Risk score for the exclusion of arrhythmic events in arrhythmogenic right ventricular cardiomyopathy at first presentation

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Abstract

Aims: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined heart muscle disorder associated with an increased risk of life-threatening arrhythmias in some patients. Risk stratification remains challenging. Therefore, we sought a non-invasive, easily applicable risk score to predict sustained ventricular arrhythmias in these patients.

Methods: Cohort of Patients who fulfilled the 2010 ARVC task force criteria were consecutively recruited. Detailed clinical data were collected at baseline and during follow up. The clinical endpoint was a composite of recurrent sustained ventricular arrhythmias and hospitalization due to ventricular arrhythmias. Multivariable logistic regression was used to develop models to predict the arrhythmic risk. A cohort including patients from other registries in UK, Canada and Switzerland was used as a validation population.

Results: One hundred and thirty-five patients were included of whom 35 patients (31.9%) reached the endpoint. A model consisting of filtered QRS duration on signal-averaged ECG, non-sustained VT (NSVT) on 24 h-ECG, and absence of negative T waves in lead aVR on 12-lead surface ECG was able to predict arrhythmic events with a sensitivity of 81.8%, specificity of 84.0% and a negative predictive value of 95.5% at the first presentation of the disease. This risk score was validated in international ARVC registry patients.

Conclusion: A risk score consisting of a filtered QRS duration ≥117 ms, presence of NSVT on 24 h-ECG and absence of negative T waves in lead aVR was able to predict arrhythmic events at first presentation of the disease.

Keywords: Arrhythmogenic right ventricular cardiomyopathy Arrhythmic risk; ventricular arrhythmia; ICD; Sudden cardiac death; Risk stratification

1. Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined heart muscle disorder characterized by disruption of the myocytic architecture resulting in electrical instability and increased risk of life-threatening ventricular arrhythmias (VA) [1].

Although the overall risk of sudden cardiac death (SCD) is low [2], ARVC has been reported to be an important cause of SCD in adults younger than 35 years, accounting for up to 11% of SCD cases [3,4] with up to 22% in athletes [5,6].

The 2006 ACC/AHA/ESC guidelines recommend the use of an implantable cardioverter-defibrillator (ICD) in patients with ARVC and documented sustained ventricular tachycardia (VT) or fibrillation (VF) [7]. The 2015 Task Force Consensus Statement on Treatment of ARVC adds syncope, non-sustained VT (NSVT) and moderate dysfunction of the right (RV), left (LV) or both ventricles as risk factors, but risk stratification remains imperfect [8]. To date, there is only retrospective data from small cohorts available (Table A.1). Both definition of outcome and selection of patients vary highly in the named studies.

The aim of this study was to identify clinically applicable, noninvasive predictors for arrhythmic risk in ARVC and to combine detected predictors into a clinically useful risk score.

2. Methods

The study cohort included unrelated patients consecutively referred to the Inherited Cardiovascular Disease Unit of The Heart Hospital in London between 2003 and 2014, and to St Georges University Hospitals NHS Foundation Trust (SGUH), London (before 2003 when the service moved to the Heart Hospital), with suspected ARVC, or with family history of SCD and/or ARVC. All patients were evaluated according to the 2010 task force criteria and classified into definite, borderline or possible ARVC [1]. Only patients who fulfilled diagnostic criteria and who have thus been diagnosed with definite ARVC according to the 2010 task force criteria [1] at any time throughout the course of their disease were included for the development of the score.

Detailed clinical and genetic data were collected at baseline and during follow up.

A cohort including patients from SGUH (not included in the first population), from the Zurich ARVC program, and from the Vancouver based BC Inherited Arrhythmia Program was used as a validation cohort.

The study was approved by the local ethics committees of each participating center.

2.1. Clinical data

Baseline clinical evaluation included personal and family history, 12-lead electrocardiogram (ECG), signal-averaged ECG (SAECG) and 24 h-ECG, 2D-echocardiography, and cardiopulmonary exercise test (CPEX).

Follow-up visits were performed as clinically necessary, usually every 6–12 months. Patients who had not been seen for at least 2 years were contacted by telephone in January 2015 using a structured questionnaire.

Paper prints of the ECGs were evaluated with regard to electrical axis, QRS duration in leads V1 and V6, duration of terminal activation measured from the nadir of the S wave to the end of the QRS in leads V1 and V2, presence of T wave inversions and Q waves in all leads, presence of low voltage (b5 mm in all limb leads and b 10 mm in all precordial leads), delayed R progression, left or right bundle branch block, presence and configuration of ventricular ectopics (VE) according to standard definition [9–12].

Automated interpretation of SAECGs was performed with regard to filtered QRS duration (fQRSd), low-amplitude signal duration (LAS) and root-mean-square voltage of the terminal 40 ms (RMS), the same parameters in only the Z-axis, the number of beats analysed and the documented noise. SAECGs with a noise ≥0.5 mV and SAECG in patients with complete right bundle branch block were excluded [1,13].

Automated interpretation of 24 h-ECGs was checked and utilised for the number of VE, couplets, triplets, tachycardias and supraventricular ectopics and tachycardias. Full disclosure was available if needed.

CPEX was performed using a standard Bruce protocol. Maximal oxygen consumption, its percentage of predicted, peak heart rate, its percentage of predicted, respiratory quotient, minutes of exercise, achieved power in Watts, occurring arrhythmias and current medication were taken from the standardized reports.

All echocardiographic measurements were taken from the standardized reports. Information on decreased RV function, dilatation and wall motion abnormalities were also taken from the written reports, unless there were conflicting reports, in which case three cardiologists with a special interest in cardiomyopathies reviewed the images independently. The consensus regarding dilatation and wall motion abnormalities was then used.

Genotyping was performed using next generation sequencing as described before for hypertrophic cardiomyopathy [14].

Magnetic resonance imaging measurements were not utilised, as results were available in less than one third of patients.

Patients from the validation cohort were analysed specifically for the parameters included in the risk score as reported above.

2.2. End point

The primary endpoint was a composite of recurrent sustained VT/VF causing patients to seek medical attention or leading to shock from their ICDs, and hospitalization due to VT/VF or SCD at any time after inclusion in the study.

2.3. Statistical analysis

Continuous variables were compared between the groups with mean ± standard deviation and categorical variables as number (percentages) of all cases. Simple logistic regression analyses were calculated for each of the candidate predictors. Predictors were evaluated using odds ratios (OR) and their area under the curve (AUC) to evaluate their accuracy with regard to discrimination of patients at risk of sustained ventricular arrhythmia. Cut-off values for balanced specificity and sensitivity as well as one for sensitivity N80% were determined. We corrected for multiple testing of the predictors selection using the false discovery rate method, implying that the level of significant p-values was lowered to reduce random findings to an expected 5% [15].

An alpha level of 0.05 was considered as statistically significant. All data were analysed with SPSS version 22 and SAS version 9.4.

2.4. Development of the risk score

The patients were compared in two groups, one consisting of those patients reaching the composite endpoint, the other consisting of the remainder. Predictors were searched using the baseline data from their first investigation at The Heart Hospital/SGUH. Parameters, which showed a statistically significant corrected p-value were grouped as SAECG, ECG, 24 h-ECG, CPEX and echocardiography parameters and subsequently entered into multiple logistic regression models. To prevent overfitting, we limited the number of variables per model to a maximum of one of each group, thus maximally five parameters per model, but fitting several models instead to cover all possible predictors. Only significant variables were retained in the models.

All models were subsequently analysed as possible risk scores. All patients were assigned points for each one of these scores, 1 point for each parameter that was positive, as all used parameters were categorized. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV), p-value, OR and AUC were computed for each risk score based on all possible numbers of points given for the specific risk score. Only patients with complete baseline information for the parameters investigated were included for this analysis.

Previously reported risk factors for sustained ventricular arrhythmia and scores were computed for our cohort if possible from our data and evaluated by calculating sensitivity, specificity, PPV, NPV, OR and AUC.

2.5. Validation

Sensitivity, specificity, PPV and NPV, p-value, OR and AUC were computed in all patients with baseline SAECG, 12-lead ECG, and 24 h-ECG data as reported for the original cohort.

3. Results

278 patients with definite, borderline and possible ARVC were identified. 135 patients (48.6%), mean age 44 ± 14 years, 82 men (60.7%) fulfilled the 2010 task force criteria for a definite diagnosis of ARVC. Fig. A.1 shows the flow chart of patients included. Patients were followed for a mean of 8.4 ± 4.8 years since their ARVC diagnosis and for 6.8 ± 3.3 years after their referral to our institution.

Of the 135 patients with definite ARVC 35 patients (31.9%) reached the composite endpoint. All patients had recurrent sustained VT documented, 8 (22.9%) experienced electrical storm and 2 (5.7%) were hospitalized for recurrent VT not identified as electrical storms. No patient with definite ARVC died suddenly. Thirty-three (94.3%) patients reaching the endpoint were treated with an ICD (15 (45.5%) for secondary prevention) at some point throughout the course of the disease, in comparison to 57 (58.2%) (14 (24.6%) for secondary prevention) in those who did not reach the endpoint.

3.1. Development of the score

Significant results from comparing candidate predictors at baseline are depicted in Table 1.

No other clinical, genetic, electrocardiographic or echocardiographic feature differed significantly between those with and without events. This includes other previously examined risk factors such as syncope or extensive T wave inversion (Tables A.2-A.8).

Parameters with a significant OR were combined into multivariable logistic regression analyses with one of each of the 12-lead ECG, SAECG, 24 h-ECG, echocardiographic and CPEX arrhythmia parameters (any arrhythmias – VE or NSVT – during exercise). The 2010 ARVC task force diagnostic criteria “arrhythmias” and “sustained VT/VF as a reason for screening” were excluded as parameters in multivariable analysis, because they were an element of the endpoint. Treatment with beta-blockers and the maximal heart rate during the first CPEX were both excluded as variables for multivariable analysis, as the first was physician's choice and the latter could have been influenced by the former.

Arrhythmias during CPEX, however, did not seem to be influenced, as they were more common in patients treated with beta-blockers, which is why we included this parameter in the analysis.

This resulted in 10 models with 3 parameters each, in which all parameters were significant. All models were significant (Table A.9). The model with the best relation between a high sensitivity and acceptable specificity, reflected in the highest AUC and OR, was a model consisting of absence of negative T waves in lead aVR, fQRSd ≥117 ms and NSVT ≥3 beats in a 24 h-ECG. This model reached an AUC of 0.90 and OR of 13.03. With one out of three parameters positive, the risk score showed a sensitivity and NPV of 100%. With three out of three parameters positive, specificity and PPV increased to 100%, however at cost of sensitivity. The sensitivity, specificity, PPV, NPV, p-value, OR and AUC, stratified for the number of positive parameters, for the risk score are presented in Table 2.

A clustered bar chart of this test is depicted in Fig. 1 panel A, the receiver operating curve in Fig. A.2. Stratification of patients based on sustained VT/VF (primary vs secondary prophylactic population) before initial investigation is shown in Fig. A.3. By applying the risk score only to patients without a history of VT/VF the AUC was 0.899, p-value 0.002, 95%CI 0.781–1.000.

Fourteen patients (82.4%) fulfilling 2 or more criteria of this risk score were treated with an ICD in comparison to 23 patients (50.0%) fulfilling 1 or less criteria (p 0.024).

3.2. Validation of risk score in other ARVC patient cohorts

Our validation cohort included 58 patients (51.7% men, mean age 41.9 ± 12.8 years) with a definite diagnosis of ARVC, of which 12 patients (20.7%) reached the endpoint over a mean follow up-time of 7.5 ± 6.0 years. When applied to all these patients, our risk score reached a specificity of 80.4% and a NPV of 88.1% with two out of three parameters positive. With only one out of three parameters positive, the NPV rose to 100% (Table 3). The overall AUC was 0.793 (0.664–0.923). The clustered bar chart is shown in Fig. 1 panel B.

3.3. Performance of other scores in our cohort

In our cohort, the parameters suggested by Protonotarios [16] reached a sensitivity of 85.7% if only one parameter had to be positive, however at a specificity of 9.0%. Corrado's parameters (syncope and NSVT in either 24 h-ECG or CPEX) [17] had a specificity of 90.8%, however, with a sensitivity of only 7.4%. The most balanced tests were Liao's [18], who used a positive SAECG in all 3 parameters as a predictor of arrhythmias, which reached a sensitivity of 59.1% and a specificity of 66.2%, Wichter's [19], with a sensitivity of 60% and a specificity of

58.8%, and Piccini's [20] with a sensitivity of 57.1% and a specificity of 78.0%. The predictor (major risk factors) recommended by the 2015 Task Force document had indeed a sensitivity and NPV of 100%, however at a specificity of only 20.2% [8] (Table A.10).

4. Discussion

We observed, that arrhythmic risk can be predicted at the first presentation of the disease, in patients with definite ARVC with and without disease-causing genetic mutations. Using simple clinical data typically gathered at the initial visit (fQRSd from SAECG of ≥117 ms, presence of NSVT beats in a 24 h-ECG and the absence of negative T waves in lead aVR at baseline) we developed a risk score that substantially improves on prior efforts to predict clinically important arrhythmias in this complex patient population. Each parameter counted as 1 point. 52.9% of patients, who had a risk score of 2, and 100% of patients with a score of 3, reached the arrhythmic endpoint over 101 ± 57 months. A score of 0 virtually excluded the occurrence of arrhythmia over 10 years follow-up. This score can therefore help in the decision about ICD implantation. The advantage of these measurements is that they are non-invasive, relatively easily accessible and not investigator-dependent.

Risk stratification in patients with ARVC is imperfect. Several risk factors have previously been published, but with significant variation in both inclusion criteria and definition of outcome. The international task force consensus statement on treatment of ARVC from 2015 underlined the sparce evidence for risk stratification [8]. Our work increases the evidence to improve risk stratification.

SAECG use in patients with ARVC was explored by Blomström-Lundqvist in 1988 [21]. Turrini [22] correlated late potentials, especially RMS with a filter of 25 Hz, to sustained VA. Late potentials in SAECG appear to correlate with fibro-fatty substitution on biopsy and magnetic resonance imaging, and may therefore be a sign of slow conduction and

hence of the substrate for arrhythmia [18]. Positivity of all three SAECG parameters was reported as a predictor for arrhythmia in a smaller series [18]. All three usually reported SAECG parameters (fQRSd, LAS and RMS), were considered for our risk score. However, only fQRSd contributed to the most sensitive and specific risk score.

Corrado et al. [17] reported NSVT ≥3 beats as a predictor of appropriate ICD interventions and shocks for VF and ventricular flutter. Our definition of the outcome differs from Corrado's in that we also included SCD and hospitalization for VT.

Lead aVR is a marker of the RV outflow tract [23]. Recently, epsilon waves in lead aVR were described in a small number of patients with ARVC [24]. To our knowledge, the morphology of the T wave in lead aVR in the context of ARVC has not been characterized. Patients with arrhythmic events characteristically did not show the usual negative T wave in aVR, but a flattened or positive T wave. T wave abnormalities in lead aVR may be a sign of electrical changes due to loss of cell-cell adhesion and fibro-fatty alteration, especially in the area of the RV outflow tract.

The absence of further predictors of arrhythmic risk in our cohort may derive from small prevalences of these factors in our cohort, as many patients have not developed a full phenotype at their first presentation yet.

No echocardiographic parameter qualified as a predictor for arrhythmias in our study. This may be related to the hypothesis that structural changes detected may occur only later in the course of the disease and may be preceded by electrical changes [25].

A history of syncope has previously been reported as a risk factor for arrhythmia [26], appropriate ICD interventions [17] and SCD [22]. In our cohort, almost 30% of patients

with an arrhythmic outcome reported syncope at baseline and another 6% during follow-up. However, similar proportions suffered from syncope in the non-arrhythmic group. Syncope may be sensitive, but not very specific and has therefore not been added to our risk score.

Reduced LV function has also been reported as a risk factor for arrhythmia [16], major adverse cardiac events [27], and appropriate ICD discharges [17,19]. LV dysfunction was relatively rare in our cohort, which explains why it has not been taken into account as an independent predictor. The low prevalence of LV dysfunction emphasizes that our patients were investigated before the occurrence of it, i.e. not at very advanced stages. However, in a patient with significant LV dysfunction, there may still be a significant arrhythmic risk and decisions upon therapy should not solely depend on our risk score.

Bhonsale et al. published a risk score, which states PKP mutations and T wave inversions as risk factors [27]. However, they have included family members without a definite diagnosis of ARVC. As both risk factors named are part of the 2010 ARVC task force criteria, they are simply likely to be associated with a definite diagnosis, which impairs the prognosis, in contrast to a possible or borderline diagnosis.

4.1. *Clinical implications*

Previously reported risk factors for arrhythmia are either very sensitive [8,16] or very specific [17,20]. This means, that by applying them, we either overestimate the risk and hence implant patients unnecessarily with ICDs from which they will not benefit, but still may experience complications, or miss patients at high risk and put them at risk of SCD. Our diagnostic score shows both a high sensitivity and specificity and therefore may

improve patient selection for prophylaxis and treatment of VA and can be used in addition to previously reported risk factors. With the very high NPV of a low risk score, this may be used to reassure patients during screening situations and the risk stratification process.

4.2. *Limitations*

This is a retrospective multicenter study. The risk factors included in our risk score were not investigated prospectively and should thus be regarded as preliminary. Our centers served as a tertiary referral center and a high referral bias is therefore to be expected. However, all patients in our database have been included, both patients with and without known genetic mutations, and therefore this cohort represents real clinical life. Additionally, we included both patients with and without previous episodes of VT/VF for the development of the score, to represent a cohort with a broad spectrum of arrhythmic risk including patients with a very high risk. Several recently researched factors such as C-reactive protein were not added to our database and could therefore not be examined. As we did not have MRI results in a large proportion of our patients we were unable to include MRI parameters into the development of the risk score. Our risk score describes an aspect of the arrhythmic phenotype, but does not predict the risk of SCD.

4.3. *Conclusion*

Ventricular arrhythmic risk in patients with ARVC can be evaluated at their first presentation based on a novel risk score comprised of SAECG measurements (fQRSd

≥117 ms), T wave morphology (absence of negative T waves in lead aVR) and arrhythmias (NSVT ≥3 beats) on 24 h-ECGs at baseline. A higher score indicates a higher arrhythmic risk, whereas a low score virtually excludes an arrhythmic risk. Our risk score has promise to form a risk stratification algorithm in the future.

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Conflict of interest

No conflict of interest declared.

Table 1. Significant baseline characteristics.

Modality	Parameter	Recurrent arrhythmia n=35	Favourable outcome n=100	p- value	p-value adapted
Reason for screening	Family history	2 (5.7%)	40 (40%)	0.000	0.017
	VT/VF	20 (57.1%)	22 (22.0%)	0.000	0.17
12-lead-ECG	Negative T wave aVR	15 (42.9%)	69 (72.6%)	0.003	0.038
Signal-averaged-ECG	fQRSd≥117ms	16 (72.7%)	22 (31.0%)	0.001	0.017
24 h-ECG	≥800 VPB	16 (80.0%)	26 (39.4%)	0.002	0.028
	Couplets present	17 (94.4%)	37 (56.1%)	0.002	0.028
	≥8 couplets	16 (88.9%)	25 (37.9%)	0.000	0.000
	Triplets present	15 (83.3%)	19 (29.2%)	0.000	0.000
	VT ≥3 beats	15 (83.3%)	25 (35.8%)	0.000	0.017
CPEX	Maximal heart rate (bpm)	129 ± 23.7	145.7 ± 29.0	0.005	0.049
Echocardiogram	Visual RV dilatation (incl. Upper normal)	31 (88.6%)	62 (63.9%)	0.005	0.049
	Visual RV dilatation (excl. Upper normal)	29 (82.9%)	52 (53.6%)	0.002	0.028
	RVOT PLAX ≥3.4cm	22 (91.7%)	41 (57.7%)	0.002	0.028
	RVIT (cm)	4.3 ± 0.8	3.6 ± 0.8	0.001	0.021
	RVIT ≥3.7	18 (81.8%)	27 (46.6%)	0.005	0.049
	RV/LV	1.3 ± 0.7	0.9 ± 0.5	0.005	0.049
	RV/LT ≥0.81	16 (80.0%) 15 (34.1%)	16 (80.0%) 15 (34.1%)	0.001	0.021

RV/LT ≥0.79	18 (90.0%)	20 (45.5%)	0.001	0.021

CPEX: cardiopulmonary exercise test, fQRSd: filtered QRS duration, LV: left ventricle, PLAX: parasternal long axis view, RV: right ventricle/ventricular, RVIT: RV inflow tract, RVOT: RV outflow tract, VF: ventricular fibrillation, VPB: ventricular premature beats, VT: ventricular tachycardia.

Table 2

Performance, effect size and accuracy of risk score.

Parameters positive	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	OR (95% CI)	P value	AUC (95% CI)
1 out of 3	100	40.4	26.2	100	NA	0.011	0.70 (0.56–0.84)
2 out of 3	81.8	84.6	52.9	95.7	24.75 (4.49–136.48)	0.000	0.83 (0.69–0.98)
3 out of 3	36.4	100	100	88.1	NA	0.001	0.68 (0.48–0.89)

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), odds ratio (OR), p-value and area under the curve (AUC) depending on number of criteria fulfilled for risk score based on filtered QRS duration ≥117 ms, non-sustained ventricular tachycardia on 24 h-ECG and absence of negative T-waves in lead aVR.

Table 3

Performance, effect size and accuracy of risk score in validation cohort.

Parameters positive	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	OR (95% CI)	p-Value	AUC (95% CI)
≥1 out of 3	100.0	39.1	30.0	100	1.429 (1.166–1.750)	0.011	0.696 (0.556–0.836)
≥2 out of 3	58.3	80.4	43.8	88.1	5.756 (1.478–22.409)	0.013	0.694 (0.514–0.874)
3 out of 3	25.0	97.8	75.0	83.3	15.000 (1.397–161.045)	0.025	0.614 (0.417–0.812)

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), odds ratio (OR), p-value and area under the curve (AUC) depending on number of criteria fulfilled for risk score based on filtered QRS duration ≥117 ms, non-sustained ventricular tachycardia on 24 h-ECG and absence of negative T-waves in lead aVR.

Figure legend

Fig. 1. ClusteredBar Chart for Risk score. Clustered Bar Chart for risk scorebasedon filtered QRS duration ≥117 ms, NSVT ≥3 beats N100 bpm on 24 h-ECG,absence of negative T wave in lead aVR. Panel A: Performance in the development cohort. Panel B: Performance in the validation cohort.

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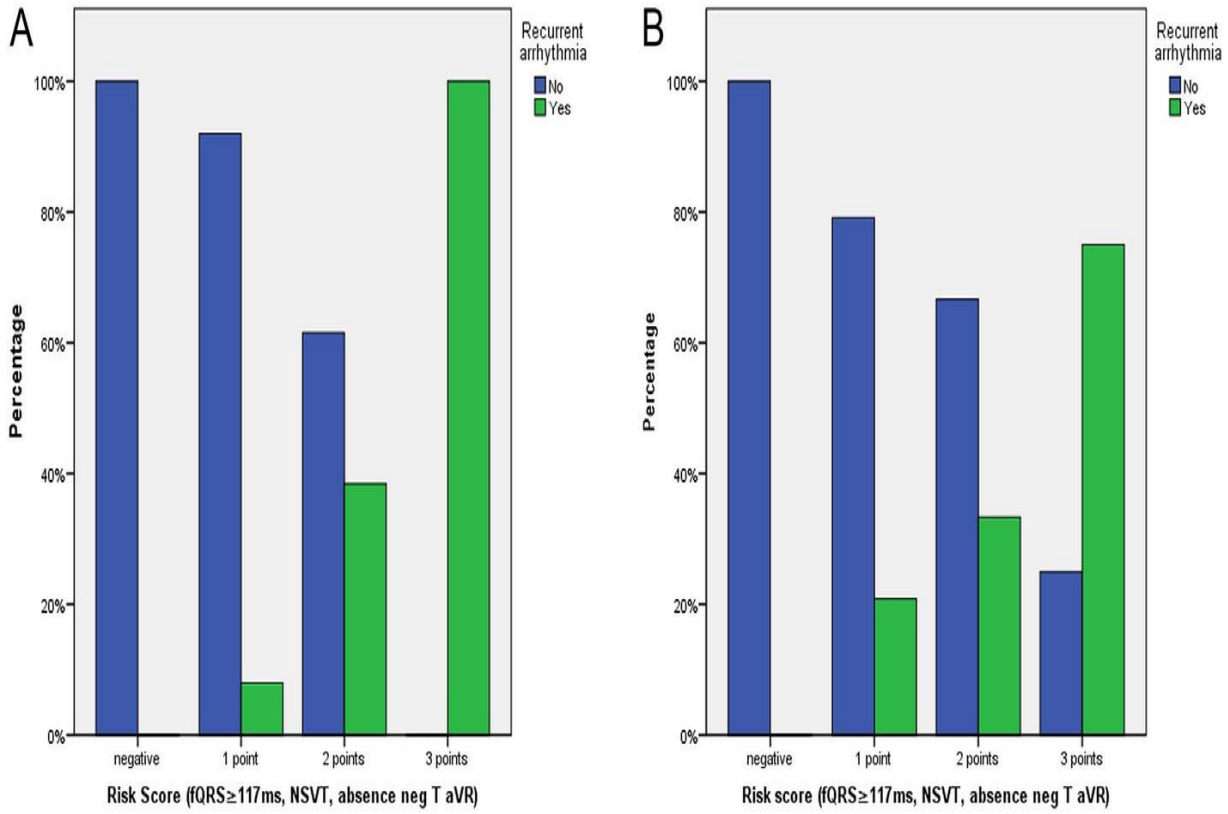
A
Recurrent arrhythmia
No
Yes
100%
80%
60%
40%
20%
0%
Percentage
negative
1 point
2 points
3 points
Risk Score (fQRS≥117ms, NSVT, absence neg T aVR)
B
Recurrent arrhythmia
No
Yes
100%
80%
60%
40%
20%
0%
Percentage
negative
1 point
2 points
3 points
Risk score (fQRS≥117ms, NSVT, absence neg T aVR)

Risk score for the exclusion of arrhythmic events in arrhythmogenic right ventricular cardiomyopathy at first presentation: Appendix

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Tables

Table A.1:

Year	Author	Analysed risk	Proposed risk factor	Quantification
2015	Protonotarios[1]	Arrhythmia	Male gender	HR 3.26
			Repolarization abnormalities	OR 6.94-9.09
			LV dysfunction	OR 7.07-8.19
2015	Mast[2]	MACE	LVEF<50%	1year event risk 50% vs 16.7%
2015	Ruwald[3]	Arrhythmia or death	Competitive sport	HR 1.99
2014	Saguner[4]	MACE (HF and arrhythmia)	inferior TWI	HR 2.44
			QRS fragmentation	HR 2.92
			precordial QRS amplitude ratio ≤0.48	HR 2.65
2014	Liao[5]	Arrhythmia	SAECG fulfilling all 3 Task Force criteria	OR 30.49
2014	Link[6]	ICD treatment	Pre-implantation SMVT or SPVT	P=0.0029
			T-wave inversions inferiorly	P=0.0159
		Life-threatening arrhythmias	Younger age	P=0.032
2014	Saguner[7]	MACE	Reduced RVFAC, per 1%	HR 1.08
			Reduced TAPSE, per unit decrease	HR 1.01
2012	Peters[8]	Development of RBBB and HF	QRS fragmentation in ≥ 3 leads	r=17.45
2013	James[9]	HF	> average annual exercise	P=0.048
		Arrhythmia	>516h/year sports before presentation	P=0.001

			>425h/year sports after presentation	P<0.001
2013	Canpolat[10]	Arrhythmia	Fragmented QRS	OR 6.52
			RVEF reduction	OR 3.76
			LV involvement	OR 2.88
			History of syncope	OR 3.12
2013	Te Riele[11]	Arrhythmia	Arrhythmic events only in patients with both electrical (ECG and/or Holter) and structural (CMR) criteria for ARVC	None given
2013	Deac[12]	Arrhythmia	Abnormal CMR	HR 16.1
2013	Bhonsale[13]	Arrhythmia	Proband status	HR 7.7
			≥ 3 T-wave inversions	HR 4.2
			Male sex	HR 1.8
2013	Migliore[14]	Arrhythmia	History of cardiac arrest or syncope	HR 2.4
			Abnormal bipolar endocardial voltage mapping	HR 1.6
2013	Saguner[15]	MACE	Inducibility of Sustained monomorphic VT	OR 2.87
2012	Santangeli[16]	Appropriate ICD interventions	Fragmented QRS	HR 21
			Abnormal electrograms within scar	HR 8.91
2012	Peters[17]	Arrhythmia	QRS fragmentation	OR 10.46
			Arrhythmia	OR 5.33
			Left precordial JT prolongation	OR 9.67
2011	Bhonsale[18]	Appropriate ICD interventions	Inducibility at electrophysiological study	HR 4.5
			Non-sustained VT	HR 10.5
2011	Paul[19]	VT	RV size (moderate vs. no dilatation)	HR 0.135
			Presence of an ICD	HR 3.012
			Presence of an abnormal ^{123}I-MIBG SPECT finding	HR 4.667
2011	Sarvari[20]	Arrhythmia	Increased RVOT diameter, RVED area, and RVES area and reduced RVFAC	P<0.001

2011	Pinamonti[21]	CV death or HTx	Significant tricuspid regurgitation	HR 7.60	AUC 0.78
			Amiodarone		
			RV dysfunction	HR 3.40	
				HR 4.12	
			Significant tricuspid regurgitation	HR 5.09	AUC 0.84
			Amiodarone		
			Ordinal ventricular dysfunction	HR 3.72	
				HR 6.30	
2010	Corrado[22]	Appropriate ICD interventions	Syncope	HR 2.95	
			NSVT	HR 1.62	
			Age ≤35y	HR 1.22	
			LV dysfunction (EF <55%)	HR 1.13	
			FH of SCD	HR 0.90	
		ICD shocks for VF/Vfl	Syncope	HR 3.16	
			NSVT	HR 1.28	
2005	Piccini[23]	Appropriate ICD interventions	Previous sustained VT/VF	OR 11.44	
2005	Lemola[24]	MACE	History of congestive heart failure	P<0.0001	
			LV involvement in echo	P=0.0003	
2004	Roguin[25]	Appropriate ICD interventions	VT induction during electrophysiological study	OR 11.2	
2004	Wichter[26]	Apropriate ICD interventions	Extensive RV dysfunction	OR 2.09	
2003	Corrado[27]	Appropriate ICD intervention for VF/Vfl	Age/5 y	OR 0.77	
			LVEF	OR 0.94	
			Cardiac arrest	OR 79	
			VT with hemodynamic compromise	OR 14	
2001	Turrini[28]	Sudden death	QRS dispersion	OR 1.22	
			History of syncope	OR 5.9	
1999	Peters[29]	Sudden death/malignant ventricular arrhythmias	LV involvement	P<0.00001	
			RV dilatation	P<0.00001	
				P<0.00001	

	Left precordial JT interval prolongation	P<0.005
	Precordial QRS dispersion ≥50 ms	P<0.0001
	Precordial T wave inversions beyond V3	

Reported risk factors for adverse outcomes in patients with ARVC. LV: left ventricular/ventricle, HR: hazard ratio, OR odds ratio, MACE: major adverse cardiac events, LVEF: left ventricular ejection fraction, HF: heart failure, TWI: T wave inversions, SAECG: signal averaged ECG, ICD: implantable cardioverter-defibrillator, SMVT: sustained monomorphic ventricular tachycardia (VT), SPVT: sustained polymorphic VT, RVFAC: fractional area of change, TAPSE: tricuspid annular plane systolic excursion, RBBB: right bundle branch block, RVEF: right ventricular ejection fraction, CMR: cardiac magnetic resonance, RV: right ventricular, ^{123}I-MIBG SPECT: I-123-*meta*iodobenzylguanidine–single photon emission computed tomography, RVOT: right ventricular outflow tract, RVED: right ventricular end-diastolic, RVES: right ventricular end-systolic, NSVT: nonsustained VT, FH: family history, SCD: sudden cardiac death, VFl: ventricular flutter

Table A.2:

	Recurrent arrhythmia **n = 35**	**Favourable outcome** **n = 100**	**p-value**	**p-value adapted**
Age at diagnosis	38.5 ± 13.0	41.8 ± 15.1	0.254	0.649
Time of follow up (months)	109.5 ± 57.4	111.1 ± 67.160	0.899	1.000
Male sex	25 (71.4%)	57 (57.0%)	0.161	0.495
Caucasians	32 (94.1%)	95 (96.0%)	0.645	0.835
Family history SCD	12 (37.5%)	46 (50.0%)	0.304	0.691
Multiple family history SCD	5 (11.6%)	21 (9.1%)	0.575	0.802
Single desmosomal pathogenic mutation	14 (40.0%)	42 (42.0%)	1.000	1.000
Desmoplakin pathogenic mutation	3 (8.6%)	15 (15.0%)	0.402	0.727
Plakophilin-2 pathogenic mutation	11 (31.4%)	32 (32.0%)	1.000	1.000
Desmoglein-2 pathogenic mutation	5 (14.3%)	11 (11.0%)	0.560	0.802
Desmocollin-2 pathogenic mutation	2 (5.7%)	2 (2.0%)	0.276	0.657
Plakoglobin pathogenic mutation	1 (2.9%)	1 (1.0%)	0.453	0.789

2 desmosomal mutations, same gene	1 (2.9%)	10 (10.0%)	0.288	0.671
2 desmosomal mutations, different genes	8 (8.0%)	5 (14.3%)	0.321	0.706
Structural major criterion	21 (60.0%)	50 (50.5%)	0.431	0.761
Structural minor criterion	2 (5.7%)	15 (15.2%)	0.237	0.615
Tissue major criterion	2 (5.7%)	3 (3.1%)	0.607	0.813
Tissue minor criterion	0 (0.0%)	0 (0.0%)	NA	NA
Repolarisation major criterion	16 (45.7%)	49 (49.5%)	0.844	0.994
Repolarisation minor criterion	5 (14.3%)	12 (12.1%)	0.771	0.927
Depolarisation major criterion	4 (11.4%)	3 (3.0%)	0.076	0.320
Depolarisation minor criterion	4 (11.4%)	16 (16.2%)	0.591	0.813
Arrhythmias major criterion	24 (68.6%)	47 (48.0%)	**0.048**	0.252
Arrhythmias minor criterion	10 (27.8%)	10 (28.6%)	1.000	1.000
Family history major criterion	24 (68.6%)	74 (75.5%)	0.503	0.802
Family history minor criterion	1 (2.9%)	3 (3.1%)	1.000	1.000

General characteristics. MACE: major adverse cardiac events, AUC: area under the curve, CI: confidence interval, OR: odds ratio. SCD: sudden cardiac death.

Table A.3:

Symptoms at initial presentation	**Recurrent arrhythmia** **n = 35**	**Favourable outcome** **n = 97**	**p-value**	**p-value adapted**
Family history as reason for screening	2 (5.7%)	40 (40.0%)	**0.000**	0.017
VT/VF as reason for screening	20 (57.1%)	22 (22.0%)	**0.000**	0.017
Cardiovascular symptoms as reason for screening	13 (37.1%)	31 (31.0%)	0.534	0.802
Incidental findings as reason for screening	0 (0.0%)	4 (4.0%)	0.572	0.802
Dyspnea	6 (18.8%)	17 (17.7%)	1.000	1.000
Chest pain	2 (6.3%)	14 (14.6%)	0.355	0.727
Palpitations	13 (40.6%)	39 (40.6%)	1.000	1.000

Presyncope	7 (21.9%)	26 (27.1%)	0.646	0.835
Syncope	9 (28.1%)	35 (36.5%)	0.520	0.802

Clinical symptoms at baseline. MACE: major adverse cardiac events, AUC: area under the curve, CI: confidence interval, OR: odds ratio, VT: ventricular tachycardia, VF: ventricular fibrillation

Table A.4:

ECG at baseline	**Recurrent arrhythmia** **n = 35**	**Favourable outcome** **n = 95**	**p-value**	**p-value adapted**
QRS duration V1	100.28 ± 18.54	94.02 ± 18.86	0.107	0.386
QRS duration V6	79.06 ± 20.12	80.22 ± 18.65	0.768	0.927
S upstroke duration V1	45.00 ± 13.74	38.09 ± 13.24	**0.014**	0.106
S upstroke duration V2	48.59 ± 16.81	42.70 ± 14.81	0.065	0.308
Abnormal axis	9 (26.5%)	19 (20.2%)	0.473	0.789
Epsilon wave V1	0 (0.0%)	3 (3.2%)	0.563	0.802
Epsilon wave V2	0 (0.0%)	3 (3.2%)	0.563	0.802
Epsilon wave V3	1 (2.9%)	2 (2.1%)	1.000	1.000
Epsilon wave II	0 (0.0%)	3 (3.2%)	0.563	0.802
Epsilon wave III	0 (0.0%)	6 (6.3%)	0.190	0.543
Epsilon wave aVF	0 (0.0%)	6 (6.3%)	0.190	0.543
Negative T wave V1	28 (80.0%)	65 (68.4%)	0.273	0.657
Negative T wave V2	25 (71.4%)	51 (53.7%)	0.075	0.320
Negative T wave V3	22 (62.9%)	44 (46.3%)	0.115	0.390
Negative T wave V4	18 (51.4%)	35 (36.8%)	0.161	0.495
Negative T wave V5	12 (34.3%)	22 (23.2%)	0.260	0.654
Negative T wave V6	6 (17.1%)	17 (17.9%)	1.000	1.000
Negative T wave I	3 (8.6%)	4 (4.2%)	0.386	0.727
Positive T wave I	21 (60.0%)	72 (75.8%)	0.084	0.324
Negative T wave II	6 (17.1%)	11 (11.6%)	0.394	0.727
Positive T wave II	17 (48.6%)	53 (55.8%)	0.553	0.802
Negative T wave III	14 (40.0%)	31 (32.6%)	0.533	0.802

Positive T wave III	7 (20.0%)	30 (31.6%)	0.273	0.657
Negative T wave aVR	15 (42.9%)	69 (72.6%)	**0.003**	0.038
Positive T wave aVR	5 (14.3%)	8 (8.4%)	0.334	0.719
Negative T wave aVL	5 (14.3%)	9 (9.5%)	0.524	0.802
Positive T wave aVL	17 (48.6%)	56 (58.9%)	0.323	0.706
Negative T wave aVF	9 (25.7%)	18 (18.9%)	0.466	0.789
Positive T wave aVF	11 (31.4%)	47 (49.5%)	0.076	0.320
Q wave V1	0 (0.0%)	3 (3.2%)	0.566	0.802
Q wave V2	0 (0.0%)	2 (2.1%)	1.000	1.000
Q wave V3	0 (0.0%)	2 (2.1%)	1.000	1.000
Q wave V4	2 (5.9%)	4 (4.2%)	0.654	0.835
Q wave V5	8 (23.5%)	15 (15.8%)	0.309	0.693
Q wave V6	8 (23.5%)	21 (22.1%)	1.000	1.000
Q wave I	7 (20.6%)	15 (15.8%)	0.597	0.813
Q wave II	6 (17.6%)	18 (18.9%)	1.000	1.000
Q wave III	5 (14.7%)	22 (23.2%)	0.338	0.719
Q wave aVR	3 (8.8%)	12 (12.6%)	0.758	0.927
Q wave aVL	6 (17.6%)	17 (17.9%)	1.000	1.000
Q wave aVF	7 (20.6%)	18 (18.9%)	0.805	0.961
Left bundle branch block (complete +incomplete)	3 (8.6%)	4 (4.2%)	0.386	0.727
Complete LBBB	1 (2.9%)	2 (2.1%)	1.000	1.000
Right bundle branch block (complete +incomplete)	2 (5.7%)	12 (12.6%)	0.350	0.727
Complete RBBB	0 (0.0%)	4 (4.2%)	0.574	0.802
Low voltage	10 (28.6%)	22 (23.2%)	0.647	0.835
Poor R wave progression	12 (35.3%)	32 (34.8%)	1.000	1.000

ECG characteristics at baseline. MACE: major adverse cardiac events, AUC: area under the curve, CI: confidence interval, OR: odds ratio, LBBB: left bundle branch block, RBBB: right bundle branch block

Table A.5:

SAECG at baseline	**Recurrent arrhythmia** **n = 22**	**Favourable outcome** **n = 71**	**p-value**	**p-value adapted**
Filtered QRS duration	124.7 ± 22.5	114.2 ± 21.2	**0.050**	0.252
Filtered QRS duration ≥ 114 ms	16 (72.7%)	29 (42.0%)	**0.012**	0.095
Filtered QRS duration ≥ 117 ms	16 (72.7%)	21 (30.4%)	**<0.001**	0.017
Filtered QRS duration ≥ 106 ms	18 (81.8%)	41 (59.4%)	0.055	0.269
Filtered QRS duration ≥ 108 ms (BL)	17 (77.3%)	39 (56.5%)	0.081	0.320
RMS 40	20.9 ± 22.6	24.8 ± 18.0	0.402	0.727
RMS 40 ≤ 20	14 (63.6%)	37 (53.6%)	0.410	0.732
RMS 40 ≤ 23.6	16 (72.7%)	37 (53.6%)	0.114	0.390
RMS 40 ≤ 30	17 (77.3%)	45 (65.2%)	0.291	0.671
LAS	51.1 ± 22.2	40.1 ± 19.6	**0.028**	0.172
LAS ≥ 36	17 (77.3%)	37 (53.6%)	**0.049**	0.252
LAS ≥ 38	15 (68.2%)	33 (47.8%)	0.096	0.354
LAS ≥ 42	15 (68.2%)	26 (38.0%)	**0.012**	0.095
All 3 parameters positive	13 (59.1%)	23 (33.3%)	**0.031**	0.183
Z QRS duration	116.3 ± 27.3	108.2 ± 15.5	0.115	0.390
Z RMS 40	22.1 ± 26.9	17.2 ± 12.1	0.277	0.657
Z LAS	50.4 ± 25.8	44.4 ± 15.5	0.235	0.615
Number of beats	326 ± 138	342 ± 189	0.724	0.904
Filtered noise	0.376 ± 0.073	0.385 ± 0.062	0.605	0.813

Signal averaged ECG (SAECG) measurements at baseline. MACE: major adverse cardiac events, AUC: area under the curve, CI: confidence interval, OR: odds ratio, RMS: Root-mean-square voltage of the terminal 40 ms, LAS: low amplitude signal < 40 µV duration, Z: Z-vector

Table A.6:

24h-ECG at baseline	**Recurrent arrhythmia**	**Favourable outcome**	**p-value**	**p-value adapted**
	n = 20	**n = 66**		

Number of VPB	3509 ± 3892	2140 ± 4672	0.237	0.615
VPB present	20 (100%)	62 (93.9%)	0.569	0.802
≥ 440 VPB	17 (85%)	33 (50.0%)	0.009	0.083
≥ 800 VPB	16 (80.0%)	26 (39.4%)	0.002	0.028
Number of couplets	308 ± 450	136 ± 356	0.091	0.343
Couplets present	17 (94.4%)	37 (56.1%)	0.002	0.028
≥ 8 couplets	16 (88.9%)	25 (37.9%)	0.000	0.000
Number of triplets	27 ± 51	9 ± 34	0.081	0.320
Triplets present	15 (83.3%)	19 (29.2%)	0.000	0.000
Polymorphic VPBs	12 (70.6%)	32 (57.1%)	0.403	0.727
VT present	7 (41.2%)	15 (22.1%)	0.128	0.425
Number of VT	1 ± 3	3 ± 15	0.754	0.927
Max beats VT	5 ± 4	3 ± 5	0.184	0.544
Max HR VT	148 ± 34	149 ± 53	0.954	1.000
Number SVE	561 ± 1343	309 ± 1499	0.541	0.802
AF present	0 (0.0%)	2 (3.0%)	1.000	1.000
SVT present	2 (11.1%)	4 (6.0%)	0.604	0.813

Holter results at baseline. MACE: major adverse cardiac events, AUC: area under the curve, CI: confidence interval, OR: odds ratio, VPB: ventricular premature beats, VT: ventricular tachycardia, SVE: supraventricular ectopics, AF: atrial fibrillation, SVT: supraventricular tachycardia

Table A.7:

CPEX at baseline	**Recurrent arrhythmia** **n = 31**	**Favourable outcome** **n = 88**	**p-value**	**p-value adapted**
Beta blockers	22 (71.0%)	41 (46.6%)	0.022	0.146
Calcium channel blockers	0 (0.0%)	1 (1.1%)	1.000	1.000
Sotalol	4 (12.9%)	7 (8.0%)	0.476	0.789
Amiodarone	3 (9.7%)	4 (4.6%)	0.377	0.727
Antiarrhythmics	2 (6.5%)	7 (8.0%)	1.000	1.000
Arrhythmias at rest	16 (51.6%)	33 (37.95)	0.207	0.582

Arrhythmias during exercise	24 (77.4%)	47 (54.0%)	0.025	0.160
NSVT during exercise	4 (12.9%)	3 (3.4%)	0.077	0.320
Arrhythmias during recovery	17 (54.8%)	36 (41.3%)	0.214	0.592
NSVT during recovery	1 (3.2%)	1 (1.1%)	0.458	0.789
%VO2max	76.7 ± 29.8	80.4 ± 22.4	0.475	0.789
VO2 max (ml/min/1.73m2)	23.4 ± 7.6	23.9 ± 7.7	0.760	0.927
RQ	1.09 ± 0.11	1.10 ± 0.10	0.680	0.862
Minutes	8.3 ± 2.7	8.6 ± 2.4	0.647	0.835
Watts	148.8 ± 55.5	149.0 ± 61.0	0.985	1.000
Max HR	129 ± 23.7	145.7 ± 29.0	0.005	0.049
Predicted max HR	159.6 ± 43.6	154.2 ± 44.4	0.573	0.802

Results from cardiopulmonary exercise test (CPEX) at baseline. MACE: major adverse cardiac events, AUC: area under the curve, CI: confidence interval, OR: odds ratio, NSVT: nonsustained VT, VO2max: maximal oxygen uptake, %VO2max: VO2max, % of predicted, RQ: respiratory quotient, HR: heart rate

Table A.8:

Echocardiogram at baseline	**Recurrent arrhythmia** **n = 35**	**Favourable outcome** **n = 97**	**p-value**	**p-value adapted**
Reduced RV function (incl. borderline)	22 (62.9%)	40 (41.2%)	0.032	0.183
Reduced RV function (excl. borderline)	21 (60.0%)	40 (41.2%)	0.075	0.320
RV dilatation (incl. upper normal)	31 (88.6%)	62 (63.9%)	0.005	0.049
RV dilatation (excl. upper normal)	29 (82.9%)	52 (53.6%)	0.002	0.028
RVOT PLAX (cm)	3.8 ± 0.4	3.5 ± 0.8	0.144	0.469
RVOT PLAX ≥ 3.6 cm	17 (70.8%)	30 (42.3%)	0.019	0.131
RVOT PLAX ≥ 3.4 cm	22 (91.7%)	41 (57.7%)	0.002	0.028
RVOT PLAX/BSA	1.9 ± 0.2	1.8 ± 0.4	0.367	0.727
RVOT PLAX/BSA ≥ 1.85	11 (64.7%)	20 (35.7%)	0.050	0.252

RVOT PLAX/BSA ≥ 1.68	15 (88.2%)	30 (53.6%)	0.011	0.095
RVOT PSAX (cm)	3.5 ± 0.6	3.2 ± 0.6	0.190	0.544
RVOT PSAX/BSA	1.7 ± 0.3	1.6 ± 0.4	0.686	0.863
RVIT (cm)	4.3 ± 0.8	3.6 ± 0.8	0.001	0.021
RVIT ≥ 3.7 cm	18 (81.8%)	27 (46.6%)	0.005	0.049
RV/LV	1.3 ± 0.7	0.9 ± 0.5	0.005	0.049
RV/LV ≥ 0.81	16 (80.0%)	15 (34.1%)	0.001	0.021
RV/LV ≥ 0.79	18 (90.0%)	20 (45.5%)	0.001	0.021
RV regional wall motion abnormalities	23 (67.6%)	51 (52.6%)	0.160	0.495
Akinesia or dyskinesia RV	9 (27.3%)	23 (23.7%)	0.815	0.966
Dyskinesia RV	6 (18.2%)	12 (12.4%)	0.395	0.727
Bulge RV	4 (12.1%)	12 (12.6%)	1.000	1.000
RV aneurysm	4 (12.1%)	11 (11.6%)	1.000	1.000
LVEDD	5.0 ± 0.5	5.2 ± 0.6	0.363	0.727
LVESD	3.5 ± 0.6	3.6 ± 0.7	0.368	0.727
IVS	0.9 ± 0.2	0.8 ± 0.2	0.363	0.727
Posterior LV wall	0.8 ± 0.2	0.8 ± 0.2	0.526	0.802
Left atrium	3.5 ± 0.7	3.7 ± 0.5	0.017	0.122
EF	57.8 ± 12.3	57.8 ± 12.2	0.988	1.000
LV regional wall motion abnormalities	9 (26.5%)	20 (20.6%)	0.480	0.789
LV akinesia or dyskinesia	4 (11.8%)	5 (5.2%)	0.237	0.615
LV dyskinesia	2 (5.9%)	4 (4.1%)	0.649	0.835
LV aneurysm	1 (3.0%)	2 (2.1%)	1.000	1.000

Echo characteristics at baseline. AUC: area under the curve, CI: confidence interval, MACE: major adverse cardiac events, OR: odds ratio, PLAX: parasternal long axis view, RV: right ventricle/ventricular, RVOT: right ventricular outflow tract, BSA: body surface area, PSAX: parasternal short axis view, RVIT: right ventricular inflow tract, LV: left ventricle/ventricular, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, IVS: interventricular septum thickness, EF: ejection fraction

Table A.9: Risk Score Proposals

	SAECG	24h-ECG	ECG	CPEX	P value	Nagelkerke R^2	PAC (%)	Sensitivity (%)	Specificity (%)	AUC	OR
Test 1	fQRSd≥106ms	≥800 VPB		Arrhythmias exercise	0.001	0.365	83.9	54.5	90.2	0.83 (0.71-0.94)	7.82 (2.16-28.32)
Test 2	fQRSd≥108ms	≥800 VPB		Arrhythmias exercise	0.001	0.320	82.0	45.5	90.0	0.81 (0.69-0.93)	6.18 (1.87-20.40)
Test 3	LAS≥38ms	≥800 VPB		Arrhythmias exercise	0.001	0.341	82.3	45.5	90.2	0.82 (0.71-0.93)	6.06 (1.90-19.37)
Test 4	LAS≥42ms	≥440 VPB		Arrhythmias exercise	0.000	0.419	85.5	54.5	92.2	0.85 (0.74-0.96)	8.76 (2.27-33.71)
Test 5	LAS≥42ms	≥800 VPB		Arrhythmias exercise	0.000	0.416	85.5	45.5	94.1	0.85 (0.74-0.95)	8.93 (2.25-35.48)
Test 6	fQRSd≥117ms	Triplets	Absence neg T aVR		0.000	0.557	86.9	36.4	100.0	0.90 (0.80-0.99)	12.14 (2.84-51.80)
Test 7	RMS≤23.6mV	Triplets	Absence neg T aVR		0.000	0.522	88.5	45.5	98.0	0.89 (0.80-0.99)	10.58 (2.57-43.54)

Test 8	LAS≥36ms	≥8 couplets	Absence neg T aVR	0.000	0.468	88.7	54.5	96.1	0.87 (0.76-0.98)	8.52 (2.36-30.78)
Test 9	LAS≥36ms	Triplets	Absence neg T aVR	0.000	0.537	90.2	54.5	98.0	0.89 (0.79-0.99)	11.72 (2.69-51.09)
Test 10	fQRSd≥117ms	NSVT ≥3 beats	Absence neg T aVR	0.000	0.556	88.9	36.4	100.0	0.90 (0.80-0.99)	13.03 (2.99-56.87)

Significant models in multivariable logistic regression. AUC: area under the curve, CPEX: cardiopulmonary exercise test, fQRSd: filtered QRS duration, LAS: low amplitude signal duration, neg: negative, OR: odds ratio, PAC: percentage accuracy in classification, RMS: root-mean-square of the last 40 ms, SAECG signal averaged ECG, VPB: ventricular premature beats.

Table A.10:

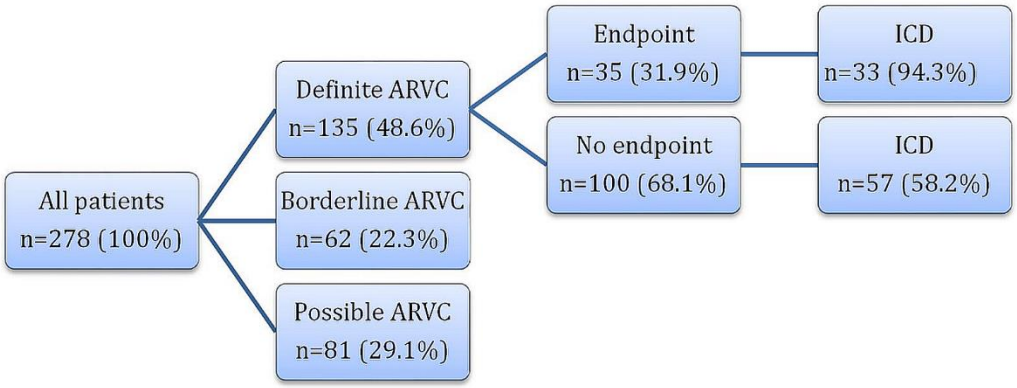
Risk Score	**Parameter**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**OR**	**AUC**
Protonotarios[1]	1 of male sex, repolarisation abnormalities, LV RWMA	85.7	9.0	24.8	64.3	0.59 (0.18-1.91)	0.53 (0.41-0.64)
Protonotarios[1]	2 of male sex, repolarisation abnormalities, LV RWMA	64.7	58.3	35.5	82.4	2.57 (1.14-5.78)	0.62 (0.51-0.73)
Protonotarios[1]	3 of male sex, repolarisation abnormalities, LV RWMA	8.6	93.0	30.0	74.4	1.25 (0.30-5.11)	0.51 (0.40-0.62)

Mast[2]	LVEF < 50%	25.7	80.4	32.1	75.0	1.42 (0.57-3.53)	0.53 (0.42-0.64)
Liao[5]	All 3 SAECG parameters positive	59.1	66.2	35.1	83.0	2.83 (1.06-7.55)	0.63 (0.049-0.76)
Bhonsale 2013[13]	Proband, Male and 3 or more TWI	31.4	77.1	33.3	75.5	1.54 (0.65-3.64)	0.54 (0.43-0.66)
Corrado 2010[22]	Syncope and NSVT	7.4	90.8	20.0	76.0	0.79 (0.16-3.97)	0.49 (0.37-0.62)
Piccini[23]	VT or VF	57.1	78.0	47.6	83.9	4.73 (2.08-10.73)	0.68 (0.57-0.78)
Wichter[26]	RV dysfunction	60.0	58.8	34.4	80.3	2.14 (0.97-4.70)	0.59 (0.48-0.70)
2015 Task Force[30]	LV/RV dysfunction, syncope or NSVT	100	20.2	30.4	100	1.44 (1.26-1.63)	0.60 (0.50-0.71)

Previously reported risk factors for arrhythmias, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), odds ratio (OR) and area under the curve (AUC) calculated in our population. LV: left ventricular, RWMA: regional wall motion abnormalities, LVEF: left ventricular ejection fraction, SAECG: signal averaged ECG, TWI: T wave inversions, NSVT: nonsustained ventricular tachycardia (VT), VF: ventricular fibrillation, RV: right ventricular

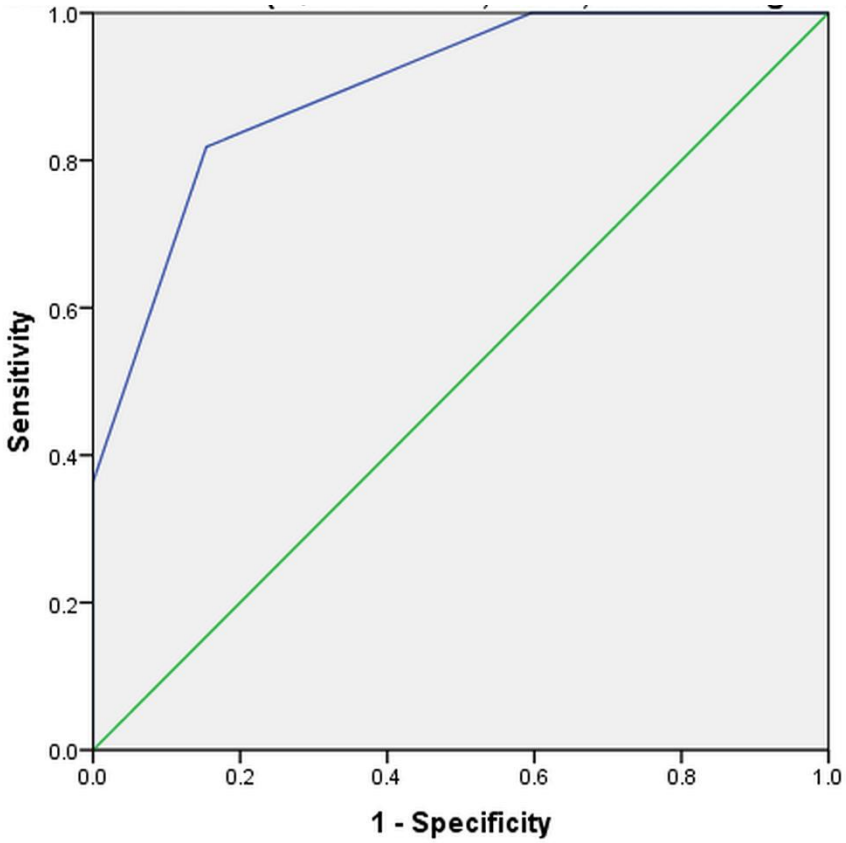
Figures

Figure A.1



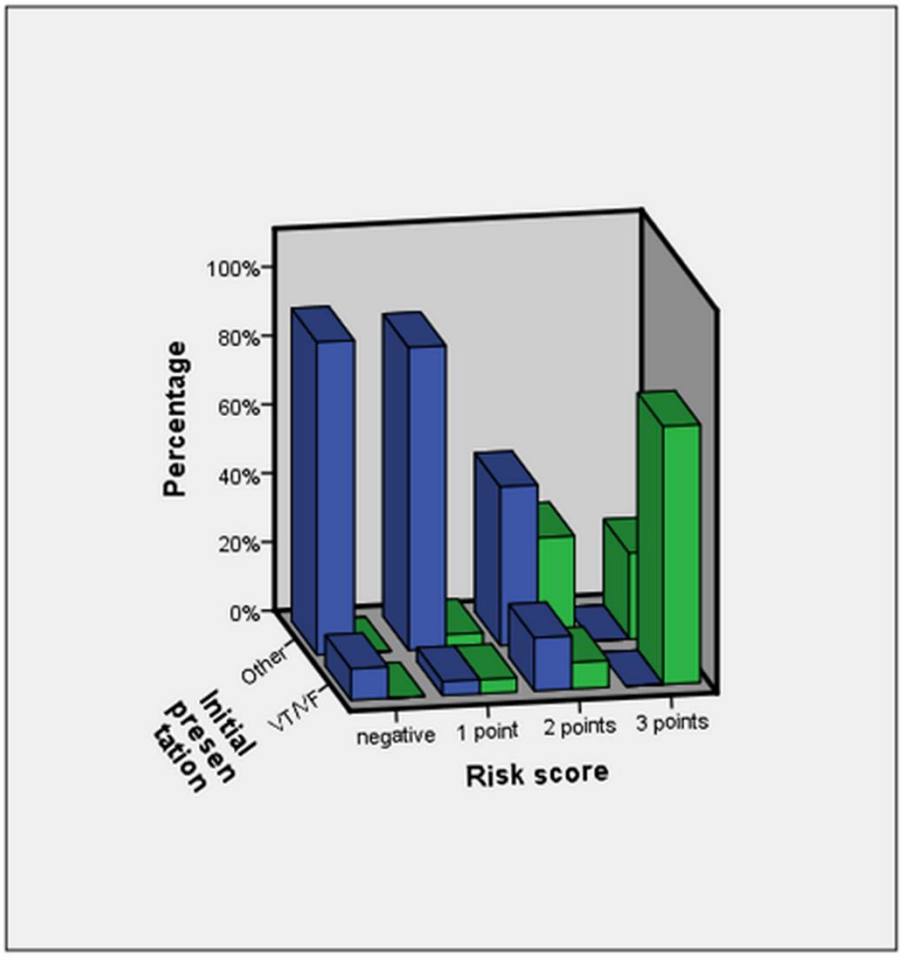
Flow-chart of patients included. ARVC: arrhythmogenic right ventricular cardiomyopathy, ICD: implantable cardioverter-defibrillator

Figure A.2



Receiver operating characteristic curves for risk score based on filtered QRS duration ≥117 ms, NSVT ≥3 beats on 24h-ECG, absence of negative T wave in lead aVR

Figure A.3



Clustered Bar Chart for risk score based on filtered QRS duration ≥117 ms, NSVT ≥3 beats on 24h-ECG, absence of negative T wave in lead aVR in patients with definite ARVC with and without VT/VF before initial investigation. Green bars: recurrent arrhythmia, blue bars: favourable outcome.

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