Supplementary Material

Supplementary Table 1: Included registries and associated hospitals

Registry	Principal investigator(s)	Included hospitals
Johns Hopkins ARVD Registry	Dr Hugh Calkins	Johns Hopkins Hospital, Baltimore, USA
Netherlands ACM Registry	Dr Richard Hauer Dr Peter van Tintelen Dr Anneline te Riele	University Medical Center, Utrecht
		University Medical Center, Groningen
		Leiden University Medical Center, Leiden
		Academic Medical Center, Amsterdam
		Vrije Universiteit Medical Center, Amsterdam
		Erasmus Medical Center, Rotterdam
Swiss ARVC Registry	Dr Firat Duru Dr Corinna Brunckhorst Dr Ardan M. Saguner	University Heart Center, Zurich
		University Hospital Bern
		Triemli Hospital Zurich
Nordic ARVC Registry sites	Dr Kristina H. Haugaa Dr Pyotr Platonov Dr Anneli Svensson	University Hospital, Rikshospitalet, Oslo, Norway
		Skane University Hospital, Lund, Sweden
		Linkoping University, Linkoping, Sweden
Canada, **Montreal Registry** **Vancouver Registry**	Dr Mario Talajic Dr Andrew Krahn	Cardiovascular Genetics Center, Montreal Heart Institute British Columbia inherited arrhythmia clinic

Supplementary Table 2: Pre-specified predictors and definitions*

Predictor	Definition
Sex	Male or female
Age	Age at diagnosis by 2010 Task Force Criteria
Cardiac syncope	Transient loss of consciousness and postural tone with spontaneous recovery with likely arrhythmic mechanism, excluding vasovagal etiology
Recent cardiac syncope	Cardiac syncope < 6 months before diagnosis
NSVT	Prior history of NSVT (hemodynamically stable VT at ≥100bpm, for ≥ 3 beats <30sec)
PVC count	Number of PVCs over a 24 hour recording
Number of leads with TWI	Number of leads with T wave inversion in anterior and inferior derivations
RVEF†	%
LVEF†	%

*All predictors were determined at diagnosis, as specified in the text.

† Cardiac magnetic resonance derived value preferred

Abbreviations: NSVT= non-sustained ventricular tachycardia; PVC= premature ventricular complex; TWI= T-wave inversion; RVEF= Right ventricular ejection fraction; LVEF= Left ventricular ejection fraction.

Supplementary Table 3: Selected and excluded predictors

Predictor	Rationale for including or excluding from the primary model
Selected predictors	
Sex	-Predictor in definite ARVC patients, as shown in prior meta-analysis(1)
Age	-Predictor in definite ARVC in prior studies(2, 3)
Cardiac syncope and recent cardiac syncope	-Predictor in definite ARVC patients as shown in prior meta-analysis(1) -The importance of the timing (recent vs remote), has also been evaluated since this factor has been demonstrated to be a modifier of the effect of this predictor(4)
Non-sustained ventricular tachycardia	-Predictor in definite ARVC patients, as shown in prior meta-analysis(1)
Number of premature ventricular complexes on a 24 hour holter	-Predictor in definite ARVC primary prevention population(1, 4, 5)
Extent of leads with T-wave inversion (sum of ante	-Predictor in definite ARVC patients, as shown in prior meta-analysis(1)
Right ventricular ejection fraction	-Predictor in definite ARVC patients, as shown in prior meta-analysis(1)
Left ventricular ejection fraction	-Not a predictor in definite ARVC patients in prior meta-analysis(1) -Plays an important role in the 2015 International Task Force Consensus Statement(6) algorithm -Important risk predictor in ischemic and other non-ischemic cardiomyopathies
Predictors not selected	
History of strenuous physical activity	-Not a predictor in patients with definite ARVC in prior meta-analysis (1) -Heterogeneity in reporting among different centers and countries limit reliability
Inductility on programmed ventricular stimulation	-Not a predictor in patients with definite ARVC in prior meta-analysis(1) - Invasiveness and availability limit widespread use.
Symptoms including pre-syncope	-Not a predictor in patients with definite ARVC in prior meta-analysis(1) -Heterogeneity in reporting by patients and physicians limit reliability
Epsilon wave	-Not a predictor in patients with definite ARVC in prior meta-analysis(1) -Not unambiguously defined(7)
Genotype	-Not a predictor in patients with definite ARVC in prior literature and in prior meta-analysis (1) -Very high risk genotype, such as TMEM43 mutations, present in a minimal number of patients
Presence of multiple mutations	-Not a predictor in patients with definite ARVC in prior meta-analysis (1) -Present in a minimal number of patients
Right ventricular volume	-Not a predictor in patients with definite ARVC in prior meta-analysis (1) -Strongly correlated with RV function which is one of our pre-specified predictors

Supplementary Table 4: Standard list of definitions for local data collection

Name of the variable	**Description and Definition**
Choices for coding and their definitions	
Patients Characteristics	
Site	Site of enrolment
Age at diagnosis	Days
Sex	Gender of patient
Male =1 Female = 0	
Pedigree	Proband or family member
1=Proband 2=Family member **Proband definition:** first affected family member seeking medical attention for ARVD/C in whom the diagnosis was confirmed (i.e. an individual ascertained independently of family history).	
Race	Ethnicity of patient
1=Caucasian, 2= African, 3=Asian	
Mutation	Pathogenic mutation associated with ARVD/C detected **Definition :** *Definition: nonsense, frameshift, splice site mutations and exon deletions are considered proven pathogenic unless previously identified as polymorphism. Missense mutations are considered pathogenic when 1) Minor allele frequency in Exome sequencing project was ≤0.05%, and 2) in silico prediction programs predicted the variant to affect protein function by score <0.02 (SIFT) and >0.900 (Polyphen2). Mutations in desmosomal genes and non-desmosomal genes (PLN) will be considered pathogenic*
1=yes, 0=no Genetic variants were reviewed by specialists in cardiac genetics (CAJ, PvT, JDHJ, BM) to confirm they met current criteria for pathogenicity (class 4 or 5)	
Gene	Gene with mutation
1=PKP2, *2=DSP,* *3=DSG2,* *4=DSC2,* *5=JUP,* *6=TMEM43,* *7=PLN,* 8=CH/HO/DG (CH: compound heterozygous mutations; DG: digenic mutations; HO: homozygous mutations) 9=other (describe in genetic remarks)	
Amino acid	Amino acid change(s)
Text	
DNA change	Nucleotide changes (cDNA)
Text	
Genetic remarks	Additional genetic screening/remarks
Text	
Genotype	Gene with mutation and base pair chain (c.DNA genotype)
Text	
Secondary prevention population	**Event at any time before or at diagnosis (Prior to diagnosis: if after, considered as an outcome)**
Variables at diagnosis **Prior to one year after dx/or first event**	

Prioritize exams in the 1-year time frame before and after dx. If not available, code the next most recent exam available	
AgeatDx	Age at which definite ARVC was attained according to 2010 Task force criteria (TFC): i. 2 major criteria (from 2 different categories) ii. 1 major and 2 minor criteria (from 3 different categories) iii. 4 minor criteria (from 4 different categories)
Days	
SymptomsDx	Presence of symptoms associated with ARVC at diagnosis as reported in the medical notes (prior to one year after dx/or first event)
1=yes, 0=no	
CardiacSyncopeDx	**Definition:** *Transient loss of consciousness and postural tone with spontaneous recovery with* ***arrhythmic mechanism likely at diagnosis. This thus excludes syncope of vaso-vagal etiology.*** (prior to one year after dx/or first event)
1=yes, 0=no	
DateCardiacSyncopeDx	Age at Syncope
Days	
ECGdx	ECG performed at diagnosis (prior to one year after dx/or first event)
1=yes, 0=no	
QRSdurationDx	Maximal QRS duration on ECG. Select ECG picked for "DateECG", if not on class 1 anti-arrhythmics or amiodarone. If on these medication on that ECG, select another one off medication that is closest from diagnosis if possible.
Milliseconds	
TAD_Dx	Terminal activation duration of QRS measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2, or V3, in the absence of complete right bundle-branch block
Milliseconds	
BBBDx	Presence of bundle branch block (on ECG selected for "DateECG")

0=no

1=Right Bundle branch block **(RBBB) :**

1- QRS duration greater than or equal to 120 ms in adults, greater than 100 ms in children ages 4-16 years and greater than 90 ms in children less than 4 years of age

2- rsr' rsR' or rSR' in leads V1, or V2. The R' or r' deflection is usually wider than the initial R wave. In a minority of patiens, a wide and often notched R wave pattern may be seen in lead V1 and/or V2

3- S wave of greater duration than R wave or greater than 40 ms in leads I and V6 in adults

4- Normal R peak time in leads V5 and V6 but greater than 50 ms in lead V1

Of the above criteria, the first 3 should be present to make the diagnosis. When a pure dominant R wave with or without a notch is present in V1, criterion 4 should be satisfied.

2=Left Bundle branch block **(LBBB) :**

1-QRS duration greater than or equal to 120 ms in adults greater than 100 ms in children 4-16 years of age and greater than 90 ms in children less than 4 years of age.

2-Broad notched or slurred R wave in leads I, aVL, V5 and V6 and an occasional RS pattern in V5 and V6 attributed to displaced transition of QRS complex.

3-Absent q waves in leads I V5 V6 but in the lead aVL, a narrow q wave may be present in the absence of myocardial pathology

4-R peak time greater than 60 ms in leads V5 and V6 but normal leads V1,V2 and V3 when small initial r waves can be discerned in the above leads

Definitions from :AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram 2009(8)	
NumLeads_Tinversion_antDx	Number of precordial leads with T-wave inversion (V1 through V6). (on ECG selected for "DateECG") **Definition:** *T-waves are considered inverted if amplitude ≥ 1 mV (1 mm).*
Number	
NumLeads_Tinversion_infDx	Number of inferior leads with T-wave inversion II, III and AVF. (on ECG selected for "DateECG") **Definition***: T-waves are considered inverted if amplitude ≥ 1 mV (1 mm).*
Number	
ECG_Comments	Comments on ECG
HolterDx	Was Holter performed at diagnosis? (prior to one year after dx/or first event)
MaxHolterPVCcountDx	Maximum PVC count on a 24 hrs Holter (prior to one year after dx/or first event, Prioritize 1-year time frame before and after dx)
NSVTDx	History of Non sustained VT (NSVT) on any exam at diagnosis (At any time prior to one year after dx/or first event) **Definition of NSVT:** 3 or more consecutive ventricular beats at a rate of >100 beats per minute with duration of less than 30 seconds and without hemodynamic compromise.
ECHODx	Transthoracic echocardiogram performed at diagnosis? (prior to one year after dx/or first event) Date transthoracic echocardiogram performed: N.B. *If a patient has more than one exam with the same imaging technique, the exam with the most complete and reliable report that is the closest from the date of diagnosis will be selected for coding.* Prioritize 1-year time frame before and after dx
ECHOdilatationRV	Qualitative global assessment of RV volume on ECHO
Normal, mild dilatation, moderate dilatation, severe dilatation	
ECHOdilatationPLAXDx	Measure of right ventricular outflow tract (RVOT) in parasternal long axis on transthoracic echocardiogram
mm	
ECHOdilatationPSAXDx	Mesure of RVOT in parasternal short axis on transthoracic echocardiogram
mm	
MRI_Dx	Magnetic resonance imaging (MRI) performed at diagnosis? (prior to one year after dx/or first event) *If a patient has more than one exam with the same imaging technique, the exam with the most complete and reliable report that is the closest from the date of diagnosis will be selected for coding.* Prioritize 1-year time frame before and after dx
BSA	Body mass index *(Ideally on MRI report, if not available take one from another test like echo or calculate from the medical chart with Mosteller formula. Use values as close as possible to the date of MRI)*
m^2	
MRIRVvolumeDx	Right ventricular end-diastolic volume (RVEDV) on MRI *(on MRI chosen for DateMRI)*
In mL ideally (if not available note as Normal, Mildly, Moderately, Severely increased)	

AngioDx	RV angiogram performed at Diagnosis
1=yes, 0=no	
RVEF	
Manual imputation for RVEF: 1-RVEF on CMR is preferred for RVEF assessment 2-For patients with assessment of RV function both with ultrasound and CMR: We will compare the qualitative ultrasound value, establish the median value of MRI RVEF associated with each qualitative category (normal function, mild dysfunction, moderate dysfunction, severe dysfunction) 3-For patient with ultrasound-only assessed RV function, the median value calculated in step 2 will be assigned for the primary analysis 4-A secondary sensitivity analysis will compare this method with the use of RVEF on MRI only with the use of standard multiple imputation based on chained equation to handle missing values 5-For patients with both FAC and RVEF by MRI, a conversion factor will be determined 6-Patients who only have RV function assessment by FAC will be assigned a RVEF with the method described in 5. 7- Patients who only have a qualitative assessment of normal RVEF by MRI, will be assigned the median value of patients with normal MRI RV function (above 45%)	
RVEFECHO_Dx	RV ejection fraction (RVEF) as measurement for RV dysfunction on transthoracic echo *(on Echo chosen for DateECHODx)* *(on Echo chosen for DateECHODx)*
% ideally (if not available note as Normal, Mildly, Moderately, Severely decreased)	
RV_FAC_Dx	Right ventricular (RV) fractional area change on transthoracic echocardiogram
%	
RVEFMRI_Dx	RV ejection fraction as measurement for RV dysfunction on MRI *(on MRI chosen for DateMRI)*
% ideally (if not available note as Normal, Mildly, Moderately, Severely decreased)	
RVEFAngio_Dx	RV ejection fraction as measurement for RV dysfunction on RV angiogram *(on Angio chosen for DateAngioDx)*
% ideally (if not available note as Normal, Mildly, Moderately, Severely decreased)	
LVEF	
Manual imputation for LVEF: 1-LVEF on CMR is preferred for LVEF assessment. 2-If LVEF on CMR is not available, quantitative assessment by cardiac ultrasound will be used **3-** For patients with assessment of LV function both with ultrasound and MRI, we will compare the qualitative ultrasound value, establish the median value of MRI LVEF associated with each qualitative category (normal, mild dysfunction, moderate dysfunction, severe dysfunction) 3-For patient who only have a qualitative ultrasound assessment of LV function, the median value calculated in step 2 will be assigned If the number of patients with both a qualitative echocardiographic assessment of LVEF and quantitative MRI assessment is too low for one category of dysfunction; Normal will be imputed to 65%, mild dysfunction 50%, moderate dysfunction 40% and severe dysfunction 30%	
LVEFECHO_Dx	Left ventricle ejection fraction (LVEF) as measurement for LV dysfunction on transthoracic echo *(on Echo chosen for DateECHODx)*
% ideally (if not available note as Normal, Mildly, Moderately, Severely decreased)	
LVEFMRI_Dx	LV ejection fraction as measurement for LV dysfunction on MRI *(on MRI chosen for DateMRI)*
% ideally (if not available note as Normal, Mildly, Moderately, Severely decreased)	
LVEFAngio_Dx	LV ejection fraction as measurement for LV dysfunction on RV angiogram **Definition:** Regional RV akinesia, dyskinesia, or aneurysm *(on Angio chosen for DateAngioDx)*
% ideally (if not available note as Normal, Mildly, Moderately, Severely decreased)	
StrenuousExerciseBeforeDx	Participation in strenuous exercise before Diagnosis

	(ACC AHA class C) **Definition** individual who participated in sports with a high dynamic demand (>70% max O_2), as defined by the 36th Bethesda Conference Classification of Sports, at vigorous intensity at any point in their life (prior to one year after dx/or first event)
Task Force criteria at diagnosis Cumulative: code the highest/most severe result a patient had for a specific test regardless of delay before dx and up to one year after dx/occurrence of the first event	
ECHOTFCDx	Results of echo if performed according to 2010 TFC (prior to one year after dx/or first event)
0=normal, 1=minor criteria, *Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): PLAX RVOT ≥29 to 33% to ≤40%* 2=major criteria, *Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m2), PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m2) or fractional area change ≤33%*	
MRITFCDx	Result of MRI if performed (prior to one year after dx/or first event)
0=normal : 1=minor criteria: *Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: Ratio of RV end-diastolic volume to BSA ≥100 to < 110 ml/m2 (male) or ≥90 to <100 mL/m2 (female) or RV ejection fraction 40% to ≤45%.* 2=major criteria: *Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: Ratio of RV end-diastolic volume to BSA ≥110 mL/m2 (male) or ≥100 mL/m2 (female) or RV ejection fraction ≤40%*	
RVangiogramTFCDx	RV angiogram performed and results (prior to one year after dx/or first event)
0=normal : 2=major criteria: Regional RV akinesia, dyskinesia, or aneurysm (no 1 because no minor criteria)	
TissueTFCDx	Tissue characterization, according to 2010 TFC (prior to one year after dx/or first event)
0=normal 1=minor criteria 2=major criteria: Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	
NMajor5Dx	Negative T wave in leads V1 to 3, major criterion (more than14 y old, no BBB) (prior to one year after dx/or first event) (see above for definition of T wave inversion) (prior to one year after dx/or first event)
1=yes, 0=no	
NegTV1-2Dx	Negative T wave in leads V1 and 2, minor criterion (prior to one year after dx/or first event) (see above for definition of T wave inversion) (prior to one year after dx/or first event)
1=yes, 0=no	
NMinor5Dx	Negative T wave in V1 to 4 in presence of complete RBBB, minor criterion (prior to one year after dx/or first event) (see above for definition of T wave inversion and RBBB) (prior to one year after dx/or first event)
1=yes, 0=no	
NMinor4Dx	Negative T wave in leads V4, V5 or 6, minor criterion (prior to one year after dx/or first event) (see above for definition of T wave inversion) (prior to one year after dx/or first event)
1=yes, 0=no	

NMajor6Dx	Epsilon wave in leads V1 to 3, major criterion (prior to one year after dx/or first event) **Definition:** *Defined as waves of small amplitude within the ST segment in V1-3 that are distinct from the QRS complex.* (prior to one year after dx/or first event)
1=yes, 0=no	
NMinor7Dx	Prolonged TAD in one of leads V1, V2 or V3 (≥ 55 ms), minor criterion (prior to one year after dx/or first event) **Definition:** *longest value in V1-3 from the nadir of S to all depolarization deflections, in the absence of CRBBB (WHO definition).* (prior to one year after dx/or first event)
1=yes, 0=no	
NMinor6Dx	Late potentials (SAECG), minor criterion (prior to one year after dx/or first event) **Definition:** *Abnormal SAECG defined as ≥ 1 abnormal parameter on SAECG* 1. *Filtered QRS duration: (≥ 114 ms = abnormal)* 2. *Duration of terminal QRS <40 uV (low-amplitude signal) (≥ 38 ms = abnormal)* 3. *Root mean square voltage of terminal 40 ms (≤ 20 uV = abnormal)* (prior to one year after dx/or first event)
1=yes, 0=no	
NMajor7Dx	LBBB VT (sustained or non sustained) with superior axis, definition: -30 to -150 degree axis, major criterion (prior to one year after dx/or first event)
1=yes, 0=no	
NMinor8Dx	LBBB VT (sustained or non sustained) with inferior or unknown axis, minor criterion (prior to one year after dx/or first event)
1=yes, 0=no	
NMinor9Dx	>500 ventricular premature ventricular complexes (PVC)/ 24 hour by Holter, minor criterion (prior to one year after dx/or first event)
1=yes, 0=no	
NMajor8DxofFU	ARVD/C confirmed in first-degree relative who meets 2010 TFC, major criterion (before end of follow-up or last outcome event coded)
1=yes, 0=no	
NMajor9DxorFU	ARVD/C confirmed pathologically at autopsy/surgery in first-degree relative, major criterion (before end of follow-up or last outcome event coded)
1=yes, 0=no	
NMajor10DxorFU	Pathogenic mutation associated with ARVD/C detected per TFC (before end of follow-up or last outcome event coded)
1=yes, 0=no	
NMinor11DxorFU	Premature sudden death (<35 years) due to suspected ARVD/C in a first-degree relative, minor criterion (before end of follow-up or last outcome event coded)
1=yes, 0=no	
Nminor10DxorFU	History of ARVD/C in FIRST DEGREE RELATIVE not possible or practical to determine whether family member meets 2010 TFC, minor criterion (before end of follow-up or last outcome event coded)
1=yes, 0=no	

Nminor12DxorFU	ARVC (confirmed pathologically or by TFC) in second degree relative (before end of follow-up or last outcome event coded)
1=yes, 0=no	
ICD history and programming	
ICD	ICD implanted at any time
AgeatICDimplantation	Date of first ICD implantation
Days	
ICD_MonitorZoneImplant	Cycle length of the Monitor zone at implant
milliseconds	
ICD_TxZone1Implant	Cycle length of the lowest therapy zone at implant
milliseconds	
ICD_MonitorZone_AryorEnd	Cycle length of the monitor zone at first LTVA or last programing available at follow-up
milliseconds	
ICD_Therapy_AryorEnd	Cycle length of the lowest therapy zone at first LTVA or last programing available at follow-up
milliseconds	
Medication history	
AAmedslistDx	
0= none 1=Amiodarone 2=Sotalol 3=Class IC(Propafenone or Flecainide) 4=Dofetilide 5=Mexiletine 6= other	
BetablockersDx	Betablockers (excluding sotalol) taken at diagnosis
AAmedslistEvent	List of all anti-arrhythmic medication taken at time of first event or censoring (list sotalol here)
0= none 1=Amiodarone 2=Sotalol 3=Class IC(Propafenone or Flecainide) 4=Dofetilide 5=Mexiletine 6= other	
BetablockersEvent	Betablockers (excluding sotalol) taken at time of first event or censoring
1=yes, 0=no	
OUTCOMES	
LTVAafterDx	Composite outcome of first life threatening ventricular arrhythmia
0 = no VT 1 = Spontanous sustained VT **Definition:** *VT lasting ≥ 30 secs or with hemodynamic compromise at ≥ 100bpm or terminated by electrical cardioversion* 2 = ICD intervention **Definition:** *ICD shock or antitachycardia overdrive pacing delivered in response to a ventricular tachyarrhythmia according to stored intracardiac ECG data* 3 = SCA (aborted) **Definition:** *An event as described above, that is reversed, usually by cardiopulmonary resuscitation and/or defibrillation or cardioversion* 4 = SCD: **Definition:** *Death of cardiac origin that occurred unexpectedly within 1 hour of the onset of new symptoms or a death that was unwitnessed and unexpected*	
AgeatfirsLTVA	Age of 1st composite outcome of first life threatening ventricular arrhythmia
Days	
LTVAafterDx_CL	Cycle length of ventricular arrhythmia coded for primary outcome
milliseconds	
SevereLTVAafterDx	VT with CL≤ 240 ms(≥250 bpm), FV, SCD or resuscitated SCD
0 = no VT 1 = spontanous sustained VT CL≤ 240 ms (≥ 250 bpm) **Definition:** *VT (*CL≤ 240 ms (≥ 250 bpm) *lasting ≥ 30 secs or with hemodynamic compromise at ≥ 100bpm or terminated by electrical cardioversion* 2 = ICD intervention for VT CL≤ 240 ms (≥ 250 bpm) *ICD shock or antitachycardia overdrive pacing delivered in response to a ventricular tachyarrhythmia according to stored intracardiac ECG data*	

3 = SCA (aborted) : **Definition:** *An event as described above, that is reversed, usually by cardiopulmonary resuscitation and/or defibrillation or cardioversion* 4 = SCD **Definition:** *Death of cardiac origin that occurred unexpectedly within 1 hour of the onset of new symptoms or a death that was unwitnessed and unexpected*	
AgeSevereLTVAafterDx	Age at 1st Severe VA (VT with CL≤ 240 ms[≥250 bpm] or FV, SCD or resuscitated SCD)
days	
SevereLTVAafterDx_CL	Cycle length of severe VA
milliseconds	
Transplant	Cardiac transplant at follow-up
1=yes, 0=no	
Age_Transplant	Age at cardiac transplant
Days	
Death	Death during follow-up
1=yes, 0=no	
Age at death	Age at death
Days	
CauseDeath_text	Cause of death
text	
CauseDeath_cat	Cause of death categorized
1=SCD, 2=heart failure, 3=arrhythmic and heart failure (eg. heart failure largely caused by arrhythmias, 4= non-cardiac	
1=yes, 0=no	
VTAblation	Endocardial or epicardial VT ablation performed at any time before last coded event
AgeVTAblation	Age of first ablation
Days	
AdditionalNotes	Additional information about the patient if necessary
text	
AgeLFU	Age at last clinical follow-up allowing assertion of outcomes : Censoring or last event coded for outcome
Days	

Supplementary Table 5: Baseline characteristics according to registry/country

	Johns Hopkins	Netherlands	Montreal	Zurich	Nordic
Total	226 (42.8)	147 (27.8)	33 (6.3)	46 (8.7)	76 (14.4)
Demographics					
Male sex	91 (40.3)	64 (43.5)	17 (51.5)	24 (52.2)	40 (52.6)
Age at diagnosis (years)	34.35 ± 14.56	42.17 ± 14.52	35.53 ± 15.06	38.54 ± 15.75	42.64 ± 17.05
Caucasian ethnicity (n=498)	217 (96.0)	145 (98.6)	4 (12.1)	45 (97.8)	74 (97.4)
Proband status	120 (53.1)	55 (37.4)	15 (45.5)	40 (87.0)	33 (43.4)
Pathogenic mutation (n=504)	147 (65.0)	115 (78.2)	14 (42.4)	11 (23.9)	19 (25.0)
PKP2	111 (49.1)	87 (59.2)	7 (21.2)	6 (13.0)	47 (61.8)
DSP	15 (6.6)	1 (0.7)	1 (3.0)	3 (6.5)	3 (3.9)
DSG2	9 (4.0)	1 (0.7)	4 (12.1)	1 (2.2)	2 (2.6)
PLN	3 (1.3)	23 (15.6)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple mutations	5 (2.2)	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)
Other	4 (1.7)	3 (2.0)	1 (3.0)	1 (2.2)	1 (1.3)
History					
Symptoms	142 (62.8)	95 (64.6)	11 (33.3)	36 (78.3)	23 (30.3)
Cardiac syncope	40 (17.7)	32 (21.8)	4 (12.1)	12 (26.1)	19 (25.0)
Recent syncope (n=519)	22 (9.7)	15 (10.2)	2 (6.1)	5 (10.9)	4 (5.3)
ECG / continuous ECG monitoring					
TWI in ≥3 precordial leads (n=517)	141 (62.4)	78 (53.1)	15 (45.5)	32 (69.6)	32 (42.1)
TWI in ≥2 inferior leads (n=506)	40 (17.7)	28 (19.0)	4 (12.1)	3 (6.5)	10 (13.2)
Non-sustained VT (n=470)	109 (48.2)	71 (48.3)	13 (39.4)	24 (52.2)	14 (18.4)
24h PVC count (n=425)	1234 [314, 4501]	1147 [517, 3398]	590 [22, 1333]	1005 [475, 3641]	516 [34, 1675]
Imaging					
RVEF (%), (n=510)	43.38 ± 11.08	45.47 ± 7.96	43.37 ± 10.40	40.46 ± 10.44	44.16 ± 11.90
LVEF (%), (n=515)	58.94 ± 8.30	57.21 ± 7.29	58.00 ± 7.60	54.40 ± 10.82	56.36 ± 8.97
LVEF <50%	26 (11.5)	19 (12.9)	4 (12.1)	8 (17.4)	10 (13.2)
Treatment at baseline					
ICD	119 (52.7)	49 (33.3)	14 (42.4)	18 (39.1)	18 (23.7)
Beta blockers (n=511)	88 (38.9)	49 (33.3)	12 (36.4)	20 (43.5)	31 (40.8)
Anti-arrhythmic drugs (n=510)	24 (10.6)	28 (19.0)	13 (39.4)	8 (17.4)	9 (11.8)
Follow-up (years)	4.11 [1.51, 8.58]	7.54 [3.93, 10.76]	3.94 [1.97, 6.19]	4.04 [2.46, 10.28]	5.38 [3.05, 9.04]

Variables are expressed as mean ± standard deviation (SD) or median (IQR) where specified.
PKP2 indicates plakophilin-2; *DSP,* desmoplakin; *DSG2*, desmoglein-2; *PLN,* phospholamban; RV, Right ventricle; ICD, implantable cardioverter defibrillator; IQR, interquartile range. Other abbreviations as per table 1. Total number of patients for a given variable mentioned in case of missing data.

Supplementary Table 6: Sensitivity analyses: RV function using multiple imputation and complete case analysis

Predictor	RVEF imputation using MICE multivariable analysis		Complete Case multivariable analysis		Final multivariable model (as presented in manuscript)	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Male Sex	1.61 (1.15-2.29)	0.0085	1.55 (0.98-2.44)	0.059	1.63 (1.17-2.29)	0.005
Age (per year increase)	0.98 (0.96-0.99)	0.0003	0.97 (0.96-0.99)	0.0005	0.98 (0.97-0.99)	< 0.001
Recent syncope	1.97(1.23-4.22)	0.0076	2.07 (1.10-3.87)	0.01	1.92 (1.20-3.11)	0.007
Prior NSVT	2.31(1.48-3.62)	0.0003	1.90 (1.16-3.11)	0.01	2.25 (1.47-3.44)	< 0.001
24 h. PVC count (ln)*	1.16(1.03-1.30)	0.0134	1.19 (1.04-1.36)	0.01	1.19 (1.05-1.34)	0.013
Leads with TWI anterior + inferior (per lead increase)	1.12 (1.03-1.22)	0.0117	1.13 (1.02-1.26)	0.02	1.12 (1.02-1.23)	0.014
RVEF (per % decrease)	1.02(1.01-1.04)	0.0015	1.02 (1.01-1.05)	0.05	1.03 (1.01-1.04)	0.002
LVEF (per % decrease)	*(Not included in the final model)*		*(Not included in the final model)*		*(Not included in the final model)*	

***PVC count had a log-linear relationship**

Abbreviations as per table 1 and 2

Supplementary Table 7: Predicted probability of survival for shorter follow-up durations

Duration	Probability of Survival ($S_0(t)$)
1 year	93.76%
2 years	90.08%
3 years	87.98%
4 years	86.95%
5 years	83.96%

Supplementary Table 8: Calculation of risk of incident sustained ventricular arrhythmia in 3 patients.

Patient 1: Low risk	Patient 2: Medium risk	Patient 3: High risk
Demographics: 48 year-old female, **Genetics/Pedigree:** family history of ARVC in daughter, no pathogenic variant. **History of recent syncope**: Absent **Arrhythmia**: No NSVT 24 hour PVC count is 1 **ECG:** TWI in V1-V4 **RV function**: RVEF: 55%	**Demographics:** 50 year-old male, **Genetics/Pedigree:** Family history of ARVC. Pathogenic variant in *PKP2* **History of recent syncope**: Absent **Arrhythmia:** No NSVT, 312 PVCs over 24 hours **ECG:** TWI in V1, III and AVf **RV function**: RVEF: 48%	**Demographics:** 22 year-old female **Genetics/Pedigree**: proband. Pathogenic *PKP2* variant **History of recent syncope**: Absent **Arrhythmia**: History of NSVT and 20527 PVCs over 24 hours **ECG**: TWI V1-V4 **RV function**: RVEF: 28%

Patient	Calculation of linear predictor (LP)																															
	.488	x	Sex (1=M 0=F)	-	.022	x	age	+	.657	x	Recent syncope (1=yes, 0=no)	+	.811	x	NSVT (1=yes 0=no	+	.170	x	Ln (PVC count in 24h)	+	.113	x	Sum of TWI ant + inf	-	.025	x	RVEF	=	PI
1	.488	x	0	-	.022	x	48	+	.657	x	0	+	.811	x	0	+	.170	x	0	+	.113	x	4	-	.025	x	55	=	-1.98
2	.488	x	1	-	.022	x	50	+	.657	x	0	+	.811	x	0	+	.170	x	5.74	+	.113	x	3	-	.025	x	48	=	-.497
3	.488	x	0	-	.022	x	22	+	.657	x	0	+	.811	x	1	+	.170	x	8.65	+	.113	x	4	-	.025	x	28	=	1.55

Calculation of 5-year risk							
	1	-	0.8396	Exp	LP	=	5-year risk of ventricular arrhythmia
1	1	-	0.8396	Exp	-1.98	=	2.4%
2	1	-	0.8396	Exp	-0.497	=	10.1%
3	1	-	0.8396	exp	1.55	=	64.1%

Link to the online calculator: https://arvcrisk.com/

ARVC, Arrhythmogenic Right Ventricular Cardiomyopathy; *PKP2* indicates plakophilin-2; PVC, Premature ventricular complexes; RV, Right ventricle; NSVT, non-sustained ventricular tachycardia; RVEF, Right ventricular ejection fraction; TWI, T-wave inversion.

Supplementary Table 9: Study of different threshold for ICD implantation at 5 years with Kaplan-Meier corrected estimates

Model-derived implant threshold	All	>2.5%	>5.0%	>7.5%	>10.0%	>15.0%	>20.0%	(Compared to ITFC*) >18.0%	ITFC
VA, ICD	139 (26.4%)	139 (26.3%)	139 (26.4%)	137 (26%)	136 (25.7%)	130 (24.7%)	122 (23.1%)	125 (23.6%)	125 (23.6%)
VA, No ICD	0 (0%)	0 (0%)	0 (0.0%)	2 (0.5%)	3 (0.5%)	9 (1.7%)	17 (3.3%)	14 (2.6%)	14 (2.6%)
No VA, ICD	389 (73.6%)	377 (71.4%)	343 (64.9%)	304 (57.6%)	265 (50.2%)	194 (36.7%)	144 (27.3%)	158 (29.9%)	230 (43.6%)
No VA, No ICD	0 (0%)	12 (2.3%)	46 (8.7%)	85 (16%)	124 (23.6%)	195 (36.9%)	245 (46.3%)	231 (43.7%)	159 (30.2%)
ICD, total	528 (100%)	516 (97.7%)	482 (91.3%)	441 (83.5%)	401 (75.9%)	324 (61.4%)	266 (50.4%)	**283 (53.6%)**	**355 (67.2%)**
ICD:VA ratio	3.8	3.7	3.5	3.2	2.9	2.5	2.2	2.3	2.8
Protection rate (%)	100.0%	100.0%	100.0%	98.6%	97.8%	93.5%	87.8%	89.9%	89.9%

*Model-derived implant threshold that would result in the same proportion ICD-treated events (89.9%) as would using the ITFC risk stratification algorithm

Abbreviations as per Table 1. ITFC designates the Treatment of Arrhythmogenic Right Ventricular Cardiomyopathy: An International Task Force Consensus Statement published in 2015(6)

Supplementary Table 10: Baseline characteristics of patients who underwent programmed ventricular stimulation with positive and negative results at baseline

	No PVS performed 312	PVS performed 214	p	PVS negative 118	PVS positive* 94	p
Male sex	134 (42.9)	102 (47.7)	0.328	49 (41.5)	53 (56.4)	0.044
Age at diagnosis (years)	38.74(16.30)	37.36 (14.24)	0.318	37.86 (15.26)	36.92 (12.81)	0.633
Caucasian ethnicity	279 (89.4)	204 (95.3)	0.102	109 (92.4)	93 (98.9)	N/A
Proband	118 (37.8)	143 (66.8)	<0.001	64 (54.2)	78 (83.0)	<0.001
Pathogenic mutation	218 (69.9)	120 (56.1)	0.005	62 (52.5)	56 (59.6)	0.305
PKP2	165 (52.9)	91 (42.5)	0.02	47 (39.8)	42 (44.7)	N/A
Symptoms	155 (49.7)	151 (70.6)	<0.001	69 (58.5)	81 (86.2)	N/A
Cardiac syncope	47 (15.1)	60 (28.0)	<0.001	25 (21.2)	34 (36.2)	0.024
Recent cardiac syncope	19 (6.1)	29 (13.6)	0.013	9 (7.6)	20 (21.3)	0.015
TWI ≥3 precordial leads	155 (49.7)	141 (65.9)	0.001	66 (55.9)	73 (77.7)	0.001
TWI ≥2 inferior leads	36 (11.5)	49 (22.9)	0.002	23 (19.5)	26 (27.7)	0.101
NSVT (n=470)	116 (37.2)	115 (53.7)	<0.001	58 (49.2)	56 (59.6)	0.063
24h PVC count	826 [140, 2937]	1624 [530, 4393]	0.001	1398 [287, 3697]	2295 [780, 6792]	0.021
RVEF (%)	45.26 (9.71)	41.53 (10.93)	<0.001	43.33 (10.57)	39.01 (10.88)	0.005
LVEF (%)	57.90 (8.59)	57.16 (8.03)	0.321	56.86 (8.17)	57.37 (7.87)	0.646
ICD	95 (30.4)	122 (57.0)	<0.001	57 (48.3)	64 (68.1)	0.006
Beta blockers	116 (37.2)	84 (39.3)	0.027	48 (40.7)	35 (37.2)	0.836
Anti-arrhythmic drugs	36 (11.5)	45 (21.0)	0.001	19 (16.1)	26 (27.7)	0.099
VA (primary outcome)	55 (17.6)	90 (42.1)	<0.001	31 (26.3)	58 (61.7)	<0.001

Abbreviations as per Table 1. PVS=Programmed ventricular stimulation

* A positive programmed ventricular stimulation study was defined as induction of sustained monomorphic VT that lasted >30 seconds or required termination because of hemodynamic compromise (loss of consciousness or systolic blood pressure ≤90 mmHg)) Induction of ventricular fibrillation was considered a negative response

Supplementary Figure Legends

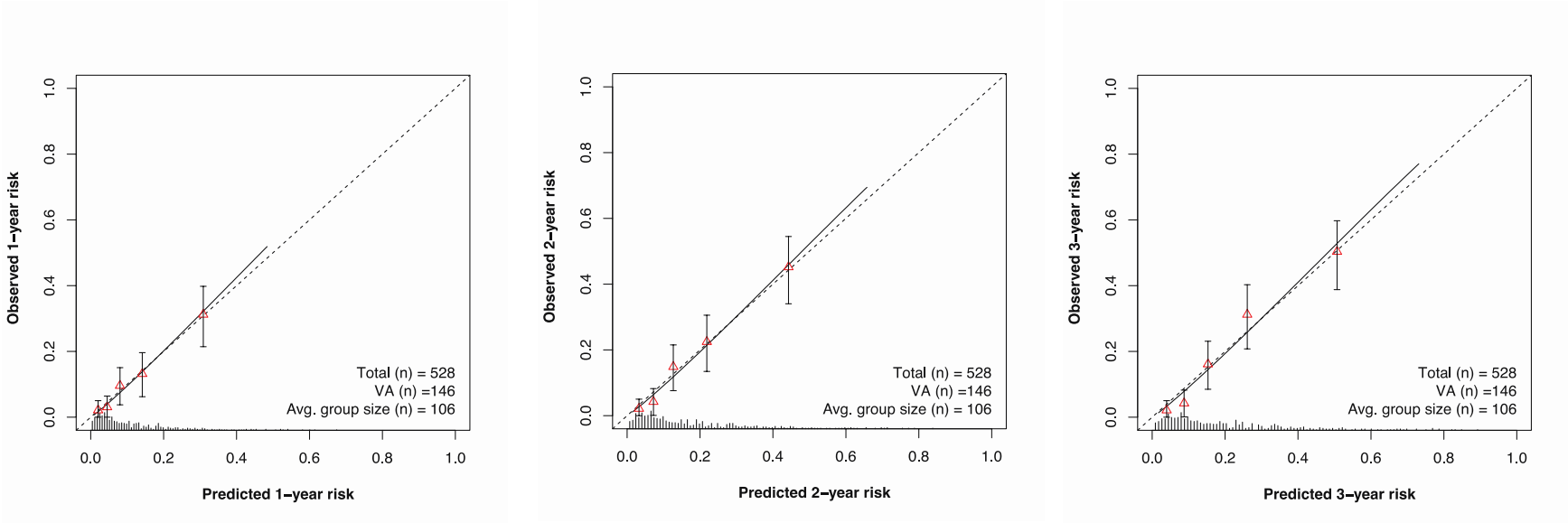
Supplementary Figure 1: Calibration plot showing the agreement between predicted (X-axis) and observed (Y-axis) 1, 2 and 3-year risk of developing any ventricular arrhythmia in different subgroups. Triangles represent binned Kaplan-Meier estimates with 95% confidence intervals for quintiles of predicted 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.

Supplementary Figure 2: Calibration plot showing the agreement between predicted (X-axis) and observed (Y-axis) 5-year risk of developing any ventricular arrhythmia in different subgroups: Description as for Figure 1.

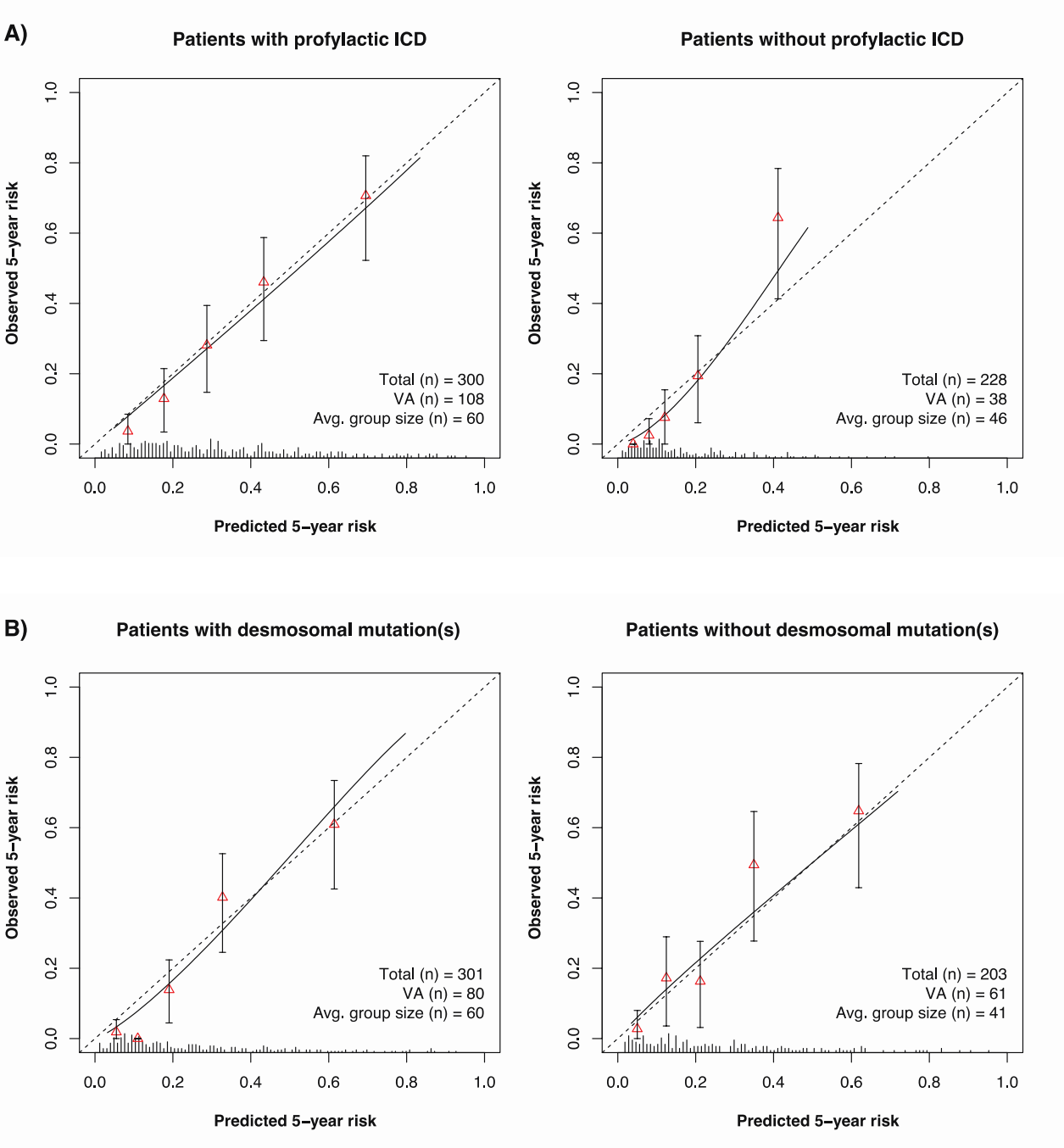
Panel A shows separate calibration plots for patients with and without an implantable cardioverter defibrillator (ICD) at censoring.

Panel B shows separate calibration plots for patients with and without desmosomal mutations.

Supplementary Figure 1:



Supplementary Figure 2:



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