ORIGINAL ARTICLE

Sudden Cardiac Death Prediction in Arrhythmogenic Right Ventricular Cardiomyopathy
A Multinational Collaboration

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BACKGROUND: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is associated with ventricular arrhythmias (VA) and sudden cardiac death (SCD). A model was recently developed to predict incident sustained VA in patients with ARVC. However, since this outcome may overestimate the risk for SCD, we aimed to specifically predict life-threatening VA (LTVA) as a closer surrogate for SCD.

METHODS: We assembled a retrospective cohort of definite ARVC cases from 15 centers in North America and Europe. Association of 8 prespecified clinical predictors with LTVA (SCD, aborted SCD, sustained, or implantable cardioverter-defibrillator treated ventricular tachycardia >250 beats per minute) in follow-up was assessed by Cox regression with backward selection. Candidate variables included age, sex, prior sustained VA (≥30s, hemodynamically unstable, or implantable cardioverter-defibrillator treated ventricular tachycardia; or aborted SCD), syncope, 24-hour premature ventricular complexes count, the number of anterior and inferior leads with T-wave inversion, left and right ventricular ejection fraction. The resulting model was internally validated using bootstrapping.

RESULTS: A total of 864 patients with definite ARVC (40±16 years; 53% male) were included. Over 5.75 years (interquartile range, 2.77−10.58) of follow-up, 93 (10.8%) patients experienced LTVA including 15 with SCD/aborted SCD (1.7%). Of the 8 prespecified clinical predictors, only 4 (younger age, male sex, premature ventricular complex count, and number of leads with T-wave inversion) were associated with LTVA. Notably, prior sustained VA did not predict subsequent LTVA (P=0.850). A model including only these 4 predictors had an optimism-corrected C-index of 0.74 (95% CI, 0.69−0.80) and calibration slope of 0.95 (95% CI, 0.94−0.98) indicating minimal over-optimism.

CONCLUSIONS: LTVA events in patients with ARVC can be predicted by a novel simple prediction model using only 4 clinical predictors. Prior sustained VA and the extent of functional heart disease are not associated with subsequent LTVA events.

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

Key Words: arrhythmogenic right ventricular dysplasia ■ calibration ■ sudden cardiac death ■ syncope ■ ventricular tachycardia

WHAT IS KNOWN?

- Improving the specific prediction of sudden cardiac death in arrhythmogenic right ventricular cardiomyopathy can help in patient selection for implantable cardioverter-defibrillators implantation.
- Life-threatening ventricular arrhythmia (LTVA; sudden cardiac death, aborted sudden cardiac death, ventricular tachycardia >250 beats per minute/ventricular fibrillation) might have different mechanisms and thus different predictors versus stable ventricular arrhythmia in arrhythmogenic right ventricular cardiomyopathy.

WHAT THE STUDY ADDS?

- LTVA events can be predicted by a new prediction model that can be easily applied to clinical practice.
- As opposed to stable arrhythmia, LTVA events are not predicted by prior sustained arrhythmic events and the extent of functional alteration of either ventricle.
- The 4 predictors of LTVA events are younger age, male sex, burden of ventricular ectopy, and the extent of repolarization abnormalities.

Nonstandard Abbreviations and Acronyms

ARVC	arrhythmogenic right ventricular cardiomyopathy
ICD	implantable cardioverter-defibrillator
LP	linear predictor
LTVA	life-threatening ventricular arrhythmia
PKP2	plakophilin 2
PVC	premature ventricular complexes
RVEF	right ventricular ejection fraction
SCD	sudden cardiac death
TWI	T-wave inversion
VA	ventricular arrhythmia
VT	ventricular tachycardia

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is associated with frequent ventricular arrhythmias (VA) and an increased risk of sudden cardiac death (SCD) particularly in young and athletic patients.[1] In the past 2 decades, significant efforts have been made to define the predictors of sustained VA in this high-risk population. Building on this work, our group recently published a model for individualized prediction of any incident sustained VA in patients with definite ARVC without sustained VA at baseline.[2]

While most clinicians agree that the risk for sustained VA events is, by itself, sufficient to merit consideration of an implantable cardioverter-defibrillator (ICD) in a patient with structural heart disease, it is an imperfect surrogate outcome for SCD as it likely overestimates SCD risk.[3] For patients with ARVC, it is furthermore uncertain if stable VA and potentially fatal VA/SCD share the same predictors. Evidence from both clinical and translational research suggests a continuum between structural and electrical disease phases in ARVC, which could potentially imply different arrhythmia mechanisms.[4,5] From a clinical perspective, it is, therefore, possible that rapid VA/SCD is not accurately predicted by a model that predicts the risk of any sustained VA.

To address this important clinical question, we sought to study the determinants of potentially fatal VA and SCD and to develop a specific prediction model for these events in an adequately powered population that represents the largest cohort of patients with definite ARVC to date.

We believe that this approach could provide valuable insights into the complex decision-making surrounding ICD placement.

METHODS

Study Design

The design of this international observational cohort study is similar to what has previously been described.[2] In brief, our cohort combines longitudinal observational data from 5 registries encompassing 6 countries (Table I in the Data Supplement). This study is in accordance with the current international guidelines for prognostic research,[6] conforms to the declaration of Helsinki and was approved by local ethics and institutional review boards.

Study Population

From our international cohort of patients with ARVC,[2] we included all who were diagnosed with definite ARVC by the 2010 Task Force Criteria.[7] The present study thus excludes patients with arrhythmogenic cardiomyopathy not fulfilling definite diagnostic criteria for ARVC. Alternate diagnoses sharing similar clinical characteristics were excluded as clinically indicated. We included patients with and without a history of sustained VA at diagnosis. This differs from the cohort used for the development of the model for any incident sustained VA in which patients with a prior history of sustained VA were excluded.[2] To maintain patient confidentiality, data and study materials will not be made available to other researchers for purposes of replicating the results. A limited data set may be made available on request.

Study Outcomes

With the aim of predicting potentially fatal VA and SCD, the primary study outcome was the time to first life-threatening VA (LTVA) during follow-up, defined by a composite of SCD, aborted SCD, ventricular fibrillation, and rapid ventricular tachycardia (VT; >250 beats per minute) that was either sustained (lasting ≥30 seconds) or terminated by ICD. The choice of 250 beats per minute as a cutoff for rapid VT was prespecified based on the widespread use of this threshold for ventricular fibrillation therapy in many ICD studies since the PAINFREE trial (The Pacing Fast VT Reduces Shock Therapies Trial) in 2001[8,9] and in clinical practice. This cutoff for life-threatening events is also consistent with

prior ARVC arrhythmic risk prediction literature.[10–12] In addition, we recorded outcomes of any sustained VA, heart transplantation, cardiovascular-, and all-cause mortality.

Predictors

Based on clinical experience and the current literature, particularly a recent published meta-analysis[13] and a prognostic model for predicting incident sustained VA in patients with ARVC,[2] 8 potential predictors were preselected and recorded at the time of diagnosis.[2,11–15] These were sex, age at diagnosis, recent (<6 months) cardiac syncope, number of premature ventricular complexes (PVCs) on 24-hour Holter monitoring, prior sustained VA events, number of anterior and inferior leads with T-wave inversion (TWI), and left and right ventricular ejection fraction (RVEF). The definitions for these predictor variables are presented in Table II in the Data Supplement. In addition, the relationship between the type of prior sustained VA event (only stable VT, as opposed to LTVA or unstable VT/ventricular fibrillation) was studied (definitions in Table II in the Data Supplement). Each predictor variable was determined at the time of definite diagnosis, defined as one year before to one year after the date of diagnosis per Task Force Criteria, but always before occurrence of the primary outcome.

Data Collection

Data were collected according to previously published standard operating procedures.[2] All ECG tracings were reviewed by a core laboratory consisting of 2 cardiac electrophysiologists (Drs Cadrin-Tourigny and Tadros) blinded to the outcome data. Adjudication of reported genetic variants was performed by consensus of a team of specialists in cardiac genetics (B. Murray, Dr Jongbloed, Dr van Tintelen, Dr James) according to the American College of Medical Genetics and Genomics guidelines as previously described.[2,16]

Statistical Analysis

Analyses were performed using R version 3.5.1 (R Foundation, Vienna, Austria). Categorical variables are presented as frequencies (percentages) and were compared using Fisher exact tests. Continuous variables were presented as mean±SD or median (interquartile range) and compared using independent sample t tests or Mann-Whitney U tests, as appropriate. The follow-up duration was calculated as the time interval from diagnosis to the outcome of interest or censoring. Censoring occurred at the most recent available clinical assessment, death from any other cause or heart transplantation. Event-free survival probabilities were estimated using the Kaplan-Meier method and Cox Proportional Hazard regression analysis.

Missing Data

Missing data patterns were evaluated, and the potential for bias was assessed by comparing the characteristics of patients with and without missing variables. Missingness was assumed to be at random and imputed using multiple imputations with chained equations or manually using qualitative assessment when available.[17] A total of 25 imputed data sets were generated in 20 iterations, and the final results of all analyses were combined using Rubin's rules.[18]

Model Development

The association between potential predictors and the primary outcome was estimated using Cox regression. The final predictors were selected via stepwise backward selection on Akaike's Information Criterion.[6] The discriminative performance of the model was calculated by Harrell's C statistic. The model was converted as a function of the individual risk prediction of having had LTVA within time t:

$$P\left(LTVA, t\right) = 1 - S_0(t)^{\exp(LP)}$$

In which $S_0(t)$ represents the estimated baseline survival probability at time t, and the linear predictor (LP) is the sum of the predictor variables in the model multiplied by their estimated coefficient.

Model Validation and Calibration

Validation of the model was performed by bootstrapping using 200 samples. Potential optimism was estimated by the pooled calibration slope of the bootstrap samples.[19] In addition, observed versus predicted values were graphically evaluated.[20]

Sensitivity Analyses

We assessed whether the predictions of LTVA were consistent in patients with and without a prior history of LTVA or unstable VT (according to the Table II in the Data Supplement definition) by performing a sensitivity analysis excluding patients who had already suffered these events.

Additionally, we performed another sensitivity analysis comparing the performance of our model in individuals with and without *PKP2* (likely) pathogenic variants.

RESULTS

A cohort of 864 patients with definite ARVC was assembled from 15 centers in 6 countries in North America and Europe, including the 528 patients from the previously published cohort.[2] The average age at diagnosis was 39.5±15.5 years and 53.4% (n=461) were male. More than half were probands (57.8%, n=499). Two-thirds (65.0%, n=539) had a (likely) pathogenic variant identified, predominantly a single heterozygous variant in plakophilin 2 (*PKP2*; 77.6%, n=418/539). Overall, 38.8% (n=335) of patients had a history of sustained VA at the time of diagnosis including 129 (14.9%, average age 39.7±15.5 years, 64% male, 57% with a [likely] pathogenic variant) with a prior history of LTVA or unstable VT. Other clinical characteristics are summarized in Table 1. The study population was evenly distributed between North America (433) and Europe (431; Table III in the Data Supplement).

Overall, only 6.6% of data for the 8 prespecified predictors were missing, 58.3% (n=504) of patients had complete data for these predictors, and none had >50% of them missing. The most common missing predictor was premature ventricular complexe count on 24-hour Holter monitor.

Table 1.　Baseline Clinical Characteristics

	Overall	Patients without LTVA in follow-up	Patients with LTVA in follow-up	P value
Total	864	771	93	
Demographics				
Male sex	461 (53.4)	398 (51.6)	63 (67.7)	0.005
Age at diagnosis, y	39.5±15.5	40.6±15.5	30.9±13.2	<0.001
White ethnicity (n=809)	784 (96.9)	701 (96.8)	83 (97.6)	0.354
Proband status	499 (57.8)	420 (54.5)	79 (84.9)	<0.001
Presence of pathogenic mutation (n=829)	539 (65.0)	474 (64.2)	65 (71.4)	0.214
Pathogenic variant (n=809)				0.022
PKP2	418 (50.4)	362 (49.1)	56 (61.5)	
DSP	28 (3.4)	24 (3.3)	4 (4.4)	
DSG2	28 (3.4)	27 (3.7)	1 (1.1)	
DSC2	5 (0.6)	4 (0.5)	1 (1.1)	
PLN	41 (4.9)	39 (5.3)	2 (2.2)	
Multiple mutations	11 (1.3)	11 (1.5)	0 (0.0)	
Other	8 (0.9)	7 (0.9)	1 (1.1)	
History				
Prior sustained VA	335 (38.8)	295 (38.3)	40 (43)	0.438
Prior LTVA and unstable VA	129 (14.9)	111 (14.4)	18 (19.4)	0.266
Symptoms (n=863)	626 (72.5)	545 (70.8)	81 (87.1)	0.001
Recent cardiac syncope (n=847)	130 (15.3)	108 (14.3)	22 (23.7)	0.028
ECG/continuous ECG monitoring				
TWI in ≥3 precordial leads (n=837)	497 (59.4)	432 (57.8)	65 (73.0)	0.008
TWI in ≥2 inferior leads (n=817)	154 (18.8)	130 (17.8)	24 (27.3)	0.046
NSVT (n=700)	566 (70.2)	495 (68.6)	71 (84.5)	0.004
24 h PVC count (n=553)	1069 (315–3955)	1007 (273–3637)	2860 (782–5406)	0.003
Imaging				
RVEF, %, (n=800)	42.5±10.4	42.7± 10.4	40.6±10.0	0.086
LVEF, %, (n=824)	57.5±8.3	57.5±8.3	57.0±8.4	0.574
Treatment at baseline				
ICD	450 (52.1)	391 (50.7)	59 (63.4)	0.027
Beta blockers (n=817)	394 (48.2)	352 (48.2)	42 (48.3)	1
Antiarrhythmic drugs (n=816)	252 (27.0)	225 (27.3)	27 (24.1)	0.522
VT ablation	152 (17.6)	142 (18.4)	10 (10.8)	0.091

Variables are expressed as frequency (%), mean±SD, or median (IQR). Total number of patients for a given variable mentioned if missing data. DSC2 indicates desmocollin-2; DSG2, desmoglein-2; DSP, desmoplakin; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LTVA, life-threatening ventricular arrhythmia; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; PKP2, plakophilin-2; PLN, phospholamban; PVC, premature ventricular complex; RVEF, right ventricular ejection fraction; TWI, T-wave inversion; VA, ventricular arrhythmia; and VT, ventricular tachycardia.

Outcomes

Over a median follow-up of 5.75 years (interquartile range, 2.77–10.58), 93 (10.8%) patients experienced a LTVA event, representing an event rate of 1.56%/y (95% CI, 1.26–1.91). This included 15 patients (1.7%) with SCD or aborted SCD. Overall, 375 (43.4%) patients experienced any sustained VA event during follow-up. Over the course of follow-up, 42 (4.9%) patients died and 35 (4.1%) had cardiac transplantation. The median cycle length of LTVA classified VT events was 224 ms

(210–230) while non-LTVA VT events had a median cycle length of 310 ms (280–350).

As depicted on Figure 1A, history of a sustained VA before diagnosis was not associated with survival free from LTVA during follow-up (P=0.43). In contrast, prior sustained VA predicted recurrence of sustained VA (P<0.0001; Figure 1B). However, no significant difference was found regarding the severity of the prior VA event, that is, unstable or life-threatening, including aborted SCD, versus stable, on the risk of sustained VA recurrence (P=0.15).
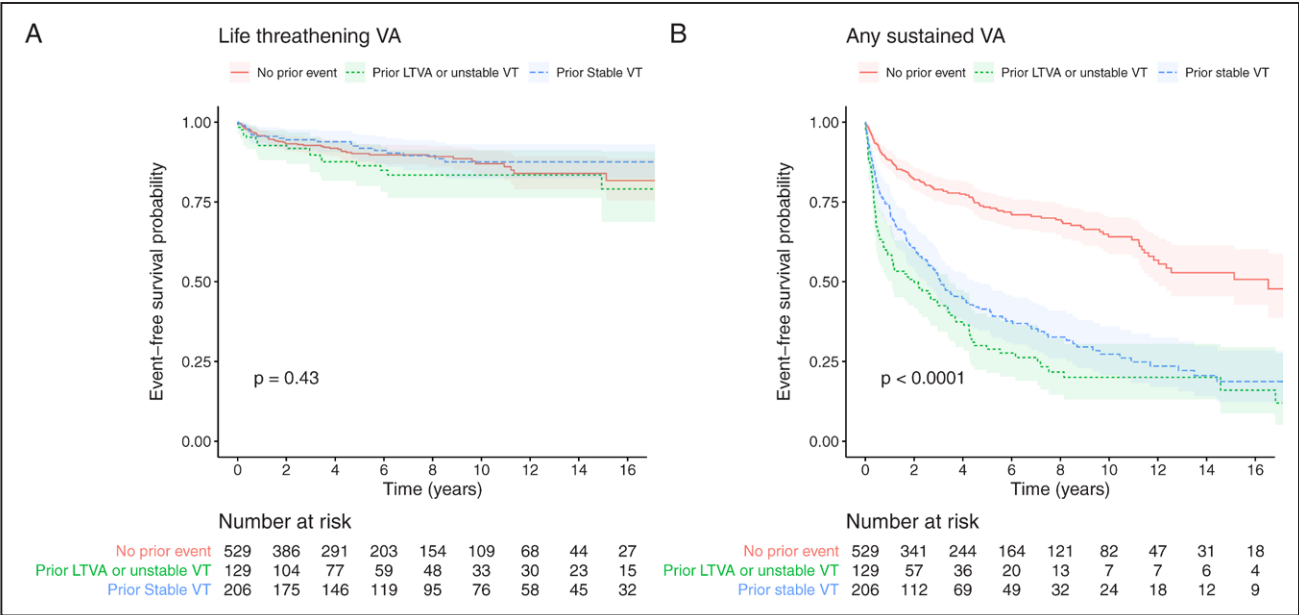
Figure 1. Survival free from life-threatening ventricular arrhythmia (LTVA) and any sustained ventricular arrhythmia (VA).
The cumulative event-free survival for LTVA is plotted in **A**. LTVA events occurred in follow-up in 52 patients with no prior sustained VA event at baseline, 19 with prior LTVA/unstable ventricular tachycardia (VT) a and 23 with prior stable VT. The cumulative event-free survival for any VA is plotted in **B**. Sustained VA events occurred in follow-up in 147 patients with no prior sustained VA event at baseline, 91 with prior LTVA/unstable VT a and 137 with prior stable VT. For both parts, 95% CIs are provided (shaded area).

Model Development

Baseline characteristics of patients with and without LTVA during follow-up are shown in Table 1. The univariable and multivariable predictors of LTVA are presented in Table 2. All predictors except prior sustained VA, left ventricular ejection fraction, and RVEF either had a significant ($P<0.05$) or borderline significant univariable linear (or log-linear) relationship with the outcome. Subsequently, all variables were fitted into a multivariable model. Only 4 predictors were independently associated with the outcome: male sex ($P=0.0021$), younger age at diagnosis ($P<0.0001$), the 24-hour PVC count (log-linear relationship; $P=0.010$), and the total number of leads with TWI ($P=0.024$).

The following formula allows for the calculation of the 5-year risk of LTVA:

$$P(\text{LTVA at 5 years}) = 1 - 0.927^{\exp(LP)}$$

Where:

$$LP = 0.6899 \times \text{sex} - 0.0439 \times \text{age} + 0.1844 \times \ln(24 \text{ hour PVC count}) + 0.1153 \times \text{sum of anterior and inferior leads with TWI}$$

Table IV in the Data Supplement provides the probability of survival ($S_0(t)$) at 1, 2, 3, and 4 years allowing calculation of risk for shorter time durations.

An online version of this new risk prediction model combined with the published sustained VA risk calculation model can be found at www.ARVCrisk.com.

Model Validation

Our prediction model had an optimism-corrected C statistic of 0.74 (95% CI, 0.69–0.80). Internal validation with bootstrapping resulted in a calibration slope of 0.95 (95% CI, 0.94–0.98), indicating only a small degree of over-optimism. Figure 2 visually shows calibration, demonstrating good concordance between predicted and observed events at 1 and 5 years. Calibration plots showing similarly good agreement for predictions of shorter duration can be found in Figure I in the Data Supplement.

Clinical Utility

We explored and presented the implications of using different risk thresholds for ICD implantation using the prediction model. Figure 3 depicts the clinical impact of using different 5-year risk thresholds for ICD use with solid colors representing patients who would get an ICD and red color representing patients with LTVA events during this period. Implanting ICDs in patients above an arbitrary 4% five-year risk threshold would result implanting ICDs in 640 patients (74.1%) leaving 2 (0.2%) patients with unprotected LTVA events during 5-years of follow-up (ie, protection rate of 97.7%, 84 patients with LTVA protected by an ICD/a total of 86 patients with LTVA at 5 years). In comparison, setting an arbitrary threshold of 10% would result in implanting ICDs in 315 (36.5%) leaving 23 (2.7%) patients with unprotected LTVA (protection rate 73.3%, 63 patients with LTVA protected by an ICD/a total of 86 patients with LTVA at 5 years). To

Table 2. LTVA Risk Prediction Model

	Univariable model		Multivariable (final model)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Male sex	1.78 (1.15–2.76)	0.009	1.99 (1.28–3.10)	0.0021
Age (per year increase)	0.96 (0.94–0.97)	<0.0001	0.96 (0.94–0.97)	<0.0001
Recent cardiac syncope	1.69 (1.04–2.72)	0.032		
Prior sustained VA	0.96 (0.63–1.46)	0.850		
24 h PVC count (ln)*	1.21 (1.06–1.39)	0.002	1.23 (1.04–1.38)	0.010
Leads with TWI anterior+inferior	1.14 (1.04–1.25)	0.005	1.12 (1.02–1.24)	0.024
RVEF (per % decrease)	1.02 (1.00–1.04)	0.095		
LVEF (per % decrease)	1.02 (0.99–1.04)	0.320		

HR indicates hazard ratio; LTVA, life-threatening ventricular arrhythmia; LVEF, left ventricular ejection fraction; PVC, premature ventricular complex; RVEF, right ventricular ejection fraction; TWI, T-wave inversion; and VA, ventricular arrhythmia.

*PVC count had a log-linear relationship.

further illustrate the use of the model, Table V in the Data Supplement depicts the characteristics of 3 patients from our cohort and their calculated LTVA risk alongside with a comparison to the published sustained VA model.[2]

Sensitivity Analyses

### LTVA Prediction in Patients With No Prior History of LTVA or Unstable VT

We performed a sensitivity analysis excluding patients with a prior history of unstable or LTVA to ensure that our predictors remain consistent in predicting incident LTVA. Patients presenting with aborted SCD or unstable and rapid VT would likely undergo ICD placement

such that it is imperative for the model to perform well in the remaining subset. Overall, 735 patients did not have such prior events and had similar characteristics as the complete cohort (Table VI in the Data Supplement). Over a median follow-up of 5.64 years (2.66–10.47) 75 of these patients experienced a LTVA including 12 SCD/aborted SCDs. The same predictors as for primary analysis were fitted into a multivariable model. As shown in Table VII in the Data Supplement, the same 4 predictors with similar weights remained in the model. This model performed well with an optimism-corrected C statistic of 0.75 (95% CI, 0.69–0.80) and a calibration slope of 0.95 (95% CI, 0.93–0.97).
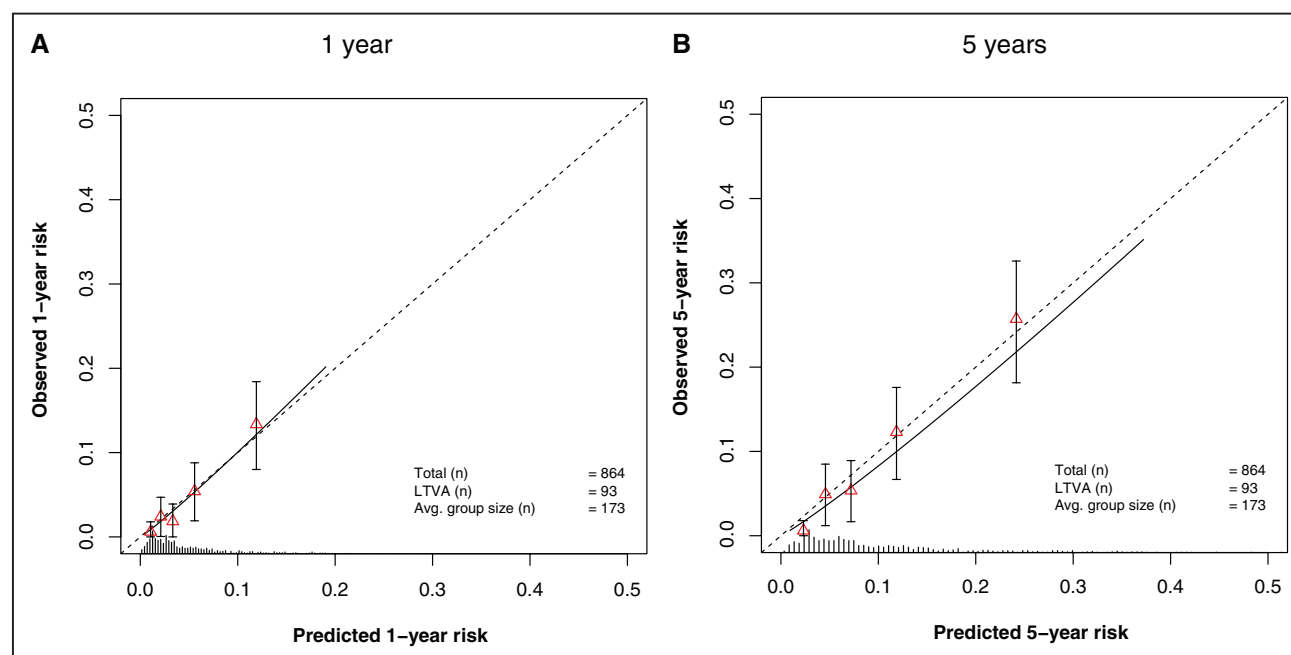
Figure 2. Calibration plot showing the agreement between predicted (*x* axis) and observed (*y* axis) 5-year risk of the primary outcome of life-threatening ventricular arrhythmia (LTVA).
Triangles represent binned Kaplan-Meier estimates with 95% CIs for quintiles of predicted risk. Straight line is the continuous calibration hazard regression. Dotted line represents perfect calibration. Spike histogram on the *x* axis reflects the number of patients with a predicted risk corresponding to the *x* axis value.
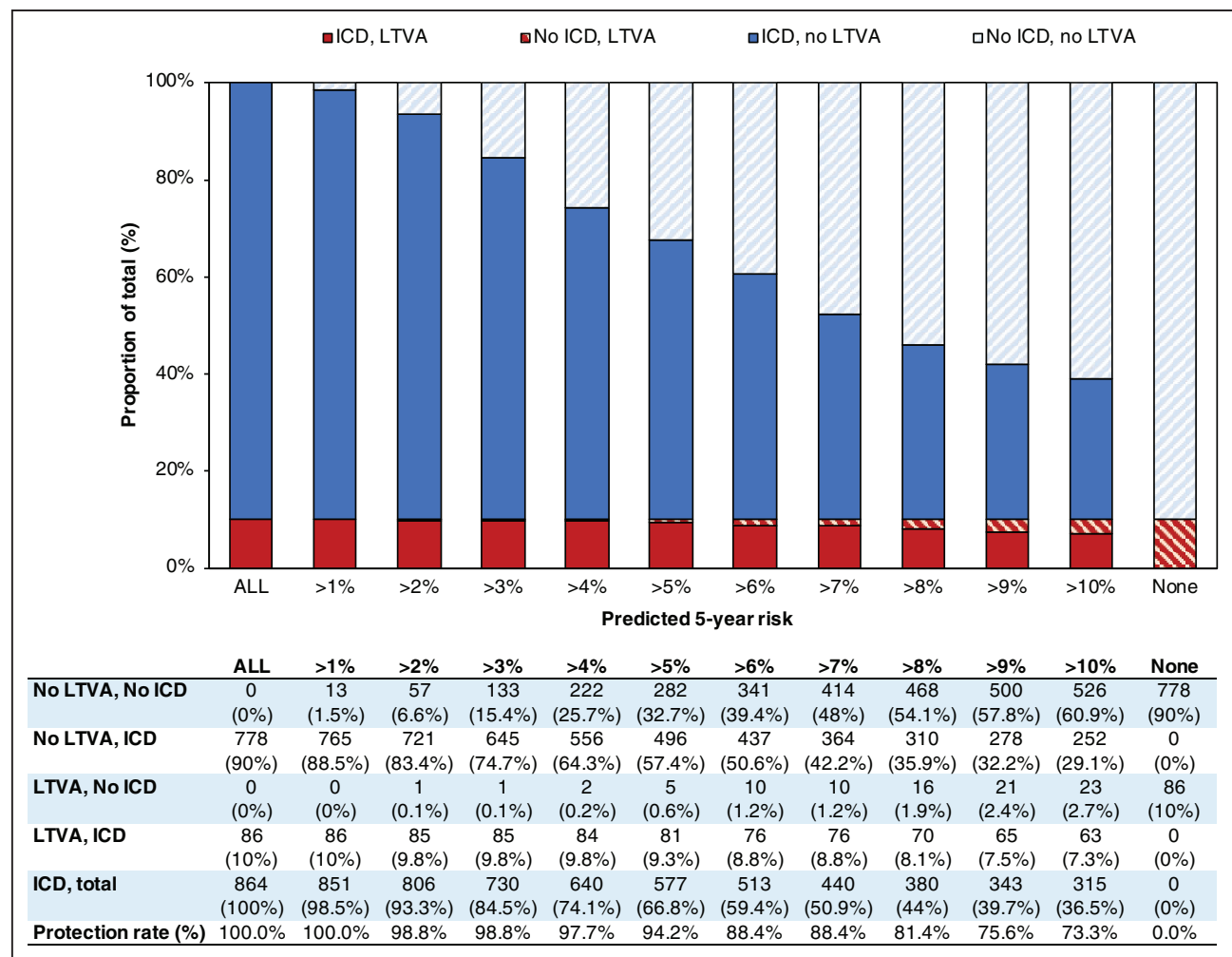
Figure 3. Outcomes of patients associated with model-based implantable cardioverter-defibrillator use thresholds.
The implications of using implantable cardioverter-defibrillators (ICD) in all (**left** bar) or none (**right** bar) of the patients are shown. The bars show the impact of using different ICD placement thresholds based on the 5-year risk calculated by our model. Each bar represents the complete cohort (n=864) and color coding represents the proportion of patients experiencing life-threatening ventricular arrhythmia (LTVA; red) or absence thereof (blue) as well as the placement (solid colors) vs the nonplacement (striped colors) of an ICD. The number of patients in each of the four categories is presented in the table below.

	ALL	>1%	>2%	>3%	>4%	>5%	>6%	>7%	>8%	>9%	>10%	None
No LTVA, No ICD	0 (0%)	13 (1.5%)	57 (6.6%)	133 (15.4%)	222 (25.7%)	282 (32.7%)	341 (39.4%)	414 (48%)	468 (54.1%)	500 (57.8%)	526 (60.9%)	778 (90%)
No LTVA, ICD	778 (90%)	765 (88.5%)	721 (83.4%)	645 (74.7%)	556 (64.3%)	496 (57.4%)	437 (50.6%)	364 (42.2%)	310 (35.9%)	278 (32.2%)	252 (29.1%)	0 (0%)
LTVA, No ICD	0 (0%)	0 (0%)	1 (0.1%)	1 (0.1%)	2 (0.2%)	5 (0.6%)	10 (1.2%)	10 (1.2%)	16 (1.9%)	21 (2.4%)	23 (2.7%)	86 (10%)
LTVA, ICD	86 (10%)	86 (10%)	85 (9.8%)	85 (9.8%)	84 (9.8%)	81 (9.3%)	76 (8.8%)	76 (8.8%)	70 (8.1%)	65 (7.5%)	63 (7.3%)	0 (0%)
ICD, total	864 (100%)	851 (98.5%)	806 (93.3%)	730 (84.5%)	640 (74.1%)	577 (66.8%)	513 (59.4%)	440 (50.9%)	380 (44%)	343 (39.7%)	315 (36.5%)	0 (0%)
Protection rate (%)	100.0%	100.0%	98.8%	98.8%	97.7%	94.2%	88.4%	88.4%	81.4%	75.6%	73.3%	0.0%

Comparison of the Performance of the Model in PKP2 Variant Carriers Versus Noncarriers

We performed another sensitivity analysis to assess the potential differences in the performance of our model in patients with and without a *PKP2* (likely) pathogenic variant. First, adding *PKP2* variant status to our model caused almost no shift in the predictive effect of any of the included variables (Table VIII in the Data Supplement). Second, we evaluated separately the performance of our model in those with and without a *PKP2* (likely) pathogenic variants. The calibration curves showed equally good performance in both groups (Figure II in the Data Supplement).

DISCUSSION

Main Findings

In this article, we used a large cohort of patients with multinational ARVC to specifically assess LTVA in ARVC

as a surrogate marker that more closely approximates SCD. This effort had 2 aims.

First, we sought to get a better understanding of the specific determinants of potentially fatal arrhythmias in an adequately powered ARVC population, with the underlying rationale that these might differ from those for stable sustained VT.

Second, we intended to refine the prediction of these events by providing a distinct prediction model for LTVA that can be used in all newly diagnosed patients with ARVC in addition to the published incident sustained VA prediction model.[2]

The 3 main findings are as follows: first, prior history of any VA or LTVA/unstable VT did not predict subsequent LTVA. This finding differs from the outcome any sustained VA which, as expected, was predicted by prior sustained VA events. Second, after evaluating several predefined clinical and demographic predictors, only 4

remained independently associated with LTVA: younger age, male sex, PVC count, and the number of leads with TWI. Notably, the severity of functional alteration (ie, RVEF, left ventricular ejection fraction) was not associated with LTVA in multivariable analyses. Third, LTVA events can be predicted with reasonable accuracy by a risk prediction model that has adequate discrimination (C statistic of 0.74) and consistency through internal validation (calibration slope of 0.95).

LTVA as a Closer Surrogate for SCD in ARVC

With the appropriate recognition of the significant risk of VA in ARVC and subsequent widespread use of ICDs, SCD has fortunately become a rare occurrence after the diagnosis of ARVC is established. Conducting a randomized controlled trial of ICD use would no longer be ethical such that surrogate outcomes are required in studies designed to inform decision-making for ICD placement. The most widely used surrogate is a composite of any sustained or ICD treated VA, as used in the recently published risk prediction model for incident VA.[2] While the underlying risk of SCD is known to be overestimated when using ICD treated events as a surrogate,[3] the extent of this overestimation might be particularly important in ARVC as the difference between the rate of VA events and underlying rate of SCD is higher than what is found in other conditions such as in hypertrophic cardiomyopathy, reflecting the higher rate of scar-related hemodynamically stable monomorphic VT in ARVC.[21] In the cohort used to develop the initial arrhythmic risk calculator for incident VA, only 36% of events (53/146 sustained VA events) were LTVA.[2] We thus believe that restricting the outcome to LTVA, while not replacing the more comprehensive outcome of any sustained VA, could provide incremental information on the risk of SCD. More closely, targeting potentially lethal arrhythmias can be of particular interest in resource-limited settings where event rates must be higher to justify ICDs. This model may also provide new information for a more comprehensive approach to the shared decision-making for ICD implantation. The LTVA model might be of particular importance in patients with borderline indications, in those who are reluctant to accept this therapy, and in cases where the risk of ICD-related complications is deemed higher.

Identified Predictors and Prior Studies

While any sustained VA has been the most commonly used outcome in ARVC risk prediction research, only a few studies have specifically reported on the prediction of LTVA using a similar definition as in the present study.[11,12,14,15] Given the limited sample size in each cohort and lower frequency of LTVA events, interpretation is uniformly hampered by insufficient power to discern the independent effect of individual predictors. Similarly to our study, identified predictors of LTVA have included younger age at presentation,[12,14] male sex,[15] and higher PVC burden.[12] Our results thus further support the importance of male sex[22] and younger age as predictors and highlight the importance of PVC count as an easily measured indicator of electrical activity and instability of the disease. On the contrary, prior sustained VA was interestingly not predictive of LTVA events in the present study. This may be surprising at first glance. Yet, the predictive value of prior sustained events for incident LTVA has been inconsistent in the literature. Two studies reported no association between prior VT[11,14] and subsequent unstable VA, with only 1% of patients with VT subsequently developing ventricular fibrillation[11] in one study. Conversely, a recent large series reported hemodynamically stable VT to be a predictor of subsequent lethal VA[23] but the end point was substantially different as it excluded rapid VT and included electrical storm. LV dysfunction[24] was associated with SCD in one study and syncope[10] with LTVA in another. RV dysfunction has not been associated specifically with LTVA in prior literature nor in this study despite being a good predictor of any sustained VA outcomes,[2,13] illustrating that unstable arrhythmias might occur before scar burden negatively affects RVEF.

The Specific Determinants of LTVA and Mechanistic Rationale

Interestingly, we found that the predictors of LTVA differ from those associated with any sustained VA by not being predicted by the extent of functional impairment (RVEF, left ventricular ejection fraction), nor by prior sustained VA or syncopal events. These findings are consistent with the long recognized notion that an early electrical phase of the disease predisposes to rapid unstable VA and is independent from the severity of the underlying substrate. This concept is now further supported by accumulating clinical[4] and experimental evidence.[5,25–27] More data now link desmosomes to other components of the intercalated disk including the sodium channel and gap junction.[25–27] More recently, conduction delays and electrogram fractionation developing before detectable cardiac imaging and histological abnormalities have also been reported in human and murine desmoplakin mutation carriers.[5] Furthermore, inflammatory infiltration has long been recognized as a histopathologic feature of ARVC,[28] and patients with ARVC have elevated levels of circulating inflammatory cytokines.[29,30] More recent work in a murine model and in induced pluripotent stem cells demonstrated that myocytes produce and secrete potent inflammatory cytokines.[31] Thus, inflammatory signaling in ARVC may act as both intrinsic and extrinsic contributors in aberrant electrophysiology and histopathologic remodeling early in disease pathogenesis. While the clinical

correlations of these phases and mechanisms of disease with arrhythmic outcomes have yet to be elucidated, they could explain why identified predictors do not depend on the burden of scar as a substrate for re-entry and do not include prior sustained or nonsustained VA. Rather, this form of disease instability could perhaps be better explained by interactions between desmosomes and other electrical cellular components as well as inflammatory signals.

Clinical Utility of a Prediction Model for LTVA

This second prediction model for arrhythmic risk in ARVC is by no means intended to replace the published model for predicting incident sustained VA in newly diagnosed patients with ARVC.[2] Rather, the intent is to expand the probabilistic framework for decision making for physicians and patients. Each model provides different information. Whereas the model with incident sustained VA is highly sensitive in capturing SCD, it is likely to overestimate the true risk of SCD. On the contrary, restricting the outcome to LTVA enhances specificity for SCD but could potentially lead to the exclusion of slower events that may degenerate into more rapid potentially fatal VA if left untreated. We thus propose that the clinical shared decision-making process should take into account the 2 predictions obtained for a patient with no prior history of VAs when considering the important decision of ICD use for primary prevention. For example, in a patient wanting to minimize risk of SCD, the decision process might rely more on the predictions of the sustained VA model than on the more stringent predictions of the LTVA model. This process in illustrated in Table V in the Data Supplement. Finally, these 2 predictive models, as any other prediction tool in medicine, are not intended to substitute for clinical judgement but rather to augment it by providing pertinent individualized information to facilitate the shared decision-making process.

Another concern stemming from the fact that these 2 outcomes, LTVA and any sustained VA, have a different set of predictors is that the sustained VA prediction model might disproportionally under-estimate the risk of LTVA in a certain profile of patients. Reassuringly however, patients with the lowest calculated risk of sustained VA as per the published sustained VA risk model, also experience a low LTVA event rate while patients who experienced a LTVA event were at significantly higher calculated risk of any sustained VA than patients who did not suffer these events (Figure III in the Data Supplement). Finally and importantly, despite not being independent predictors of LTVA, prior sustained events are powerful predictors of recurrent sustained VA events with >50% of patients suffering recurrences at 5 years (Figure 1B). We thus do not suggest that our findings should impact the usually recommended approach of ICD implantation in secondary prevention for patients with structural heart disease.

Limitations

Our cohort is drawn from North-European and North American academic centers with a population predominantly of white descent with a high rate of pathogenic *PKP2* variants. Caution should thus be exerted when extrapolating our results to different populations. While the model performed equally well in patients with and without pathogenic *PKP2* variants, external validation of our model will be an important additional step in the future. In particular, the model may underperform in cohorts with genotypes poorly represented in this study for instance Naxos disease patients or patients with a *TMEM43* founder variant. Importantly, we only included patients with a definite diagnosis of ARVC thus excluding patients in the concealed phase of the disease, patients with a possible or borderline ARVC diagnosis or with non-ARVC forms of arrhythmogenic cardiomyopathy in which our results cannot be applied. Although a widely used measure of RV function, RVEF might lack sensitivity in detecting subtle changes in early structural disease[32,33] that could potentially be valuable predictors of LTVA.

Finally, while being a closer surrogate for SCD than all sustained VA, LTVA still represents an imperfect outcome. Despite being a widely used threshold and typically indicative of a significant clinical event, the cutoff of 250 beats per minute may nevertheless still overestimate the underlying risk for SCD while potentially missing slower events that could degenerate into lethal arrhythmias.

Conclusions

In patients with ARVC, LTVA events are not independently predicted by prior sustained VA events, nor by the extent of functional heart disease. Independent predictors of LTVA are young age, male sex, burden of ventricular ectopy and total number of anterior and inferior leads with TWI. These life-threatening events can be accurately predicted by a novel prediction model that can be used in any newly diagnosed patient with definite ARVC. An integrative approach using both prediction models (ie, all sustained VA and LTVA) has the potential to provide clinicians and patients with complementary data to inform shared decision making for ICD implantation in ARVC.

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