHODS

SUBJECTS. We retrospectively studied 90 patients with ARVC/D who met the definitive diagnosis of the 2010 TFC. All patients admitted to the Department of Cardiology, Tokyo Women's Medical University Hospital, for evaluation of sustained VT or VF and/or cardiomyopathy between 1974 and 2012 and with available follow-up were included in this study. All patients underwent 12-lead ECG and echocardiography or magnetic resonance imaging or RV angiography. Eighty-one patients also underwent endomyocardial biopsy of the right ventricle. Eighty-five patients underwent signal-averaged ECG (SAECG) (Predictor BSM-32, Arrhythmia Research Technology, Fitchburg, Massachusetts), and 79 patients underwent 24-h Holter ECG.

Antiarrhythmic drugs were prescribed for ventricular and supraventricular arrhythmias. In Japan, amiodarone and sotalol were approved in 1992 and 1998, respectively, and the implantable cardioverter-defibrillator (ICD) was approved in 1996.

Available data were obtained retrospectively from the medical records of our hospital. The patients were followed until December 31, 2013. Information regarding deceased subjects was obtained from medical records, family members, their local hospitals or general practitioners, and the admitting hospital. The patients were followed until the end of the follow-up period (December 31, 2013). The protocol was approved by the Institutional Review Board of Tokyo Women's Medical University.

ARVC/D RISK SCORE. ARVC/D risk score was calculated as the sum of major and minor criteria in all 6 subdivided categories of the 2010 TFC, with major criteria given 2 points and minor criteria given 1 point. The definite diagnosis of ARVC/D according to the 2010 TFC was fulfilled by the presence of 2 major criteria, 1 major plus 2 minor criteria, or 4 minor criteria from different categories. Thus, the minimum score of the ARVC/D risk was 4, and the range of this score was between 4 and 12. The patients were divided into 3 subgroups on the basis of the ARVC/D risk score tertiles: group A (first tertile, 4 to 6 points), group B (second tertile, 7 to 9 points), and group C (third tertile, 10 to 12 points).

OUTCOMES. The primary endpoints were major adverse cardiovascular events (MACEs), a composite of cardiovascular death, hospitalization for worsened HF, and sustained VT or VF. Worsened HF was defined by signs and symptoms, such as dyspnea, rales, and ankle edema, as well as the need for treatment with diuretic agents, vasodilators, positive inotropic drugs, or an intra-aortic balloon pump. Sustained VT was defined as a rate of more than 100 beats/min or more than 30 s in duration (or less if treated by electrocardioversion within 30 s) of VT on ECG, VT that required external defibrillation, intravenous antiarrhythmic agents such as amiodarone, and ICD therapy for termination. The occurrence of these events was validated through a review of medical records by 3 investigators (N.K., D.Y., and A.S.). The details of cardiovascular death were based on the clinical history obtained from medical charts or information from other hospitals. Sudden death was defined as unexpected endogenous death within 24 h after last having been observed alive, unrelated to a specific cause of circulatory failure.

STATISTICAL ANALYSIS. Summary data are presented either as the median and range or the number of patients. Cumulative probabilities of cardiovascular death, first HF hospitalization, and first

sustained VT or VF after the diagnosis were estimated using the Kaplan-Meier method and by means of a comparison of cumulative events according to 3 groups on the basis of the ARVC/D risk score with a log-rank test. The risk for MACEs associated with each increase of 1 point in the ARVC/D risk score was assessed using a Cox proportional hazards model, with adjustment for age and sex. The proportionality assumption was checked by inspection of log-log plots. Univariate Cox regression analysis was used to estimate the relationship between each major or minor criterion of the 2010 TFC and the long-term outcomes: cardiovascular death, HF hospitalization, and sustained VT or VF. A p value <0.05 was considered to indicate statistical significance. Data analyses were performed using SPSS version 11.01 (SPSS, Inc., Chicago, Illinois).

RESULTS

PATIENT CHARACTERISTICS. The patients' baseline characteristics are shown in Table 1. The mean age of the cohort at diagnosis of ARVC/D was 44 ± 15 years, and 68 (76%) were men.

Sustained VT or VF was documented in 64 patients (71%), and 3 patients had cardiac arrest. Nine patients (10%) had family histories of definite ARVC/D, which were confirmed in first-degree relatives who met the 2010 TFC. Nonsustained or sustained VT with left bundle-branch block was the most frequent. Electrocardiographic abnormalities were observed, especially T-wave inversion in the right precordial leads (V_1 through V_3) in 47 patients (52%) and epsilon waves in 39 patients (43%). SAECG showed ventricular late potentials in 85 patients (94%). RV angiography revealed signs suggesting ARVC/D, such as RV dilation, reduction of the RV ejection fraction, and RV aneurysms, in 98% of the patients. Histological examinations were performed in 81 patients using myocardial tissue. Any abnormality of the myocardium, such as fibrofatty replacement, was observed (Table 1). At the end of the follow-up period (December 31, 2013), 16 patients (18%) were lost to follow-up because they did not visit our hospital and provided no explanation.

ARVC/D RISK SCORE AND LONG-TERM OUTCOMES. The mean ARVC/D risk score of our patients was 8 ± 2 points. The distribution of patients according to the score is shown in Figure 1. The number of patients in each group was as follows: 25 patients in group A, 49 patients in group B, and 16 patients in group C.

TABLE 1 Clinical Characteristics in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (n = 90)

Male	69 (76)
Age at diagnosis, yrs	44 ± 15
Family history of ARVC/D	9 (10)
Previous sustained VT	64 (71)
Previous VF/cardiac arrest	3 (3)
Nonsustained or sustained VT of LBBB	74 (82)
LVEF, %	52 ± 14
RVEF, %	30 ± 12
NYHA functional class at diagnosis	
I	74 (82)
II	12 (13)
III/IV	4 (4)
ECG	
Inverted T-wave in right precordial leads (V_1–V_3)	47 (52)
Epsilon wave	39 (43)
SAECG (n = 85)	
Ventricular late potential	79 (92)
Holter recording (n = 79)	
VPB (>500/24 h)	63 (93)
Right ventricular biopsy (n = 81)	
Regional myocytes <60% with fibrous replacement	40 (49)
Regional myocytes 60%–75% with fibrous replacement	41 (51)
ICD implantation	16 (18)
Catheter ablation	31 (34)
Medications	
Beta-blockers	22 (24)
ACE inhibitors/ARBs	28 (31)
Amiodarone	38 (42)
Sotalol	2 (2)
Other antiarrhythmic agents	17 (19)
Digitalis	4 (4)
Diuretic agents	13 (14)
Anticoagulation	14 (16)

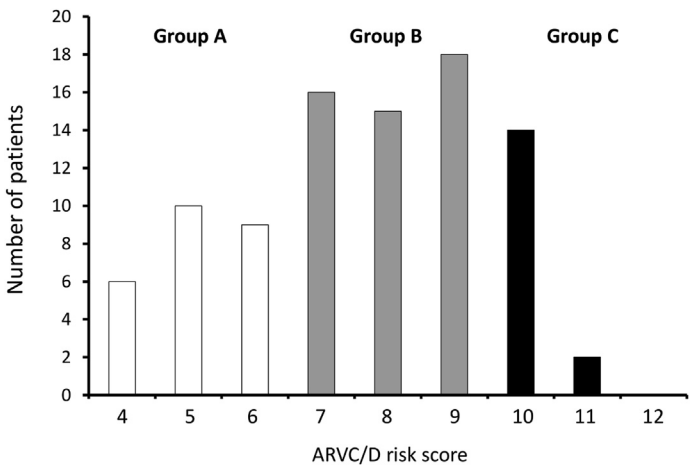
Values are n (%) or mean ± SD.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ARVC/D = arrhythmogenic right ventricular cardiomyopathy/dysplasia; ECG = electrocardiography; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RVEF = right ventricular ejection fraction; SCD = sudden cardiac death; VF = ventricular fibrillation; VPB = ventricular premature beat; VT = ventricular tachycardia.

During the follow-up period of 10.2 ± 7.1 years, 19 patients died because of cardiovascular causes, 28 patients were admitted because of worsened HF, and 47 patients experienced sustained VT or VF (Figure 2). The 19 cardiovascular deaths included HF death (n = 16) and SCD (n = 3).

The Kaplan-Meier curves for MACEs in the 3 groups are shown in Figure 3. Patients in groups B and C were at increased risk for MACEs compared with those in group A (Table 2). There was a significantly higher

FIGURE 1 Distribution of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia Risk Scores

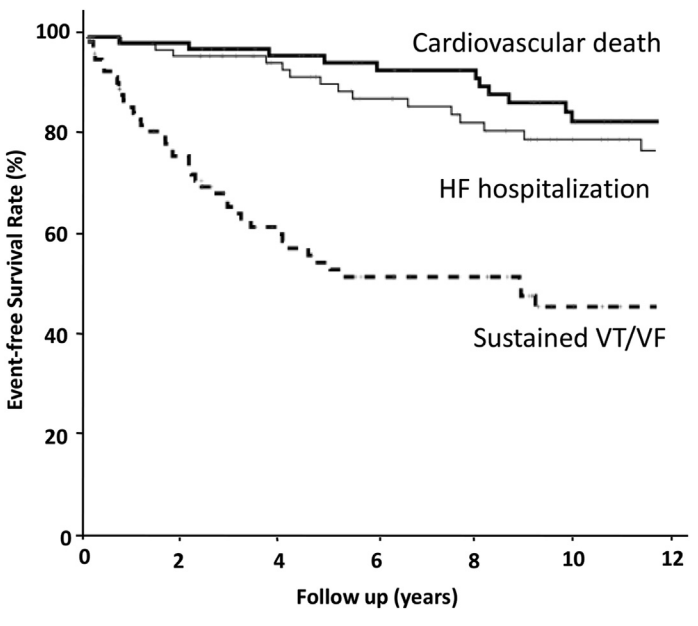


ARVC/D = arrhythmogenic right ventricular cardiomyopathy/dysplasia.

incidence of MACEs with a higher score (per 1 point; hazard ratio [HR]: 2.29; 95% confidence interval [CI]: 1.52 to 3.45; $p < 0.001$). After adjusting for age and sex, the score was associated with MACEs (per 1 point; HR: 2.29; 95% CI: 1.51 to 3.46; $p < 0.001$).

Patients in groups B and C were at increased risk for sustained VT or VF compared with those in group A. Patients in group C, but not those in group B, were also at increased risk for cardiovascular death and HF hospitalization compared with those in group A (Table 3, Figure 4).

FIGURE 2 Kaplan-Meier Analysis of Cardiovascular Death, First Heart Failure Hospitalization, and First Sustained Ventricular Tachycardia or Ventricular Fibrillation After Diagnosis in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia



HF = heart failure; VF = ventricular fibrillation; VT = ventricular tachycardia.

CATEGORIES OF TFC AND LONG-TERM OUTCOMES. Univariate analysis for each major and minor criterion in the 6 categories of MACEs and each event showed that repolarization and depolarization abnormalities were significantly related to all events. The major criteria, but not the minor criteria, of RV dysfunction (global and/or regional dysfunction and structural alterations with dilation of the RV outflow tract or severely reduced RV systolic function) and the major criteria of depolarization abnormalities (epsilon waves) were significantly related to the occurrence of sustained VT or VF, as well as the major criteria of arrhythmias (nonsustained or sustained VT with left bundle branch block with superior axis) (Table 3).

DRUG THERAPY AND LONG-TERM OUTCOMES. Our study failed to show the benefit of beta-blockers in the prevention of sustained VT or VF (HR: 1.05; 95% CI: 0.53 to 2.07; $p = 0.891$) or cardiovascular death (HR: 0.43; 95% CI: 0.10 to 1.88; $p = 0.557$). In 64 patients who had previous sustained VT, there was no difference in the first recurrence rate of sustained VT or VF between amiodarone users ($n = 31$) and non-amiodarone users ($n = 33$) (8.4% per year vs. 9.6% per year, $p = 0.457$).

DISCUSSION

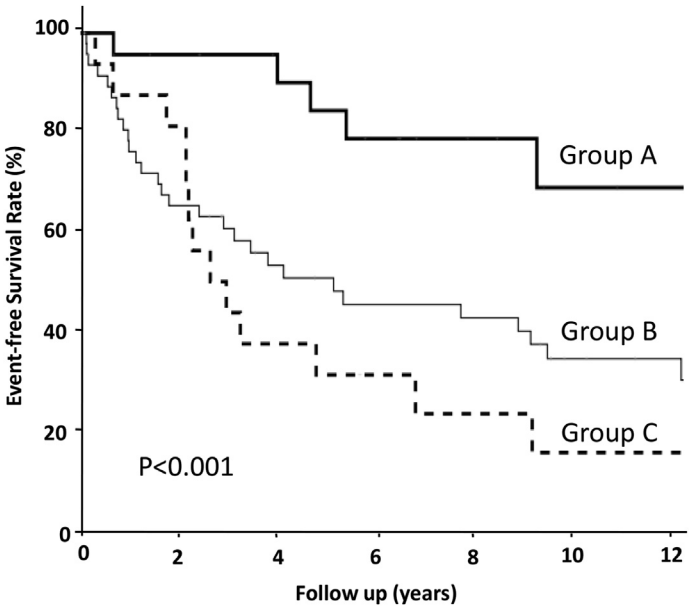
Our long-term observational study suggested that risk scoring on the basis of the 2010 TFC is useful to predict adverse events in patients with ARVC/D: 1) the categories of the TFC include the risk factors of cardiovascular mortality and SCD in patients with ARVC/D; 2) a higher incidence of MACEs was associated with a higher score; 3) higher incidences of cardiovascular death, HF hospitalization, and sustained VT or VF were associated with the highest score; and 4) electrocardiographic (repolarization and depolarization) abnormalities were related to all major events. Additionally, RV dysfunction was related to the occurrence of sustained VT or VF, and family history was related to cardiovascular death.

ARVC/D DIAGNOSTIC CRITERIA AND RISK FACTORS FOR SCD. SCD is the most common cause of death in

patients with ARVC/D (1–8). For risk stratification of SCD in patients with ARVC/D, previous reports suggested prior cardiac arrest caused by hemodynamically unstable VT and VF, a history of syncope, electrocardiographic depolarization abnormalities, such as QRS prolongation in the right precordial leads, QRS dispersion and ventricular late potential on SAECG, electrocardiographic repolarization abnormalities such as a significant extent of negative T and epsilon waves, RV dysfunction, and LV involvement (8). Most of these clinical findings overlapped the major or minor criteria in 4 of the 6 categories of the 2010 TFC for the diagnosis of ARVC/D (7). Thus, most patients who met the definitive diagnosis of ARVC/D also have the risk factors for SCD. The 2010 TFC does not include aborted SCD, hemodynamically unstable sustained VT, and syncope, which are strong predictors of SCD, because these criteria were developed only for the diagnosis of ARVC/D. In these specific patients, ICD therapy should be considered regardless of the diagnostic criteria.

ARVC/D SCORE AND RISK STRATIFICATION OF MACES. This approach can be challenging for the risk stratification of MACEs in patients with ARVC/D. There are no powerful risk factors for SCD and other cardiovascular events in patients with ARVC/D, and there is no standard diagnostic tool. However, a high score indicates multiple risk factors. In fact, our results suggested that the high-score group showed a higher incidence of MACEs. Recently, ICDs have been placed to avoid SCD in high-risk patients with ARVC/D with primary or secondary indications (9,10). Amiodarone is used as a first-line antiarrhythmic drug to suppress ventricular arrhythmia because it has superior efficacy in preventing sustained VT or VF compared with beta-blockers or sotalol (11). Therefore, the cause of death in patients who were recently diagnosed with ARVC/D may shift from SCD to death due to HF in the later phase. Our study showed that the most common cause of cardiovascular death was worsened HF. Risk factors of death in patients with ARVC/D will change in the future if the strategies for the prevention and treatment of SCD are recognized.

FIGURE 3 Kaplan-Meier Analysis of Major Adverse Cardiovascular Events According to the 3 Groups on the Basis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia Risk Score



Although the RV abnormalities were not significantly related to HF hospitalization and cardiovascular death, other markers, including parameters that show RV and/or LV failure, are risk factors of cardiovascular death.

CATEGORIES AND LONG-TERM OUTCOMES. Our findings show that the ARVC/D score is an effective predictor of adverse events, including ventricular arrhythmia, HF, and cardiovascular mortality. Although more than one-half of the patients did not undergo magnetic resonance imaging, because our study included historical cases, most patients underwent RV angiography. In our study, the majority of patients met the major criteria of RV dysfunction. They had severely reduced RV systolic function, and this criterion was a significant factor for the occurrence of sustained VT or VF. Hulot et al. (12)

TABLE 2 Groups According to Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia Risk Score and Long-Term Outcomes

	MACEs		Cardiovascular Death		HF Hospitalization		Sustained VT/VF	
Group	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
A (4–6 points) (n = 25)	1.00 (reference)		1.00 (reference)		1.00 (references)		1.00 (references)	
B (7–9 points) (n = 49)	4.80 (1.87–12.33)	0.001	3.45 (0.44–27.37)	0.240	7.24 (0.97–54.38)	0.054	6.64 (2.00–22.03)	0.002
C (10–12 points) (n = 16)	6.15 (2.20–17.21)	0.001	8.10 (1.01–65.02)	0.049	10.91 (1.38–86.61)	0.024	9.18 (2.60–32.40)	0.001

CI = confidence interval; HF = heart failure; HR = hazard ratio; MACE = major adverse cardiac event; other abbreviations as in Table 1.

TABLE 3 The 2010 Task Force Criteria and Long-Term Outcomes

	MACEs		Cardiovascular Death		HF Hospitalization		Sustained VT/VF	
Criteria	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
RV systolic function and structure								
Major (n = 71)	4.79 (1.73–13.28)	0.003	26.80 (0.09–8094)	0.259	5.10 (0.69–37.73)	0.111	5.12 (1.59–16.48)	0.006
Minor (n = 17)	0.26 (0.09–0.72)	0.010	0.04 (0.00–17.44)	0.275	0.24 (0.03–1.75)	0.157	0.24 (0.07–0.77)	0.017
Tissue characterization								
Major (n = 40)	0.75 (0.42–1.33)	0.325	0.44 (0.15–1.25)	0.122	0.59 (0.27–1.29)	0.187	0.91 (0.49–1.67)	0.760
Minor (n = 41)	1.33 (0.75–2.36)	0.325	2.29 (0.80–6.53)	0.122	1.69 (0.78–3.69)	0.187	1.10 (0.60–2.02)	0.760
Repolarization abnormalities								
Major (n = 47)	1.02 (0.50–2.08)	0.966	1.31 (0.37–4.58)	0.676	2.31 (0.93–5.77)	0.072	0.78 (0.33–1.84)	0.565
Minor (n = 14)	2.10 (1.35–4.29)	0.003	3.18 (1.05–9.65)	0.041	1.96 (0.87–4.41)	0.104	2.72 (1.42–5.20)	0.002
Depolarization abnormalities								
Major (n = 39)	1.71 (0.99–2.95)	0.054	1.67 (0.67–4.18)	0.270	2.56 (1.17–5.61)	0.019	1.86 (1.03–3.34)	0.039
Minor (n = 79)	1.93 (0.47–8.00)	0.364	22.00 (0.00–54104)	0.604	0.95 (0.12–7.24)	0.957	1.66 (0.40–6.93)	0.484
Arrhythmias								
Major (n = 74)	1.55 (0.66–3.65)	0.315	0.84 (0.19–3.70)	0.816	0.43 (0.14–1.30)	0.134	3.29 (1.02–10.61)	0.046
Minor (n = 63)	1.43 (0.66–3.09)	0.366	1.01 (0.28–3.67)	0.989	0.74 (0.28–1.91)	0.529	1.84 (0.71–4.76)	0.210
Family history								
Major (n = 8)	0.87 (0.12–6.33)	0.887	0.05 (0.00–11266)	0.734	3.35 (0.44–25.40)	0.242	0.05 (0.00–445.0)	0.514
Minor (n = 1)	1.59 (0.63–4.00)	0.330	1.53 (0.35–6.66)	0.572	2.17 (0.74–6.31)	0.157	1.02 (0.32–3.30)	0.972

RV = right ventricular; other abbreviations as in Tables 1 and 2.

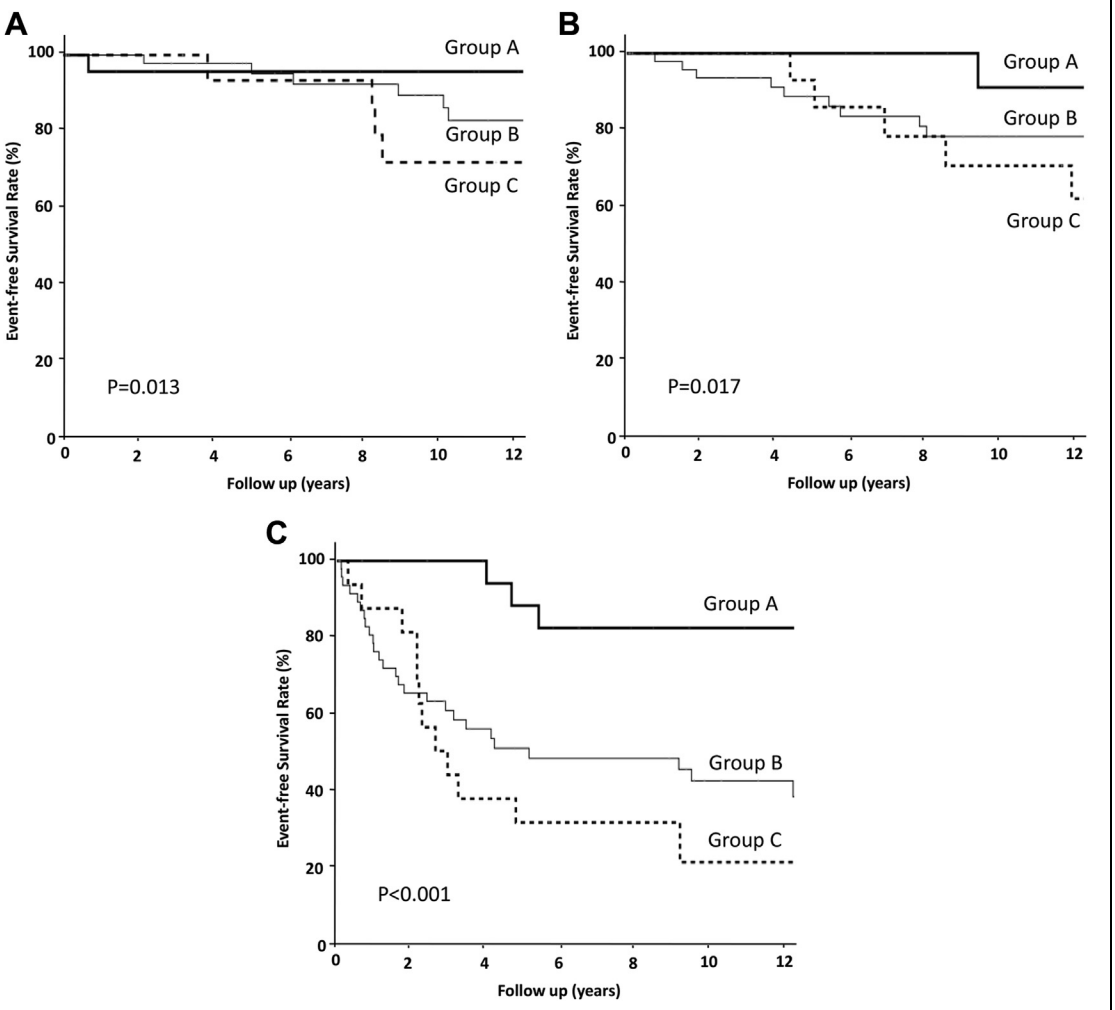
reported that clinical signs of RV and LV dysfunction were associated with cardiovascular death. Other studies reported that RV dysfunction is associated with VT or VF and SCD (13–15). Because RV dysfunction is related to the presence of late potentials (13), it may show the presence of the arrhythmogenic substrate of the right ventricle. However, RV dysfunction as a category of the 2010 TFC for the diagnosis of ARVC/D did not include RV dilation or hemodynamic state. Meanwhile, the minor criterion of RV dysfunction was a negative factor for the occurrence of sustained VT or VF. Minor structural abnormalities, such as mild segmental dilation of the right ventricle or regional RV hypokinesis, might contribute less to the development or recurrence of sustained VT, and the small number of patients who met this criterion (n = 17) might have influenced this result.

Electrocardiographic repolarization abnormalities have 2 meanings: the extent of the RV scar and the arrhythmogenic substrate of the right ventricle, which lead to the occurrence of arrhythmia (13,16–18). The former may be related to the hemodynamic state of the right ventricle as well as the presence of the arrhythmogenesis. T-wave inversion in leads V_1, V_2, and V_3 and beyond in patients >14 years of age as a major criterion is reasonable for the diagnosis of ARVC/D, especially in the early stage (19). Previous reports showed that the extent of T-wave inversion is related to RV enlargement and the progressed stage (1,20,21). However, it is not clear whether major or minor criteria for repolarization abnormalities as a diagnostic tool on the basis of the extent of T-wave inversion and the presence or absence of complete right bundle-branch block indicate the degree of arrhythmogenesis.

Late potentials on SAECG (minor criteria of depolarization abnormalities) have diagnostic value for ARVC/D, but there is no evidence of their predictive value for arrhythmic events (8,22–24). The epsilon wave is a potential electrocardiographic feature of ARVC/D that indicates delayed RV activation, but it is not common (3,17,20,25–28). It appears in patients with diffuse RV involvement, but not in the early phase (27,28). In our study, the presence of an epsilon wave, but not a late potential on SAECG, was significantly associated with the occurrence of VT or VF and HF hospitalization. However, its prognostic value remains unclear (12,28).

DRUG THERAPY AND LONG-TERM OUTCOMES. Beta-blocker therapy to prevent the occurrence of sustained VT or VF and delay disease progression in patients with ARVC/D is controversial. Our retrospective analysis failed to show the clear benefit of beta-blockers in the prevention of sustained VT or

FIGURE 4 **Kaplan-Meier Analysis of Cardiovascular Death, Heart Failure Hospitalization, and Sustained Ventricular Tachycardia or Ventricular Fibrillation According to the 3 Groups on the Basis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia Risk Score**



(A) Cardiovascular death; **(B)** HF hospitalization; **(C)** sustained VT or VF. HF = heart failure; VF = ventricular fibrillation; VT = ventricular tachycardia.

VF or cardiovascular death. The role of antiarrhythmic drugs, such as sotalol or amiodarone, is considered to prevent the recurrence of VT in low- or intermediate-risk patients and reduce VT-required ICD therapy in high-risk patients (11,29). One-half of our patients received amiodarone therapy, and the others received class I antiarrhythmic drugs or sotalol. We could not prove the benefit of amiodarone to prevent the first recurrence of sustained VT in patients with sustained VT. However, these results could not counteract the effect of these drugs in the prevention of worsening of arrhythmia or disease progression, because this study was retrospective and small in size, and the backgrounds of these compared patients were not identical. Further evaluation will be required to confirm this issue.

STUDY LIMITATIONS. First, it was a retrospective, observational study at a single center. Some patients were lost to follow-up. Data concerning clinical condition at the time of MACEs were not available. In addition, there was a treatment bias.

Second, we could not assess the patients with ARVC/D whose first presentation of the disease was with SCD. In the early stage of ARVC/D, the diagnosis may be challenging (2).

Third, we used the parameters at the diagnosis of ARVC/D as the ARVC/D risk scoring. In this study, the time-dependent changes in markers, such as ECG and

the structures of the right and left ventricles, were not evaluated.

Fourth, the outcome assessment of each criterion in the 6 categories was limited by the small number of patients in our study.

Fifth, this study included patients from a single referral hospital who were enrolled over a long sampling period. The treatments that were administered were not controlled for during this long sampling period and may thus have influenced the outcome and prognoses of these patients. Moreover, the treatment strategies used for each patient were changed during the follow-up period. The potential confounding factors associated with time and era could not be completely excluded.

CONCLUSIONS

Our long-term observational study suggested that risk scoring on the basis of the 2010 TFC for diagnosis is useful to predict MACEs in patients with ARVC/D.

ACKNOWLEDGMENTS The authors thank Dr. Naoki Serizawa, Dr. Yuichiro Minami, Dr. Koichiro Ejima, Dr. Tsuyoshi Suzuki, Dr. Kenta Uto, Dr. Junichi Yamaguchi, Dr. Kyomi Ashihara, Dr. Noritoshi Fukushima, and Prof. Morio Shoda for their support and helpful suggestions.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: MACEs in patients with ARVC/D include cardiovascular death and worsened HF, as well as sustained VT or VF, which may lead to SCD.

COMPETENCY IN MEDICAL KNOWLEDGE 2: Risk scoring on the basis of the 2010 TFC for diagnosis is useful to predict MACEs in patients with ARVC/D.

TRANSLATIONAL OUTLOOK: Additional studies are needed to develop the risk stratification and management of cardiovascular death and worsening HF for patients with ARVC/D in the ICD era.

REFERENCES

1. Marcus FI, Fontaine GH, Guiraudon G, et al. Right ventricular dysplasia: a report of 24 adult cases. Circulation 1982;65:384–98.

2. Basso C, Corrado D, Marcus FI, et al. Arrhythmogenic right ventricular cardiomyopathy. Lancet 2009;373:1289–300.

3. Corrado D, Basso C, Thiene G, et al. Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study. J Am Coll Cardiol 1997;30:1512–20.

4. Thiene G, Nava A, Corrado D, et al. Right ventricular cardiomyopathy and sudden death in young people. N Engl J Med 1988;318:129–33.

5. Corrado D, Thiene G, Nava A, et al. Sudden death in young competitive athletes: clinicopathologic correlations in 22 cases. Am J Med 1990;89:588–96.

6. McKenna WJ, Thiene G, Nava A, et al., on behalf of the Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. Diagnosis of arrhythmogenic right ventricular dysplasia cardiomyopathy. Br Heart J 1994;71:215–8.

7. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation 2010;121:1533–41.

8. Zorzi A, Corrado D. Risk stratification and prognosis. In: Brunckhorst C, Duru F, editors. Current Concepts in Arrhythmogenic Right Ventricular Cardiomyopathy Cardiomyopathy/Dysplasia. Minneapolis, MN: Cardiotext Publishing, 2014:105–16.

9. Corrado D, Leoni L, Link MS, et al. Implantable cardioverter-defibrillator therapy for prevention of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. Circulation 2003;108:3084–91.

10. Corrado D, Calkins H, Link MS, et al. Prophylactic implantable defibrillator in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and no prior ventricular fibrillation or sustained ventricular tachycardia. Circulation 2010;122:1144–52.

11. Marcus GM, Glidden DV, Polonsky B, et al., for the Multidisciplinary Study of Right Ventricular Dysplasia Investigators. Efficacy of antiarrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: a report from the North American ARVC Registry. J Am Coll Cardiol 2009;54:609–15.

12. Hulot JS, Jouven X, Empana JP, et al. Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circulation 2004;110:1879–84.

13. Turrini P, Angelini A, Thiene G, et al. Late potentials and ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy. Am J Cardiol 1999;83:1214–9.

14. Wichter T, Paul M, Wollmann C, et al. Implantable cardioverter/defibrillator therapy in arrhythmogenic right ventricular cardiomyopathy: single-center experience of long-term follow-up and complications in 60 patients. Circulation 2004;109:1503–8.

15. Roguin A, Bomma CS, Nasir K, et al. Implantable cardioverter-defibrillators in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. J Am Coll Cardiol 2004;43:1843–52.

16. Zorzi A, Migliore F, Elmaghawry M, et al. Electrocardiographic predictors of electroanatomic scar size in arrhythmogenic right ventricular cardiomyopathy: implications for arrhythmic risk stratification. J Cardiovasc Electrophysiol 2013;24:1321–7.

17. te Riele AS, James CA, Bhonsale A, et al. Malignant arrhythmogenic right ventricular dysplasia/cardiomyopathy with a normal 12-lead electrocardiogram: a rare but underrecognized clinical entity. Heart Rhythm 2013;10:1484–91.

18. Bhonsale A, James CA, Tichnell C, et al. Risk stratification in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. Circ Arrhythm Electrophysiol 2013;6:569–78.

19. Marcus FI. Prevalence of T-wave inversion beyond V1 in young normal individuals and

usefulness for the diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia. Am J Cardiol 2005;95:1070–1.

20. Marcus FI, Zareba W. The electrocardiogram in right ventricular cardiomyopathy/dysplasia. How can the electrocardiogram assist in understanding the pathologic and functional changes of the heart in this disease? J Electrocardiol 2009;42:136.e1–5.

21. Nava A, Canciani B, Buja G, et al. Electrovectorcardiographic study of negative T waves on precordial leads in arrhythmogenic right ventricular dysplasia: relationship with right ventricular volumes. J Electrocardiol 1988;21:239–45.

22. Blomström-Lundqvist C, Hirsch I, Olsson SB, et al. Quantitative analysis of the signal-averaged QRS in patients with arrhythmogenic right ventricular dysplasia. Eur Heart J 1988;9:301–12.

23. Leclercq JF, Coumel P. Late potentials in arrhythmogenic right ventricular dysplasia. Prevalence, diagnostic and prognostic values. Eur Heart J 1993;14 Suppl E:80–3.

24. Nava A, Folino AF, Bauce B, et al. Signal-averaged electrocardiogram in patients with arrhythmogenic right ventricular cardiomyopathy and ventricular arrhythmias. Eur Heart J 2000;21:58–65.

25. Saguner AM, Ganahl S, Kraus A, et al. Electrocardiographic features of disease progression in arrhythmogenic right ventricular cardiomyopathy/dysplasia. BMC Cardiovasc Disord 2015;15:4.

26. Nasir K, Bomma C, Tandri H, et al. Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity: a need to broaden diagnostic criteria. Circulation 2004;110:1527–34.

27. Steriotis AK, Bauce B, Daliento L, et al. Electrocardiographic pattern in arrhythmogenic right ventricular cardiomyopathy. Am J Cardiol 2009;103:1302–8.

28. Lemola K, Brunckhorst C, Helfenstein U, et al. Predictors of adverse outcome in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy: long term experience of a tertiary care centre. Heart 2005;91:1167–72.

29. Wichter T, Paul TM, Eckardt L, et al. Arrhythmogenic right ventricular cardiomyopathy. Antiarrhythmic drugs, catheter ablation, or ICD? Herz 2005;30:91–101.

KEY WORDS **arrhythmia, arrhythmogenic right ventricular cardiomyopathy/dysplasia, diagnosis, heart failure, prognosis, risk stratification**