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ORIGINAL ARTICLE

Longitudinal Prediction of Ventricular Arrhythmic Risk in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy

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BACKGROUND: The arrhythmogenic right ventricular cardiomyopathy (ARVC) risk calculator stratifies risk for incident sustained ventricular arrhythmias (VA) at the time of ARVC diagnosis. However, included risk factors change over time, and how well the ARVC risk calculator performs at follow-up is unknown.

METHODS: This was a retrospective analysis of patients with definite ARVC and without prior sustained VA. Risk factors for VA including age, nonsustained ventricular tachycardia, premature ventricular complex burden, T-wave inversions on electrocardiogram, cardiac syncope, right ventricular function, therapeutic medication use, and exercise intensity were assessed at the time of 2010 Task Force Criteria based ARVC diagnosis and upon repeat evaluations. Changes in these risk factors were analyzed over 5-year follow-up. The 5-year risk of VA was predicted longitudinally using (1) the baseline ARVC risk calculator prediction, (2) the ARVC risk prediction calculated using updated risk factors, and (3) time-varying Cox regression. Discrimination and calibration were assessed in comparison to observed VA event rates.

RESULTS: Four hundred eight patients with ARVC experiencing 132 primary VA events were included. Matched comparison of risk factors at baseline versus at 5 years of follow-up revealed decreased burdens of premature ventricular complexes (−1200/day) and nonsustained ventricular tachycardia (−14%). Presence of significant right ventricular dysfunction and number of T-wave inversions on electrocardiogram were unchanged. Observed risk for VA decreased by 13% by 5 years follow-up. The baseline ARVC risk calculator's ability to predict 5-year VA risk worsened during follow-up (C statistics, 0.83 at diagnosis versus 0.68 at 5 years). Both the updated ARVC risk calculator (C statistics of 0.77) and time-varying Cox regression model (C statistics, 0.77) had strong discrimination. The updated ARVC risk calculator overestimated 5-year VA risk by an average of +6%.

CONCLUSIONS: Risk factors for VA in ARVC are dynamic, and overall risk for incident sustained VA decreases during follow-up. Up-to-date risk factor assessment improves VA risk stratification.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cardiomyopathy ■ death, sudden, cardiac ■ defibrillator, implantable ■ risk factors ■ tachycardia

Arrhythmogenic right ventricular (RV) cardiomyopathy (ARVC), the most common form of arrhythmogenic cardiomyopathy, is a heterogeneous genetic disease characterized by fibro-fatty infiltration of the myocardium and the development of potentially lethal ventricular arrhythmias (VA).[1] Although ARVC is rare with a prevalence of only 1 in 1000 to 1 in 5000,[2,3] it accounts for 10% to 20% of sudden cardiac deaths (SCD) in young

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WHAT IS KNOWN?

- Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic cardiomyopathy associated with a high burden of ventricular arrhythmias.
- The ARVC risk calculator is a clinical tool used for identifying high-risk patients who may benefit from a primary prevention implantation of cardioverter defibrillator.

WHAT THE STUDY ADDS

- Following initial ARVC diagnosis, average risk for developing ventricular arrhythmias events decreases with time, as does the burden of premature ventricular complexes and prevalence of nonsustained ventricular tachycardia.
- While the ARVC risk calculator maintains excellent ventricular arrhythmias risk discrimination out to 5 years of follow-up, it should be recalculated at each follow-up using the most recent set of clinical risk factors.
- Ventricular arrhythmias risk predictions from the ARVC risk calculator are overestimated by an average of +6% by 5 years of follow-up.

Nonstandard Abbreviations and Acronyms

ARVC	arrhythmogenic right ventricular cardiomyopathy
CMR	cardiac magnetic resonance
ICD	implantable cardioverter defibrillator
NSVT	nonsustained ventricular tachycardia
PVC	premature ventricular contraction
RVEF	right ventricular ejection fraction
SCD	sudden cardiac death
TWI	T-wave inversions
VA	ventricular arrhythmias
VT	ventricular tachycardia

adults.[4] The judicious implantation of cardioverter defibrillators (ICDs) in high-risk patients with ARVC is thus a core component of disease management. However, device-related risks are well known and may be particularly impactful among patients with ARVC who are generally diagnosed at younger ages.[5,6] Prospectively identifying those patients who are at high risk for VA, and consequently more likely to derive benefit from ICD placement, is, therefore, of critical importance in implantation decision-making.

The ARVC risk calculator was recently proposed as a tool for individualized VA risk assessment.[7] The Cox proportional hazards-based ARVC risk calculator incorporates a series of seven clinical predictors (age, sex, RV ejection fraction [RVEF], premature ventricular complex [PVC] burden on ambulatory cardiac monitoring, history of nonsustained VT [NSVT], the total number of T-wave inversions (TWI) in precordial and inferior leads on ECG, and history of recent cardiac syncope) to determine a particular patient's likelihood of developing incident VA over the 5-year period following his or her ARVC diagnosis. This tool has demonstrated excellent ability to discriminate between low- and high-risk patients with ARVC (C statistics, of 0.77) and has been increasingly adopted into clinical ICD decision-making algorithms.[8] However, ARVC is a progressive condition, and clinical predictors included in the ARVC risk calculator may be dynamic.[9–11] How reliably this tool performs at subsequent evaluations after initial diagnosis is, therefore, unknown, limiting longitudinal risk assessment in these patients.

To address this question, we analyzed data from a large, multicenter cohort of patients with ARVC without prior sustained VA which included repeat clinical, imaging, and electrophysiologic assessments during routine follow-up. We hypothesized that VA risk predictors change over time, and that incorporation of these changes is necessary for accurate longitudinal risk prediction in ARVC.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

We conducted an observational, retrospective, longitudinal cohort study in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement.[12]

Study Population

The study population comprised patients enrolled in the Johns Hopkins ARVC registry and the Netherlands Arrhythmogenic Cardiomyopathy registry. In brief, consecutive patients were included in the current study if (1) they were diagnosed with definite ARVC by the 2010 Task Force Criteria,[1] (2) had not experienced prior sustained VA at the time of ARVC diagnosis, and (3) had longitudinal clinical follow-up of at least 1 day. This study conforms to the Helsinki declaration and was approved by local ethics or institutional review boards. Participants signed informed consent to have their data included in the registry.

Data Collection

As described previously,[7] data were collected independently by each participating center using uniform definitions (Table S1). Outcomes and baseline characteristics were adjudicated at each center via review of clinical visit documentation, ECG tracings, ICD interrogation tracings, ambulatory cardiac monitoring reports, echocardiography reports, cardiac magnetic resonance imaging (CMR) reports, as well as medical and death records. Genetic variants were adjudicated according to the American

College of Medical Genetics and Genomics guidelines by consensus of specialists in cardiac genetics.[13] Additional longitudinal data from subsequent clinical follow-up were also collected, including repeat ECG tracings, echocardiography reports, ambulatory cardiac monitoring reports, prescribed medication reviews, and exercise histories. Due to high prevalence of ICD implantation in these patients and the resulting low number of repeat CMR studies performed during follow-up, longitudinal CMR data was not included.

Study Outcomes

Consistent with the published ARVC risk calculator,[7] the primary outcome was first sustained VA following confirmed ARVC diagnosis. Sustained VA was defined as a composite of SCD, sudden cardiac arrest, spontaneous sustained ventricular tachycardia (VT; lasting ≥30 s at ≥100 beats per minute or with hemodynamic compromise requiring cardioversion), ventricular fibrillation, or appropriate ICD intervention (defined as anti-tachycardia pacing or defibrillation). Incident heart transplantation, cardiovascular mortality, and all-cause mortality were also collected.

Predictor Variables and the ARVC Risk Calculator

Variables included in the ARVC risk calculator were considered.[7] These include sex, age, recent cardiac syncope (defined as transient loss of consciousness and postural tone with spontaneous recovery with a likely arrhythmic mechanism within the preceding 6 months), presence of NSVT (defined as hemodynamically stable VT at ≥100 beats per minute, for ≥3 beats <30 s), burden of PVCs on most recent 24-hour ambulatory cardiac monitoring, extent (defined as sum) of TWI on anterior and inferior leads on ECG, and RVEF. Each predictor variable was determined at the time of diagnosis, defined as within 1 year of ARVC diagnosis but always before arrhythmic outcome, and at each follow-up visit. The timing of clinical follow-up was based upon the discretion of local physicians.

Due to the limited availability of CMR-derived RVEF assessments during follow-up, the ARVC risk calculator was modified by replacing the RVEF variable with presence of moderate or severe RV dysfunction as a dichotomous, echocardiographically-derived variable (Supplemental Methods S1). We will refer to this model as the modified ARVC risk calculator, the formula of which is presented in Equation 1,

$$P(\text{Sustained VA by5 years}) = 1 - 0.791^{\exp(\text{Prognostic Index})} \quad (1)$$

where prognostic index is calculated according to Equation 2.

$$\begin{aligned}\text{Prognostic Index} = &-\text{Age} * 0.022 + \text{Male sex} * 0.558 + \\ &\text{Presence of NSVT} * 0.754 + \text{Cardiac Syncope} * 0.441 + \\ &\text{Burden TWI} * 0.096 + \ln(24 - \text{PVC count}) * 0.278 + \\ &\text{Presence of Moderate or Severe RV dysfunction} * 0.351 - 2.176\end{aligned} \quad (2)$$

Discrimination of this model was assessed using concordance-based C statistics and 5-fold cross-validation.

Longitudinal VA Risk. Risk Predictor Trends, and Risk Prediction at Follow-Up

Longitudinal trends in risk factors included in the ARVC risk calculator, as well as those of alternative risk modifiers (left ventricular ejection fraction, prescription rates of antiarrhythmic medications and beta blockers, and level of athletic activity) were assessed by plotting the change in risk factor values relative to their patient-matched value at the time of diagnosis as a function of follow-up time. A window size equal to 2 years was used for the moving average, and analysis was limited to those patients for whom relevant testing/evaluation was available at both time of diagnosis and follow-up. Patient data was not censored by VA events.

Longitudinal VA risk was estimated by repeating Kaplan-Meier analysis at each follow-up time out to 5 years. Patients were included in these analyses if they remained free of VA at the assessed follow-up time. Longitudinal prediction of 5-year VA risk was performed using three methods for interval follow-up risk estimation:

1. Baseline ARVC risk calculator: risk prediction calculated using only risk factors available at the time of diagnosis.
2. Updated ARVC risk calculator: risk prediction calculated using the most recent set of risk factors available at the time of follow-up evaluation.
3. Time-varying Cox regression: non-proportional Cox regression model that predicts risk as a function of both changing risk factors and the baseline hazard function (Supplemental Methods S2).

Statistical Analysis

Analyses were performed using PyCharm software version 2021.2 (JetBrains, Inc, Boston, MA) and open-source Pandas data analysis library, Lifelines survival analysis library, and statsmodels statistical modeling library. Missingness in data for the predictors included in the baseline ARVC calculator was assumed to be at random and imputed using multiple imputation with chained equations.[14] The final model included all predictors included in the ARVC risk calculator together with VA outcome and a cumulative baseline hazard estimation. A total of 20 imputed datasets were generated using 20 iterations each, and the final estimates were combined using Rubin rule.[15] Categorical variables were summarized as frequencies (%) and compared using proportional Z test. Continuous variables were presented as mean±SD or median (interquartile range) and compared using the independent sample Students t test or the Mann-Whitney U test, as appropriate.

For patients with known risk factor values at both the time of diagnosis and at least 3 years of follow-up, Wilcoxon signed-rank tests were used to assess differences between risk factor values at the 2 time points. For patients with >1 repeat risk factor assessment, the value from closest to 5 years of follow-up was selected. Follow-up duration was calculated from the date of diagnosis to the date of composite outcome occurrence or censoring (defined as death from any other cause, heart transplantation, or the most recent follow-up visit). Survival curves were estimated using the Kaplan-Meier method. The strengths of associations between risk factor variables and VA events were reported as hazard ratios derived from Cox proportional hazards modeling of baseline risk factors and from unrestricted Cox regression analysis of all available longitudinal risk factor data.

The longitudinal performances of the 3 methods for estimating 5-year VA risk were compared by generating time-dependent receiver operator characteristics and calculating the area under these curves for each follow-up time between time of diagnosis and 5 years[16]; error was reported with 95% CIs and curves were smoothed to facilitate visual interpretation using locally weighted

scatterplot smoothing with a weighting fraction of 0.2. Calibration was assessed by calculating the mean risk predictions for low (0%–10%), intermediate (10%–25%), and high (>25%) risk patients as assessed by the modified ARVC risk calculator at time of diagnosis, and comparing to mean observed risk as estimated by the Kaplan-Meier method in these risk groups. Differences in predicted versus observed risk (miscalibration) were assessed using empiric exponential decay functions (Supplemental Methods S3) for both the overall cohort and each of the 3 risk groups.

RESULTS

Study Population

The study included 408 patients, of whom 146 were from the Netherlands Arrhythmogenic Cardiomyopathy registry (36%) and 262 were from the Johns Hopkins ARVC registry (64%). Patient characteristics by registry are shown in Table S2. A minority were male (n=164, 40%). The age at ARVC diagnosis was 37±15 years, and about two-thirds had symptoms attributable to ARVC at the time of diagnosis (n=232, 64%). Most patients were identified as having pathogenic genetic variants (n=298, 74%), most commonly in *PKP2* (n=197, 49%). More than half the patients were probands (n=240, 58.8%). Table 1 summarizes other clinical and demographic characteristics.

Overall, 282 patients (69%) had complete baseline risk factor data allowing for estimation of the ARVC calculator 5-year VA risk. Missing data occurred for 5 of the 8 predictors: NSVT (n=38, 9.3%), PVC count (n=65,

Table 1. Baseline Characteristics of Patients at the Time of ARVC Diagnosis

Variable (patients with available data at diagnosis)	All patients (N=408)	Absence of VA event (276)	Occurrence of VA event (132)	*P* value
Age at diagnosis (n=408)	37 (±15.1)	38 (±15.8)	33 (±12.6)	<0.001
Male sex (n=408)	164 (40.2%)	96 (34.8%)	68 (51.5%)	0.001
White race (n=407)	397 (97.5%)	269 (97.5%)	128 (97.7%)	0.881
Proband (n=408)	240 (58.8%)	135 (48.9%)	105 (79.5%)	<0.001
Pathogenic/likely pathogenic variant (n=405)	298 (73.6%)	211 (77.0%)	87 (66.4%)	0.024
PKP2	197 (48.6%)	133 (48.5%)	64 (48.9%)	0.953
DSP	13 (3.2%)	10 (3.6%)	3 (2.3%)	0.468
DSG2	11 (2.7%)	5 (1.8%)	6 (4.6%)	0.111
PLN	27 (6.7%)	20 (7.3%)	7 (5.3%)	0.46
Other	13 (3.2%)	7 (2.6%)	6 (4.6%)	0.279
Symptoms* (n=361)	232 (64.3%)	131 (55.3%)	101 (81.5%)	<0.001
History of cardiac syncope (n=408)	77 (18.9%)	39 (14.1%)	38 (28.8%)	<0.001
Anterior T-wave inversions (n=398)	3 [2.0–4.0]	3 [1.0–4.0]	3 [3.0–4.0]	<0.001
Inferior T-wave inversions (n=387)	0 [0.0–1.0]	0 [0.0–1.0]	0 [0.0–1.0]	0.028
Total T-wave inversions (ant.+inf.; n=387)	3 [2.0–5.0]	3 [2.0–4.0]	4 [3.0–5.0]	<0.001
24 h PVC count (n=343)	1186 [361–4095]	860 [183–2751]	2879 [1151–60785]	<0.001
Presence of NSVT (n=370)	195 (52.7%)	114 (44.4%)	81 (71.7%)	<0.001
RVEF, % (n=348)	44 (±10.1)	45 (±8.8)	40 (±11.6)	<0.001
LVEF, % (n=355)	58 (±8.0)	58 (±7.9)	57 (±8.3)	0.304
ICD at any point (n=407)	277 (68.1%)	150 (54.5%)	127 (96.2%)	<0.001
ICD prior to dx.	18 (4.4%)	16 (5.8%)	2 (1.5%)	0.049
ICD within 6 mo. of dx.	129 (31.6%)	59 (21.4%)	70 (53.0%)	<0.001
ICD arrhythmia monitoring zone cycle length, ms	350 [323–400]	350 [328–375]	351 [322–400]	0.520
ICD arrhythmia treatment zone cycle length, ms	300 [286–320]	300 [285–316]	300 [289–333]	0.017
Baseline antiarrhythmic prescription (n=391)	59 (15.1%)	36 (13.5%)	23 (18.4%)	0.21
Amiodarone prescription	8 (2%)	5 (2%)	3 (2%)	0.753
Sotalol prescription	45 (11%)	27 (10%)	18 (14%)	0.245
Baseline beta-blocker prescription (n=392)	153 (39.0%)	96 (36.0%)	57 (45.6%)	0.068
ARVC calculator predicted 5-y VA risk, %	29 (±23%)	21 (±19%)	45 (±23%)	<0.001
Observed 5-y VA risk, %	29% [95% CI, 24–34]	...	...	...

Continuous variables are presented as mean±SD or median [IQR], as appropriate. ant indicates anterior; ARVC, arrhythmogenic right ventricular cardiomyopathy; dx, diagnosis; ICD, implantation of cardioverter defibrillator; inf, inferior; IQR, interquartile range; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular complex; RVEF, right ventricular ejection fraction; and VA, ventricular arrhythmias.

*Presence of symptoms associated with ARVC, including palpitations, dyspnea, and chest pain.

15.9%), number of TWI (n=21, 5.1%), RVEF (n=60, 14.7%). After imputation, mean 5-year VA risk was estimated at 29% (95% CI, 24%–34%) using the ARVC risk calculator.

Outcomes

During median follow-up of 5.2 [interquartile range, 2.8–9.6] years, 132 (32%) patients experienced the composite VA outcome at a rate of 6.3 events per 100 patient-years. Figure 1 shows the cumulative VA-free survival. Events occurred throughout follow-up, with a cumulative VA-free survival at 5 years of 71.3% (95% CI, 75.8–66.1). Of these events, 87 (66%) were ICD interventions, including either appropriate shock or antitachycardic pacing, and had median cycle length of 270 ms (interquartile range, 235–300). Rapid sustained VAs (VT with cycle length <240 ms, sudden cardiac arrest, or SCD) occurred in 41 (10.0%) patients during follow-up at a rate of 1.6 events per 100 patient-years. At last follow-up, 6 (1.5%) patients had died, and 10 (2.5%) had undergone heart transplantation. Of these alternative outcomes, 0 deaths and 1 transplant occurred without prior VA event; competing-risk sensitivity analysis was performed and did not impact results.

Longitudinal Predictive Variables

Table 2 details the number and timing of VA risk factor reevaluations during clinical follow-up, the distributions of which are presented as histograms in Figures S1 and S2. Average changes in risk factor values between time of ARVC diagnosis and 5-year follow-up are presented in Table 3. On repeat ambulatory cardiac monitoring assessment, the prevalence of NSVT decreased by 14% and the burden of PVCs decreased by an average of 1200 PVC per 24 hours. There was a nonsignificant trend toward increased prevalence of moderate to severe RV dysfunction. Sensitivity analysis was performed by looking at changes between individual RV functional categories (eg, normal, mild, moderate, and severe dysfunction) and likewise did not reveal significant changes. There was a small but statistically significant 2% decrease in left ventricular ejection fraction. There were no significant changes in the number of TWI on repeat ECG. There was a significant increase of 16% in the prescription rates of antiarrhythmic medications, but no change in the rates of beta-blocker prescriptions. On average, patients decreased their exercise by 4 MET×h/wk. Figure 2 shows the longitudinal trends of the changes in these variables.

Longitudinal Risk Prediction

Associations between individual elements of the modified ARVC risk calculator and VA events are presented in Table 4. The C statistics of the modified ARVC risk calculator for 5-year VA events was 0.76±0.02 and was similar to that of the original ARVC risk calculator (C statistics 0.78). Figure 3A presents longitudinal trends in model discrimination of 5-year VA events for the 3 risk prediction methods (baseline ARVC risk calculator, updated ARVC risk calculator, and time-varying Cox regression). As shown in Figure 3A, the ability to discriminate VA event risk decreased for the baseline ARVC risk calculator after ≈3 years, and the C statistics decreased

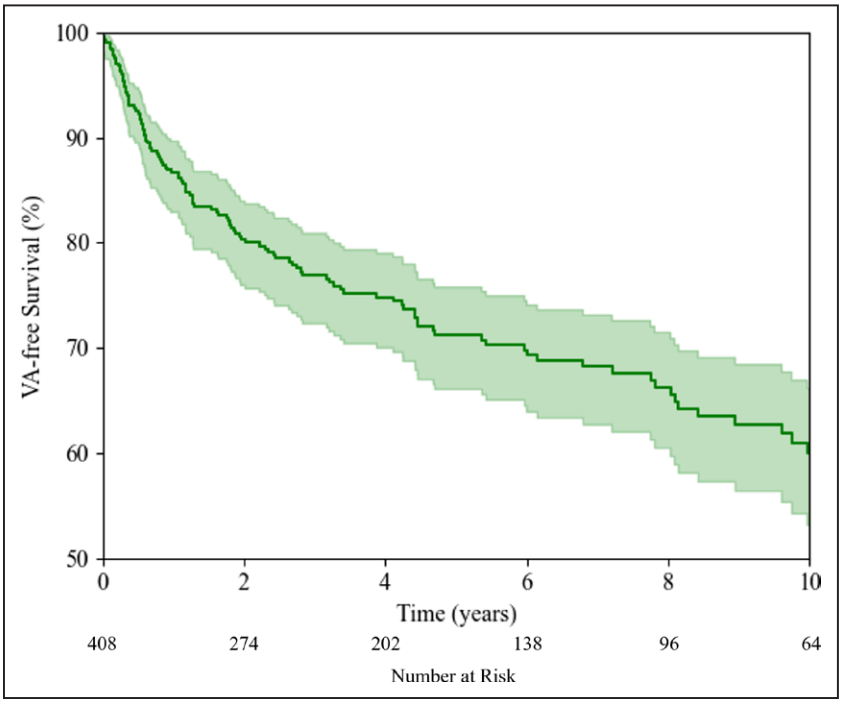

Figure 1. Kaplan-Meier estimate of ventricular arrhythmia (VA) free survival for patients with arrhythmogenic right ventricular cardiomyopathy without prior sustained VA.

Table 2. Number and Timing of VA Risk Predictor Reevaluations During Clinical Follow-Up

Evaluation	Number of pts. w/ additional evals.	Number of additional eval. (per pt.)	Time of eval. [IQR]
Ambulatory cardiac monitor (PVC, NSVT)	294	951 (2.3)	3.0 [1.0–6.8]
ECG (TWI)	344	1,429 (3.5)	3.5 [1.1–7.6]
Echo (RV function)	173	483 (1.2)	5.1 [2.1–9.6]
Echo (LVEF)	251	735 (1.8)	4.4 [1.7–8.9]
Medication review	104	220 (0.5)	3.6 [0.6–8.5]
Exercise histories	102	102 (0.25)	4.7 [1.9–9.0]

Echo indicates echocardiogram; eval., evaluation; IQR, interquartile range; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; pt., patient; PVC, premature ventricular complex; RV, right ventricular; TWI, T-wave inversions; and VA, ventricular arrhythmias.

from 0.83±0.03 at time of diagnosis to 0.69±0.06 at 5 years, while the updated ARVC risk calculator and time-varying Cox regression risk remained relatively stable out to 5 years (C statistics of 0.83±0.03–0.79±0.06 and 0.84±0.03–0.78±0.06, respectively).

Mean VA risk predictions from the three models are shown in Figure 3B, where they are compared to observed VA risk. Observed 5-year risk decreased from 29% to 16% between the time of initial ARVC diagnosis and at 5-year follow-up. Although all models showed a decrease in predicted 5-year VA risk at 5-year follow-up, these decreases were smaller in magnitude for both baseline ARVC risk calculator (29% decreasing to 22%) and updated ARVC risk calculator (29% decreasing to 20%). The time-varying Cox regression risk predictions (31% decreasing to 14%) more closely matched the observed drop in 5-year risk. Risk predictions from the updated ARVC risk calculator were recalibrated using an empiric exponential decay function, resulting in close approximation of observed risk (29% decreasing to 14%). The average risk discrepancy estimated using this calibration model was +6%. Risk discrepancies in the low, intermediate, and high-risk groups were +2%, +9%, and +13%, respectively. Subgroup calibration plots are shown in Figure S3, and details of empiric calibration models are presented in Table S3.

DISCUSSION

In this study, we leveraged a large, deeply phenotyped, multicenter cohort of patients with ARVC with long-term follow-up to characterize how VA risk factors change over time and to define how these changes can be incorporated into models for longitudinal VA risk prediction. Our findings shed important new insights into the dynamic nature of the disease course of ARVC following initial diagnosis. In particular, we demonstrated the importance of changes in ventricular ectopy, with both prevalence of NSVT and PVC burden acting as independent risk factors for VA events that decrease during follow-up. Overall likelihood of primary VA events likewise decreased over time. Applying the same baseline ARVC risk calculator prediction to follow-up evaluations resulted in decreasing VA risk discrimination after 3 years. However, this decrement was negated by updating the ARVC risk calculator prediction with changes in risk factor values (i.e. assessing 5-year VA risk using the ARVC risk calculator and the most recent set of available risk factor data). Mean risk for initial VA event during the subsequent 5-year period was overestimated by an average of +6% compared with both observed risk, although this overestimate was smaller in low-risk patients. We created a time-varying Cox regression model for predicting 5-year VA risk that maintained excellent discrimination and accuracy at 5-year follow-up.

Table 3. Changes in Risk Factor Values at the Time of ARVC Diagnosis and at Repeat Evaluation Closest to 5-Year Follow-Up Time

	Change from diagnosis to >5 years follow-up	*P* value
ARVC risk calculator variables		
Log(24 h PVC count; n=112)	−0.64±2.5	0.009
Presence of NSVT (n=122)	−14%	0.006
Number of TWI (n=161)	0.0 [−1.0 to 1.0]	0.456
Presence of RV dysfunction (mod/sev; n=102)	+6%	0.181
Other risk predictors		
LVEF, % (n=150)	−2.2±7.5	<0.001
Antiarrhythmic medication prescribed (n=49)	+16%	0.044
Beta-blocker prescribed (n=49)	+10%	0.255
Exercise (MET×h/wk; n=46)	−4 [−42 to 7]	0.016

Of note, these changes include only patients for whom clinical predictor values were available at both time of diagnosis and at least 3-y of follow-up; the total number of patients is shown. ARVC indicates arrhythmogenic RV cardiomyopathy; LVEF, left ventricular ejection fraction; MET, metabolic equivalent; mod, moderate; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular complex; RV, right ventricular; sev, severe; and TWI, T-wave inversions.

Comparison to Other Study Findings

Although there have been a handful of studies reporting longitudinal changes in individual ARVC risk factors, our study represents the first examination of how these risk factors change in concert with one another. Similar to our findings, one recent observational study examining patients with multiple Holter monitors found that the average burden of PVC decreased after initial diagnosis.[10] This study likewise demonstrated the importance of changes in PVC count, with both presence of NSVT and increase in PVC burden independently identifying increased risk for VA events in the year following assessment. Cappelletto et al[17] likewise found that both NSVT and PVC burden decreased progressively at both 2-year and 8-year follow-up in their cohort of patients with repeat Holter monitoring and that NSVT remained

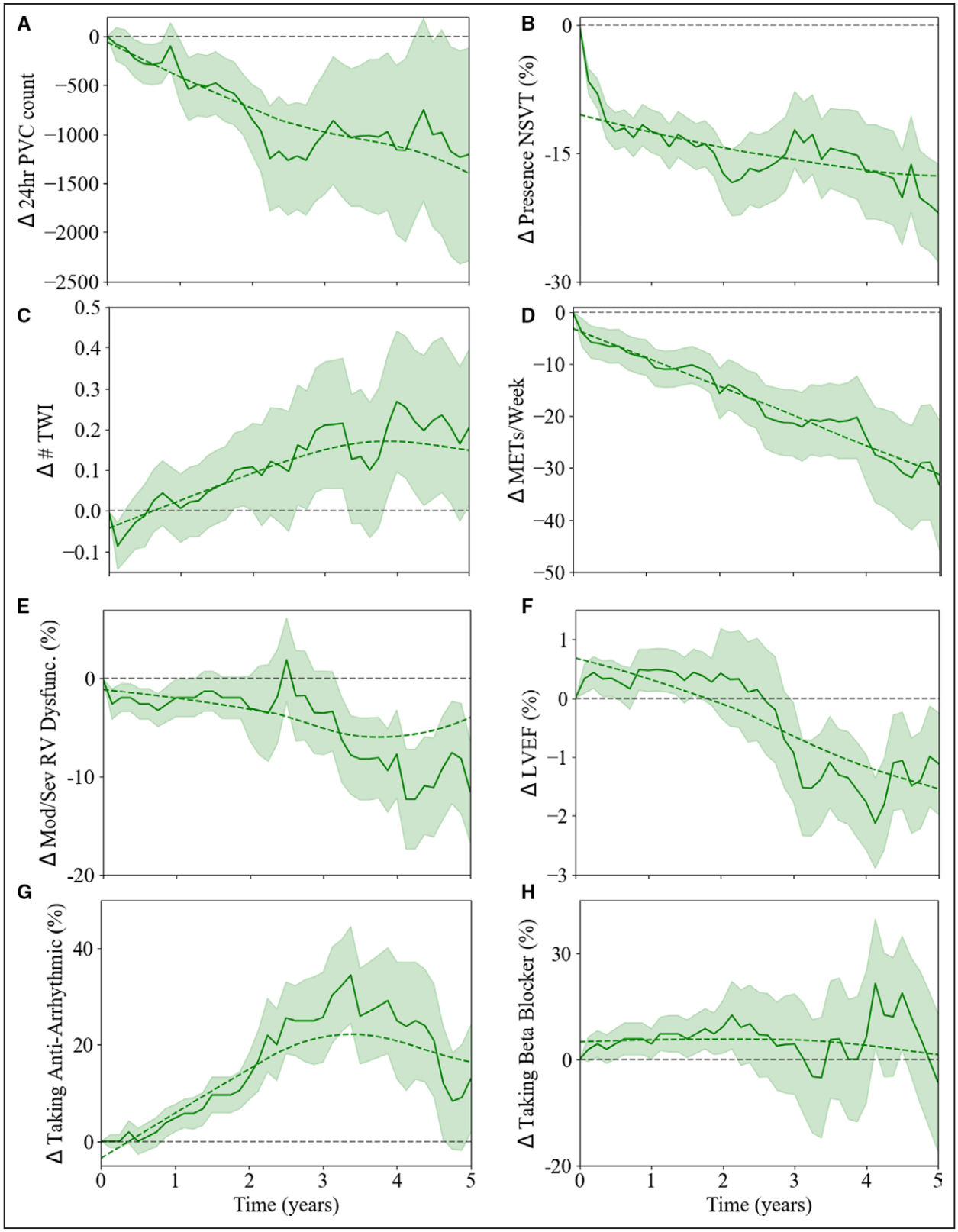

Figure 2. Longitudinal trends in predictors of ventricular arrhythmia (VA) events, presented as the change in predictor value at follow-up relative to time of arrhythmogenic right ventricular (RV) cardiomyopathy diagnosis.
A, Log of 24-hour premature ventricular complex (PVC) burden, (**B**) presence of nonsustained ventricular tachycardia (NSVT) on cardiac ambulatory monitoring, (**C**) number of T-wave inversions (TWI) in precordial and inferior leads, (**D**) the extent of strenuous exercise per week, (**E**) presence of moderate or severe RV dysfunction from echocardiography, (**F**) left ventricular ejection fraction (LVEF) from echocardiography, (**G**) antiarrhythmic prescription, and (**H**) beta-blocker prescriptions. dysfunc indicates dysfunction; MET, metabolic equivalent; mod, moderate; and sev, severe.

Table 4. Associations Between Clinical Risk Factors Included in the Modified ARVC Risk Calculator and 5-Year VA Event Risk

	Cox proportional hazards regression using baseline variables hazard ratios [95% CI]				Time-varying Cox regression hazard ratios [95% CI]			
Variable	Univariable	*P* value	Multivariable	*P* value	Univariable	*P* value	Multivariable	*P* value
Age, y (per year)	0.983 [0.972–0.995]	0.004	0.978 [0.966–0.989]	<0.001	0.983 [0.972–0.995]	0.004	0.983 [0.971–0.994]	0.003
Male sex (vs female)	1.843 [1.307–2.600]	<0.001	1.746 [1.234–2.471]	0.002	1.843 [1.307–2.600]	<0.001	1.730 [1.222–2.449]	0.002
Presence of NSVT (vs absence)	3.653 [2.434–5.484]	<0.001	2.126 [1.350–3.347]	0.001	3.012 [2.082–4.356]	<0.001	1.758 [1.165–2.652]	0.007
History of cardiac syncope (vs absence)	2.197 [1.504–3.209]	<0.001	1.554 [1.050–2.298]	0.027	2.470 [1.713–3.562]	<0.001	1.794 [1.232–2.612]	0.002
No. of TWI (per lead)	1.199 [1.107–1.297]	<0.001	1.100 [1.004–1.206]	0.04	1.176 [1.090–1.269]	<0.001	1.079 [0.994–1.171]	0.071
log (24 h PVC count)	1.536 [1.366–1.729]	<0.001	1.321 [1.156–1.510]	<0.001	1.381 [1.243–1.533]	<0.001	1.207 [1.080–1.348]	0.001
Presence of mod./sev. RV dysfunction (vs absence)	2.745 [1.922–3.920]	<0.001	1.421 [0.968–2.084]	0.073	2.961 [2.076–4.225]	<0.001	1.807 [1.239–2.637]	0.002

Hazard ratios are presented with 95% CIs. ARVC indicates arrhythmogenic RV cardiomyopathy; mod./sev., moderate or severe; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular complex; RV, right ventricular; TWI, T-wave inversions; and VA, ventricular arrhythmias.

an important independent risk factor for VA at follow-up. It is unclear whether these changes are part of the natural disease course in ARVC, or if decreased ventricular ectopy is the result of initiating pharmacologic therapy and lifestyle modification. It is also plausible that the observed improvements in electrophysiologic properties may be exaggerated due to selection bias, as both PVC count and NSVT are important arrhythmic components of the ARVC diagnostic criteria.

For patients with repeat echocardiographic assessment, we found that cardiac function was stable between ARVC diagnosis and 5-year follow-up. On average, patients did not have progressive RV dysfunction during that period. While patients did demonstrate a statistically significant 2% decrease in left ventricular ejection fraction, this small change is unlikely to be clinically significant. These findings are consistent with other studies that have looked at changes in cardiac function in ARVC over time. In a smaller study of patients with ARVC with serial echocardiograms, Malik et al. found small but significant decreases in left ventricular ejection fraction without significant changes in RV fractional area change over a similar time frame.[18] Contrasting this, Taha et al[19] found that RV fractional area change decreased by 5% over 7-year follow-up of patients with ARVC with serial imaging. Kalantarian et al[11] found that about a quarter of patients with ARVC had a drop of at least 10% in RV fractional area change over 10-year follow-up. Thus, significant functional cardiac changes in ARVC seem to occur over longer time scales (>5 years) than our present study was able to examine. It is also possible that our evaluation of RV function as a dichotomous rather than continuous variable (eg, fractional area change or ejection fraction) may have overlooked more subtle, early progression of RV dysfunction. We likewise did not explore more sensitive markers such as echocardiographic or CMR-based RV strain that have been shown to be associated with progression of RV dysfunction.[18] However, we did not find that substitution of RVEF with a categorical definition of RV dysfunction negatively impacted the ARVC risk calculator's ability to discriminate VA risk, suggesting that these early changes are less important for predicting incident VA. This is consistent with prior studies showing that RV strain did not add incremental value to prediction of VA over broader assessments of RV dysfunction.[20]

We also found that the number of TWI on ECG was relatively stable out to 5 years of follow-up. These findings are consistent with prior work demonstrating that although TWI in both the inferior and precordial leads are common, they change little by around 5 years of follow-up.[21,22] In contrast, studies examining longer-term follow-up with serial ECGs out to 10 years have demonstrated increased numbers of ECG leads with TWI.[11,23,24] As with cardiac functional changes, these findings suggest that the progression of ECG changes, and thus the electrophysiologic and structural changes they reflect, likely change over longer time spans (>5 years) than the present study was able to examine.

Longitudinal Trends in VA Risk and Risk Prediction

We found that average risk for first sustained VA event decreased by nearly half (absolute risk reduction of 13%) between initial evaluation and 5-year clinical follow-up (Figure 3, black line). This may in part be due to the selection bias inherent to this type of analysis. Those high-risk patients present in the initial cohort who go on to have VA events are by definition no longer at risk for a first VA event. They are thus removed from the pool of patients for whom risk of initial VA events are

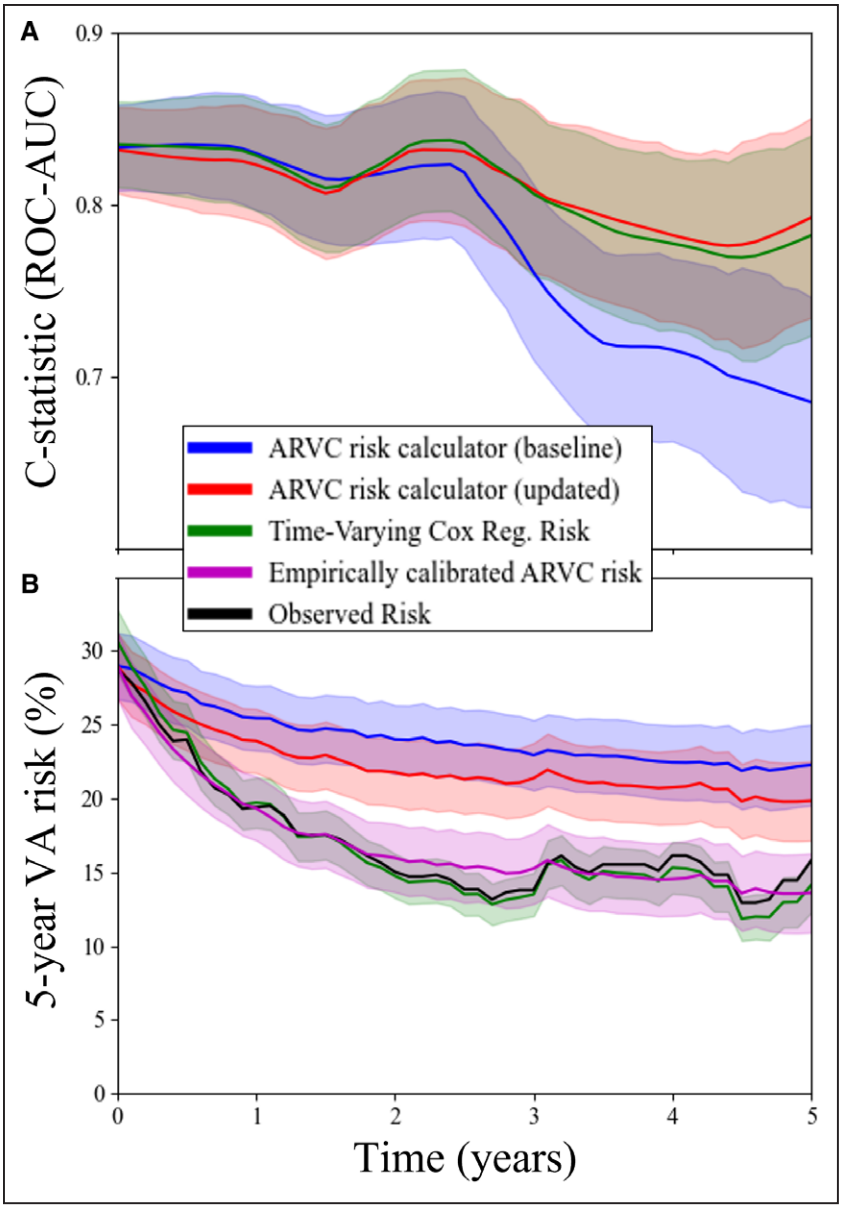

Figure 3. Longitudinal performance of ventricular arrhythmias (VA) risk prediction models.
A, Longitudinal changes in model discrimination for (blue) the baseline arrhythmogenic right ventricular cardiomyopathy (ARVC) risk calculator, (red) the updated ARVC risk calculator, and (green) time-varying Cox regression risk. Plots are shown with LOWESS smoothing and SEs of the mean. **B**, Longitudinal calibration between predictions made by (blue) baseline ARVC risk calculator, (red) updated ARVC risk calculator, (green) time-varying Cox regression risk, compared to observed risk (black). The updated ARVC risk calculator risk was recalibrated using an empiric exponential decay function (magenta). Here observed risk is shown with 95% CIs, and model predictions are shown with SEs of the mean. reg. indicates regression; LOWESS, locally weighted scatterplot smoothing; ROC AUC, receiver operator characteristics and calculating the area under these curves; and VA, ventricular arrhythmias.

subsequently assessed. This is reflected by the negative trend in risk predicted by the baseline ARVC risk calculator (Figure 3, blue lines) and accounts for an approximately 7% decrease in average risk by 5 years. This only partially explains the total 13% decrease in observed risk, however. The discrimination of the baseline ARVC risk calculator also drops off significantly after 3 years, suggesting that there is also heterogeneity in the way that individual patient risk changes over time. Accounting for changing patient characteristics by recalculating the predicted risk with the most recent set of risk factor data results in significantly improved discrimination of VA likelihood (Figure 3, red lines) but a persistent overestimation of mean risk (+6% at 5-year follow-up). In contrast, the time-varying Cox regression model for risk prediction had both good discrimination and well-calibrated mean risk (Figure 3, green lines). This model takes advantage of complete knowledge of the baseline hazard function (eg, the instantaneous VA risk at all follow-up times for a patient with null risk factors) and thus incorporates empiric changes to risk that exceed those accounted for by the included VA risk factors. Similarly, we were able to recalibrate the updated ARVC risk calculator predictions using an empiric exponential decay function (Figure 3, magenta lines), which resulted in both excellent discrimination and closely calibrated mean risk. Thus, there appear to be three distinct sources of decreasing VA risk: survivorship bias, improving risk factors included within the ARVC risk calculator (age, NSVT, and PVC count), and additional risk modifiers that are currently unaccounted for by the ARVC risk calculator but that do not impact risk discrimination.

Two risk modifiers that may decrease longitudinal VA risk but are not included in the ARVC risk calculator are reductions in exercise and initiation of medical therapy. We found that patients significantly reduced

the amount and intensity of their exercise between initial diagnosis and 5-year clinical follow-up (Figure 2D). Prior studies have shown that competitive sports activity is associated with as much as a 5-fold increase in risk for SCD in young adults[25,26] and that this association is dose-dependent.[27,28] Even recreational sports contribute significantly to risk of VA and SCD.[29] In this context, our results support decreasing exercise as a plausible mechanism for reducing risk for VA. We also found that patients in our cohort were more likely to be prescribed antiarrhythmic medications at 5-year follow-up compared with at the time of initial diagnosis (Figure 2G). Although evidence for the use of antiarrhythmic medications in ARVC is mixed,[30] observational data suggest that these medications, particularly amiodarone and sotalol, may reduce the rate of VA events in patients with high burdens of PVC and NSVT.[31–34] We did not find that rates of beta-blocker prescriptions changed significantly between initial ARVC diagnosis and 5-year follow-up. This may be because of the moderately high rates (≈40%) of baseline beta-blocker prescriptions, and the lack of strong evidence supporting their efficacy in isolated right-sided dysfunction or for prevention of VA events.[26] In addition, it has been hypothesized that episodes of acute inflammation elicited by environmental triggers may play a role in modulating disease progression.[35] As inflammation increases both VA risk and symptom burden, it follows that ARVC diagnosis is most likely to be made during an inflammatory episode, thus leading to the observed pattern of heightened initial VA risk followed by risk attenuation as the episode recedes.

Clinical Implications

Our time-varying Cox regression model provided a combination of strong discrimination and accurate VA risk prediction. However, its clinical use would likely be cumbersome due to the need for providers to enter a significant quantity of risk factor data to generate risk predictions. Ultimately, this could be achieved via integration into electronic health records systems. Alternatively, our findings suggest that the ARVC risk calculator remains a useful clinical tool for discriminating between low- and high-risk patients during follow-up evaluation, provided that predictions are made using updated risk factor data. Predictions made by the ARVC risk calculator overestimate the observed risk at follow-up evaluations, the average magnitude of which was +6%. This overestimation is smaller (+2%) in patients with low baseline risk and larger in patients with high baseline risk (+13%; Table S3). Since those patients at low baseline risk are least likely to have ICD placement at time of ARVC diagnosis, the updated ARVC risk calculator, therefore, performed best in the population for whom longitudinal VA risk reassessment was most relevant.

Additionally, we present a modified version of the ARVC risk calculator which makes use of a dichotomous RV dysfunction variable, rather than continuous RVEF. This modification did not decrease the model's discrimination in this cohort and has the added benefit of eliminating the score's reliance on CMR imaging data which may be unavailable at follow-up (particularly after ICD implantation) or granular RV fractional area change which may not be routinely available in clinical echocardiograms. External validation will also be required before this modified risk prediction tool should be used clinically.

Finally, our findings are consistent with the hypothesis that reduction in exercise and initiation of antiarrhythmic medications may help to reduce the likelihood of VA events. Although Bosman et al[28] examined the incremental value of adding exercise to the ARVC risk calculator and found no improvement in VA risk prediction, their analyses were restricted to risk prediction at the time of initial ARVC diagnosis. It is possible that reducing exercise and initiating antiarrhythmic medications may be important for improving individualized, longitudinal risk predictions. That said, in one small cohort of athletic patients with ARVC, ARVC risk calculator predictions also seemed to hold despite clinical detraining.[36] Further analyses of cohorts with more complete exercise history and medication review data are therefore needed to clarify the incremental value of these variables in longitudinal VA risk prediction. Regardless, the updated ARVC risk calculator had excellent discrimination without inclusion of either exercise or medication data.

Limitations

We acknowledge the observational nature of this study as a limitation. All longitudinal reassessments of risk predictors were obtained at the discretion of the local clinicians introducing possible observation bias. However, this observation bias most likely takes the form of increased surveillance in high-risk patients and those with clinical symptoms, which represent the population for whom VA risk prediction is of most relevance. Additionally, while many repeat diagnostic tests were available during follow-up, the number of patients for whom complete exercise histories and longitudinal medication reviews were available represent a small fraction of the overall cohort, and may have therefore increased the risk of type 2 error (eg, our failure to detect change in beta-blocker prescription rate) or be less representative of the full cohort. To confirm our hypotheses that the differences between observed VA event rates and uncalibrated ARVC risk predictions are due to these risk modifiers, further studies with more complete exercise and medication review data should be performed. Finally, our study population was drawn from tertiary, academic centers in North America and Northern Europe which may have created a referral bias that could lead to overestimation of VA risk in a community-derived

population. External validation of our model for longitudinal VA risk assessment is essential to confirm its clinical utility. Additionally, as in the original ARVC risk calculator, we used a surrogate composite end point that included appropriate ICD therapy to infer risk of SCD. Although clinically recognized as significant arrhythmic events, ICD therapies are an imperfect substitute for SCD.[37] As a further limitation of our multicenter, longitudinal registry-based study of a rare disease, we do not have granular data regarding the breakdown of these ICD therapies into antitachycardic pacing versus appropriate shock, or of the programmed detection times for therapies.

Conclusions

In the present study, we leveraged a well-characterized, international multicenter cohort of patients with ARVC with long-term clinical follow-up to explore the ways in which risk factors for VA change over time, how these changing risk factors impact overall rates of sustained VA, and how well current risk assessment tools perform on serial evaluation. On average, we found that ventricular ectopy, including both burden of PVCs and prevalence of NSVT decreased significantly between time of diagnosis and 5-year follow-up, whereas structural and functional risk factors including RV function and number of TWI on ECG remained largely static. We found that updating the ARVC risk prediction using the most recent set of VA risk factors was important in maintaining discrimination during follow-up. Additionally, observed 5-year VA risk decreased quickly relative to predicted risk, suggesting the influence of risk modifiers that are not explicitly included in the ARVC risk calculator. Mean VA risk was overestimated by +6% at 5-year follow-up, and this overestimation should be accounted for when providing clinical risk assessments.

ARTICLE INFORMATION

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Supplemental Material

Supplemental Methods S1–S3
Tables S1–S3
Figures S1–S3
Reference[38]

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