

## Supplementary Material

**Supplementary Table 1: Included registries and associated hospitals**

<b>Registry</b>	<b>Principal investigator(s)</b>	<b>Included hospitals</b>
<b>Johns Hopkins ARVD Registry</b>	Dr Hugh Calkins	Johns Hopkins Hospital, Baltimore, USA
<b>Netherlands ACM Registry</b>	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
<b>Swiss ARVC Registry</b>	Dr Firat Duru Dr Corinna Brunckhorst Dr Ardan M. Saguner	University Heart Center, Zurich
		University Hospital Bern
		Triemli Hospital Zurich
<b>Nordic ARVC Registry sites</b>	Dr Kristina H. Haugaa Dr Pyotr Platonov Dr Anneli Svensson	University Hospital, Rikshospitalet, Oslo, Norway
		Skane University Hospital, Lund, Sweden
		Linkoping University, Linkoping, Sweden
<b>Canada, Montreal Registry Vancouver Registry</b>	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\***

<b>Predictor</b>	<b>Definition</b>
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 $\geq 100$ bpm, for $\geq 3$ 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 <sup>†</sup>	%
LVEF <sup>†</sup>	%

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

<sup>†</sup> 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
<b>Selected predictors</b>	
<b>Sex</b>	-Predictor in definite ARVC patients, as shown in prior meta-analysis(1)
<b>Age</b>	-Predictor in definite ARVC in prior studies(2, 3)
<b>Cardiac syncope and recent cardiac syncope</b>	-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)
<b>Non-sustained ventricular tachycardia</b>	-Predictor in definite ARVC patients, as shown in prior meta-analysis(1)
<b>Number of premature ventricular complexes on a 24 hour holter</b>	-Predictor in definite ARVC primary prevention population(1, 4, 5)
<b>Extent of leads with T-wave inversion (sum of ante</b>	-Predictor in definite ARVC patients, as shown in prior meta-analysis(1)
<b>Right ventricular ejection fraction</b>	-Predictor in definite ARVC patients, as shown in prior meta-analysis(1)
<b>Left ventricular ejection fraction</b>	-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
<b>Predictors not selected</b>	
<b>History of strenuous physical activity</b>	-Not a predictor in patients with definite ARVC in prior meta-analysis (1) -Heterogeneity in reporting among different centers and countries limit reliability
<b>Inducibility on programmed ventricular stimulation</b>	-Not a predictor in patients with definite ARVC in prior meta-analysis(1) - Invasiveness and availability limit widespread use.
<b>Symptoms including pre-syncope</b>	-Not a predictor in patients with definite ARVC in prior meta-analysis(1) -Heterogeneity in reporting by patients and physicians limit reliability
<b>Epsilon wave</b>	-Not a predictor in patients with definite ARVC in prior meta-analysis(1) -Not unambiguously defined(7)
<b>Genotype</b>	-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
<b>Presence of multiple mutations</b>	-Not a predictor in patients with definite ARVC in prior meta-analysis (1) -Present in a minimal number of patients
<b>Right ventricular volume</b>	-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
<b>Choices for coding and their definitions</b>	
<b>Patients Characteristics</b>	
<b>Site</b>	Site of enrolment
<b>Age at diagnosis</b>	Days
<b>Sex</b>	Gender of patient
Male =1 Female = 0	
<b>Pedigree</b>	Proband or family member
1=Proband 2=Family member	
<b>Proband definition:</b> 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).	
<b>Race</b>	Ethnicity of patient
1=Caucasian, 2= African, 3=Asian	
<b>Mutation</b>	Pathogenic mutation associated with ARVD/C detected <b>Definition :</b> <i>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 <math>\leq 0.05\%</math>, and 2) in silico prediction programs predicted the variant to affect protein function by score <math>&lt; 0.02</math> (SIFT) and <math>&gt; 0.900</math> (Polyphen2). Mutations in desmosomal genes and non-desmosomal genes (PLN) will be considered pathogenic</i>
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)	
<b>Gene</b>	Gene with mutation
1= <i>PKP2</i> , 2= <i>DSP</i> , 3= <i>DSG2</i> , 4= <i>DSC2</i> , 5= <i>JUP</i> , 6= <i>TMEM43</i> , 7= <i>PLN</i> , 8=CH/HO/DG (CH: compound heterozygous mutations; DG: digenic mutations; HO: homozygous mutations) 9=other (describe in genetic remarks)	
<b>Amino acid</b>	Amino acid change(s)
Text	
<b>DNA change</b>	Nucleotide changes (cDNA)
Text	
<b>Genetic remarks</b>	Additional genetic screening/remarks
Text	
<b>Genotype</b>	Gene with mutation and base pair chain (c.DNA genotype)
Text	
<b>Secondary prevention population</b>	Event at any time before or at diagnosis (Prior to diagnosis: if after, considered as an outcome)
<b>Variables at diagnosis</b>	
<b>Prior to one year after dx/or first event</b>	

Prioritize exams in the 1-year time frame before and after dx. If not available, code the next most recent exam available	
<b>AgeatDx</b>	Age at which definite ARVC was attained according to 2010 Task force criteria (TFC): <ul style="list-style-type: none"> <li>i. 2 major criteria (from 2 different categories)</li> <li>ii. 1 major and 2 minor criteria (from 3 different categories)</li> <li>iii. 4 minor criteria (from 4 different categories)</li> </ul>
Days	
<b>SymptomsDx</b>	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	
<b>CardiacSyncopeDx</b>	<b>Definition:</b> <i>Transient loss of consciousness and postural tone with spontaneous recovery with <b>arrhythmic mechanism likely at diagnosis. This thus excludes syncope of vaso-vagal etiology.</b></i> (prior to one year after dx/or first event)
1=yes, 0=no	
<b>DateCardiacSyncopeDx</b>	Age at Syncope
Days	
<b>ECGdx</b>	ECG performed at diagnosis (prior to one year after dx/or first event)
1=yes, 0=no	
<b>QRSdurationDx</b>	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	
<b>TAD_Dx</b>	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	
<b>BBBDx</b>	Presence of bundle branch block (on ECG selected for "DateECG" )
<b>0=no</b> <b>1=Right Bundle branch block (RBBB) :</b> 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 patients, 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.  <b>2=Left Bundle branch block (LBBB) :</b> 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)	
<b>NumLeads_Tinversion_antDx</b>	Number of precordial leads with T-wave inversion (V1 through V6). (on ECG selected for "DateECG" ) <b>Definition:</b> <i>T-waves are considered inverted if amplitude <math>\geq 1</math> mV (1 mm).</i>
Number	
<b>NumLeads_Tinversion_infDx</b>	Number of inferior leads with T-wave inversion II, III and AVF. (on ECG selected for "DateECG" ) <b>Definition:</b> <i>T-waves are considered inverted if amplitude <math>\geq 1</math> mV (1 mm).</i>
Number	
<b>ECG_Comments</b>	Comments on ECG
<b>HolterDx</b>	Was Holter performed at diagnosis? (prior to one year after dx/or first event)
<b>MaxHolterPVCcountDx</b>	Maximum PVC count on a 24 hrs Holter (prior to one year after dx/or first event, <u>Prioritize 1-year time frame before and after dx</u> )
<b>NSVTDx</b>	History of Non sustained VT (NSVT) on any exam at diagnosis ( <u>At any time</u> prior to one year after dx/or first event) <b>Definition of NSVT:</b> 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.
<b>ECHODx</b>	Transthoracic echocardiogram performed at diagnosis? (prior to one year after dx/or first event) Date transthoracic echocardiogram performed: <i>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. <u>Prioritize 1-year time frame before and after dx</u></i>
<b>ECHODilatationRV</b>	Qualitative global assessment of RV volume on ECHO
Normal, mild dilatation, moderate dilatation, severe dilatation	
<b>ECHODilatationPLAXDx</b>	Measure of right ventricular outflow tract (RVOT) in parasternal long axis on transthoracic echocardiogram
mm	
<b>ECHODilatationPSAXDx</b>	Mesure of RVOT in parasternal short axis on transthoracic echocardiogram
mm	
<b>MRI_Dx</b>	Magnetic resonance imaging (MRI) performed at diagnosis? (prior to one year after dx/or first event) <i>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. <u>Prioritize 1-year time frame before and after dx</u></i>
<b>BSA</b>	Body mass index ( <i>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</i> )
m <sup>2</sup>	
<b>MRIrVvolumeDx</b>	Right ventricular end-diastolic volume (RVEDV) on MRI ( <i>on MRI chosen for DateMRI</i> )

In mL ideally (if not available note as Normal, Mildly, Moderately, Severely increased)	
<b>AngioDx</b>	RV angiogram performed at Diagnosis
1=yes, 0=no	
<b>RVEF</b>	
<b>Manual imputation for RVEF:</b>	
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%)	
<b>RVEFECHO_Dx</b>	RV ejection fraction (RVEF) as measurement for RV dysfunction on transthoracic echo ( <i>on Echo chosen for DateECHODx</i> ) ( <i>on Echo chosen for DateECHODx</i> )
% ideally (if not available note as Normal, Mildly, Moderately, Severely decreased)	
<b>RV_FAC_Dx</b>	Right ventricular (RV) fractional area change on transthoracic echocardiogram
%	
<b>RVEFMRI_Dx</b>	RV ejection fraction as measurement for RV dysfunction on MRI ( <i>on MRI chosen for DateMRI</i> )
% ideally (if not available note as Normal, Mildly, Moderately, Severely decreased)	
<b>RVEFAngio_Dx</b>	RV ejection fraction as measurement for RV dysfunction on RV angiogram ( <i>on Angio chosen for DateAngioDx</i> )
% ideally (if not available note as Normal, Mildly, Moderately, Severely decreased)	
<b>LVEF</b>	
<b>Manual imputation for LVEF:</b>	
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%	
<b>LVEFECHO_Dx</b>	Left ventricle ejection fraction (LVEF) as measurement for LV dysfunction on transthoracic echo ( <i>on Echo chosen for DateECHODx</i> )
% ideally (if not available note as Normal, Mildly, Moderately, Severely decreased)	
<b>LVEFMRI_Dx</b>	LV ejection fraction as measurement for LV dysfunction on MRI ( <i>on MRI chosen for DateMRI</i> )
% ideally (if not available note as Normal, Mildly, Moderately, Severely decreased)	
<b>LVEFAngio_Dx</b>	LV ejection fraction as measurement for LV dysfunction on RV angiogram <b>Definition:</b> Regional RV akinesia, dyskinesia, or aneurysm ( <i>on Angio chosen for DateAngioDx</i> )
% ideally (if not available note as Normal, Mildly, Moderately, Severely decreased)	

<b>StrenuousExerciseBeforeDx</b>	Participation in strenuous exercise before Diagnosis (ACC AHA class C) <b>Definition</b> individual who participated in sports with a high dynamic demand (>70% max O <sub>2</sub> ), 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)
<b>Task Force criteria at diagnosis</b> 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	
<b>ECHOTFCDx</b>	Results of echo if performed according to 2010 TFC (prior to one year after dx/or first event)
0=normal, 1= <u>minor criteria</u> , Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): PLAX RVOT ≥29 to 33% to ≤40% 2= <u>major criteria</u> , 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/m <sup>2</sup> ), PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m <sup>2</sup> ) or fractional area change ≤33%	
<b>MRITFCDx</b>	Result of MRI if performed (prior to one year after dx/or first event)
0=normal : 1= <u>minor criteria</u> : 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/m <sup>2</sup> (male) or ≥90 to <100 mL/m <sup>2</sup> (female) or RV ejection fraction to 40% to ≤45%. 2= <u>major criteria</u> : Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: Ratio of RV end-diastolic volume to BSA ≥110 mL/m <sup>2</sup> (male) or ≥100 mL/m <sup>2</sup> (female) or RV ejection fraction ≤40%	
<b>RVangiogramTFCDx</b>	RV angiogram performed and results (prior to one year after dx/or first event)
0=normal : 2= <u>major criteria</u> : Regional RV akinesia, dyskinesia, or aneurysm (no 1 because no minor criteria)	
<b>TissueTFCDx</b>	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	
<b>NMajor5Dx</b>	Negative T wave in leads V1 to 3, major criterion (more than 14 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	
<b>NegTV1-2Dx</b>	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	
<b>NMinor5Dx</b>	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	
<b>NMinor4Dx</b>	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	
<b>NMajor6Dx</b>	Epsilon wave in leads V1 to 3, major criterion (prior to one year after dx/or first event) <b>Definition:</b> <i>Defined as waves of small amplitude within the ST segment in V1-3 that are distinct from the QRS complex.</i> (prior to one year after dx/or first event)
1=yes, 0=no	
<b>NMinor7Dx</b>	Prolonged TAD in one of leads V1, V2 or V3 ( $\geq 55$ ms), minor criterion (prior to one year after dx/or first event) <b>Definition:</b> <i>longest value in V1-3 from the nadir of S to all depolarization deflections, in the absence of CRBBB (WHO definition).</i> (prior to one year after dx/or first event)
1=yes, 0=no	
<b>NMinor6Dx</b>	Late potentials (SAECG), minor criterion (prior to one year after dx/or first event) <b>Definition:</b> <i>Abnormal SAECG defined as <math>\geq 1</math> abnormal parameter on SAECG</i> <ol style="list-style-type: none"> <li>1. <i>Filtered QRS duration: (<math>\geq 114</math> ms = abnormal)</i></li> <li>2. <i>Duration of terminal QRS <math>&lt;40</math> uV (low-amplitude signal) (<math>\geq 38</math> ms = abnormal)</i></li> <li>3. <i>Root mean square voltage of terminal 40 ms (<math>\leq 20</math> uV = abnormal)</i></li> </ol> <p>(prior to one year after dx/or first event)</p>
1=yes, 0=no	
<b>NMajor7Dx</b>	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	
<b>NMinor8Dx</b>	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	
<b>NMinor9Dx</b>	$>500$ ventricular premature ventricular complexes (PVC)/ 24 hour by Holter, minor criterion (prior to one year after dx/or first event)
1=yes, 0=no	
<b>NMajor8DxorFU</b>	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	
<b>NMajor9DxorFU</b>	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	
<b>NMajor10DxorFU</b>	Pathogenic mutation associated with ARVD/C detected per TFC (before end of follow-up or last outcome event coded)
1=yes, 0=no	
<b>NMinor11DxorFU</b>	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	
<b>Nminor10DxorFU</b>	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	
<b>Nminor12DxorFU</b>	ARVC (confirmed pathologically or by TFC) in second degree relative (before end of follow-up or last outcome event coded)
1=yes, 0=no	
<b><u>ICD history and programming</u></b>	
<b>ICD</b>	ICD implanted at any time
<b>AgeatICDimplantation</b>	Date of first ICD implantation
Days	
<b>ICD_MonitorZoneImplant</b>	Cycle length of the Monitor zone at implant
milliseconds	
<b>ICD_TxZone1Implant</b>	Cycle length of the lowest therapy zone at implant
milliseconds	
<b>ICD_MonitorZone_AryorEnd</b>	Cycle length of the monitor zone at first LTVA or last programming available at follow-up
milliseconds	
<b>ICD_Therapy_AryorEnd</b>	Cycle length of the lowest therapy zone at first LTVA or last programming available at follow-up
milliseconds	
<b><u>Medication history</u></b>	
<b>AAmedslistDx</b>	
0= none 1=Amiodarone 2=Sotalol 3=Class IC( Propafenone or Flecainide) 4=Dofetilide 5=Mexiletine 6= other	
<b>BetablockersDx</b>	Betablockers (excluding sotalol) taken at diagnosis
<b>AAmedslistEvent</b>	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	
<b>BetablockersEvent</b>	Betablockers (excluding sotalol) taken at time of first event or censoring
1=yes, 0=no	
<b><u>OUTCOMES</u></b>	
<b>LTVAafterDx</b>	Composite outcome of first life threatening ventricular arrhythmia
0 = no VT	
1 = <u>Spontaneous sustained VT</u> <b>Definition:</b> VT lasting $\geq 30$ secs or with hemodynamic compromise at $\geq 100$ bpm or terminated by electrical cardioversion	
2 = ICD intervention <b>Definition:</b> ICD shock or antitachycardia overdrive pacing delivered in response to a ventricular tachyarrhythmia according to stored intracardiac ECG data	
3 = <u>SCA (aborted)</u> <b>Definition:</b> An event as described above, that is reversed, usually by cardiopulmonary resuscitation and/or defibrillation or cardioversion	
4 = <u>SCD</u> : <b>Definition:</b> Death of cardiac origin that occurred unexpectedly within 1 hour of the onset of new symptoms or a death that was unwitnessed and unexpected	
<b>AgeatfirsLTVA</b>	Age of 1st composite outcome of first life threatening ventricular arrhythmia
Days	
<b>LTVAafterDx_CL</b>	Cycle length of ventricular arrhythmia coded for primary outcome
milliseconds	
<b>SevereLTVAafterDx</b>	VT with $CL \leq 240$ ms ( $\geq 250$ bpm), FV, SCD or resuscitated SCD
0 = no VT	
1 = spontaneous sustained VT $CL \leq 240$ ms ( $\geq 250$ bpm) <b>Definition:</b> VT ( $CL \leq 240$ ms ( $\geq 250$ bpm) lasting $\geq 30$ secs or with hemodynamic compromise at $\geq 100$ bpm or terminated by electrical cardioversion	

2 = ICD intervention for VT CL $\leq$ 240 ms ( $\geq$ 250 bpm) <i>ICD shock or antitachycardia overdrive pacing delivered in response to a ventricular tachyarrhythmia according to stored intracardiac ECG data</i>	
3 = SCA (aborted) : <b>Definition:</b> <i>An event as described above, that is reversed, usually by cardiopulmonary resuscitation and/or defibrillation or cardioversion</i>	
4 = SCD <b>Definition:</b> <i>Death of cardiac origin that occurred unexpectedly within 1 hour of the onset of new symptoms or a death that was unwitnessed and unexpected</i>	
<b>AgeSevereLTVAafterDx</b>	Age at 1st Severe VA (VT with CL $\leq$ 240 ms[ $\geq$ 250 bpm] or FV, SCD or resuscitated SCD)
days	
<b>SevereLTVAafterDx_CL</b>	Cycle length of severe VA
milliseconds	
<b>Transplant</b>	Cardiac transplant at follow-up
1=yes, 0=no	
<b>Age_Transplant</b>	Age at cardiac transplant
Days	
<b>Death</b>	Death during follow-up
1=yes, 0=no	
<b>Age at death</b>	Age at death
Days	
<b>CauseDeath_text</b>	Cause of death
text	
<b>CauseDeath_cat</b>	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	
<b>VTAblation</b>	Endocardial or epicardial VT ablation performed at any time before last coded event
<b>AgeVTAblication</b>	Age of first ablation
Days	
<b>AdditionalNotes</b>	Additional information about the patient if necessary
text	
<b>AgeLFU</b>	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**

	<b>Johns Hopkins</b>	<b>Netherlands</b>	<b>Montreal</b>	<b>Zurich</b>	<b>Nordic</b>
<b>Total</b>	226 (42.8)	147 (27.8)	33 (6.3)	46 (8.7)	76 (14.4)
<b>Demographics</b>					
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)
<i>PKP2</i>	111 (49.1)	87 (59.2)	7 (21.2)	6 (13.0)	47 (61.8)
<i>DSP</i>	15 (6.6)	1 (0.7)	1 (3.0)	3 (6.5)	3 (3.9)
<i>DSG2</i>	9 (4.0)	1 (0.7)	4 (12.1)	1 (2.2)	2 (2.6)
<i>PLN</i>	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)
<b>History</b>					
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)
<b>ECG / continuous ECG monitoring</b>					
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]
<b>Imaging</b>					
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)
<b>Treatment at baseline</b>					
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)
<b>Follow-up (years)</b>	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 if there is 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)	<i>(Not included in the final model)</i>		<i>(Not included in the final model)</i>		<i>(Not included in the final model)</i>	

**\*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	0.921
2 years	0.876
3 years	0.849
4 years	0.837
5 years	0.801

**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									
<b>Demographics:</b> 48 year-old female, <b>Genetics/Pedigree:</b> family history of ARVC in daughter, no pathogenic variant. <b>History of recent syncope:</b> Absent <b>Arrhythmia:</b> No NSVT 24 hour PVC count is 1 <b>ECG:</b> TWI in V1-V4 <b>RV function:</b> RVEF: 55%										<b>Demographics:</b> 50 year-old male, <b>Genetics/Pedigree:</b> Family history of ARVC. Pathogenic variant in <i>PKP2</i> <b>History of recent syncope:</b> Absent <b>Arrhythmia:</b> No NSVT, 312 PVCs over 24 hours <b>ECG:</b> TWI in V1, III and AVf <b>RV function:</b> RVEF: 48%										<b>Demographics:</b> 22 year-old female <b>Genetics/Pedigree:</b> proband. Pathogenic <i>PKP2</i> variant <b>History of recent syncope:</b> Absent <b>Arrhythmia:</b> History of NSVT and 20527 PVCs over 24 hours <b>ECG:</b> TWI V1-V4 <b>RV function:</b> 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	=	-0.497
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	-	0.801	Exp	LP	=	5-year risk of ventricular arrhythmia																						
1	1	-	0.801	Exp	-1.98	=	2.6%																						
2	1	-	0.801	Exp	-0.497	=	12.7%																						
3	1	-	0.801	exp	1.55	=	72.8%																						
Link to the online calculator: <a href="https://arvcrisk.com/">https://arvcrisk.com/</a>																													

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**

<b>Model-derived implant threshold</b>	<b>All</b>	<b>&gt;2.5%</b>	<b>&gt;5.0%</b>	<b>&gt;7.5%</b>	<b>&gt;10.0%</b>	<b>&gt;15.0%</b>	<b>&gt;20.0%</b>	<b>(Comparison to ITFC*) &gt;22.5%</b>	<b>ITFC</b>
<b>VA, ICD</b>	139 (26.4%)	139 (26.4%)	139 (26.4%)	138 (26.1%)	136 (25.8%)	134 (25.4%)	127 (24.1%)	125 (23.7%)	125 (23.6%)
<b>VA, No ICD</b>	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)	3 (0.5%)	5 (1%)	12 (2.4%)	14 (2.6%)	14 (2.6%)
<b>No VA, ICD</b>	389 (73.6%)	382 (72.3%)	363 (68.7%)	332 (62.9%)	298 (56.4%)	228 (43.1%)	182 (34.5%)	157 (29.7%)	230 (43.6%)
<b>No VA, No ICD</b>	0 (0%)	7 (1.3%)	26 (4.9%)	57 (10.8%)	91 (17.3%)	161 (30.4%)	207 (39.1%)	232 (44%)	159 (30.2%)
<b>ICD, total</b>	528 (100%)	521 (98.7%)	502 (95.1%)	470 (89%)	434 (82.2%)	362 (68.6%)	309 (58.5%)	<b>282 (53.4%)</b>	<b>355 (67.2%)</b>
<b>ICD:VA ratio</b>	3.8	3.7	3.6	3.4	3.2	2.7	2.4	2.3	2.8
<b>Protection rate (%)</b>	100.0	100.0	100.0	99.3	97.8	96.4	91.4	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
<i>PKP2</i>	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

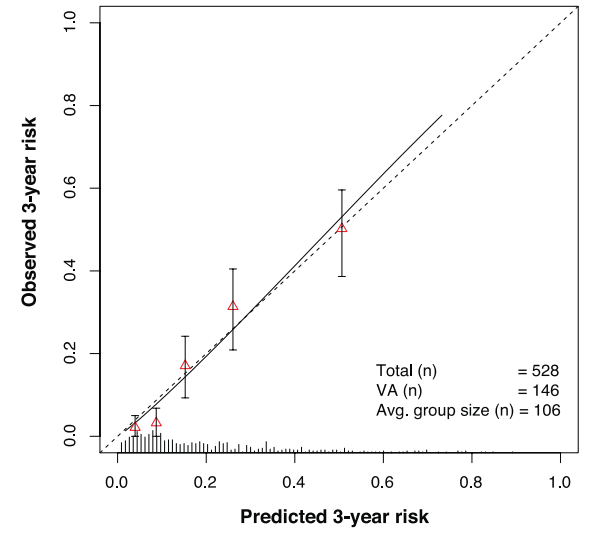
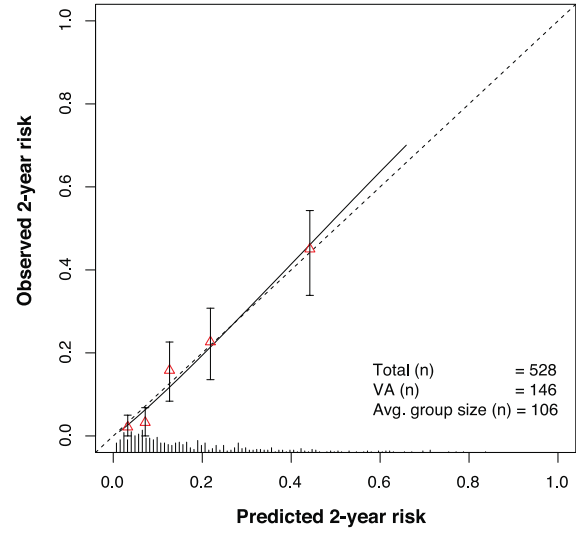
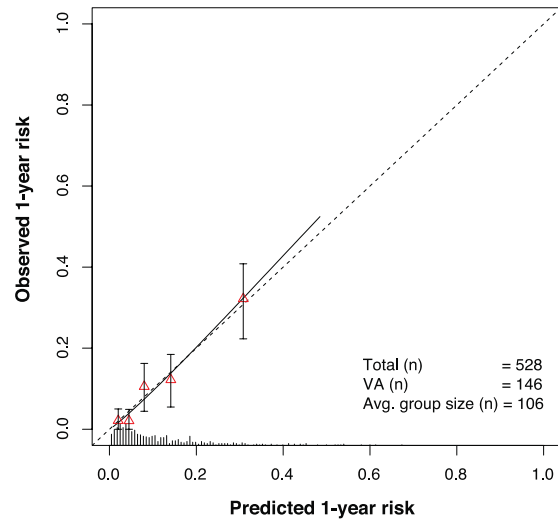
**Supplementary Figure 1: Calibration plot showing the agreement between predicted (X-axis) and observed (Y-axis) 1, 2 and 3-year risk of developing any ventricular arrhythmia in different subgroups.** Triangles represent binned Kaplan-Meier estimates with 95% confidence intervals for quintiles of predicted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

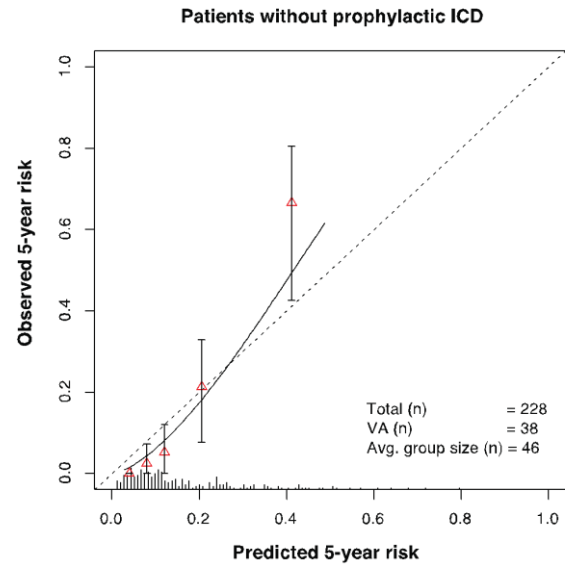
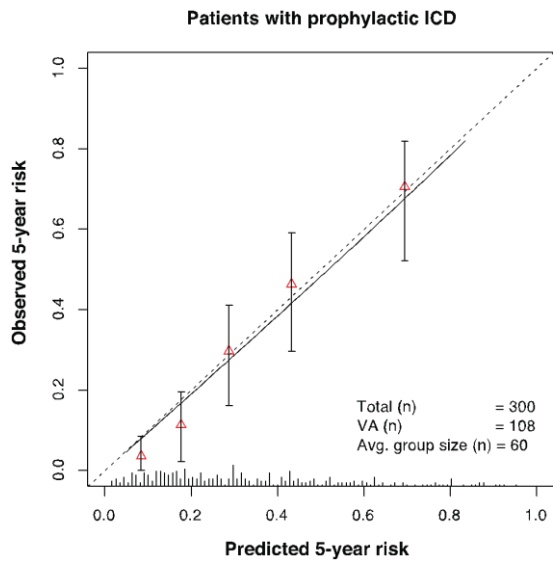
**Panel B** shows separate calibration plots for patients with and without desmosomal mutations.

Supplementary Figure 1:

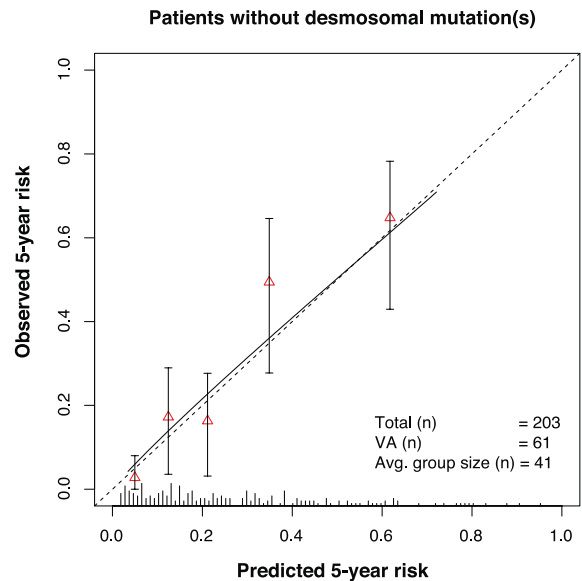
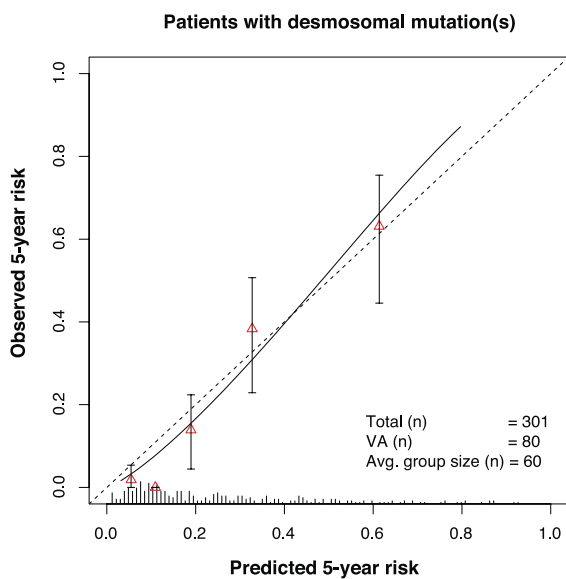


## Supplementary Figure 2:

A)



B)



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