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 (L TVA) 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 L TVA (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 L TVA 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 L TVA. Notably, prior sustained VA did not predict subsequent L TVA (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: L TVA 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 L TVA events.

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

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

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rhythmogenic 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. 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 which patients with a prior history of sustained VA 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. 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 (LTVAs) 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 and in clinical practice. This cutoff for life-threatening events is also consistent with outcome for SCD as it likely overestimates SCD risk. 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. 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. 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, 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, we included all who were diagnosed with definite ARVC by the 2010 Task Force Criteria. 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. 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.

Nonstandard Abbreviations and Acronyms

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ARVC</td>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
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<tr>
<td>ICD</td>
<td>Implantable cardioverter-defibrillator</td>
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<td>LP</td>
<td>Linear predictor</td>
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<td>LTVAs</td>
<td>Life-threatening ventricular arrhythmia</td>
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<td>PKP2</td>
<td>Plakophilin 2</td>
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<td>PVC</td>
<td>Premature ventricular complexes</td>
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<tr>
<td>RVEF</td>
<td>Right ventricular ejection fraction</td>
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<td>SCD</td>
<td>Sudden cardiac death</td>
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<td>TWI</td>
<td>T-wave inversion</td>
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<tr>
<td>VA</td>
<td>Ventricular arrhythmia</td>
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<td>VT</td>
<td>Ventricular tachycardia</td>
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prior ARVC arrhythmic risk prediction literature. 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 and a prognostic model for predicting incident sustained VA in patients with ARVC, 8 potential predictors were preselected and recorded at the time of diagnosis. 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 LTV 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. 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.

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. 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.

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. 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 LTV within time t:

$$P(LTV, t) = 1 - S_0(t)^\text{exp(LP)}$$

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. In addition, observed versus predicted values were graphically evaluated.

Sensitivity Analyses
We assessed whether the predictions of LTV were consistent in patients with and without a prior history of LTV 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. 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 LTV 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.
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).
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 ($S(t)$) 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 in 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
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 SCVs. 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).

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

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.
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. While the underlying risk of SCD is known to be overestimated when using ICD treated events as a surrogate, 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. In the cohort used to develop the initial risk prediction model for incident VA, only 36% of events (53/146 sustained VA events) were LTVA. 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. 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, male sex, and higher PVC burden. Our results thus further support the importance of male sex 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 and subsequent unstable VA, with only 1% of patients with VT subsequently developing ventricular fibrillation in one study. Conversely, a recent large series reported hemodynamically stable VT to be a predictor of subsequent lethal VA but the end point was substantially different as it excluded rapid VT and included electrical storm. LV dysfunction was associated with SCD in one study and syncope 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, 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 and experimental evidence. More data now link desmosomes to other components of the intercalated disk including the sodium channel and gap junction. 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. Furthermore, inflammatory infiltration has long been recognized as a histopathologic feature of ARVC and patients with ARVC have elevated levels of circulating inflammatory cytokines. More recent work in a murine model and in induced pluripotent stem cells demonstrated that myocytes produce and secrete potent inflammatory cytokines. Thus, inflammatory signaling in ARVC may act as both intrinsic and extrinsic contributors to 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. 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 rapidly 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 is 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 underestimate 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 but 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 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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