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# Yield of Serial Evaluation in At-Risk Family Members of Patients With ARVD/C

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## ABSTRACT

**BACKGROUND** Incomplete penetrance and variable expressivity of arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) complicate family screening.

**OBJECTIVES** The objective of the present study was to determine the optimal approach to longitudinal follow-up regarding: 1) screening interval; and 2) testing strategy in at-risk relatives of ARVD/C patients.

**METHODS** We included 117 relatives (45% male, age 33.3 ± 16.3 years) from 64 families who were at risk of developing ARVD/C by virtue of their familial predisposition (72% mutation carriers [92% plakophilin-2]; 28% first-degree relatives of a mutation-negative proband). Subjects were evaluated by electrocardiography (ECG), Holter monitoring, signal-averaged ECG, and cardiac magnetic resonance (CMR). Disease progression was defined as the development of a new criterion by the 2010 Task Force Criteria (not the "Hamid criteria") at last follow-up that was absent at enrollment.

**RESULTS** At first evaluation, 43 subjects (37%) fulfilled an ARVD/C diagnosis according to the 2010 Task Force Criteria. Among the remaining 74 subjects (63%), 11 of 37 (30%) with complete re-evaluation experienced disease progression during 4.1 ± 2.3 years of follow-up. Electrical progression (n = 10 [27%], including by ECG [14%], Holter monitoring [11%], or signal-averaged ECG [14%]) was more frequently observed than structural progression (n = 1 [3%] on CMR). All 5 patients (14%) with clinical ARVD/C diagnosis at last follow-up had an abnormal ECG or Holter monitor recording, and the only patient with an abnormal CMR already had an abnormal ECG at enrollment.

**CONCLUSIONS** Over a mean follow-up of 4 years, our study showed that: 1) almost one-third of at-risk relatives have electrical progression; 2) structural progression is rare; and 3) electrical abnormalities precede detectable structural changes. This information could be valuable in determining family screening protocols. (J Am Coll Cardiol 2014;64:293–301) © 2014 by the American College of Cardiology Foundation.

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is an inherited cardiomyopathy characterized by a high incidence of ventricular arrhythmias and an increased risk of sudden cardiac death (1,2). The genetic era has significantly improved our understanding of heritability in ARVD/C, and a familial basis of the disease is now well established (3,4). Once the diagnosis of

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**ABBREVIATIONS AND ACRONYMS**

**ARVD/C** = arrhythmogenic right ventricular dysplasia/cardiomyopathy

**CI** = confidence interval

**CMR** = cardiac magnetic resonance

**ECG** = 12-lead electrocardiography

**ICD** = implantable cardioverter-defibrillator

**IQR** = interquartile range

**RV** = right ventricle/ventricular

**SAECG** = signal-averaged electrocardiography

**TFC** = Task Force Criteria

**VT** = ventricular tachycardia

ARVD/C is made in an index patient with positive gene identification, guidelines exist on the optimal testing strategy to diagnose ARVD/C in first-degree relatives (5,6).

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However, in our experience, only a subgroup of at-risk family members meet diagnostic Task Force Criteria (TFC) for ARVD/C at the time of their initial evaluation; the majority have minor electrocardiographic (ECG) criteria or reveal no additional criteria other than the positive family history (7). Although guidelines exist on how to evaluate at-risk family members at an initial visit, both the optimal longitudinal screening strategy and the timing of subsequent evaluations to monitor development of ARVD/C criteria are unknown. Periodic reassessment with ECG recording, Holter monitoring, and echocardiography/cardiac magnetic resonance (CMR) imaging is performed by many referral centers, including ours, but objective evidence to support this approach is lacking. The burden on clinical resources is significant, as is the psychosocial impact on patients and their families (8). As such, there is an enormous need for objective data on the impact of serial screening on both the development of ARVD/C criteria and clinical outcome in these at-risk people. The purpose of our study was to examine the utility of serial noninvasive follow-up evaluation in individuals at risk of developing ARVD/C.

## METHODS

**STUDY POPULATION.** The study population was recruited from the Johns Hopkins ARVD/C registry (9). For the purpose of this study, we identified all families in which the proband fulfilled 2010 diagnostic TFC for ARVD/C (6) and had undergone comprehensive genetic testing for an ARVD/C-associated mutation in 5 desmosomal genes. 1) Among families with a mutation-positive proband, we included all relatives who were genotyped and found to carry the same mutation as the proband. Nongenotyped and mutation-negative relatives were excluded. 2) Among families with a mutation-negative proband, we included all first-degree relatives of the proband. According to clinical practice and genetics guidelines (5), genetic testing is not recommended in relatives of a mutation-negative proband, although a genetic cause of ARVD/C cannot be ruled out. Therefore, we only included first-degree relatives of a mutation-negative proband.

This yielded a total of 239 relatives from 107 families who were regarded as being at risk of developing ARVD/C. Among these subjects, 117 subjects underwent at least 1 full evaluation that included 12-lead ECG and CMR with the images available for analysis. Therefore, the study population comprised 117 relatives from 64 families who were regarded as being at risk of developing ARVD/C and who underwent full evaluation with the studies available for analysis. A patient flowchart is shown in **Figure 1**. The majority of subjects were at risk by virtue of the presence of an ARVD/C-associated pathogenic mutation (n = 84; 92% plakophilin-2; Online Table 1); the remainder were first-degree relatives of a mutation-negative ARVD/C proband (n = 33). All patients provided written informed consent. The Johns Hopkins School of Medicine Institutional Review Board approved the study.

**CLINICAL CHARACTERIZATION.** The 2010 TFC were used for clinical characterization of family members (6) and not the criteria proposed by Hamid et al. (7). Patients were evaluated as described previously (10). All 117 subjects underwent routine 12-lead ECG (recorded at rest; 10 mm/mV at paper speed 25 mm/s), which was evaluated for repolarization (precordial T-wave inversion in $V_1$ to $V_2$ or beyond) or depolarization (epsilon waves or terminal activation duration ≥55 ms) criteria for ARVD/C (6). No subject was taking antiarrhythmic or other medications known to affect the QRS complex at the time of ECG acquisition. In addition, 24-h Holter monitoring was evaluated for premature ventricular complex count, which according to the 2010 TFC was regarded as abnormal if >500 premature ventricular complexes were recorded (6). Exercise stress testing and loop recordings were evaluated for evidence of (non)sustained ventricular tachycardia (VT). Signal-averaged ECG (SAECG) recordings, obtained by time-domain analysis with a band-pass filter of 40 Hz, were evaluated for evidence of late potentials. SAECG was regarded as abnormal if 1 of 3 parameters showed evidence of late potentials, as stated in the 2010 TFC (6).

CMR examinations for all 117 subjects were performed according to standard protocols for ARVD/C, which have been described previously in detail (11,12). All CMRs were acquired on a 1.5T scanner with a phased-array cardiac coil during repeated end-expiratory breath holds. ECG-gated cine images, fast spin-echo images, and contrast-enhanced images after administration of a gadolinium chelate were acquired in both axial and short-axis planes covering the entire right ventricle (RV) and left ventricle. Global ventricular volumes and function were

calculated from the short-axis cine images with the software program QMASS (Medis, Leiden, the Netherlands). Three experienced CMR physicians blinded to all other patient information performed the CMR image analysis. CMR studies were analyzed for fulfillment of diagnostic criteria for ARVD/C according to the revised 2010 TFC (6).

**FOLLOW-UP AND OUTCOME MEASURES.** This study's primary outcome was the diagnosis of ARVD/C according to the revised 2010 TFC (6), and not according to the criteria as described by Hamid et al. (7). Because all subjects were either an ARVD/C-associated pathogenic mutation carrier or a first-degree relative of a mutation-negative ARVD/C proband, they all received a major criterion for family history. Therefore, an additional 2 minor criteria or 1 major criterion sufficed for meeting diagnostic criteria for ARVD/C. In addition, we describe fulfillment of the criteria for familial ARVD/C as previously described by Hamid et al. (7) in the Online Appendix (Online Tables 2 and 3). As a secondary outcome, we ascertained the occurrence of a life-threatening ventricular arrhythmia, which was a composite measure of the occurrence of spontaneous sustained VT, aborted sudden cardiac death, sudden cardiac death, or appropriate implantable cardioverter-defibrillator (ICD) intervention for a ventricular arrhythmia, as described previously (10).

**STATISTICAL ANALYSIS.** All continuous data are presented as mean ± SD or median (interquartile range [IQR]) and categorical variables as numbers (percentages). Continuous variables were compared between 2 groups with the independent Student *t* test or Mann-Whitney *U* test; comparisons between 3 groups were performed with analysis of variance or Kruskal-Wallis test. Categorical data were compared with the chi-square test or Fisher exact test where appropriate. To evaluate differences between baseline and last follow-up for continuous variables, paired Student *t* tests were used. For categorical variables, the proportion of disease progression (i.e., 2010 TFC fulfillment) was estimated with the Clopper-Pearson 95% confidence interval (CI). The freedom from disease progression (i.e., 2010 TFC fulfillment) was evaluated by Kaplan-Meier analysis. A p value of $<0.05$ was considered significant. Statistical calculations were performed with SPSS version 21.0 (IBM, Chicago, Illinois).

## RESULTS

**STUDY POPULATION.** The study population comprised 117 relatives from 64 families who were at risk of developing ARVD/C. Characteristics of the study participants are shown in Table 1. Mean age at first evaluation was 33.3 ± 16.3 years, and 53 patients (45%) were men. The majority (n = 72 [61%]) of subjects were asymptomatic at presentation; the remainder (n = 45 [39%]) had a history of syncope, presyncope, or palpitations.

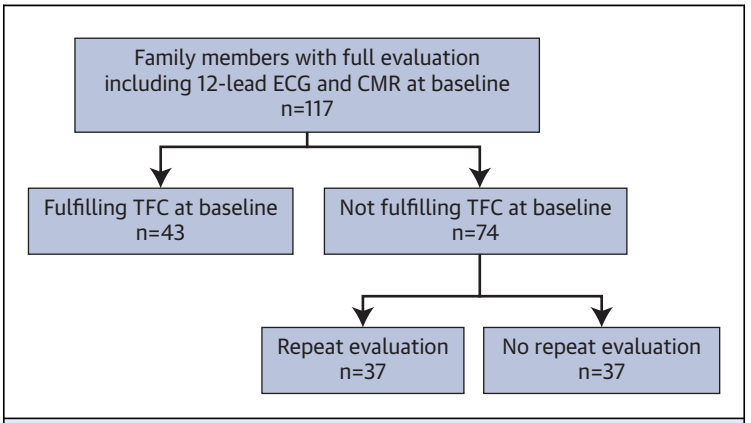



**FIGURE 1 Patient Flowchart**

Determination of the study population. CMR = cardiac magnetic resonance; ECG = electrocardiogram; TFC = Task Force Criteria.

**DEFINITE ARVD/C DIAGNOSIS AT ENROLLMENT.** Results for baseline clinical evaluation are shown in Table 1. At first evaluation, 43 subjects (37%) were diagnosed with ARVD/C according to the 2010 TFC. Mean age of these patients was 36.0 ± 14.3 years, and 15 (35%) were male (Table 1). Patients with definite ARVD/C were more often symptomatic than subjects without ARVD/C diagnosis (26 [61%] vs. 19 [26%]; $p < 0.001$). All 43 patients with definite ARVD/C had electrical abnormalities on ECG, Holter monitor, or SAECG (Table 1). Structural changes on CMR were observed in 21 subjects (49%).

**NO ARVD/C DIAGNOSIS AT ENROLLMENT. Baseline evaluation.** Overall, 74 subjects (63%) did not have an ARVD/C diagnosis according to the 2010 TFC at first evaluation. These patients were 31.7 ± 17.3 years of age at time of first evaluation, and 38 (51%) were male. At enrollment, 31 (42%) of these subjects had minor electrical abnormalities on ECG, Holter monitoring, or SAECG; none met TFC on CMR (Table 1).

**Disease progression.** Patients without ARVD/C diagnosis were followed for a mean period of 4.1 ± 2.3 years. Disease progression was defined as the development of a new ECG, Holter monitoring, SAECG, or CMR TFC according to the 2010 TFC at last follow-up that was absent at enrollment. Among 37 subjects with a complete re-evaluation, 28 (76%) were mutation carriers.

**TABLE 1 Baseline Characteristics of Family Members**

| | | No ARVD/C | | ARVD/C | |
|---|---|---|---|---|---|
| | Overall (n = 117) | Completely Normal Evaluation (n = 40) | Borderline/Suspected ARVD/C* (n = 34) | Definite ARVD/C Diagnosis* (n = 43) | p Value† |
| Age at enrollment (yrs) | 33.3 ± 16.3 | 28.5 ± 16.9 | 35.5 ± 17.2 | 36.0 ± 14.3 | 0.038 |
| Male | 53 (45) | 17 (43) | 21 (62) | 15 (35) | NS |
| Mutation carrier | 84 (72) | 27 (68) | 24 (71) | 33 (77) | NS |
| Symptomatic | 45 (39) | 9 (23) | 10 (29) | 26 (61) | 0.001 |
| Palpitations | 36 (31) | 9 (23) | 9 (27) | 18 (42) | NS |
| Syncope | 11 (9) | 4 (10) | 0 (0) | 7 (16) | NS |
| Pre-syncope | 15 (13) | 4 (10) | 3 (9) | 8 (19) | NS |
| ECG, Holter monitor, or SAECG fulfilling TFC | 74 (63) | 0 (0) | 31 (91) | 43 (100) | NS |
| ECG fulfilling TFC | 46 (39) | 0 (0) | 11 (32) | 35 (81) | <0.001 |
| T-wave inversion $V_1$ to $V_3$ | 24 (21) | 0 (0) | 0 (0) | 24 (56) | <0.001 |
| T-wave inversion $V_1$ and $V_2$ | 11 (9) | 0 (0) | 4 (12) | 7 (16) | 0.034 |
| T-wave inversion $V_4$ to $V_6$ | 4 (3) | 0 (0) | 1 (3) | 3 (7) | NS |
| T-wave inversion $V_1$ to $V_4$ in presence of CRBBB | 1 (1) | 0 (0) | 0 (0) | 1 (2) | NS |
| Epsilon wave | 1 (1) | 0 (0) | 0 (0) | 1 (2) | NS |
| Prolonged TAD | 8 (7) | 0 (0) | 6 (18) | 2 (5) | 0.009 |
| Holter monitoring fulfilling TFC‡ | 19/91 (16) | 0/26 (0) | 2/30 (7) | 17/35 (49) | <0.001 |
| PVC count | 10 (1–267) | 2 (0–10) | 2 (0–46) | 462 (39–2,558) | <0.001 |
| SAECG fulfilling TFC§ | 40/86 (74) | 0/29 (0) | 23/32 (72) | 17/25 (68) | <0.001 |
| CMR fulfilling TFC | 21 (18) | 0 (0) | 0 (0) | 21 (49) | <0.001 |
| RV wall motion abnormalities | 31 (27) | 1 (3) | 4 (12) | 26 (61) | <0.001 |
| RV EDV/BSA (ml/m$^2$) | 81.2 ± 25.8 | 70.7 ± 12.6 | 81.7 ± 21.1 | 95.0 ± 26.1 | <0.001 |
| RVEF (%) | 51.1 ± 8.3 | 54.6 ± 7.1 | 52.4 ± 6.5 | 47.2 ± 9.0 | 0.004 |
| LVEF (%) | 57.7 ± 6.5 | 59.0 ± 6.8 | 58.2 ± 5.7 | 56.0 ± 6.6 | NS |

Values are mean ± SD, n (%), median (interquartile range), or n/N (%). *Borderline/suspected ARVD/C defined as 3 TFC points; definite ARVD/C defined as ≥4 TFC points. The 2010 revised TFC were used for diagnostic categorization, and not the Hamid criteria. †p value constitutes comparison of all 3 groups. ‡Holter monitoring fulfilled TFC when >500 PVCs/24 h. §SAECG fulfilled TFC when at least 1 of 3 parameters was abnormal.

ARVD/C = arrhythmogenic right ventricular dysplasia/cardiomyopathy; BSA = body surface area; CMR = cardiac magnetic resonance; CRBBB = complete right bundle branch block; ECG = electrocardiogram; EDV = end-diastolic volume; IQR = interquartile range; LVEF = left ventricular ejection fraction; NS = not significant; PVC = premature ventricular complex; RV = right ventricular; RVEF = right ventricular ejection fraction; SAECG = signal-averaged electrocardiogram; TAD = terminal activation duration; TFC = Task Force Criteria.

Eleven subjects (30%) showed evidence of disease progression (**Fig. 2**). Five (45%) of these subjects were men, with a mean age of 29.3 ± 16.0 years (median, 22.0 years; IQR: 15.0 to 42.5 years) at time of first evaluation. The vast majority of these patients (10 of 11 [91%]) showed evidence of electrical progression on ECG, Holter monitor, or SAECG. Electrical progression was frequently observed on ECG (n = 5 [14%, 95% CI: 5% to 29%]). Holter monitoring progression was observed in 3 of 27 subjects (11%; 95% CI: 2% to 29%). SAECG showed evidence of late potentials in 3 of 22 subjects (14%; 95% CI: 3% to 35%). In addition to the 10 patients with progression on ECG, Holter monitoring, or SAECG, 1 patient (3%) had a run of nonsustained VT of left bundle branch block superior axis morphology on exercise testing, thereby fulfilling a major arrhythmia TFC that was absent at enrollment. None of the tests that were abnormal at baseline reverted to normal during follow-up (Online Fig. 1). A graphic representation of disease progression is shown in **Figure 3**.

Online Figure 2 and Online Table 4 show the prevalence of CMR findings in 37 subjects with serial structural evaluation. One patient had structural progression and fulfilled a minor 2010 TFC for CMR at last follow-up. This patient, who also had nonsustained VT during exercise testing, already had an abnormal ECG with T-wave inversions in $V_1$ and $V_3$ (not $V_2$) both at enrollment and at last follow-up. Her baseline CMR showed RV dyskinesia with borderline RV end-diastolic volume of 88.3 ml/m$^2$ and an RV ejection fraction of 50%, which increased to an RV end-diastolic volume of 93.5 ml/m$^2$ and RV ejection fraction of 45% at last follow-up, thereby fulfilling a minor CMR TFC according to the 2010 TFC. In the overall group, RV and left ventricular volumes and function did not change significantly during follow-up (Online Fig. 2).

**Outcome.** Five subjects (14%) with an initially normal clinical evaluation were diagnosed with ARVD/C according to the 2010 TFC during follow-up. Their clinical characteristics are described in **Table 2**. There was no statistically significant difference in length of follow-up between those with and without a definite

ARVD/C diagnosis (median 5.9 [IQR: 2.7 to 7.2] years vs. 3.6 [IQR: 2.4 to 5.1] years; p = NS). The majority of subjects (n = 4 [80%]) with definite ARVD/C were female, with a median age of 39.0 years (IQR: 19.5 to 51.0 years) at the time of diagnosis.

Patients fulfilling the 2010 TFC for ARVD/C at last follow-up were more often symptomatic at enrollment (3 of 5 [60%] vs. 4 of 32 [13%] asymptomatic; p = 0.012) and more often had an abnormal baseline ECG (2 of 5 [40%] vs. 1 of 32 [3%] with a normal ECG; p = 0.005) than patients who did not fulfill ARVD/C TFC at last follow-up. All other clinical characteristics and tests at enrollment were similar between those with and without a definite ARVD/C diagnosis at last follow-up. Among all clinical tests at last follow-up, SAECG was the only modality that did not distinguish between patients with and without a definite ARVD/C diagnosis (1 of 2 [50%] vs. 9 of 25 [36%]; p = NS).

**ADVERSE EVENTS.** Among the overall cohort, 29 of 117 subjects (25%) had an ICD, all of whom had a definite ARVD/C diagnosis at the time of ICD implantation. During 4.1 ± 2.3 years of follow-up, none of the 74 subjects without definite ARVD/C diagnosis at first evaluation experienced a sustained ventricular arrhythmia. In comparison, 8 of 43 patients with ARVD/C diagnosis at first evaluation (19%) experienced an arrhythmic event during 3.2 ± 2.4 years of follow-up. Two events were spontaneous sustained VTs, and 6 were appropriate ICD discharges. All patients who experienced an arrhythmic event were successfully diagnosed with ARVD/C before the arrhythmia. No subjects died or required heart transplantation during follow-up.

## DISCUSSION

Our study aimed to describe the utility of serial noninvasive follow-up evaluation in at-risk family members of ARVD/C probands (predominantly plakophilin-2 mutation carriers). This study has several interesting results. First, we showed that relatives of ARVD/C probands who did not fulfill 2010 TFC for ARVD/C at first evaluation had a low short-term risk of sustained arrhythmia during a mean follow-up of 4 years. Second, during the 4-year follow-up period, we only observed minimal disease progression, which should be taken into account when determining the optimal screening interval for these patients. Third, electrical progression on ECG, Holter monitoring, or SAECG was seen to a much greater extent than structural progression on CMR, and all patients with a definite ARVD/C diagnosis at last follow-up had an abnormal ECG or Holter monitor. These results add to the growing body of evidence that electrical abnormalities precede detectable structural changes in ARVD/C, which should be reflected by the screening strategy used in these subjects (Central Illustration).

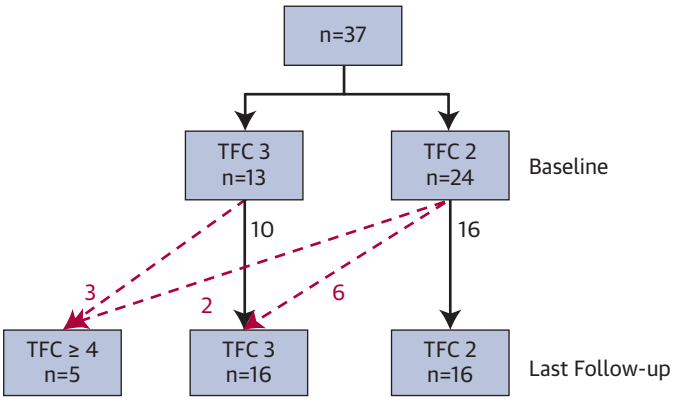



**FIGURE 2 Disease Progression in 37 Subjects With Complete Re-Evaluation**

Disease progression (defined as the development of a new 2010 TFC at last follow-up that was absent at enrollment) is shown as **red dotted lines**; **numbers in red** depict the number of patients. ARVD/C = arrhythmogenic right ventricular dysplasia/cardiomyopathy; TFC = Task Force Criteria.

**FAVORABLE PROGNOSIS.** The high risk of ventricular arrhythmias in ARVD/C is well established. However, the arrhythmic propensity of the index patient must not necessarily be applied to at-risk relatives, who by virtue of the incomplete penetrance and

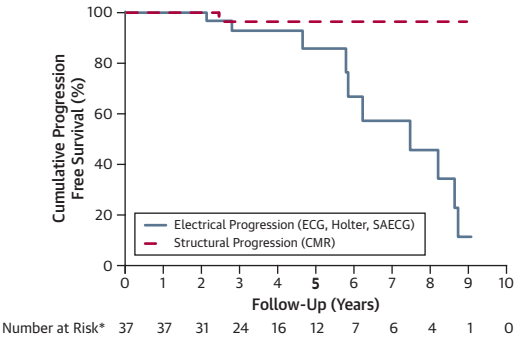



**FIGURE 3 Time to Disease Progression Among 37 Subjects With Complete Re-Evaluation**

*Per study design, time to progression (i.e., fulfillment of TFC) and time to last follow-up were the same or within a 1-year range for electrical and structural progression in all subjects. Therefore, numbers at risk apply to both electrical and structural progression. CMR = cardiac magnetic resonance; ECG = electrocardiogram; SAECG = signal-averaged electrocardiogram; TFC = Task Force Criteria.

**TABLE 2 Characteristics of 5 Patients With a Definite ARVD/C Diagnosis at Last Follow-up**

| | Patient #1 | Patient #2 | Patient #3 | Patient #4 | Patient #5 |
|---|---|---|---|---|---|
| Sex | F | F | M | F | F |
| Age at time of diagnosis (yrs) | 21 | 43 | 59 | 39 | 18 |
| Pathogenic mutation | – | + (*PKP2*) | + (*PKP2*) | + (*PKP2*) | + (*PKP2*) |
| Length of follow-up (yrs) | 5.9 | 6.2 | 8.2 | 2.4 | 2.8 |
| Symptoms | Palpitations | Palpitations, pre-syncope | Palpitations, pre-syncope | Palpitations, syncope | Palpitations |
| Disease progression | | | | | |
| Electrical progression* | Yes | Yes | Yes | Yes | Yes |
| Repolarization progression | BL: None<br>FU: TWI $V_1$ to $V_3$ | … | … | … | BL: None<br>FU: TWI $V_1$ to $V_2$ |
| Arrhythmia progression | … | BL: 1 PVC/24 h<br>FU: 502 PVCs/24 h | BL: 29 PVCs/24 h<br>FU: 1,105 PVCs/24 h | BL: None<br>FU: LBS NSVT | BL: 2 PVCs/24 h<br>FU: 4,559 PVCs/24 h |
| Depolarization progression | … | … | … | … | BL: None<br>FU: > TAD |
| Structural progression† | No | No | No | Yes | No |
| Clinical phenotype | | | | | |
| Repolarization TFC | TWI $V_1$ to $V_3$ (major) | TWI $V_1$ and $V_2$ (minor) | None | None | TWI $V_1$ and $V_2$ (minor) |
| Depolarization TFC | Late potentials (minor) | None | > TAD + late potentials (minor) | None | > TAD (minor) |
| Arrhythmia TFC | None | 502 PVCs/24 h (minor) | 1,105 PVCs/24 h (minor) | Nonsustained VT, LBBB superior axis (major) | 4,559 PVCs/24 h (minor) |
| Structural TFC | None | None | None | Minor | None |
| Family history TFC | Major | Major | Major | Major | Major |
| TFC points at enrollment | 3 | 3 | 3 | 2 | 2 |
| TFC points at last follow-up | 5 | 4 | 4 | 5 | 5 |

Disease progression was defined as the presence of a new 2010 TFC at last follow-up that was absent at baseline. *Progression on electrocardiography, Holter monitoring, or signal-averaged electrocardiography. †Progression on cardiac magnetic resonance imaging.

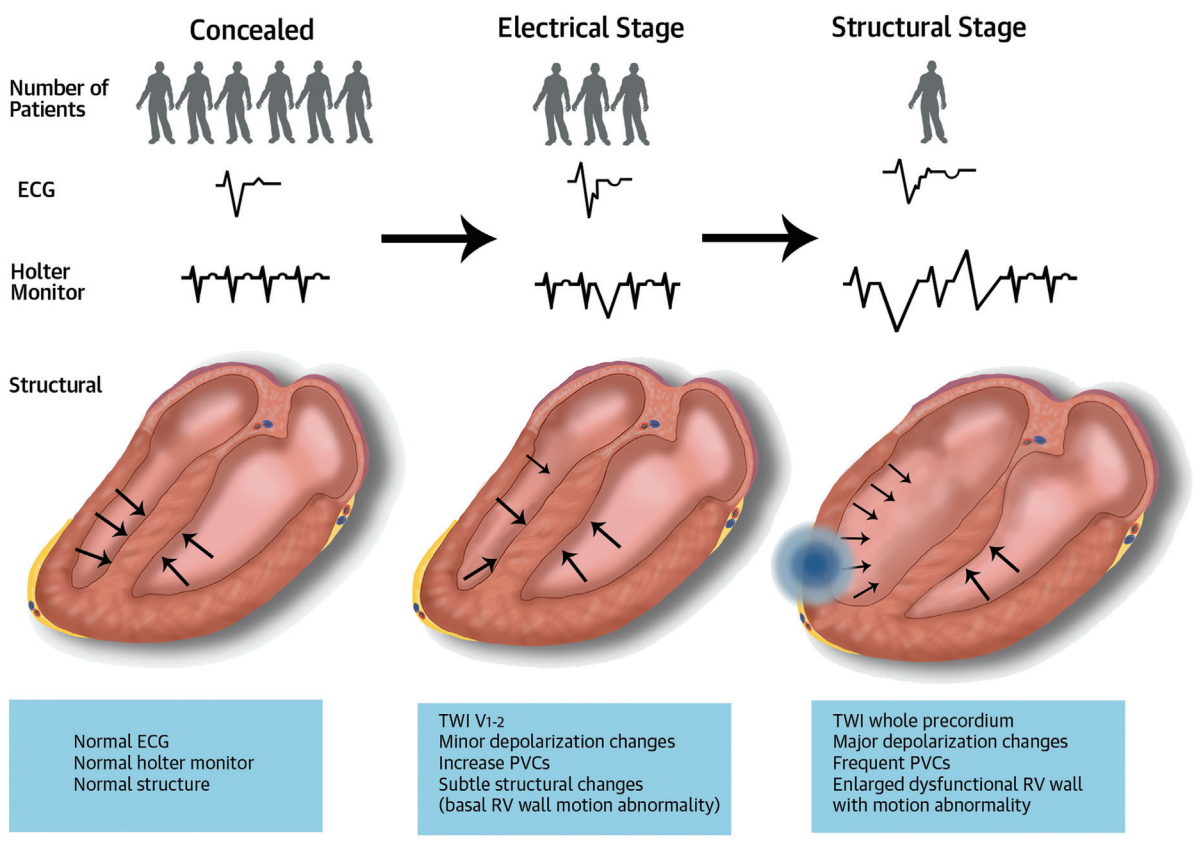
ARVD/C = arrhythmogenic right ventricular dysplasia/cardiomyopathy; BL = baseline; FU = follow-up; LBBB = left bundle branch block; LBS NSVT = nonsustained ventricular tachycardia of left bundle branch superior axis morphology; *PKP2* = plakophilin-2; PVC = premature ventricular complex; > TAD = prolonged terminal activation duration; TFC = Task Force Criteria; TWI = T-wave inversion; VT = ventricular tachycardia.

variable expressivity of this disease have a different, lower level of risk (10). In fact, our study shows that family members of ARVD/C patients who do not fulfill diagnostic 2010 TFC at first evaluation have a low risk of arrhythmia during a mean follow-up of 4 years. It is important to note in this regard that more than one-third of at-risk relatives fulfilled diagnostic 2010 TFC for ARVD/C at first evaluation, and that 8 of these 43 subjects experienced a ventricular arrhythmia during follow-up. This emphasizes the importance of complete screening in relatives after diagnosis in a proband, and underscores the fact that the low risk of arrhythmias in short-term follow-up only applies to those who do not fulfill 2010 TFC at initial evaluation.

**DETERMINING THE OPTIMAL SCREENING INTERVAL.** An important result of our study is that the overall rate of progression in relatives of ARVD/C probands is slow and unlikely to be appreciated on short-term screening. Disease progression was observed in 30% of subjects with an initially normal clinical investigation during 4 years of follow-up. However, only minimal changes were observed for all single testing modalities between baseline and last follow-up. These results are in alignment with prior reports that showed limited change on electroanatomic scar mapping and CMR during a follow-up period of approximately 4 years (13,14). This lack of short-term progression is important to consider when re-evaluating family members of ARVD/C index patients at a 2- to 3-year interval. The pre-test probability of finding new abnormalities is low, and the observed changes are likely to be minor, with questionable clinical significance. Although our mean follow-up duration was relatively short, and the results by no means provide definite reassurance for patients at risk of developing ARVD/C, these data provide important information for clinical care, in which follow-up protocols are still largely based on consensus opinions and clinical judgments. One recent study from our group described that endurance exercise and frequent physical activity contribute to disease development and arrhythmic occurrence in ARVD/C-associated desmosomal mutation carriers (15), which suggests that at-risk individuals should not participate in high-level athletics. It is certainly possible, and perhaps likely, that the absence of disease progression that we observed in the present study may not apply to subjects who continue to participate in athletic training.

**DETERMINING THE OPTIMAL SCREENING STRATEGY.** Over the past decade, CMR has gained enormous popularity as the modality of choice for structural evaluation in ARVD/C. However, in our cohort of subjects with high a priori risk of ARVD/C, there was only 1 patient with an initially normal structural evaluation who had a minor CMR criterion at last follow-up. In addition, other qualitative CMR parameters, such as RV delayed enhancement and fat, did not increase the yield of CMR screening.

On the basis of a cross-sectional study in ARVD/C mutation carriers, we have previously proposed that electrical abnormalities precede detectable structural changes in people at risk of developing ARVD/C (16). This is also supported by a study by Protonotarios et al. (17), which reported on 205 at-risk subjects who were similarly followed over a median of 4 years. In their study, 16 mutation carriers were newly diagnosed with ARVD/C during follow-up, of whom 100% had ECG abnormalities, whereas only 31% had structural alterations. The present study extends prior reports by showing that electrical abnormalities are not only more prevalent in a cross-sectional setting in ARVD/C, but also precede structural abnormalities in a longitudinal fashion. Only 1 patient in this study had structural progression on CMR, but whether this really represents disease progression is arguable. This patient already had an abnormal CMR with RV free wall dyskinesia at baseline and showed a minimal volume increase (RV end-diastolic volume increased from 88.3 ml/m$^2$ to 93.5 ml/m$^2$), fulfilling a minor TFC. Moreover, she had an abnormal ECG with T-wave inversion in leads $V_1$ and $V_3$ (but not $V_2$) and a run of nonsustained VT on exercise testing, which fulfilled a major arrhythmia TFC for ARVD/C.




**CENTRAL ILLUSTRATION** **Disease Progression in ARVD/C**

Family members of a proband with arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) have a long latent stage without signs or symptoms of disease (concealed stage). Electrical changes on electrocardiogram or Holter monitoring are usually the first sign of disease, and structural abnormalities may be observed later. Disease progression is typically slow. ECG = electrocardiogram; PVC = premature ventricular complex; RV = right ventricular; TWI = T-wave inversion.

Interestingly, all patients who fulfilled diagnostic TFC for ARVD/C at last follow-up had electrical abnormalities on ECG or Holter monitor in addition to their familial predisposition. This suggests that electrical abnormalities precede detectable structural changes in subjects at risk for ARVD/C. Importantly, this study and prior reports have shown that no single test should be relied upon for diagnosis and risk stratification purposes in ARVD/C, because even a 12-lead ECG can be normal in definite ARVD/C cases (18). Therefore, a full baseline evaluation remains necessary in determining an at-risk individual's phenotype. In our cohort, SAECG was the only test that did not distinguish between subjects with and without a definite ARVD/C diagnosis at last follow-up. Although this calls into question the significance of an abnormal SAECG in the evaluation of subjects at risk for ARVD/C, SAECG was shown to have incremental value for ARVD/C evaluation among newly diagnosed ARVD/C probands in a prior study (19). Adding to the results of prior studies (10,17,18), this supports a screening strategy that includes serial ECG and Holter monitoring in all subjects at risk of developing ARVD/C and using CMR in selected cases when symptoms and/or ECG or Holter monitoring abnormalities are present. Prior studies have shown that arrhythmic risk in ARVD/C is very low in children before the age of puberty (20). Further studies are needed to validate our findings and identify the age window at which screening is particularly likely to detect disease expression.

**STUDY LIMITATIONS.** Studies on ARVD/C, in particular involving CMR, are typically small in size. Only 37 subjects without ARVD/C diagnosis at enrollment underwent complete re-evaluation using at least ECG and CMR. The other 37 subjects did not undergo repeat CMR, but also re-evaluation by ECG was not performed in the majority of these subjects. Because baseline characteristics and endpoints were similar between subjects with and without repeat evaluation, a significant selection bias seems unlikely. The presence of multiple pathogenic mutations in ARVD/C probands has been described previously (21). Although only one pathogenic mutation was identified in all mutation-positive families of this study, the presence of modifier genes could be responsible for disease progression in some family members. Although the majority of subjects carried a pathogenic ARVD/C-causing mutation, a subset of our cohort was made up of family members of a mutation-negative proband. This provided us with the opportunity to study a reasonably large cohort of family members at risk of developing disease. ICDs were implanted in 25% of our cohort, only among those with a definite ARVD/C diagnosis. This may have increased our ability to identify ventricular arrhythmias among those with an ICD.

## CONCLUSIONS

To the best of our knowledge, this study is the first to describe the yield of serial cardiac evaluation using a combination of ECG, Holter monitoring, SAECG, and CMR in at-risk relatives of ARVD/C probands. Our results reassure the practicing physician that patients who do not fulfill the 2010 revised TFC at first evaluation have a low risk of arrhythmia during a mean follow-up of 4 years. Disease progression is minimal and likely not appreciated on biennial or triennial screening. Because electrical abnormalities precede detectable structural changes, the use of serial CMR screening may be restricted to symptomatic family members with electrical abnormalities on ECG and Holter monitoring.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** ARVD/C is a slowly progressive disease in which electrical abnormalities precede detectable structural changes.

**COMPETENCY IN PATIENT CARE 1:** After comprehensive evaluation of relatives of patients with ARVD/C, physicians may reassure those not fulfilling the 2010 Task Force criteria that progression occurs slowly, if at all, and that the risk of arrhythmia is generally low.

**COMPETENCY IN PATIENT CARE 2:** Cardiac magnetic resonance imaging of relatives of patients with ARVD/C may be restricted to subjects who are symptomatic and those with depolarization or repolarization abnormalities on ECG or Holter monitoring.

**TRANSLATIONAL OUTLOOK:** Genetic characterization and longer-term follow-up of families of patients with ARVD/C are needed to define additional factors associated with early and late development of structural and electrical abnormalities.

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**KEY WORDS** cardiomyopathy, electrocardiography, magnetic resonance imaging, progression, screening

**APPENDIX** For supplemental figures and tables, please see the online version of this article.