Check for updates

Circulation

ORIGINAL RESEARCH ARTICLE

# Family Screening in Relatives at Risk for Plakophilin-2–Associated Arrhythmogenic Right Ventricular Cardiomyopathy

Steven A. Muller, MD; Babken Asatryan, MD, PhD; Alessio Gasperetti, MD, PhD; Maarten J. Cramer, MD, PhD; Ahmad S. Amin, MD, PhD; Peter Loh, MD, PhD; Richard T. Carrick, MD, PhD; Moniek G.P.J. Cox, MD, PhD; Pim van der Harst, MD, PhD; Marish I.F.J. Oerlemans, MD, PhD; Crystal Tichnell, MGC, RN; Sing-Chien Yap, MD, PhD; Brittney Murray, MS, CGC; Stefan L. Zimmerman, MD; J. Peter van Tintelen, MD, PhD; Hugh Calkins, MD; Anneline S.J.M. te Riele, MD, PhD*; Cynthia A. James, PhD, CGC*

**BACKGROUND:** Penetrance and risk of ventricular arrhythmias (VAs) in arrhythmogenic right ventricular cardiomyopathy (ARVC) are increasingly recognized as being genotype specific. Therefore, genotype-informed family screening protocols may lead to safer and more personalized recommendations than the current one-size-fits-all screening recommendations. We aimed to develop a safe, evidence-based plakophilin-2 (*PKP2*)–specific longitudinal screening algorithm.

**METHODS:** We included 295 relatives (41% male; age 30.9 years [18.0–47.7 years]) with a pathogenic or likely pathogenic *PKP2* variant from 145 families. Phenotype was ascertained with ECG, Holter monitoring, and cardiac imaging and classified by the 2010 Task Force Criteria. VA was defined as a composite of sudden cardiac arrest or death, spontaneous sustained ventricular tachycardia, ventricular fibrillation, or appropriate implantable cardioverter defibrillator intervention. We performed Cox regression to determine predictors of ARVC development and multistate modeling to assess the probability of ARVC development and occurrence of VA.

**RESULTS:** At baseline, 110 relatives (37%) had definite ARVC. During 8.5 years (4.2–12.9 years) of follow-up, 62 of 185 relatives (34%) without definite ARVC at baseline progressed to definite ARVC diagnosis, and 35 of 295 of all relatives (12%) had VA. VAs occurred only in relatives who previously fulfilled definite ARVC diagnosis. Relatives with borderline ARVC (fulfillment of one minor criterion plus the major family history criterion) progressed 5 times faster in the multistate model to definite ARVC diagnosis and compared with genotype-positive/phenotype-negative (G+/P–) relatives (ie, major family history criterion alone). Relatives 20 to 40 years of age had increased risk for developing definite ARVC (hazard ratio, 2.23; *P*=0.012) compared with those ≥40 years of age. New Task Force Criteria fulfillment most commonly occurred first on ECGs, followed by Holter monitoring and cardiac imaging. Consequently, 3 risk profiles were identified, and appropriate screening protocols were derived: relatives with borderline ARVC (annual ECG and Holter monitoring; complete evaluation [ie, ECGs, Holter monitoring, and imaging] every 2 years), younger (<40 years of age) or symptomatic G+/P– relatives (every 2 years an ECG and Holter monitoring; complete evaluation every 4 years), and older (≥40 years of age) and asymptomatic G+/P– relatives (complete evaluation every 5 years).

**CONCLUSIONS:** An evidence-based longitudinal screening algorithm that integrates age, symptoms, and baseline clinical phenotype may improve patient care and improve efficiency of clinical resource allocation.

**Key Words:** cardiomyopathies ■ death, sudden, cardiac ■ genetics ■ genotype ■ precision medicine

Correspondence to: Steven A Muller, MD, Johns Hopkins ARVC Program, Division of Cardiology, Department of Medicine, Johns Hopkins University, Blalock 545, 600 N Wolfe St, Baltimore, MD 21287. Email s.a.muller-5@umcutrecht.nl
*A.S.J.M. te Riele and C.A. James contributed equally
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.125.074058.
For Sources of Funding and Disclosures, see page XXX.
© 2025 The Authors. *Circulation* is published on behalf of the American Heart Association, Inc., by Wolters Kluwer Health, Inc. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial-NoDerivs License, which permits use, distribution, and reproduction in any medium, provided that the original work is properly cited, the use is noncommercial, and no modifications or adaptations are made.
*Circulation* is available at www.ahajournals.org/journal/circ

Circulation FIRST PROOF ONLY

Downloaded from http://ahajournals.org by on June 17, 2025

ORIGINAL RESEARCH ARTICLE

## Clinical Perspective

### What Is New?

- Relatives with a pathogenic or likely pathogenic variant plakophilin-2 (*PKP2*) variant with borderline arrhythmogenic right ventricular cardiomyopathy (ARVC) progress ≈5 times faster to definite ARVC diagnosis compared with relatives who are genotype positive/phenotype negative (G+/P–).
- Relatives 20 to 40 years of age or who are symptomatic have an ≈2 times higher risk of progressing to definite ARVC diagnosis.
- Relatives with a pathogenic or likely pathogenic *PKP2* variant without definite ARVC diagnosis at baseline rarely develop ventricular arrhythmias during medium-term follow-up and only after fulfilling definite ARVC diagnostic criteria.

### What Are the Clinical Implications?

- We identified 3 risk profiles for at-risk relatives: (1) borderline ARVC; (2) symptomatic or <40 years of age and G+/P–; and (3) asymptomatic ≥40 years of age and G+/P–.
- Using these risk profiles, we developed longitudinal screening algorithms that ensured diagnosis >5 years before ventricular arrhythmias occur: (1) for borderline ARVC, annual screening with an ECG and Holter monitoring and a complete evaluation every 2 years; (2) for symptomatic or <40 years of age and G+/P–, screening every 2 years with an ECG and Holter monitoring and a complete evaluation every 4 years; and (3) for asymptomatic ≥40 years of age and G+/P–, screening every 5 years with a complete evaluation.

## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **ACM** | arrhythmogenic cardiomyopathy |
| **ARVC** | arrhythmogenic right ventricular cardiomyopathy |
| **CMR** | cardiac magnetic resonance imaging |
| ***DSP*** | desmoplakin |
| **G+/P–** | genotype-positive/phenotype-negative |
| **IQR** | interquartile range |
| **P/LP** | pathogenic or likely pathogenic variant |
| ***PKP2*** | plakophilin-2 |
| ***PLN*** | phospholamban |
| **TFC** | Task Force Criteria |
| ***TMEM43*** | transmembrane protein 43 |
| **VA** | ventricular arrhythmia |

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited disease that is most commonly caused by a pathogenic or likely pathogenic (P/LP) variant in plakophilin-2 (*PKP2*).[1] The hallmark features of the disease are sustained ventricular arrhythmias (VAs), including sudden cardiac death.[1,2] Because a familial predisposition to *PKP2*-associated ARVC can be identified through genetic testing, longitudinal screening of relatives of patients with ARVC is strongly recommended.[3–6] Indeed, the current guidelines recommend initiation of screening at 10 to 12 years of age and reevaluation with an ECG, Holter monitoring, and an imaging modality every 1 to 3 years.[3–6]

Unfortunately, the currently recommended screening algorithms do not account for genotype-specific differences in penetrance, risk of VA, or their associated risk factors.[1,7–20] Therefore, this one-size-fits-all family screening algorithm may result in overscreening of patients with a low likelihood of developing penetrant ARVC and underscreening of those who are at the highest risk, leading to inefficient use of clinical resources and potential missed windows of opportunity for primary prevention. Although longitudinal family screening studies have been performed previously, these studies enrolled relatives of patients with ARVC with different underlying genotypes, as well as gene-elusive families.[21–23] Thus, to date, there is limited evidence to support genotype-specific longitudinal screening algorithms.[24]

To address this gap, we evaluated outcomes of a large cohort of relatives of patients with ARVC with P/LP *PKP2* variants to develop such an algorithm. The purpose of this study was to develop a safe, evidence-based longitudinal screening algorithm for relatives with a P/LP *PKP2* variant.

FIRST PROOF ONLY

## METHODS

### Study Population

The study population was recruited from the Netherlands ACM registry (Arrhythmogenic Cardiomyopathy[25]; www.acmregistry.nl; UCC-UNRAVEL No. 12-387[26]) and the Johns Hopkins ARVC registry. From both registries, we identified all families in which the proband fulfilled definite ARVC diagnosis as per 2010 Task Force Criteria (TFC)[27] and who carried a P/LP *PKP2* variant. All *PKP2* variant classifications were adjudicated by an experienced cardiac genetic counselor (B.M.) according to the standards and guidelines for the interpretation of sequence variants set forth by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.[28] Among the families identified, all relatives with a P/LP *PKP2* variant who underwent a baseline screening evaluation in which definite ARVC diagnosis could be ascertained were included, as described later. We excluded relatives who had a sustained VA before their first clinical evaluation because they were no longer at risk for a first VA. The study population partially consisted of relatives who had been included in previous ARVC studies.[22,23,29–33] The data used in this study are available on reasonable request. This study followed the code of conduct and the use of data in health research and was approved by local ethics or institutional review boards.

Downloaded from http://ahajournals.org by on June 17, 2025

## Clinical Evaluation

Participants were evaluated as described previously.[22,23,34] Medical history was obtained by review of medical records or clinical evaluation. Detailed clinical information on demographics, presentation, symptom onset, and noninvasive testing was obtained. Pedigree analysis was performed by genetic counselors with expertise in ARVC. Relatives were categorized according to their relationship to the proband as first-, second-, or third-degree relatives; first-degree relatives were subdivided into parents, siblings, and children of the proband.

All relatives underwent guideline-recommended baseline screening evaluation in which definite ARVC diagnosis could be ascertained, defined as a 12-lead ECG, Holter monitor of at least 24 hours, and an imaging evaluation of cardiac structure and function (echocardiogram or cardiac magnetic resonance imaging [CMR]).[3–6] Testing results from other modalities (eg, electrophysiology studies) were also collected. For follow-up evaluations, we included all available clinical testing performed at the discretion of the treating cardiologist, including 12-lead ECG, Holter monitoring of ≥24 hours, and repeat imaging (echocardiogram or CMR).

## ARVC Diagnosis

Diagnostic evaluation was based on the 2010 TFC,[27] with definite ARVC diagnosis defined by fulfillment of 2 major, one major plus 2 minor, or 4 minor criteria. By study design, all subjects fulfilled one major criterion in the family history category given their genetic predisposition (ie, harboring a P/LP *PKP2* variant). Thus, relatives were stratified by their baseline clinical phenotype: (1) genotype positive/phenotype negative (G+/P—; ie, only the major family history criterion without any other TFC fulfillment on diagnostic tests), (2) borderline ARVC (ie, fulfillment of one minor criterion plus the major family history criterion), or (3) definite ARVC (ie, fulfillment of 2 minor or one major plus the major family history criterion).

## Study Outcomes

The primary outcomes of this study were the development of definite ARVC during follow-up as per 2010 TFC and the occurrence of sustained VA during follow-up. For the purpose of this study, sustained VA was defined as a composite of sudden cardiac death, sudden cardiac arrest, spontaneous sustained ventricular tachycardia (ventricular tachycardia lasting ≥30 seconds at ≥100 bpm or with hemodynamic compromise requiring cardioversion), ventricular fibrillation/flutter, or appropriate implantable cardioverter defibrillator intervention, as done previously.[29]

The secondary outcome of this study was the occurrence of a new TFC during follow-up that was absent at the first evaluation. This was evaluated for each diagnostic test (ie, ECG, Holter monitor, echocardiogram, and CMR) separately.

## Statistical Analysis

Nominal variables were expressed as number (percent) and continuous variables as mean±SE or median (interquartile range [IQR]) as appropriate. Comparisons for binary variables were performed by the $\chi^2$ or Fisher exact test. For continuous variables, independent *t* tests or Mann-Whitney *U* tests were used. To visualize progression to definite ARVC diagnosis, new TFC, and VA, Kaplan-Meier curves were plotted, and groups were compared with the log-rank test. The event rates for VA, including the 95% CI, were calculated with the Kaplan-Meier method. Because progression to definite ARVC diagnosis and fulfillment of new TFC are dependent on diagnostic test results, our analysis could potentially be biased because of the unavailability of tests. To assess this potential bias, we repeated the analyses for progression to definite ARVC diagnosis and progression to a new TFC including only relatives who had a complete repeat evaluation (ie, those who had an ECG, Holter monitoring, echocardiography, and CMR during follow-up available) as a sensitivity analysis. No missing data were imputed. A value of $P<0.05$ was considered statistically significant. Data were analyzed with R version 4.1.2 (Boston, MA), including the msm package for the multistate model.[35]

### Overcoming Interval Censoring

Because this was a retrospective study without predefined follow-up dates, the date of diagnosis in our study population was dependent on the timing of outpatient clinic visits; that is, our analyses are sensitive to interval censoring. To overcome that limitation, we created a multistate model (continuous-time Markov chain). In this model, we determined G+/P—, borderline ARVC, definite ARVC, and VA as separate clinical states through which an individual can progress unidirectionally to a more advanced disease stage (Figure 1A shows a visualization of how an individual could progress). Transitioning to a less severe disease state (eg, from borderline ARVC to G+/P—) was deemed impossible. The multistate model considers transitions from one disease state to another to occur at an unknown time point between 2 outpatient clinic evaluations at which the current disease state could be assessed. The model therefore estimates the probability of transitioning to a more severe disease state between 2 time points. VA, in contrast to the other disease states, was modeled as a time-stamped event. An in-depth description of the type of Markov chain and the assumptions and restrictions of the model is provided in the Supplemental Methods.

### Determining When to Screen

We used the fitted risks from the multistate model as mentioned in 3 complementary ways to determine clinically acceptable risks for progression to definite ARVC. First, because the current guidelines[3–6] recommend a 1- to 3-year screening interval, we evaluated the 1- to 3-year risk for definite ARVC and VA for G+/P— relatives and relatives with borderline ARVC. Second, we determined which screening intervals for G+/P— relatives and relatives with borderline ARVC had comparable risks for definite ARVC and VA. Third, we determined which screening intervals for G+/P— relatives and relatives with borderline ARVC would hold acceptable risks in daily clinical practice. To do so, we deemed a clinically acceptable risk for definite ARVC development to be between 6% and 16%, as previously reported for risk for definite ARVC development in the overall at-risk ARVC population.[22] For VA, a clinically acceptable risk was deemed to be <0.5% in the setting of family screening.

To determine how (ie, by which modalities) relatives should be screened, we created multistate models for every diagnostic test separately in which no progression and progression were the available states (Figure 1B shows a visualization of how an individual could progress). We performed these analyses only in those who did not fulfill definite ARVC diagnosis at baseline evaluation.

Circulation FIRST PROOF ONLY

Downloaded from http://ahajournals.org by on June 17, 2025

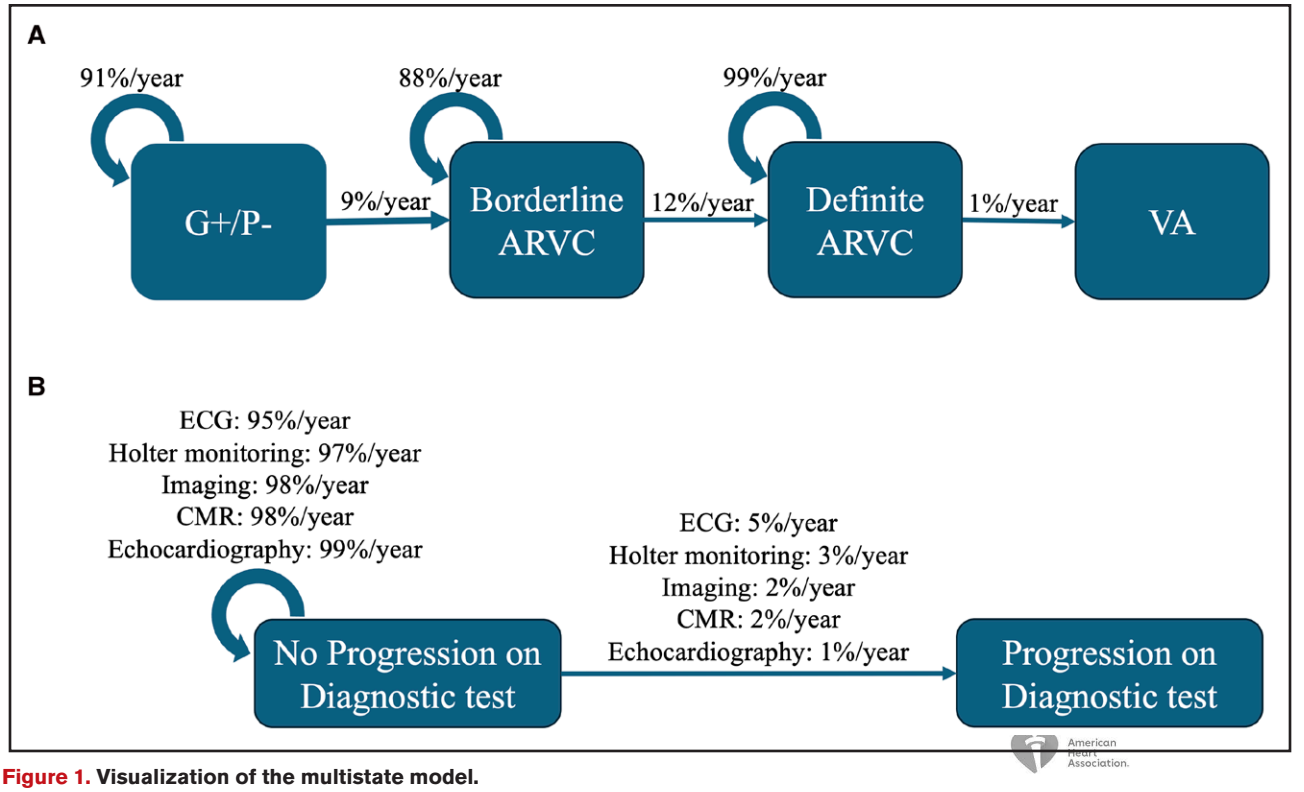


**Figure 1. Visualization of the multistate model.**
**A**, Multistate model of progression of disease using the diagnostic 2010 Task Force Criteria (TFC) consisted of 4 states: genotype positive/phenotype negative (G+/P−), borderline arrhythmogenic right ventricular cardiomyopathy (ARVC), definite ARVC, and ventricular arrhythmia (VA). A relative could only stay in the same state or progress to a more severe state during follow-up, which is shown by the blue arrows. Numbers represent the estimated transition intensities per year. **B**, Multistate models of progression to new TFC by diagnostic test. Numbers represent the estimated transition intensities per diagnostic test per year.

Circulation FIRST PROOF ONLY

### *Establishing Predictors of Progression*

To determine which individuals were at a higher risk of progression (ie, who would benefit from more frequent follow-up visits), we additionally examined individual risk predictors for progression of development of ARVC using predefined variables known to be associated with progression to definite ARVC.[22,29] Predictors for the definite ARVC diagnosis were tested by a frailty Cox proportional hazard regression to adjust for a potential effect of family membership, and hazard ratios were reported with their 95% CIs. The Cox proportional hazard assumptions were tested with the Schoenfeld residuals.[36]

### *Longitudinal Screening Algorithm Development*

To develop a safe, evidence-based longitudinal screening algorithm, we combined the natural rate of progression (ie, fitted risk from all multistate models) and the risk factors to identify different risk profiles. Using these different risk profiles, we subsequently proposed a longitudinal screening algorithm accounting for the natural progression of disease (ie, when to screen) and new TFC per diagnostic test (ie, how to screen) for relatives in each of these risk groups.

## RESULTS

### Study Population

Our study cohort consisted of 295 relatives of probands from 145 families (relatives per family: median, 1 [IQR, 1–3]; range, 1–9) who harbored a familial P/LP *PKP2* variant (Table S1 gives P/LP *PKP2* variants) and had follow-up evaluations available (Figure 2). Median age at first evaluation was 30.9 years (IQR, 18.0–47.7 years); 122 (41%) were male; and 205 (69%) were first-degree relatives (Table 1). Most relatives were asymptomatic (n=159/236; 67%), whereas among the symptomatic relatives (n=77; 33%), palpitations were the most prevalent symptom (n=41/77; 53%). During the follow-up period (median, 8.5 years [IQR, 4.2–12.9 years]); 7 of 295 relatives (2.4%) died. All causes of death were likely not ARVC related, and no sudden cardiac deaths were observed. Table S2 summarizes individual causes of death.

### Progression of Disease

#### *Progression to Definite ARVC Diagnosis*

Sixty-two of the 185 relatives (34%) without definite ARVC diagnosis at first clinical evaluation (dotted box in Figure 2; median follow-up time, 8.2 years [IQR, 4.0–12.1 years]) progressed to definite ARVC diagnosis at a median time after initial evaluation of 5.3 years (IQR, 2.5–8.7 years; Figure 3A). Relatives with borderline ARVC (4.1 years [IQR, 1.6–7.0 years]) progressed significantly faster to definite ARVC diagnosis compared

Downloaded from http://ahajournals.org by on June 17, 2025

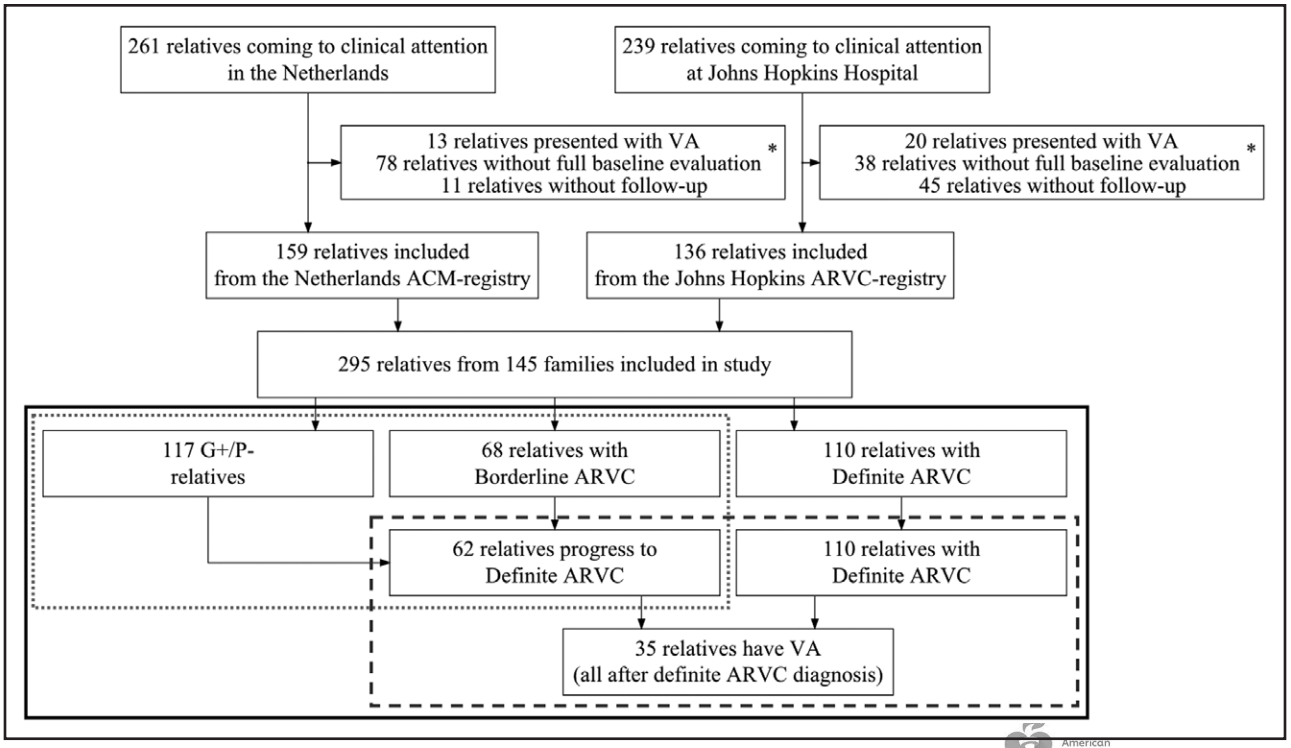


**Figure 2. Flowchart of the study population.**

*Complete baseline evaluation defined as at least 12-lead ECG, Holter monitoring, and imaging (cardiac magnetic resonance imaging [CMR] or echocardiography). Boxes around the study population visualize specific analyses as described in the text.

Circulation
FIRST PROOF ONLY

Downloaded from http://ahajournals.org by on June 17, 2025

with G+/P− relatives (7.7 years [IQR, 4.6–9.5 years]; $P<0.001$; Figure 3B).

### Occurrence of VA

Of all 295 relatives, including those with definite ARVC (solid box, Figure 2; median follow-up, 8.5 years [IQR, 4.2–12.9 years]), 35 (12%) had a VA during follow-up, with a corresponding annual rate of 1.4% (95% CI, 0.9%–1.8%). In those 35 relatives, median time to VA was 6.0 years (IQR, 2.3–9.3 years; Figure 4A). The youngest relative experiencing VA was 14 years of age. Of note, no VAs occurred before a definite ARVC diagnosis. Consequently, of the 172 relatives with a definite ARVC diagnosis by last follow-up (dashed box in Figure 2; Table S3), the 35 VAs corresponded to an annual rate of VA of 2.7% (95% CI, 1.7%–3.5%) while fulfilling definite ARVC diagnosis (Figure 4B).

In total, 3 of 185 relatives (1.6%) without a definite ARVC diagnosis at baseline had a VA during follow-up. These events all occurred after definite ARVC diagnosis (time from definite ARVC diagnosis to VA, 6.8, 9.6, and 14.5 years). It is notable that these 3 relatives without a definite ARVC diagnosis at baseline progressed significantly more slowly and less often to VA from baseline evaluation (time from baseline evaluation to VA, 7.8, 14.9, and 18.3 years) compared with those with definite ARVC diagnosis at baseline (median time to VA, 5.5 years [IQR, 2.1–8.4 years]; $P<0.001$; Figure 4C and 4D). Phenotypic expression at time of diagnosis was less severe in those who developed diagnosis during follow-up compared with those who were diagnosed at baseline (Table S3).

### Yield of Diagnostic Testing in Relatives Without ARVC

We analyzed the development of new TFC fulfillment per diagnostic test in the 185 relatives without definite ARVC diagnosis at the baseline evaluation. Disease trajectory for every relative is visualized in Figure S1.

Overall, 84 of 185 relatives (45%) developed a new TFC during follow-up. Median time to a new TFC was 4.5 years (IQR, 2.1–7.1 years; Figure S2A). New TFC were most commonly first observed on ECG (n=45/84, 54%), followed by Holter monitoring (n=25/84; 30%) and imaging (n=14/84; 17%; Figure S2B). New imaging criteria were most commonly observed first on CMR (n=11/14, 79%), followed by echocardiography (n=2/14; 14%) and both modalities at one time point (n=1/14; 7%; Figure S2C).

G+/P− relatives and relatives with borderline ARVC progressed at rates similar to those for new TFC ($P=0.380$; Figure S3A). In addition, no significant difference in rate of progression to a new TFC per diagnostic test was found between G+/P− relatives and those with borderline ARVC (all $P>0.05$; Figure S3B through S3F).

**Table 1. Baseline Characteristics**

| | Complete cohort (N=295) | Nondefinite ARVC | | | Definite ARVC (n=110) | *P* value, G+/P– vs borderline ARVC | *P* value, definite ARVC vs nondefinite ARVC |
|---|---|---|---|---|---|---|---|
| | | Overall nondefinite ARVC (n=185) | G+/P– (n=117) | Borderline ARVC (n=68) | | | |
| Age at presentation, y | 30.9 (18.0–47.7) | 26.2 (15.2–43.4) | 21.3 (13.5–41.3) | 32.9 (21.7–47.2) | 37.3 (22.2–50.5) | 0.001 | <0.001 |
| Age (categorical), n (%) | | | | | | 0.004 | <0.001 |
| <14 y | 38 (12.9) | 37 (20.0) | 32 (27.4) | 5 (7.4) | 1 (0.9) | | |
| 14–20 y | 56 (19.0) | 36 (19.5) | 25 (21.4) | 11 (16.2) | 20 (18.2) | | |
| 20–30 y | 50 (16.9) | 29 (15.7) | 17 (14.5) | 12 (17.6) | 21 (19.1) | | |
| 30–40 y | 46 (15.6) | 28 (15.1) | 13 (11.1) | 15 (22.1) | 18 (16.4) | | |
| >40 y | 105 (35.6) | 55 (29.7) | 30 (25.6) | 25 (36.8) | 50 (45.5) | | |
| Sex, n (%) | | | | | | 0.181 | 0.222 |
| Male | 122 (41.4) | 82 (44.3) | 47 (40.2) | 35 (51.5) | 40 (36.4) | | |
| Female | 173 (58.6) | 103 (55.7) | 70 (59.8) | 33 (48.5) | 70 (63.6) | | |
| Relationship to the proband, n (%) | | | | | | 0.388 | <0.001 |
| Sibling | 89 (30.3) | 38 (20.7) | 22 (18.8) | 16 (23.9) | 51 (46.4) | | |
| Child | 76 (25.9) | 54 (29.3) | 40 (34.2) | 14 (20.9) | 22 (20.0) | | |
| Parent | 39 (13.3) | 21 (11.4) | 12 (10.3) | 9 (13.4) | 18 (16.4) | | |
| Second degree | 56 (19.0) | 43 (23.4) | 27 (23.1) | 16 (23.9) | 13 (11.8) | | |
| Third degree or further | 34 (11.6) | 28 (15.2) | 16 (13.7) | 12 (17.9) | 6 (5.5) | | |
| Symptoms at baseline presentation (n=236), n (%) | | | | | | 0.894 | <0.001 |
| Asymptomatic | 159 (67.4) | 119 (77.3) | 78 (78.8) | 41 (74.5) | 40 (48.8) | | |
| Palpitations | 41 (17.4) | 21 (13.6) | 12 (12.1) | 9 (16.4) | 20 (24.4) | | |
| Presyncope | 17 (7.2) | 5 (3.2) | 3 (3.0) | 2 (3.6) | 12 (14.6) | | |
| Syncope | 19 (8.1) | 9 (5.8) | 6 (6.1) | 3 (5.5) | 10 (12.2) | | |
| Electrical TFC fulfillment, n (%) | 168 (56.9) | 66 (35.7) | 0 (0.0) | 66 (97.1) | 102 (92.7) | <0.001 | <0.001 |
| Repolarization TFC fulfillment, n (%) | 92 (31.2) | 13 (7.0) | 0 (0.0) | 13 (19.1) | 79 (71.8) | <0.001 | <0.001 |
| T-wave inversions $V_1$–$V_2$ | 34 (11.5) | 13 (7.0) | 0 (0.0) | 13 (20.0) | 21 (19.1) | <0.001 | 0.002 |
| T-wave inversions $V_1$–$V_3$ | 51 (17.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 51 (49.0) | <0.001 | <0.001 |
| T-wave inversions $V_4$–$V_6$ | 5 (1.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 5 (4.8) | … | 0.006 |
| T-wave inversions with CRBBB $V_1$–$V_4$ | 2 (0.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (1.9) | … | 0.253 |
| Depolarization TFC fulfillment, n (%) | 65 (22.0) | 36 (19.5) | 0 (0.0) | 36 (52.9) | 29 (26.6) | <0.001 | 0.192 |
| Prolonged TAD | 41 (13.9) | 22 (11.9) | 0 (0.0) | 22 (32.4) | 19 (17.4) | <0.001 | 0.222 |
| Late potentials on SAECG | 30 (38.0) | 16 (29.1) | 0 (0.0) | 16 (55.2) | 14 (58.3) | <0.001 | 0.027 |
| Holter TFC fulfillment, n (%) | 83 (28.1) | 17 (9.2) | 0 (0.0) | 17 (25.0) | 66 (60.6) | <0.001 | <0.001 |
| PVC count/24h (n=275) | 46 (2–681) | 5 (1–59) | 2 (0–37) | 18 (2–411) | 831 (178–2813) | <0.001 | <0.001 |
| Imaging TFC fulfillment, n (%) | 51 (17.3) | 2 (1.1) | 0 (0.0) | 2 (2.9) | 49 (45.0) | 0.134 | <0.001 |
| CMR TFC fulfillment (n=163), n (%) | | | | | | 0.361 | <0.001 |
| Minor TFC | 14 (7.1) | 1 (1.0) | 0 (0.0) | 1 (2.9) | 13 (13.0) | | |
| Major TFC | 30 (15.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 30 (30.0) | | |
| Presence of RV WMAs (n=163), n (%) | 48 (29.4) | 9 (8.8) | 5 (8.2) | 4 (9.8) | 39 (63.9) | 1.000 | <0.001 |

(*Continued*)

Downloaded from http://ahajournals.org by on June 17, 2025

Circulation

**Table 1. Continued**

| | Complete cohort (N=295) | Nondefinite ARVC | | | Definite ARVC (n=110) | *P* value, G+/P– vs borderline ARVC | *P* value, definite ARVC vs nondefinite ARVC |
|---|---|---|---|---|---|---|---|
| | | Overall nondefinite ARVC (n=185) | G+/P– (n=117) | Borderline ARVC (n=68) | | | |
| RVEDV/BSA (n=123), mL/m² | 93.6±23.1 | 88.8±19.9 | 86.7±19.0 | 92.0±21.1 | 102.9±26.0 | 0.243 | 0.001 |
| RVEF (n=133), % | 52±9 | 54±7 | 55±6 | 53±9 | 47±8 | 0.176 | <0.001 |
| LVEF (n=126), % | 60±6 | 60±5 | 60±5 | 59±6 | 59±7 | 0.307 | 0.757 |
| Echocardiographic TFC fulfillment (n=206) | | | | | | 0.387 | <0.001 |
| Minor TFC | 6 (2.3) | 1 (0.6) | 0 (0.0) | 1 (1.7) | 5 (4.9) | | |
| Major TFC | 11 (4.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 11 (10.7) | | |
| Presence of RV WMAs (n=206) | 32 (15.5) | 6 (4.5) | 2 (2.4) | 4 (7.8) | 26 (36.6) | 0.201 | <0.001 |
| RVOT PLAX/BSA (n=50), mL/m² | 16.1±3.3 | 15.2±1.8 | 15.3±2.1 | 15.2±1.4 | 17.9±4.9 | 0.981 | 0.009 |
| RVOT PSAX/BSA (n=40), mL/m² | 17.0±3.4 | 16.6±2.0 | 16.9±2.1 | 16.1±2.0 | 17.8±5.5 | 0.335 | 0.340 |
| LVEF (n=91), % | 60±6 | 60±6 | 61±6 | 58.7±6 | 60±6 | 0.116 | 0.929 |

Variables are expressed as frequency (percentage), mean±SD, or median (IQR). Total number of patients for a given variable is mentioned when there are missing data; for all other variables, n=295.

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; BSA, body surface area; CMR, cardiac magnetic resonance imaging; CRBBB, complete right bundle-branch block; G+/P–, genotype positive/phenotype negative; LVEF, left ventricular ejection fraction; PLAX, parasternal long axis; PSAX, parasternal short axis; PVC, premature ventricular complex; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVOT, right ventricular outflow tract; SAECG, signal-averaged ECG; TAD, terminal activation duration; TFC, Task Force Criteria; and WMA, wall motion abnormality.

American Heart Association.

## Sensitivity Analyses

We next repeated these analyses in patients with complete repeat evaluations (ie, all had a repeat ECG, Holter monitoring, echocardiography, and CMR during follow-up available). Of note, relatives with a complete repeat evaluation were significantly younger (*P*=0.002) and more often had a prolonged terminal activation duration (*P*=0.019) compared with those without a full repeat evaluation (Table S4). Nonetheless, these sensitivity analyses yielded similar results for both progression to definite ARVC diagnosis (Figure S4) and progression to new TFC criterion per diagnostic test (Figure S5), including when the full repeat evaluation cohort was stratified by baseline clinical phenotype (Figures S6 and S7).

## Multistate Modeling of Progression of Disease to Overcome Interval Censoring

### *Probabilities of Definite ARVC and VA*

The probabilities of progression to definite ARVC diagnosis, VA, and new TFC based on multistate modeling are presented in Figure 5 (Figures S8 and S9 show the continuous-time Markov model survival curves). Patients with borderline ARVC had a 5-fold higher rate of progressing to definite ARVC and occurrence of VA compared with G+/P– relatives, which was consistent throughout the follow-up period (Figure 5A and Figure S10 for smaller fitted risks for VA; *P*<0.001 for definite ARVC and *P*<0.05 for VA). Calibration plots are presented in Figures S11 and S12.

The 1- to 3-year risk for definite ARVC and VA in relatives with borderline ARVC was as follows: risk for definite ARVC at 1 year, 11% (95% CI, 9%–14%) and at 3 years, 29% (95% CI, 23%–35%); risk for VA at 1 year, 0.05% (95% CI, 0.02%–0.1%) and at 3 years 0.5% (95% CI, 0.2%–1%). These risks were higher compared with G+/P– relatives (risk for definite ARVC at 1 year, 0.5% [95% CI, 0.3%–0.7%] and at 3 years, 4% [95% CI, 3%–5%]; risk for VA at 1 year, <0.01% [95% CI, <0.01%–<0.01%] and at 3 years, 0.04% [95% CI, 0.02%–0.1%]). The 1- to 3-year risk for definite ARVC or VA in relatives with borderline ARVC was similar to the 4- to 7-year risk for definite ARVC or VA in G+/P– relatives (Figure 5A). Both the 1-year screening interval in relatives with borderline ARVC and the 4- to 7-year screening interval in G+/P– relatives fell within the clinically acceptable thresholds (ie, 6% to 16% and <0.5% screening risk for definite ARVC and VA, respectively; Figure 5A).

### *Probabilities of New TFC by Diagnostic Test*

Patients without definite ARVC were more likely to progress to new TFC based on electrocardiographic findings (1-year risk of new TFC, 5.3% [95% CI, 4.2%–6.9%]; 3-year risk of new TFC, 15.2% [95% CI, 11.4%–20.5%]), followed by Holter monitoring (1-year risk of new TFC, 3.3% [95% CI, 2.3%–4.5%]; 3-year risk of new TFC, 9.5% [95% CI, 6.5%–14.1%]) and then imaging criteria (1-year risk of new TFC, 2.0% [95% CI, 1.4%–3.0%]; 3-year risk of new TFC, 6.0% [95% CI, 3.9%–9.1%]; $P_{\text{ECG-imaging}}$<0.05, $P_{\text{Holter-imaging}}$ and

Downloaded from http://ahajournals.org by on June 17, 2025

Circulation FIRST PROOF ONLY

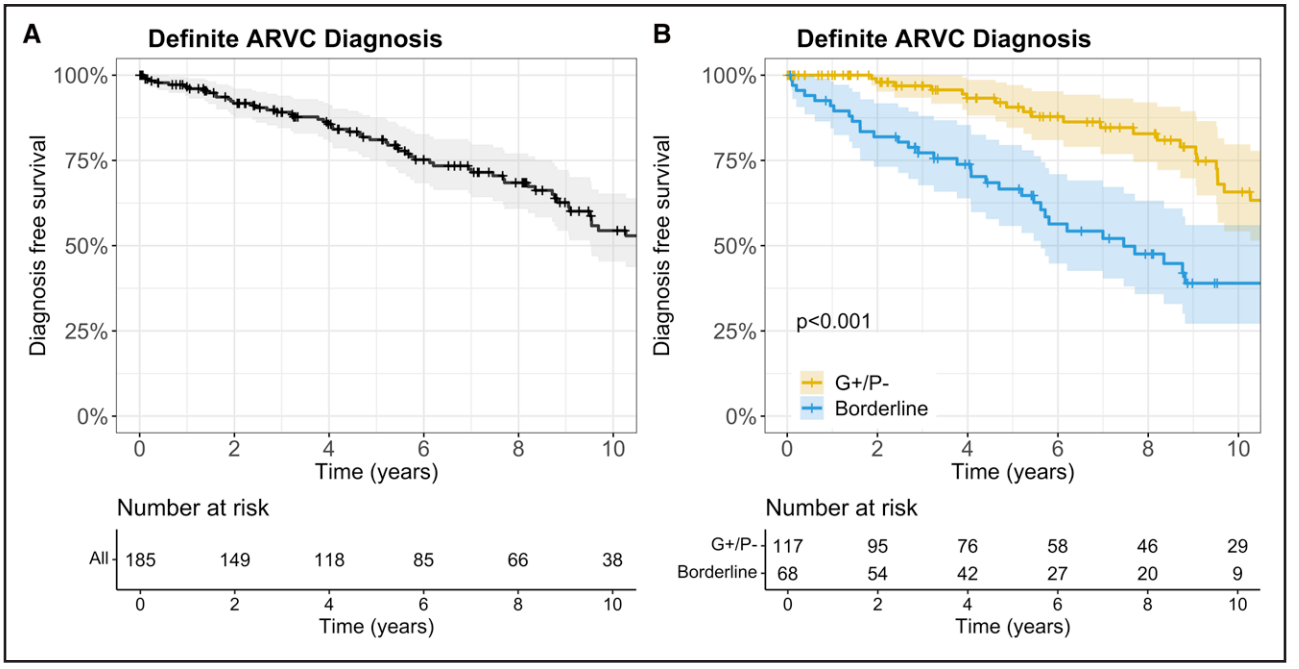


**Figure 3. Progression of disease.**
Survival curve of definite arrhythmogenic right ventricular cardiomyopathy (ARVC) diagnosis in the overall, nondefinite population (**A**) and stratified by baseline clinical phenotype (**B**). Relatives who are genotype positive/phenotype negative (G+/P−) and who have borderline ARVC are depicted as yellow and blue lines, respectively. Shaded areas indicate 95% CI. Censoring is indicated by a vertical bar.

$P_{ECG\text{-}Holter}$>0.05; Figure 5B). A nonsignificant trend was observed showing that the progression to new imaging criteria was driven mostly by new CMR TFC, which was followed at a later stage by echocardiography TFC (*P*>0.05; Figure 5C).

## Predictors of Progression

Relatives 20 to 40 years of age showed a significantly higher hazard for definite ARVC (hazard ratio, 2.33; *P*=0.012) compared with relatives ≥40 years of age (Table 2). Female sex was associated with higher risk of definite ARVC diagnosis at follow-up (hazard ratio, 2.38; *P*=0.002). In addition, symptomatic patients had a trend toward development of definite ARVC (hazard ratio, 1.79; *P*=0.058).

## Risk Profiles and Longitudinal Screening Algorithm

We defined 3 distinct risk profiles for relatives of patients with ARVC based on multistate modeling and the predictors: (1) relatives with borderline ARVC (n=68/185; 37%); (2) G+/P− relatives who were <40 years of age or symptomatic (n=94/185; 51%), and (3) asymptomatic G+/P− relatives who were ≥40 years of age (n=23/185; 12%). The proposed longitudinal screening algorithm derived from the 3 risk profiles is shown in Figure 6 and described in detail here.

### *Borderline ARVC*

Relatives with borderline ARVC had an 11% risk for development of definite ARVC and a 0.06% risk for VA at the 1-year follow-up (Figure 5A). Of note, the majority of new diagnoses were based on new ECG- and Holter monitoring–based TFC, with only 2% of new diagnoses explained by new imaging TFC (Figure 5B). Consequently, the number needed to image at a 1-year screening interval was 50. Therefore, proposing to annually screen relatives with borderline ARVC with only an ECG and Holter monitoring and a complete evaluation (ie, ECG, Holter monitoring, and imaging) every 2 years to use resources efficiently while still upholding a safe screening interval concerning the risk of definite ARVC and VA is clinically acceptable. Regardless, if a new TFC on ECG or Holter monitoring is established and a definite ARVC diagnosis is made, an imaging test is warranted for VA risk stratification.

### *Younger (<40 Years of Age) or Symptomatic G+/P− Relatives*

Because a 4-year screening interval is well within the clinically acceptable risk for definite ARVC (6.4% [95% CI, 4.5%–8.9%]) and VA (0.09% [95% CI, 0.04%–0.25%]) in younger or symptomatic G+/P− relatives, a complete evaluation (ie, ECG, Holter monitoring, and imaging) at a 4-year interval is adequate (Figure 5A). However, to avoid missing any relevant disease progression but also to use clinical resources efficiently, we propose an additional evaluation every 2 years with an ECG

Circulation FIRST PROOF ONLY

Downloaded from http://ahajournals.org by on June 17, 2025

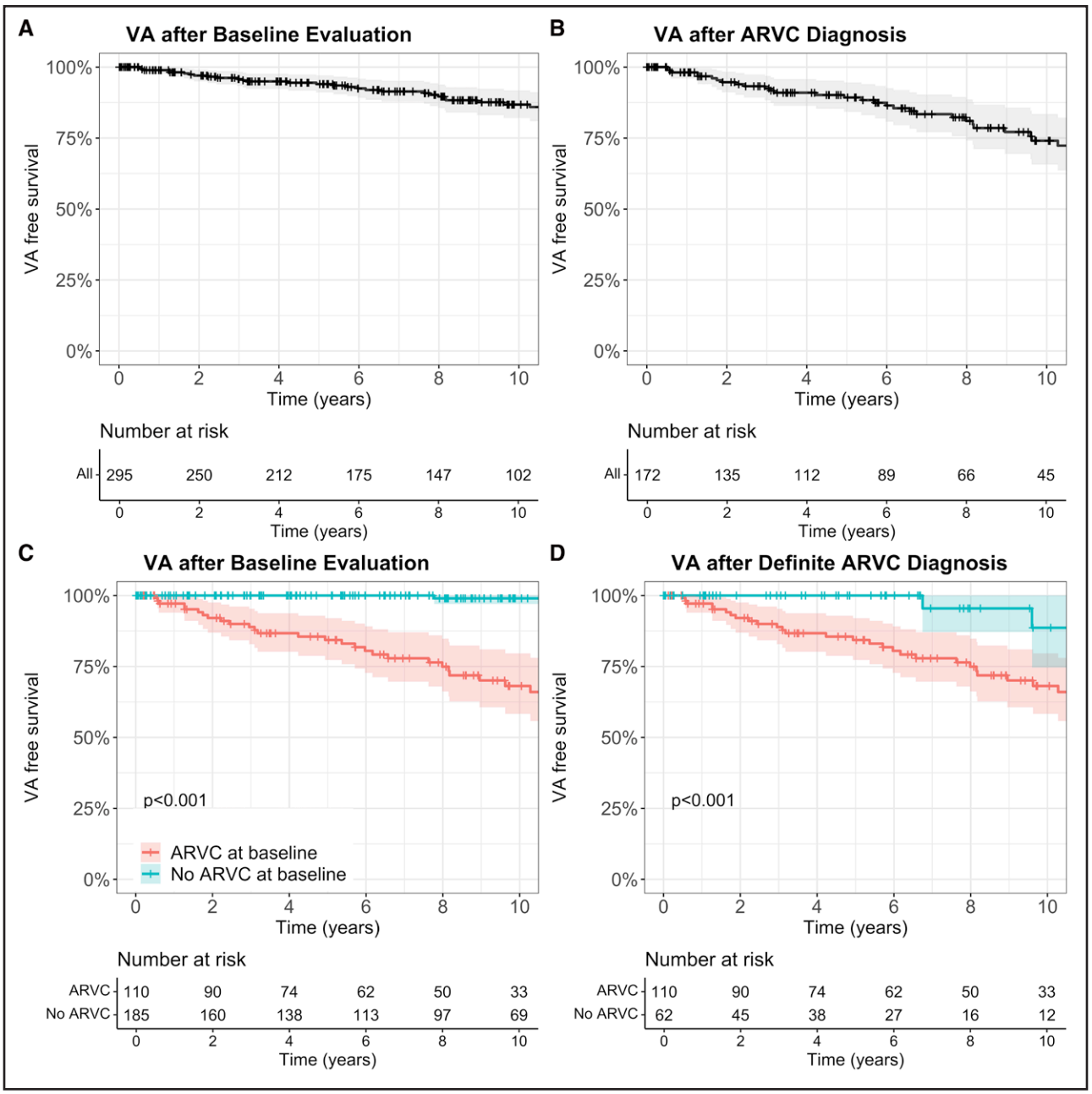


**Figure 4. Occurrence of VA.**
Survival curve of ventricular arrhythmia (VA) after baseline evaluation (**A**), arrhythmogenic right ventricular cardiomyopathy (ARVC) diagnosis (**B**), baseline evaluation stratified by baseline clinical phenotype (**C**), and ARVC diagnosis stratified by baseline clinical phenotype (**D**). Relatives with and without definite ARVC diagnosis at baseline are depicted as red and turquois lines, respectively. Because only 3 relatives (1.6%) without definite ARVC had a VA during follow-up, we combined the genotype-positive/phenotype-negative (G+/P−) relatives and relatives with borderline ARVC into a "no ARVC at baseline" group for visual purposes in **C** and **D**. Shaded areas indicate 95% CI. Censoring is indicated by a vertical bar.

and Holter monitoring. The combined yield for new TFC on ECG and Holter monitoring at a 2-year interval was 16.8% (95% CI, 12.4%–23.2%), and the added yield of an imaging modality for new TFC was 4.0% (95% CI, 2.7%–6.2%; Figure 5B). Of note, if a new TFC on ECG or Holter monitoring is established, an additional imaging test is warranted to adjudicate a potential definite ARVC diagnosis.

### *Older (≥40 Years of Age), Asymptomatic G+/P− Relatives*

A 5-year interval (9.3% [95% CI, 6.5%–13.0%] for definite ARVC; 0.2% [95% CI, 0.07%–0.45%] for VA; Figure 5A) for older and asymptomatic G+/P− relatives is well within the acceptable risk. Therefore, a 5-year screening interval with an ECG, Holter monitor, and an imaging test in older (≥40 years of age),

Downloaded from http://ahajournals.org by on June 17, 2025

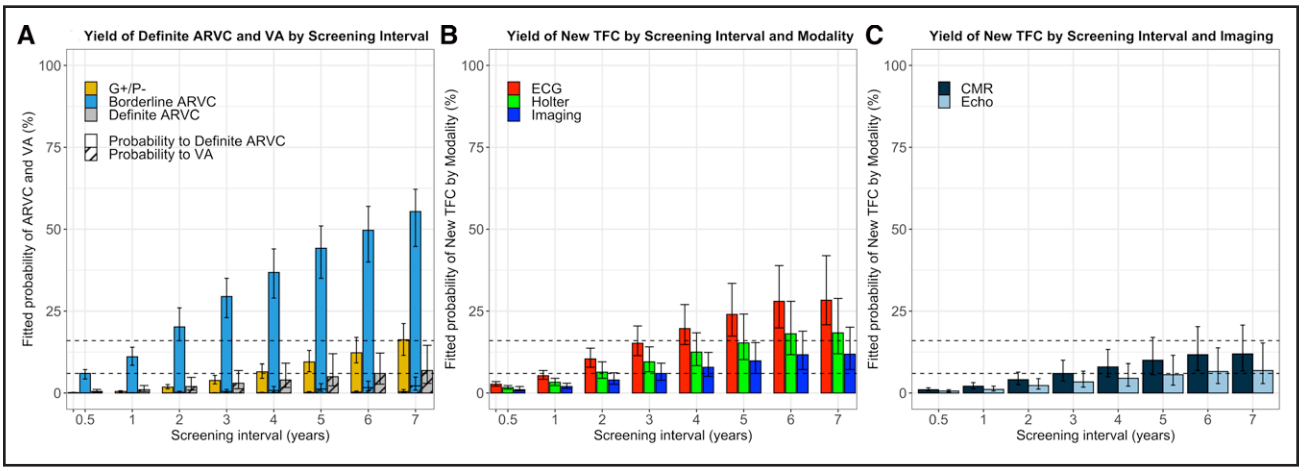


**Figure 5. Progression to developing definite ARVC, VA, and new TFC.**
**A**, Yield of screening stratified by baseline clinical phenotype for definite arrhythmogenic right ventricular cardiomyopathy (ARVC) and ventricular arrhythmia (VA; *y* axis) over different screening intervals (*x* axis). Every screening interval consists of 3 bars, which depict the genotype-positive/phenotype-negative (G+/P−; yellow), borderline ARVC (blue), and definite ARVC (gray) groups. The bars are divided into solid and striped bars, which differentiate between the probability of definite ARVC and VA, respectively. Of note, because relatives with definite ARVC have a 100% "probability of VA" probability of definite ARVC, we visualize only the probability of VA in that population. **B**, Yield of screening new Task Force Criteria (TFC) and ECG, Holter monitoring, and imaging TFC over different screening intervals. **C**, Yield of screening for new cardiac magnetic resonance imaging (CMR) and echocardiography TFC over different screening intervals. ECG, Holter monitoring, imaging, CMR, and echocardiography are indicated by red, green, blue, dark blue, and light blue bars, respectively. Dotted black line indicates the clinically acceptable risk for definite ARVC (ie, 6%–16%). Error bars indicate 95% CI.

asymptomatic G+/P− relatives is acceptable in daily clinical practice.

## DISCUSSION

This study represents the first systematic investigation of genotype-specific progression to definite ARVC and VA in relatives who harbor a familial P/LP *PKP2* variant. These results provide direct evidence to support a genotype-specific longitudinal family screening approach. From our findings, we propose distinct intervals of longitudinal screening for: (1) relatives with borderline ARVC (every year with an ECG and Holter monitoring and every 2 years with a complete evaluation [ie, ECG, Holter monitoring, and imaging]); (2) G+/P− relatives who were <40 years of age or symptomatic (every 2 years with an ECG and Holter monitoring and every 4 years with a complete evaluation), and (3) asymptomatic G+/P− relatives ≥40 years of age (every 5 years with a complete evaluation; Figure 6).

**Table 2. Frailty Cox Proportional Hazard Regression for Definite ARVC Diagnosis**

| | Analysis for definite ARVC diagnosis, adjusted for baseline clinical phenotype* | | | |
|---|---|---|---|---|
| | HR | Lower 95% CI | Upper 95% CI | *P* value |
| Age (referent: ≥40 y)† | … | … | … | |
| <14 y | 1.33 | 0.58 | 3.02 | 0.500 |
| 14–20 y | 1.34 | 0.61 | 2.97 | 0.470 |
| 20–40 y | 2.33 | 1.21 | 4.48 | 0.012 |
| Female sex | 2.38 | 1.39 | 4.17 | 0.002 |
| Sibling of the proband | 1.14 | 0.62 | 2.08 | 0.680 |
| Symptomatic | 1.79 | 0.98 | 3.25 | 0.058 |

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; and HR, hazard ratio.

Frailty Cox regression was used to adjust for family membership. No significant association between family membership and outcome was objectified in all analyses ($P>0.05$).

*The Cox regression consisted only of relatives without definite ARVC diagnosis at baseline; hence, the adjustment for baseline clinical phenotype consisted only of genotype positive/phenotype negative and borderline ARVC.

†Age was subdivided into groups because of nonlinearity.

### Relationship Among Family Screening, Early Diagnosis, and VA

Contemporary clinical guidelines recommending genetic testing in patients with ARVC and families have brought an increasing number of G+ relatives at risk for ARVC to clinical attention. Since the inception of family screening recommendations,[37] a number of studies have established the rate of progression to definite ARVC in G+ relatives.[21–23] a recent study found that the rate of structural progression does not differ between relatives and probands, regardless of phenotypic expression.[38] Our results enforce and extend these findings by showing that the rates of both structural and electrical progression are similar between clinical phenotypes. These findings are important to recognize because they underline that *PKP2*-associated ARVC follows a specific mode of progression, which is in contrast to other types of arrhythmogenic cardiomyopathy such as desmoplakin (*DSP*) cardiomyopathy.[7,8,12]

Downloaded from http://ahajournals.org by on June 17, 2025

Circulation FIRST PROOF ONLY

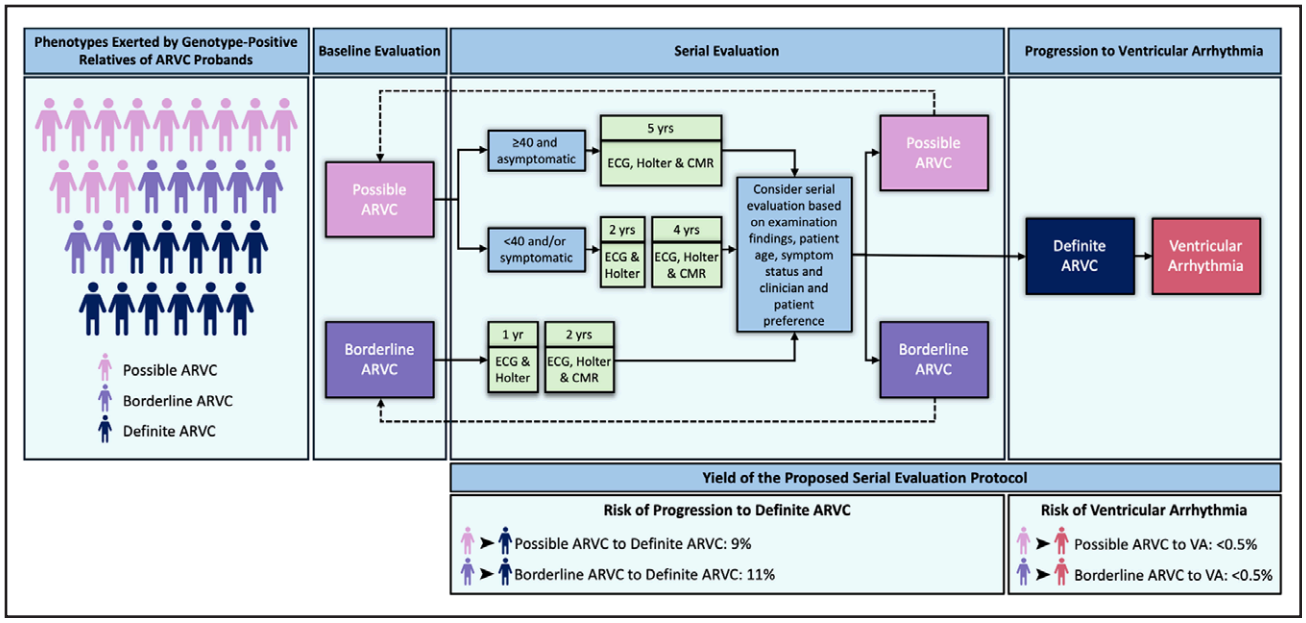


**Figure 6. Longitudinal screening algorithm for at-risk pathogenic or likely pathogenic *PKP2* carriers.**
The longitudinal screening algorithm. The baseline evaluation should start between 8 and 10 years of age, and the serial evaluation depends on the baseline clinical phenotype, presence of symptoms, and age: (1) genotype-positive/phenotype-negative (G+/P−) relatives who are ≥40 years of age and are asymptomatic should be evaluated every 5 years with an ECG, Holter monitoring, and imaging test; (2) G+/P− relatives who are <40 years of age or are symptomatic should be evaluated every 2 years with an ECG and Holter monitoring and every 4 years with an ECG, Holter monitoring, and imaging test; and (3) relatives with borderline arrhythmogenic right ventricular cardiomyopathy (ARVC) should be evaluated every year with an ECG and Holter monitoring and every 2 years with an ECG, Holter monitoring, and imaging test. If a relative remains in the same clinical phenotype (G+/P− or borderline ARVC) or progresses from G+/P− to borderline ARVC, screening intervals and management should be adjusted accordingly as shown by the dotted lines. If a relative progresses to definite ARVC, management and risk stratification should follow the most current guideline recommendations. Following this screening algorithm ensures that all relatives will be screened at a similar risk for progressing to definite ARVC (G+/P−, 9%; borderline ARVC, 11%) and ventricular arrhythmia (VA; both G+/P− and borderline ARVC, <0.5%). CMR indicates cardiac magnetic resonance imaging.

Circulation FIRST PROOF ONLY

Prior studies have shown that up to one-third of relatives have definite ARVC at baseline.[39] Indeed, more recent studies have confirmed this yield of baseline evaluation and extended it by showing that, after a median follow-up of 4 years, an additional one-third of relatives without definite ARVC at baseline progressed to definite ARVC diagnosis,[21–23] thus demonstrating the benefit of longitudinal family screening in at-risk relatives for ARVC. However, these studies did not model the impact of genotype on the development of ARVC.[21–23] The present study extends previous findings by including solely relatives harboring the familial P/LP *PKP2* variant and establishing a safe, evidence-driven, genotype-specific longitudinal screening algorithm, including risk of VA.

## Impact of Family Screening on Relatives Not Fulfilling Definite ARVC Diagnosis

Similar to previous family screening studies,[21–23] we found that the baseline yield of screening is approximately one-third and that an additional one-third can be diagnosed after 4 to 5 years of follow-up. We extended these findings by showing that relatives with the familial P/LP *PKP2* variant who progress to definite ARVC diagnosis during follow-up had less severe phenotypic expression at the time of diagnosis compared with those with definite ARVC at baseline. This is important because these relatives with *PKP2*-associated ARVC are diagnosed in a phase when lifestyle modification (ie, limiting exercise) may have a great influence on slowing ARVC progression and first VA occurrence.[40–43] Although we are fully aware that G+/P− relatives are recommended and should adhere to the exercise restrictions to slow ARVC progression,[42] a recent survey[44] showed that a nonnegligible portion of patients with ARVC will start to limit their exercise intensity at the time of definite ARVC diagnosis. This shows that early diagnosis, besides risk stratification for VA, has a practical implication in daily clinical practice to initiate lifestyle modification in *PKP2*-associated ARVC, which is in contrast to relatives with phospholamban (*PLN*)-associated ARVC in whom lifestyle modification does not influence progression of disease.[17]

Furthermore, we established that the rate of VA is very low and VA occurred only in those who fulfilled 2010 TFC during follow-up. In contrast to other studies,[1,45] we did not report any VAs in the "concealed ARVC" phase (ie, P/LP *PKP2* carriers not fulfilling definite ARVC diagnosis). This is reassuring for relatives

Downloaded from http://ahajournals.org by on June 17, 2025

harboring a P/LP *PKP2* variant because it shows that, when following our proposed longitudinal screening algorithm, all relatives are diagnosed with definite ARVC well before their first VA. These *PKP2*-specific findings are notably different from the much higher risks of G+ relatives with other genotypes, for example, the risks seen in relatives with the ARVC-associated transmembrane protein 43 (*TMEM43*) *P*.S358L variant.[13]

We also established clinical characteristics that are associated with definite ARVC in *PKP2* relatives. We showed that age-related progression peaked in early adulthood with a 2-fold higher hazard for definite ARVC diagnosis in relatives 20 to 40 years of age compared with those ≥40 years of age and shows that age-specific screening intervals are justified. Our results showed that female sex is associated with an ≈2-fold higher hazard of developing definite ARVC. However, previous studies have shown that female sex is associated with a lower hazard of VA. The well-established high risk of VA in young male patients with ARVC partially explains why men are more likely to be the proband of a family,[29,46] leading to a female predominance in this and other ARVC family screening studies.

## Diagnostic Tests Used in Family Screening

We also investigated how relatives progressed to new TFC to ultimately determine which diagnostic tests should be prioritized in the outpatient clinic. In line with our previous studies,[21,22] we showed that G+/P− relatives and relatives with borderline ARVC progress to new TFC at a similar rate. We extended this finding by showing that the modality of progression (ie, ECG, Holter monitoring, or imaging) in these relatives is also similar. In addition, a trend was observed in relatives without definite ARVC diagnosis who develop imaging TFC, indicating that CMR TFC precede echocardiography TFC. This may reflect the expertise required to perform precise right ventricular structural and functional quantification on echocardiography.

## Longitudinal Screening Algorithm in At-Risk Relatives

When a longitudinal screening algorithm is proposed, a major consideration is given to when to initiate family screening. Consistent with prior studies,[1,23] we found that the penetrance of definite ARVC diagnosis at <14 years of age is rare (n=1/110; 0.9%) and that VAs can occur in adolescence (youngest individual who experienced VA in our study population was 14 years of age). Therefore, initiating screening at 8 to 10 years of age is justifiable to diagnose severe cases before VA occurrence. After a baseline evaluation, 2 scenarios are possible: (1) if a definite ARVC diagnosis is made, decisions on the management (including VA risk stratification[29–31,47]) should be based on guideline-directed recommendations[3–6]; and (2) if no definite ARVC diagnosis is made, the evidence-driven *PKP2*-specific and personalized algorithm can be used for longitudinal screening (Figure 6).

Although our longitudinal screening algorithm warrants external validation, we believe that the findings of this study are reassuring for clinicians and families, considering the large sample size of relatives not fulfilling 2010 TFC at baseline with long-term follow-up, yielding a very low VA rate that occurred only after being diagnosed with definite ARVC for ≥5 years when our longitudinal screening algorithm was followed.

## Study Limitations

Although our cohort of comprehensively evaluated relatives with *PKP2* P/LP variants is a relatively large cohort of relatives of an individual with ARVC, we were underpowered to perform extensive multivariable analyses to ascertain independent predictors, particularly in the occurrence of VA. In addition, we did not include medication use (eg, beta-blockers) as a factor for disease progression, but they were initiated in some patients. In addition, because of the unavailability of exercise data for many relatives, we did not include exercise as a factor for disease progression despite its well-documented influence on development of ARVC and VA in *PKP2*-associated ARVC.[40,42,43] Certainly, screening intervals should be shortened in family members who choose to participate in competitive or frequent high-intensity exercise. Last, our multistate model was built mostly on G+/P− relatives who were younger or symptomatic, which could have led to a slight overestimation of progression of older asymptomatic G+/P− relatives.

## Conclusions

In this study, we showed that although the development of ARVC is slow in relatives with P/LP *PKP2* variants, younger relatives are at higher risk of disease progression. In addition, disease-related abnormalities were typically appreciated first on ECG and Holter monitoring. We propose a longitudinal screening algorithm that differentiates between relatives with: (1) borderline ARVC (annual screening with ECG and Holter monitoring and a complete evaluation every 2 years), (2) G+/P− relatives who are younger (<40 years of age) or symptomatic (an evaluation with ECG and Holter monitoring every 2 years with complete evaluation every 4 years), and (3) older (≥40 years of age), asymptomatic G+/P− relatives (complete evaluation every 5 years). When the proposed algorithm was evaluated in the present cohort, all potentially at-risk relatives were diagnosed with definite ARVC diagnosis at least 5 years before their VA.

Downloaded from http://ahajournals.org by on June 17, 2025

Circulation FIRST PROOF ONLY

## ARTICLE INFORMATION

Received February 9, 2025; accepted May 19, 2025.

### Affiliations

Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD (S.A.M., B.A., A.G., R.T.C., C.T., B.M., S.L.Z., H.C., C.A.J.). Department of Cardiology, University Medical Center Utrecht, Netherlands (S.A.M., M.J.C., P.L., P.v.d.H., M.I.F.J.O., A.S.J.M.t.R.). Member of the European Reference Network for rare, low prevalence and complex diseases of the heart: ERN GUARD-Heart' (S.A.M., M.J.C., A.S.A., P.L., P.v.d.H., M.I.F.J.O., S.-C.Y., J.P.v.T., A.S.J.M.t.R.). Amsterdam University Medical Centers, Department of Cardiology, University of Amsterdam, Netherlands (A.S.A.). Heart Center, University Medical Center Groningen, Department of Cardiology, University of Groningen, Netherlands (M.G.P.J.C.). Department of Cardiology, Thoraxcenter, Cardiovascular Institute, Erasmus Medical Center, Rotterdam, Netherlands (S.-C.Y.). Department of Genetics, University Medical Center Utrecht, Utrecht University, Netherlands (J.P.v.T.).

### Acknowledgments

The authors thank the ARVC relatives who have made this work possible.

### Sources of Funding

Dr Muller is supported by the Netherlands Heart Foundation, grant CVON 2018-30 Predict2 Young Talent Program. Dr Asatryan is supported by the 2022 research fellowship for aspiring electrophysiologists from the Swiss Heart Rhythm Foundation and a postdoctoral research fellowship grant from the Gottfried und Julia Bangerter-Rhyner-Stiftung (Switzerland). Dr Carrick is funded by a National Institutes of Health T32 grant (T32HL007227) and the National Institutes of Health loan repayment program (L30HL165535). Dr te Riele is supported by the ZonMW clinical fellows grant 2024 and ERC HORIZON IMPACT (#101115536). The Johns Hopkins ARVC Program is supported by the Leonie-Wild Foundation; the Leyla Erkan Family Fund for ARVD Research; The Hugh Calkins, Marvin H. Weiner, and Jacqueline J. Bernstein Cardiac Arrhythmia Center; the Dr Francis P. Chiramonte Private Foundation; the Dr Satish, Rupal, and Robin Shah ARVD Fund at Johns Hopkins; the Bogle Foundation; the Campanella family; the Patrick J. Harrison Family; the Peter French Memorial Foundation; and the Wilmerding Endowments. The Netherlands ACM Registry is supported by the Netherlands Heart Institute (project 06901).

### Disclosures

Dr James has received research support from Stride Bio Inc, Lexeo Therapeutics, and ARVADA Therapeutics. C. Tichnell has received salary support on these grants. Dr te Riele is a consultant for Tenaya, Rocket Pharmaceuticals, and BioMarin for unrelated work (gene therapy trials). Drs James and Gasperetti have served as compensated consultants for LEXEO Therapeutics for unrelated work. Dr Yap has received honoraria (speaker or consultancy fees) from Boston Scientific, Medtronic, Biotronik, and Acutus Medical. In addition, he has received research grants from Medtronic, Biotronik, and Boston Scientific. The other authors report no conflicts.

### Supplemental Material

Methods
Tables S1–S4
Figures S1–S13

## REFERENCES


1. Bhonsale A, Groeneweg JA, James CA, Dooijes D, Tichnell C, Jongbloed JDH, Murray B, te Riele ASJM, van den Berg MP, Bikker H, et al. Impact of genotype on clinical course in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated mutation carriers. *Eur Heart J*. 2015;36:847–855. doi: 10.1093/eurheartj/ehu509
2. Marcus FI, Fontaine GH, Guiraudon G, Frank R, Laurenceau JL, Malergue C, Grosgogeat Y. Right ventricular dysplasia: a report of 24 adult cases. *Circulation*. 1982;65:384–398. doi: 10.1161/01.cir.65.2.384
3. Towbin JA, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC, Daubert JP, de Chillou C, DePasquale EC, Desai MY, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm*. 2019;16:e301–e372. doi: 10.1016/j.hrthm.2019.05.007
4. Corrado D, Wichter T, Link MS, Hauer RNW, Marchlinski FE, Anastasakis A, Bauce B, Basso C, Brunckhorst C, Tsatsopoulou A, et al. Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement. *Circulation*. 2015;132:441–453. doi: 10.1161/CIRCULATIONAHA.115.017944
5. Hershberger RE, Givertz MM, Ho CY, Judge DP, Kantor PF, McBride KL, Morales A, Taylor MRG, Vatta M, Ware SM. Genetic evaluation of cardiomyopathy: a Heart Failure Society of America practice guideline. *J Card Fail*. 2018;24:281–302. doi: 10.1016/j.cardfail.2018.03.004
6. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, Bezzina CR, Biagini E, Blom NA, de Boer RA, et al; ESC Scientific Document Group. 2023 ESC guidelines for the management of cardiomyopathies. *Eur Heart J*. 2023;44:3503–3626. doi: 10.1093/eurheartj/ehad194
7. Smith ED, Lakdawala NK, Papoutsidakis N, Aubert G, Mazzanti A, McCanta AC, Agarwal PP, Arscott P, Dellefave-Castillo LM, Vorovich EE, et al. Desmoplakin cardiomyopathy, a fibrotic and inflammatory form of cardiomyopathy distinct from typical dilated or arrhythmogenic right ventricular cardiomyopathy. *Circulation*. 2020;141:1872–1884. doi: 10.1161/CIRCULATIONAHA.119.044934
8. Wang W, Murray B, Tichnell C, Gilotra NA, Zimmerman SL, Gasperetti A, Scheel P, Tandri H, Calkins H, James CA. Clinical characteristics and risk stratification of desmoplakin cardiomyopathy. *Europace*. 2022;24:268–277. doi: 10.1093/europace/euab183
9. Protonotarios A, Bariani R, Cappelletto C, Pavlou M, García-García A, Cipriani A, Protonotarios I, Rivas A, Wittenberg R, Graziosi M, et al. Importance of genotype for risk stratification in arrhythmogenic right ventricular cardiomyopathy using the 2019 ARVC risk calculator. *Eur Heart J*. 2022;43:3053–3067. doi: 10.1093/eurheartj/ehac235
10. Carrick RT, Gasperetti A, Protonotarios A, Murray B, Laredo M, van der Schaaf I, Dooijes D, Syrris P, Cannie D, Tichnell C, et al. A novel tool for arrhythmic risk stratification in desmoplakin gene variant carriers. *Eur Heart J*. 2024;45:2968–2979. doi: 10.1093/eurheartj/ehae409
11. Gasperetti A, Carrick R, Protonotarios A, Laredo M, van der Schaaf I, Syrris P, Murray B, Tichnell C, Cappelletto C, Gigli M, et al. Long-term arrhythmic follow-up and risk stratification of patients with desmoplakin-associated arrhythmogenic right ventricular cardiomyopathy. *JACC Adv*. 2024;3:100832. doi: 10.1016/j.jacadv.2024.100832
12. Gasperetti A, Carrick RT, Protonotarios A, Murray B, Laredo M, van der Schaaf I, Lekanne RH, Syrris P, Cannie D, Tichnell C, et al. Clinical features and outcomes in carriers of pathogenic desmoplakin variants. *Eur Heart J*. 2025;46:362–376. doi: 10.1093/eurheartj/ehae571
13. Hodgkinson K, Connors S, Merner N, Haywood A, Young T, McKenna W, Gallagher B, Curtis F, Bassett A, Parfrey P. The natural history of a genetic subtype of arrhythmogenic right ventricular cardiomyopathy caused by a p.S358L mutation in <scp>TMEM43</scp>. *Clin Genet*. 2013;83:321–331. doi: 10.1111/j.1399-0004.2012.01919.x
14. Protonotarios I, Asimaki A, Xylouri Z, Protonotarios A, Tsatsopoulou A. Clinical and molecular aspects of Naxos disease. *Heart Fail Clin*. 2022;18:89–99. doi: 10.1016/j.hfc.2021.07.010
15. Bermudez-Jimenez FJ, Protonotarios A, García-Hernández S, Pérez Asensio A, Rampazzo A, Zorio E, Brodehl A, Arias MA, Macías-Ruiz R, Fernández-Armenta J, et al. Phenotype and clinical outcomes in desmin-related arrhythmogenic cardiomyopathy. *JACC Clin Electrophysiol*. 2024;10:1178–1190. doi: 10.1016/j.jacep.2024.02.031
16. Verstraelen TE, van Lint FHM, Bosman LP, de Brouwer R, Proost VM, Abeln BGS, Taha K, Zwinderman AH, Dickhoff C, Oomen T, et al. Prediction of ventricular arrhythmia in phospholamban p.Arg14del mutation carriers-reaching the frontiers of individual risk prediction. *Eur Heart J*. 2021;42:2842–2850. doi: 10.1093/eurheartj/ehab294
17. van Lint FHM, Hassanzada F, Verstraelen TE, Wang W, Bosman LP, van der Zwaag PA, Oomen T, Calkins H, Murray B, Tichnell C, et al. Exercise does not influence development of phenotype in PLN p.(Arg14del) cardiomyopathy. *Neth Heart J*. 2023;31:291–299. doi: 10.1007/s12471-023-01800-4
18. Muller SA, Bertoli G, Wang J, Gasperetti A, Cox MGPJ, Calkins H, Te Riele ASJM, Judge DP, Delmar M, Hauer RNW, et al. Arrhythmogenic cardiomyopathy: towards genotype based diagnoses and management [published online December 2, 2024]. *J Cardiovasc Electrophysiol*. doi: 10.1111/jce.16519. https://onlinelibrary.wiley.com/doi/10.1111/jce.16519
19. Asatryan B, Rieder M, Murray B, Muller SA, Tichnell C, Gasperetti A, Carrick RT, Joseph E, Leung DG, Te Riele ASJM, et al. Natural history, phenotype spectrum, and clinical outcomes of desmin (DES)-associated cardiomyopathy. *Circ Genom Precis Med*. 2025;18:e004878. doi: 10.1161/CIRCGEN.124.004878
20. Chen L, Hu Y, Saguner AM, Bauce B, Liu Y, Shi A, Guan F, Chen Z, Bueno Marinas M, Wu L, et al. Natural history and clinical outcomes of patients with *DSG2/DSC2* variant-related arrhythmogenic right


Downloaded from http://ahajournals.org by on June 17, 2025

Circulation FIRST PROOF ONLY

ventricular cardiomyopathy. *Circulation*. 2025;151:1213–1230. doi: 10.1161/CIRCULATIONAHA.124.072226
21. te Riele ASJM, James CA, Rastegar N, Bhonsale A, Murray B, Tichnell C, Judge DP, Bluemke DA, Zimmerman SL, Kamel IR, et al. Yield of serial evaluation in at-risk family members of patients with ARVD/C. *J Am Coll Cardiol*. 2014;64:293–301. doi: 10.1016/j.jacc.2014.04.044
22. Muller SA, Gasperetti A, Bosman LP, Schmidt AF, Baas AF, Amin AS, Houweling AC, Wilde AAM, Compagnucci P, Targetti M, et al. Individualized family screening for arrhythmogenic right ventricular cardiomyopathy. *J Am Coll Cardiol*. 2023;82:214–225. doi: 10.1016/j.jacc.2023.05.005
23. te Riele ASJM, James CA, Groeneweg JA, Sawant AC, Kammers K, Murray B, Tichnell C, van der Heijden JF, Judge DP, Dooijes D, et al. Approach to family screening in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Eur Heart J*. 2016;37:755–763. doi: 10.1093/eurheartj/ehv387
24. Stroeks SLVM, Muller S, Beelen NJ, Venner MFGHM, Baas AF, van Empel VPM, Krapels IPC, Hazebroek MR, te Riele ASJM, Verdonschot JAJ. Family screening in patients with dilated and arrhythmogenic cardiomyopathy: the road toward gene-specific recommendations. *Circ Genom Precis Med*. 2025;18:e004778. doi: 10.1161/CIRCGEN.124.004778
25. Bosman LP, Verstraelen TE, van Lint FHM, Cox MGPJ, Groeneweg JA, Mast TP, van der Zwaag PA, Volders PGA, Evertz R, Wong L, et al; Netherlands ACM Registry. The Netherlands Arrhythmogenic Cardiomyopathy Registry: design and status update. *Neth Heart J*. 2019;27:480–486. doi: 10.1007/s12471-019-1270-1
26. Sammani A, Jansen M, Linschoten M, Bagheri A, de Jonge N, Kirkels H, van Laake LW, Vink A, van Tintelen JP, Dooijes D, et al. UNRAVEL: big data analytics research data platform to improve care of patients with cardiomyopathies using routine electronic health records and standardised biobanking. *Neth Heart J*. 2019;27:426–434. doi: 10.1007/s12471-019-1288-4
27. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MGPJ, Daubert JP, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. *Eur Heart J*. 2010;31:806–814. doi: 10.1093/eurheartj/ehq025
28. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, et al; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17:405–424. doi: 10.1038/gim.2015.30
29. Cadrin-Tourigny J, Bosman LP, Nozza A, Wang W, Tadros R, Bhonsale A, Bourfiss M, Fortier A, Lie OH, Saguner AM, et al. A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J*. 2022;43:e1–e9. doi: 10.1093/eurheartj/ehac180
30. Carrick RT, Te Riele ASJM, Gasperetti A, Bosman L, Muller SA, Pendleton C, Tichnell C, Murray B, Yap S-C, van den Berg MP, et al. Longitudinal prediction of ventricular arrhythmic risk in patients with arrhythmogenic right ventricular cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2022;15:e011207. doi: 10.1161/CIRCEP.122.011207
31. Cadrin-Tourigny J, Bosman LP, Wang W, Tadros R, Bhonsale A, Bourfiss M, Lie OH, Saguner AM, Svensson A, Andorin A, et al. Sudden cardiac death prediction in arrhythmogenic right ventricular cardiomyopathy: a multinational collaboration. *Circ Arrhythm Electrophysiol*. 2021;14:e008509. doi: 10.1161/CIRCEP.120.008509
32. Carrick RT, De Marco C, Gasperetti A, Bosman LP, Gourraud J-B, Trancuccio A, Mazzanti A, Murray B, Pendleton C, Tichnell C, et al. Implantable cardioverter defibrillator use in arrhythmogenic right ventricular cardiomyopathy in North America and Europe. *Eur Heart J*. 2024;45:538–548. doi: 10.1093/eurheartj/ehad799
33. Muller SA, Asatryan B, Murray B, Tichnell C, Cox MGPJ, Amin AS, Yap S-C, Gasperetti A, Carrick RT, Cadrin-Tourigny J, et al. Performance of ARVC risk calculators in (likely) pathogenic plakophilin-2 variant carriers without definite ARVC diagnosis. *Circ Arrhythm Electrophysiol*. 2024;18:e013144. doi: 10.1161/CIRCEP.124.013144
34. Carrick RT, Carruth ED, Gasperetti A, Murray B, Tichnell C, Gaine S, Sampognaro J, Muller SA, Asatryan B, Haggerty C, et al. Improved diagnosis of arrhythmogenic right ventricular cardiomyopathy using electrocardiographic deep-learning. *Heart Rhythm*. 2025;22:1080–1088. doi: 10.1016/j.hrthm.2024.08.030
35. Jackson CH. Multi-state models for panel data: the msm package for *R*. *J Stat Softw*. 2011;38:1–28. doi: 10.18637/jss.v038.i08
36. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika*. 1982;69:239–241. doi: 10.2307/2335876
37. McKenna WJ, Thiene G, Nava A, Fontaliran F, Blomstrom-Lundqvist C, Fontaine G, Camerini F. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy: 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. *Br Heart J*. 1994;71:215–218. doi: 10.1136/hrt.71.3.215
38. Chivulescu M, Lie OH, Popescu BA, Skulstad H, Edvardsen T, Jurcut RO, Haugaa KH. High penetrance and similar disease progression in probands and in family members with arrhythmogenic cardiomyopathy. *Eur Heart J*. 2020;41:1401–1410. doi: 10.1093/eurheartj/ehz570
39. Dalal D, Tandri H, Judge DP, Amat N, Macedo R, Jain R, Tichnell C, Daly A, James C, Russell SD, et al. Morphologic variants of familial arrhythmogenic right ventricular dysplasia/cardiomyopathy a genetics-magnetic resonance imaging correlation study. *J Am Coll Cardiol*. 2009;53:1289–1299. doi: 10.1016/j.jacc.2008.12.045
40. Wang W, Orgeron G, Tichnell C, Murray B, Crosson J, Monfredi O, Cadrin-Tourigny J, Tandri H, Calkins H, James CA. Impact of exercise restriction on arrhythmic risk among patients with arrhythmogenic right ventricular cardiomyopathy. *J Am Heart Assoc*. 2018;7:e008843. doi: 10.1161/JAHA.118.008843
41. Gasperetti A, Cappelletto C, Carrick R, Targetti M, Tichnell C, Martino A, Murray B, Compagnucci P, Stolfo D, Bisson J, et al. Association of premature ventricular contraction burden on serial Holter monitoring with arrhythmic risk in patients with arrhythmogenic right ventricular cardiomyopathy. *JAMA Cardiol*. 2022;7:378–385. doi: 10.1001/jamacardio.2021.6016
42. Wang W, Tichnell C, Murray BA, Agafonova J, Cadrin-Tourigny J, Chelko S, Tandri H, Calkins H, James CA. Exercise restriction is protective for genotype-positive family members of arrhythmogenic right ventricular cardiomyopathy patients. *Europace*. 2020;22:1270–1278. doi: 10.1093/europace/euaa105
43. James CA, Bhonsale A, Tichnell C, Murray B, Russell SD, Tandri H, Tedford RJ, Judge DP, Calkins H. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. *J Am Coll Cardiol*. 2013;62:1290–1297. doi: 10.1016/j.jacc.2013.06.033
44. Sweeney J, Tichnell C, Christian S, Pendelton C, Murray B, Roter DL, Jamal L, Calkins H, James CA. Characterizing decision-making surrounding exercise in ARVC: analysis of decisional conflict, decisional regret, and shared decision-making. *Circ Genom Precis Med*. 2023;16:e004133. doi: 10.1161/CIRCGEN.123.004133
45. Zorzi A, Rigato I, Pilichou K, Perazzolo Marra M, Migliore F, Mazzotti E, Gregori D, Thiene G, Daliento L, Iliceto S, et al. Phenotypic expression is a prerequisite for malignant arrhythmic events and sudden cardiac death in arrhythmogenic right ventricular cardiomyopathy. *Europace*. 2016;18:1086–1094. doi: 10.1093/europace/euv205
46. Jordà P, Bosman LP, Gasperetti A, Mazzanti A, Gourraud JB, Davies B, Frederiksen TC, Weidmann ZM, Di Marco A, Roberts JD, et al. Arrhythmic risk prediction in arrhythmogenic right ventricular cardiomyopathy: external validation of the arrhythmogenic right ventricular cardiomyopathy risk calculator. *Eur Heart J*. 2022;43:3041–3052. doi: 10.1093/eurheartj/ehac289
47. Gasperetti A, Carrick RT, Costa S, Compagnucci P, Bosman LP, Chivulescu M, Tichnell C, Murray B, Tandri H, Tadros R, et al. Programmed ventricular stimulation as an additional primary prevention risk stratification tool in arrhythmogenic right ventricular cardiomyopathy: a multinational study. *Circulation*. 2022;146:1434–1443. doi: 10.1161/CIRCULATIONAHA.122.060866

Downloaded from http://ahajournals.org by on June 17, 2025

Circulation FIRST PROOF ONLY