



Personalized Medicine in Arrhythmogenic Right Ventricular Cardiomyopathy

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Laurens P. Bosman

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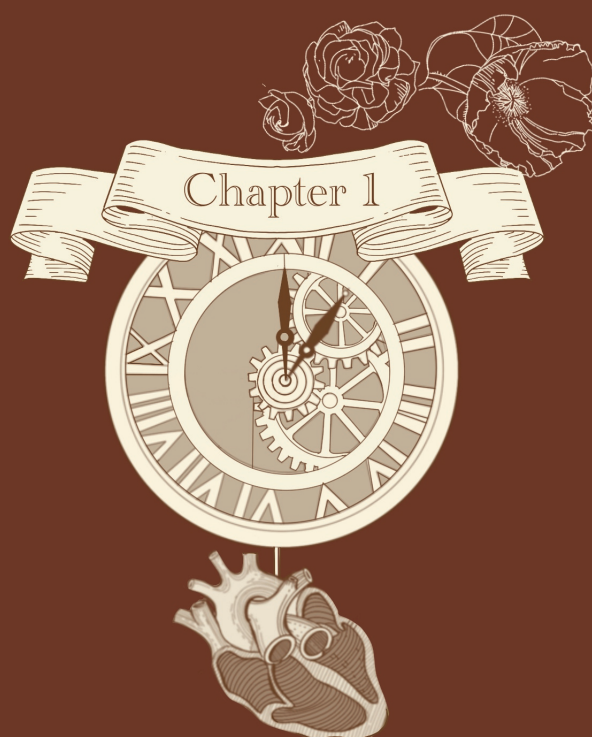
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***Science, my lad,
is made up of mistakes,
but they are mistakes which it is useful to make,
because they lead little by little to the truth.***

Jules Verne

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Chapter 1

Preface

Sudden cardiac death (SCD) is a significant public health issue worldwide. In Western populations, SCD is reported to account for up to 15-20% of all deaths.¹ Especially in young individuals, such a sudden unexpected death is often associated with a devastating emotional and economic impact on family and society. In the Netherlands, every three days an individual below the age of 40 dies suddenly.² Characteristic of SCD in young individuals is that it is commonly caused by congenital disease, familial/genetic channelopathy, or familial/genetic cardiomyopathy. The subject of this thesis, arrhythmogenic right ventricular cardiomyopathy (ARVC), is one of these common causes of SCD in young individuals.

ARVC is a familial cardiomyopathy characterized by fibrofatty replacement of predominantly the right ventricular myocardium.³ The prevalence of ARVC is estimated between 1 in 2000-5000, although as ARVC is thought to be underrecognized some claim the true prevalence to be closer to 1 in 1000.⁴ The disease typically manifests in late adolescence or early adulthood, with possible first symptoms ranging from mild palpitations to SCD. In the majority of patients, a disease-causing variant is found in genes encoding the desmosome. Others may carry one of several non-desmosomal gene variants also associated with ARVC, and in the remaining cases no variants are found.⁵ Most genetic variants show an autosomal dominant inheritance pattern, but with incomplete penetrance.⁵ Besides the variety in genetic background, the phenotypic disease expression and risk of life-threatening ventricular arrhythmias is also highly variable among individual ARVC patients. The cause of this high individual variation, even within the same family, is not well understood. Physical exercise is thought to be one of the factors that promote disease progression, but the nature of this association needs to be further investigated. As a result of this individual variation, diagnosing patients with ARVC as well as estimating their risk of SCD is complex and challenging. The tools for providing personalized medicine to ARVC patients are still fairly limited. In **Chapter 2**, we provide a detailed description and discussion of the current state-of-the-art in our disease understanding, clinical diagnosis, risk prediction and treatment options.

As there is no cure for ARVC, a principle aim in the clinical management of ARVC patients is prevention of SCD. The only proven therapy that prevents SCD in ARVC patients, the placement of an implantable cardioverter defibrillator (ICD), greatly depends on timely and accurate diagnosis and risk prediction. Hence, the challenges in diagnosis and risk prediction in ARVC have been an important topic of research in recent years. While progress has been made, many challenges still remain. Motivated by these clinical challenges, and inspired by the preceding work of many national and international researchers, I started my research career in 2016 focused to find potential solutions. In this thesis I present the results of my research on personalized medicine in ARVC.

Aims and outline of this thesis

Our aim to find ways to improve arrhythmic risk prediction in ARVC started with a systematic review and meta-analysis of the current literature in **Chapter 3**. In this study we identified several risk factors with consistent evidence supporting their association with increased risk of ventricular arrhythmia. These results led to our hypothesis that we could use these risk factors combined in a multivariable prediction model to estimate the risk of ventricular arrhythmia risk of individual patients. In order to conduct such a study, we needed to have a large longitudinal dataset of ARVC patients, for which we had to redesign the Netherlands ACM Registry database as described in **Chapter 4**.

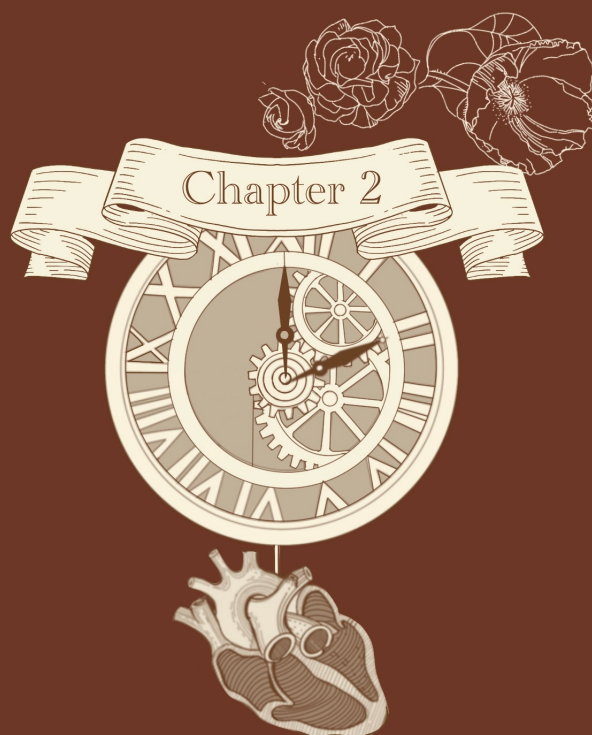
In **Chapter 5** we confirmed our hypothesis by successfully developing a risk prediction model using the eight risk predictors we pre-selected (based on the results in **Chapter 3**). The resulting model predicts the risk of a first sustained ventricular arrhythmia in ARVC patients without a prior sustained event (i.e. primary prevention). In **Chapter 6** we study the relation between physical exercise and arrhythmic risk in ARVC patients, and explore if adding exercise as a risk factor would improve the risk prediction model we developed. As the prediction model in **Chapter 5** was designed to be used for primary prevention patients only, we subsequently developed a model for all ARVC patients as described in **Chapter 7**. Furthermore, instead of predicting any type of sustained ventricular arrhythmia, this second model predicts fast (>250 beats per minute) events to closer approximate the risk of SCD.

Alternative to our two prediction models, there are several risk stratification flow-charts available from published guidelines and consensus documents.⁶⁻⁸ In contrast to our models, these flow-charts are designed by expert consensus, hence their actual clinical performance was unknown. The aim of our study in **Chapter 8** was to estimate and compare the clinical performance of these stratification flow-charts.

Moving away from prognosis, in **Chapter 9** we focus on the clinical diagnosis of ARVC. There is no single gold standard test to diagnose ARVC, instead, the diagnosis is determined by a complex set of different tests and criteria as specified in the Task Force Criteria (TFC).³ While many studies focus on finding ways to improve the diagnostic performance of the TFC, no study had validated the clinical performance of the TFC as a whole in a real-life consecutive diagnostic cohort. Therefore, in **Chapter 9** we validate the performance and evaluate strengths and weaknesses that could guide future studies regarding criteria improvements.

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Chapter 2

Arrhythmogenic Right Ventricular Cardiomyopathy: a focused update on diagnosis and risk stratification

Heart 2021

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Abstract

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by fibrofatty replacement of predominantly the right ventricle, and high risk of ventricular arrhythmias and sudden cardiac death (SCD). Early diagnosis and accurate risk assessment are challenging, yet essential for SCD prevention. This manuscript summarizes the current state-of-the-art on ARVC diagnosis and risk stratification.

Improving the 2010 diagnostic criteria is an ongoing discussion. Several studies suggest that early diagnosis may be facilitated by including deformation imaging ("strain") for objective assessment of wall motion abnormalities, which was shown to have high sensitivity for preclinical disease. Adding fibrofatty replacement detected by late gadolinium enhancement or T1-mapping in cardiac magnetic resonance imaging as criterion for diagnosis is increasingly suggested, but requires more supporting evidence from consecutive patient cohorts. In addition to the traditional right-dominant ARVC, standard criteria for arrhythmogenic cardiomyopathy (ACM) and arrhythmogenic left ventricular cardiomyopathy (ALVC) are on the horizon.

After diagnosis confirmation, the primary management goal is SCD prevention, for which an implantable cardioverter-defibrillator is the only proven therapy. Prior studies determined that younger age, male sex, previous (non-)sustained ventricular tachycardia, syncope, extent of T-wave inversion, frequent premature ectopic beats and lower biventricular ejection fraction are risk factors for subsequent events. Previous ICD indication guidelines were however limited to three expert-opinion flowcharts stratifying patients in risk groups. Now, two multivariable risk prediction models (arvcrisk.com) combine the abovementioned risk factors to estimate individual risks. Of note, both the flowcharts and prediction models require clinical validation studies to determine which should be recommended.

Introduction

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a familial disease characterized by fibrofatty replacement of predominantly right ventricular (RV) myocardium, ventricular arrhythmias, sudden cardiac death (SCD) and/or heart failure. While the first historical description was in 1763 by Giovanni Maria Lancisi in *De Motu Cordis et Aneurysmatibus*, Dr. Marcus was the first to describe ARVC in modern literature.¹ Now, after four decades of research in electrophysiology, molecular genetics and cardiac imaging, much has changed in our understanding and clinical management of ARVC.

While originally classified as dysplasia (i.e. developmental birth defect), we now recognize ARVC as a genetic cardiomyopathy with an autosomal dominant inheritance pattern with incomplete penetrance. The rise of cardiogenetic clinics enabled cascade screening of relatives identifying those at risk of developing ARVC. The at-risk population started growing rapidly, resulting in a noticeable shift in the clinical population from patients with overt disease towards asymptomatic patients with little or no disease expression. This urged clinical management to focus on early disease detection and risk prediction, while guidance from research and guidelines was limited. As a first step, the original 1994 diagnostic “Task Force Criteria” (TFC) were revised in 2010 to improve sensitivity for early and familial disease.²

Despite the revised criteria, many clinical challenges remain, which mainly result from incomplete penetrance and highly variable disease expression. In this review, we provide an overview of the state-of-the-art in pathophysiology, genetics, and management of ARVC, and focus on the recent developments in diagnosis and risk stratification.

ARVC, ALVC, ACM: what is in a name?

Over the years, several terms were introduced related to this disease (**Figure 1**). The original term arrhythmogenic right ventricular dysplasia (ARVD) refers to the developmental disorder (“dysplasia”) that this disease was thought to be at the time.¹ With increasing knowledge, ARVD was recognized as a progressive disease that developed after birth (“cardiomyopathy”) leading to its replacement by the more correct term ARVC³: hence, ARVD, ARVC, or ARVD/C can be considered synonyms. These terms relate to our most classic understanding of this disease: predominant RV involvement, fulfilment of the 2010 TFC, and pathogenic variants in desmosomal genes.

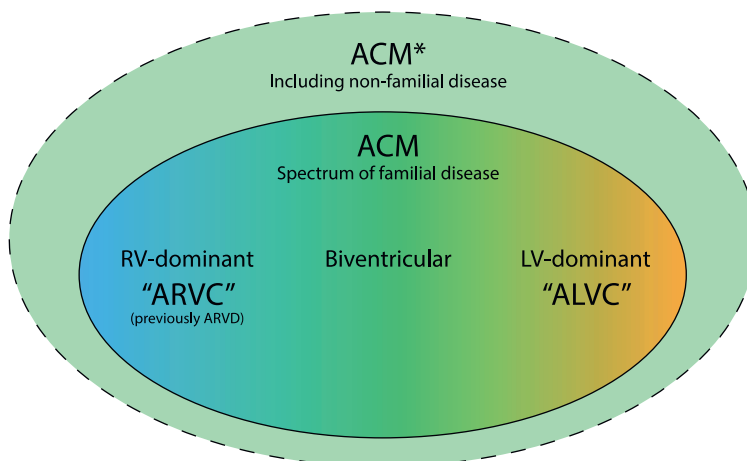


Figure 1. Schematic representation of terminology: ARVC, ALVC and ACM.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) refers to the most classical right ventricular (RV) dominant concept of this familial cardiomyopathy characterized by fibrofatty replacement of the myocardium predisposing to ventricular dysfunction and arrhythmias, and arrhythmogenic left ventricular cardiomyopathy (ALVC) in case of left ventricular (LV) dominant disease. Arrhythmogenic cardiomyopathy (ACM) refers of the entire spectrum of ARVC, ALVC, and biventricular phenotypes, but some literature includes non-familial diseases in the ACM definition as well. *The inclusion of non-familial disease such as inflammatory (e.g. sarcoidosis) or infectious (e.g. Chagas disease) is subject of debate.

While almost all ARVC patients show some degree of left ventricular (LV) involvement, a proportion of patients has predominant LV disease.⁴ Since this does not fit the classical ARVC concept, the terms left-dominant arrhythmogenic cardiomyopathy (LDAC), or arrhythmogenic left ventricular cardiomyopathy (ALVC) were introduced. ALVC occurs more frequently with *DSP* and non-desmosomal (e.g. *PLN*, *LMNA*) gene variants.^{4,5} However, most gene variants are observed in both ARVC and ALVC patients.

To cover the whole spectrum of biventricular involvement, the term arrhythmogenic cardiomyopathy (ACM or AC) was introduced to describe this familial disease with a common genetic background.⁶ At present, however, a uniform definition of ACM remains absent: the range of diseases designated as ACM varies from classical ARVC to almost any arrhythmogenic myocardial disorder. To most, it seems obvious to restrict the definition to familial disease, ensuring a similar aetiology.⁷⁻⁹ However, some define ACM as any arrhythmogenic disorder of the myocardium not secondary to ischemic, hypertensive or valvular disease, thereby including infectious and inflammatory diseases (e.g. Chagas and sarcoidosis).¹⁰ Nonetheless, it can be appreciated that every ARVC is considered ACM, but

not every ACM is ARVC. For clarity, we focus on familial/genetic disease with predominant RV involvement (i.e. “ARVC”) throughout the remainder of this manuscript.

Epidemiology and clinical presentation

The estimated population prevalence of ARVC ranges from 1:5000 to 1:2000,¹¹ although under-recognition is probably an important problem. Affected patients typically present between the ages of 20-40 years, with symptoms ranging from palpitations, (pre-)syncope, to even SCD as first manifestation.¹² Upon clinical evaluation, ARVC can be categorized into three stages: (1) the early “concealed phase”, with non-apparent or subtle structural RV changes at which patients can already be at risk of SCD; (2) the “electrical phase”, characterized by T-wave inversions and terminal QRS prolongation on electrocardiogram (ECG), premature ventricular complexes (PVCs), and ventricular tachycardias (VT) with left bundle-branch block (LBBB) morphology; (3) the “structural phase” when structural modifications progressed into right- or biventricular dilatation and potentially heart failure.¹³ Important differential diagnostic considerations (**Table 1**) include idiopathic RV outflow tract (RVOT) VT, Brugada syndrome, myocarditis, sarcoidosis and non-ischemic dilated cardiomyopathy (DCM).¹⁴ Differentiation can be challenging, yet is crucial for appropriate clinical management.

Table 1. Most common differential diagnostic considerations for ARVC

Differential diagnosis	Comparison of clinical features
Cardiac sarcoidosis	<ul style="list-style-type: none"> • Similarities with ARVC: focal myocardial lesions, (regional) ventricular dysfunction, arrhythmias, and LGE with non-ischemic pattern. • Contrasting with ARVC: non-familial pattern, AV-conduction delay, extra-cardiac manifestations, and predominant intraventricular septal involvement.
Myocarditis	<ul style="list-style-type: none"> • Similarities with ARVC: non-ischemic LGE and arrhythmias. • Contrasting with ARVC: history of viral prodromes, imaging findings suggesting myocardial oedema (acute phase) as well as pericardial involvement.
Dilated cardiomyopathy	<ul style="list-style-type: none"> • Similarities with ARVC: familial pattern, phenotype may mimic ARVC/ACM with LV involvement. • Contrasting with ARVC: ventricular arrhythmias predominantly in context of impaired ventricular structure/function, usually preceded by heart failure.
Uhl's anomaly	<ul style="list-style-type: none"> • Similarities with ARVC: loss of RV myocardium, RV dilatation • Contrasting with ARVC: non-familial, RV birth defect, deficiency of myocardium appearing as “parchment”, symptoms early childhood, primarily heart failure.
Brugada syndrome	<ul style="list-style-type: none"> • Similarities with ARVC: ventricular arrhythmias, pseudo-right bundle branch block. • Contrasting with ARVC: ventricular arrhythmias predominantly at rest, structural abnormalities absent.
Athlete's heart	<ul style="list-style-type: none"> • Similarities with ARVC: cardiac remodelling may mimic ARVC, exercise accelerates structural modifications • Contrasting with ARVC: reversible, balanced biventricular dilatation and hypertrophy, no dysfunction, no regional wall motion abnormalities.
Idiopathic RVOT VT	<ul style="list-style-type: none"> • Similarities with ARVC: VTs with LBBB inferior axis morphology. • Contrasting with ARVC: benign prognosis, curative catheter ablation, structural/ECG abnormalities usually absent.

Abbreviations: as in text.

Pathophysiology

Structural changes

Focal structural myocardial lesions in ARVC typically manifest as fibrofatty replacement in the RV basal inferior wall, RV basal anterior wall, and LV posterolateral wall, i.e. the “triangle of dysplasia”.¹⁵ This is the result of progressive cardiomyocyte loss, starting in the subepicardial layer extending towards the endocardium leading to transmural thinning lesions.⁸ Although the exact molecular pathophysiology remains unclear, several hypotheses have been proposed.⁵ Most commonly, cardiomyocyte loss and fibrofatty replacement in ARVC are thought to be due to abnormal cell-cell adhesion with disruption of desmosomes and adherens junctions. This predisposes myocyte detachment and cell death, especially in combination with mechanical wall stress, for example during exercise.

Arrhythmogenesis

In ARVC, monomorphic VTs most likely arise from fibrofatty lesions shaping highly arrhythmogenic re-entry circuits.¹⁶ However, as life-threatening arrhythmias can occur during the ‘concealed phase’ in the absence of (recognizable) structural heart disease, other mechanisms are likely involved as well. Recent preclinical studies revealed that loss of desmosomal integrity results in decreased gap junction protein (Connexin43) levels and sodium channel dysfunction, leading to abnormal impulse conduction.⁵ Furthermore, desmosomal mutations lead to dysregulated calcium handling, contributing to arrhythmogenesis in animal models.¹⁷ Concordantly, pathogenic variants in calcium handling protein genes (e.g. *PLN*, *RYR2*) are found in some patients. Future research is required to further elucidate the pathological mechanisms underlying this early arrhythmic substrate.

Molecular genetics

Advances in molecular genetic research have led to the identification of various genetic substrates associated with ARVC. Most pathogenic variants are found in genes encoding the desmosome, predominantly *PKP2* (**Table 2**).¹⁸ The majority of variants have an autosomal dominant inheritance pattern with incomplete penetrance, with exceptions such as the fully penetrant *TMEM43* p.S35L variant.¹⁹ Of note, some variants appear more frequent in LV-dominant phenotypes or DCM (e.g. *DSP*, *DSG2*, *DES*, *LMNA*, *PLN*), and overlapping phenotypes are the rule rather than exception.²⁰ Still, in approximately 30-40% of index patients no genetic substrate is found,²¹ indicating the role of other (epi)genetic, metabolic, or even external causes for ARVC that have yet to be determined.

Table 2. Genes associated with ARVC

Cell component	Gene	Protein	Estimated frequency	Reported features
Desmosome	<i>PKP2</i>	Plakophilin-2	34-74%	Associated with the most classical ARVC (RV-dominant) phenotype.
	<i>JUP</i>	Plakoglobin	<1%	First gene associated with ARVC, autosomal recessive variant associated with Naxos disease (cardiocutaneous disease).
	<i>DSG2</i>	Desmoglein-2	5-26%	More frequent in Asian countries. LV involvement common, overlap with DCM phenotype.
	<i>DSC2</i>	Desmocollin-2	1-5%	Autosomal dominant, recessive and homozygous mutations reported in ARVC patients.
	<i>DSP</i>	Desmoplakin	1-14%	More prevalent in the UK and Italy. Associated with LV-dominant disease, DCM, and autosomal recessive with Carvajal syndrome (cardiocutaneous disease).
Adherens junction	<i>CTNNA3</i>	Catenin-a3	Rare	Influences <i>PKP2</i> protein distribution, but variants considered to cause ARVC are rare and evidence is limited.
	<i>CDH2</i>	Cadherin-2	Rare	Associated with (biventricular) ARVC, but evidence is limited to reports of a few families.
Cytoskeleton	<i>DES</i>	Desmin	Rare	Associated with high penetrance, LV-dominant disease overlapping DCM, and combination with myopathies.
	<i>TMEM43</i>	Transmembrane protein 43	Rare	Founder missense variant (p.S358L) in Newfoundland, with full penetrance and early onset severe phenotype.
	<i>LMNA</i>	Lamin A/C	Rare	Associated with AV block, high risk of arrhythmia, biventricular disease overlapping DCM, but evidence in ARVC/ACM is limited.
	<i>TTN</i>	Titin	Rare	Associated with biventricular dysfunction and conduction block, overlap with DCM phenotype, but evidence in ARVC/ACM is limited.
	<i>FLNC</i>	Filamin-C	Rare	Associated with biventricular dysfunction and high risk of arrhythmias, overlap with DCM phenotype, but evidence in ARVC/ACM is limited.
Ion-transporters	<i>PLN</i>	Phospholamban	Rare	Founder variant with single amino acid deletion (p.R14del) in the Netherlands (up to 12%), associated with LV-dominant disease and heart failure, overlap with DCM.
	<i>SCN5A</i>	Sodium channel NaV1.5	Rare	Associated with conduction disturbances, overlap with Brugada/long QT syndrome and sometimes DCM. Evidence in ARVC/ACM is limited.
Cytokines	<i>TGF-β3</i>	Transforming growth factor-β3	Rare	Associated with ARVC in a few families, evidence is limited.

Visit <https://clinicalgenome.org/> for a complete list of associated genes including those currently disputed.

Abbreviations: as in text

Diagnosis

The 2010 Task Force Criteria

No single test has sufficient sensitivity and specificity to serve as gold standard for ARVC diagnosis. Therefore, diagnosis is determined by a combination of clinical tests defined by a Task Force in 1994, the TFC, which was modified in 2010.² Criteria considered to have high

specificity (>90%) are classified as major, others as minor. The criteria are divided into six categories: (1) structure/function, (2) tissue characterization, (3) repolarization abnormalities, (4) depolarization abnormalities, (5) arrhythmias, and (6) family history. Per category, patients can fulfil only one minor or major criterion. At least 2 major, 1 major with 2 minor, or 4 minor criteria are required for diagnosis (**Table 3**). We will discuss some of the important new developments in ARVC diagnosis below.

Table 3. The 2010 TFC for diagnosis of ARVC

I. Structure/function assessment	
Major	2D Echocardiography: <ul style="list-style-type: none"> Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following at end diastole: <ul style="list-style-type: none"> PLAX RVOT $\geq 32\text{mm}$ or PLAX/BSA $\geq 19\text{mm/m}^2$ PSAX RVOT $\geq 36\text{mm}$ or PSAX/BSA $\geq 21\text{mm/m}^2$ Fractional area change $\leq 33\%$ CMR: <ul style="list-style-type: none"> Regional RV akinesia or dyskinesia or dyssynchronous contraction and 1 of the following: <ul style="list-style-type: none"> RV EDV/BSA $\geq 110\text{mL/m}^2$ (male) or $\geq 100\text{mL/m}^2$ (female) RVEF $\leq 40\%$ RV angiography: <ul style="list-style-type: none"> Regional RV akinesia, dyskinesia, or aneurysm
Minor	2D Echocardiography: <ul style="list-style-type: none"> Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following at end diastole: <ul style="list-style-type: none"> PLAX RVOT ≥ 29 to $<32\text{mm}$ or PLAX/BSA ≥ 16 to $<19\text{mm/m}^2$ PSAX RVOT ≥ 32 to $<36\text{mm}$ or PSAX/BSA ≥ 18 to $<21\text{mm/m}^2$ Fractional area change $>33\%$ to $\leq 40\%$ CMR: <ul style="list-style-type: none"> Regional RV akinesia or dyskinesia or dyssynchronous contraction and 1 of the following (end diastole): <ul style="list-style-type: none"> RV EDV/BSA ≥ 100 to $<110\text{mL/m}^2$ (male) or ≥ 90 to $<100\text{mL/m}^2$ (female) RVEF >40 to $\leq 45\%$
II. Tissue characterization	
Major	<ul style="list-style-type: none"> 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.
Minor	<ul style="list-style-type: none"> Residual myocytes 60-75% by morphometric analysis (or 50-65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy.
III. Repolarization abnormalities	
Major	<ul style="list-style-type: none"> Inverted T-waves in leads V1, V2, and V3 or beyond, in individuals >14 years of age (in absence of complete RBBB QRS $\geq 120\text{ms}$).
Minor	<ul style="list-style-type: none"> Inverted T-waves in leads V1 and V2, in individuals >14 years of age (in absence of complete RBBB) or in V4, V5, or V6. Inverted T-waves in leads V1, V2, V3, and V4 in individuals >14 years of age in the presence of complete RBBB.
IV. Depolarization abnormalities	
Major	<ul style="list-style-type: none"> Epsilon wave (reproducible low-amplitude signals between end of QRS complete to onset of the T-wave) in V1-3.
Minor	<ul style="list-style-type: none"> Late potentials by SAECD in ≥ 1 of 3 parameters in absence of a QRS of $\geq 110\text{ms}$ on standard ECG: <ul style="list-style-type: none"> Filtered QRS duration $\geq 114\text{ms}$ Duration of terminal QRS $<40\mu\text{V}$ $\geq 38\text{ms}$ Root-mean-square voltage of terminal 40ms $\leq 20\mu\text{V}$ Terminal activation duration of QRS $\geq 55\text{ms}$, measured from the nadir of the S-wave to the end of the QRS, including R', in V1, V2, or V3, in absence of complete RBBB.

V. Arrhythmias	
Major	<ul style="list-style-type: none"> • Non-sustained or sustained VT of LBBB morphology with superior axis.
Minor	<ul style="list-style-type: none"> • Non-sustained or sustained VT of RVOT configuration, LBBB morphology with inferior axis or with unknown axis. • >500 PVCs per 24 hours on Holter monitoring
VI. Family history	
Major	<ul style="list-style-type: none"> • First-degree relative with ARVC confirmed by TFC • First-degree relative with ARVC confirmed pathologically at autopsy or surgery • Identification of a pathogenic mutation categorized as associated or probably associated with ARVC in the patient under evaluation
Minor	<ul style="list-style-type: none"> • First-degree relative with ARVC history not possible to confirm by TFC • First-degree relative with SCD <35 years of age due to suspected ARVC • Second-degree relative with ARVC confirmed by TFC or pathologically

Abbreviations: BSA=body surface area; EDV=end diastolic volume; PLAX=parasternal long axis; PSAX=parasternal short axis; PVC=premature ventricular complex; RBBB=right bundle-branch block; RV=right ventricle; RVEF=right ventricular ejection fraction; RVOT=right ventricular outflow tract; SAECG=signal-averaged electrocardiogram; SCD=sudden cardiac death; TFC=task force criteria; VT=ventricular tachycardia.

Structure and function assessment

The 2010 TFC introduced quantitative echocardiography and cardiac magnetic resonance imaging (CMR) criteria as alternatives to the previous standard of invasive angiography. While these criteria were recently shown to have high specificity (88-99%), their sensitivity is relatively poor: 21-29% for echocardiography and 46-69% for CMR.^{22,23} A possible explanation for this limited sensitivity is that the primary condition for criteria fulfilment, detection of wall motion abnormalities, depends on subjective visual assessment. Besides being operator-dependent, visual assessment may be insensitive for early signs of disease given the RV geometry and limited spatial resolution (particularly in echocardiography). Confirming this, echocardiography and CMR studies have shown objective assessment by deformation imaging ("strain") to be superior in detecting subtle motion abnormalities in early disease.^{13,24-26} Another limitation in the 2010 TFC may be the absence of multidetector computed tomography (MDCT) as a useful alternative when obtaining CMR images is not possible due to implanted devices or claustrophobia.¹⁴

Tissue characterization

Fibrofatty replacement is a typical sign of ARVC and histological analysis has been a diagnostic tool for many years. Unfortunately, endomyocardial biopsy has a high rate of sampling error due to the segmental distribution of fibrofatty lesions.²⁷ As the diagnostic yield is too low to justify the procedural complication risk, endomyocardial biopsy is usually reserved for cases in which mimics such as sarcoidosis cannot be otherwise excluded.

However, non-invasive detection of fat and fibrosis by CMR and MDCT is rapidly improving. Localized myocardial lesions may be detected by late gadolinium enhancement

(LGE) CMR, with studies reporting sensitivities up to 88%.²⁰ Alternatively, T1-mapping allows quantification of diffuse fibrosis and may detect ARVC preceding LGE, although the thin RV wall precludes T1-mapping analysis.²⁸ Furthermore, contrast-enhanced MDCT low attenuation regions are also suggested to indicate fibrofatty infiltration.²⁹ Although promising, future studies should determine if these techniques can differentiate ARVC from mimics. Advocating their use as diagnostic criterion seems premature as their true specificity for ARVC has yet to be determined.

Repolarization abnormalities

The extent of precordial T-wave inversions (TWI) on ECG in ARVC correlates to the degree of RV dilatation and is used for diagnosis.³⁰ In addition to leads V1-3, indicating RV disease, the 2010 TFC includes TWI in V4-V6 as minor criterion, which may indicate LV involvement.³¹ As a result, this enables the inclusion of more LV-dominant cases in the TFC definition of ARVC, while in the future this criterion may be more suitable as ALVC criterion.⁷

Depolarization abnormalities

Depolarization abnormalities in ARVC may manifest as prolonged terminal activation duration or epsilon waves on ECG, or as late potentials on signal-averaged ECG (SAECG). Of these, SAECG and epsilon waves are currently under debate: SAECG had poor diagnostic performance in a recent validation study,²² and epsilon waves had high interobserver variability in an international expert panel.³² The latter is especially concerning considering its high impact as major criterion. Fortunately, the expert panel found that no patients depended on epsilon waves for their diagnosis, suggesting that it is a sign of advanced disease. As such, removing epsilon wave as diagnostic criterion will not affect ARVC diagnosis, while it may prevent harm caused by adjudication errors.

Arrhythmias

Both PVCs and VTs are included as diagnostic criteria for ARVC. While the PVC criterion depends on 24-hour count without requirements on morphology, strict morphologic criteria apply for VT. In doing so, the Task Force aimed to avoid the overlap with idiopathic RVOT tachycardia. Since then, some authors have suggested that similar morphologic criteria for PVCs would improve ARVC diagnosis.³³ However, the feasibility of reliable morphology detection during ambulant Holter monitoring remains to be investigated.

Family history and genetics

Since the 2010 TFC family history and genetics criteria, all first-degree relatives and pathogenic variant carriers fulfil a major criterion. While this reflects the strong familial inheritance pattern of ARVC, this “head start” in relatives could lead to false-positive diagnoses especially in the context of the incomplete penetrance. Indeed, a recent study revealed that relatives who depend on family history for diagnosis have generally benign follow-up.³⁴ It is remarkable that the TFC considers having a first-degree relative with ARVC of equal weight as a confirmed pathogenic variant, since family history indicates 50% probability of harbouring a genetic predisposition (assuming an autosomal dominant inheritance pattern), while a confirmed genetic variant confers 100% probability. Indeed, the family membership criterion had much lower diagnostic value than positive genetic testing in a recent validation study.²² Future studies should systematically evaluate the role of family history and genetics in ARVC diagnosis.

Proposal for new ARVC, ACM and ALVC criteria: the Padua criteria

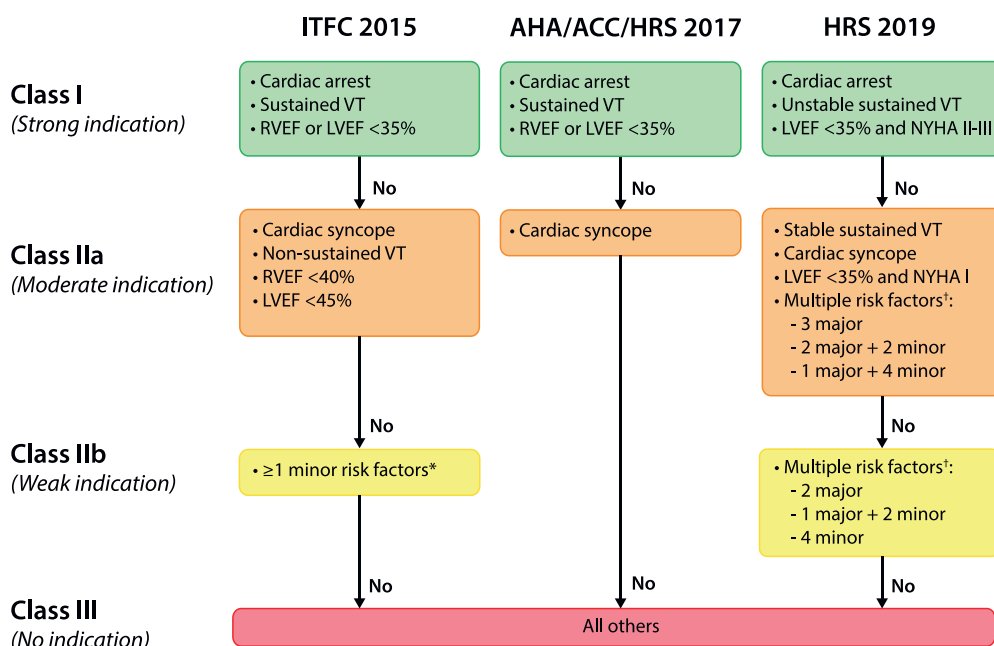
While the above outlined limitations of the 2010 TFC are widely recognized,³⁵ changing the diagnostic criteria requires a strong evidence base as any change has major consequences for clinical practice and research.

A first step has recently been taken by Corrado et al., proposing new criteria for ARVC, ALVC, and ACM: the Padua Criteria.⁷ This proposal defines ACM as “a genetic heart muscle disease involving the RV, LV, or both, characterized by fibrofatty replacement predisposing to global and/or regional dysfunction, and ventricular arrhythmias independent of the ventricular dysfunction”. In this framework, ACM is subdivided as ARVC, ALVC, or biventricular, with separate criteria for each entity. For ARVC, the main changes to the 2010 TFC include: wall motion abnormalities directly qualifying as minor criterion, transmural CMR LGE as major criterion. In addition, the Padua criteria remove SAECG, and apply VT morphology criteria to the PVC criterion. As suggested by the authors, we emphasize that the Padua criteria should be evaluated in clinical validation studies prior to their clinical implementation.

Prognosis

Patients with ARVC have an average risk of 10%/year to develop ventricular arrhythmias including SCD.³⁶ Of note, the only effective treatment to prevent SCD is the placement of an implantable cardioverter-defibrillator (ICD), which is invasive, has inherent complication risk, and can impose physical and psychological burden to patients. As ARVC patients are often

young, these burdens affect a significant part of their lives. Careful consideration of ICD indications is therefore warranted. However, the heterogeneity of SCD risk complicates decision-making for ICD implantation. We will discuss the recent developments aimed at addressing this issue.



* ITFC 2015 Minor: RV or RA dilatation, young age, male sex, compound or digenic heterozygosity, proband status, inducible VT/VF, electroanatomic scar or fragmented electrograms on endocardial voltage mapping, T-wave inversions inferior or in >3 precordial lead QRS fragmentation, QRS amplitude ratio V1-3/V1-6 <0.48.

[†] HRS 2019 Major: non-sustained VT, inducible VT, LVEF ≤49%. Minor: male sex, >1000 PVCs/24h (in absence of non-sustained VT), RV dysfunction as per major 2010 TFC, proband status, multiple desmosomal variants.

Figure 2. Expert statement / guideline ICD indication algorithms.

Overview of the three flow diagram algorithms for implantable cardioverter-defibrillator (ICD) indication, from the 2015 ARVC international task force consensus (ITFC 2015),¹⁶ the 2017 AHA/ACC/HRS ventricular arrhythmia guideline (AHA/ACC/HRS 2017),³⁷ and the 2019 ACM HRS consensus (HRS 2019).¹⁰

Abbreviations: LVEF=left ventricular ejection fraction; PVC=premature ventricular complex; RA=right atrium; RVEF=right ventricular ejection fraction; VT=ventricular tachycardia; VF=ventricular fibrillation.

Expert statements and guidelines

Although many studies identified risk factors for arrhythmic events, translation to absolute risks relevant for clinical practice was lacking. Several expert consensus documents consolidated

the available evidence in flow diagram algorithms to recommend ICD placement. Today, three algorithms are available: the 2015 international task force consensus statement on management of ARVC,¹⁶ the 2017 AHA/ACC/HRS guideline for management of ventricular arrhythmias,³⁷ and the 2019 HRS consensus statement on evaluation, risk stratification and management of ACM (**Figure 2**).¹⁰ Of note, all three algorithms are based on expert opinion, and clinical validation studies to estimate their accuracy are lacking. Moreover, the algorithms do not account for incremental or interactive effects of multiple risk factors, which may limit their real-life accuracy.

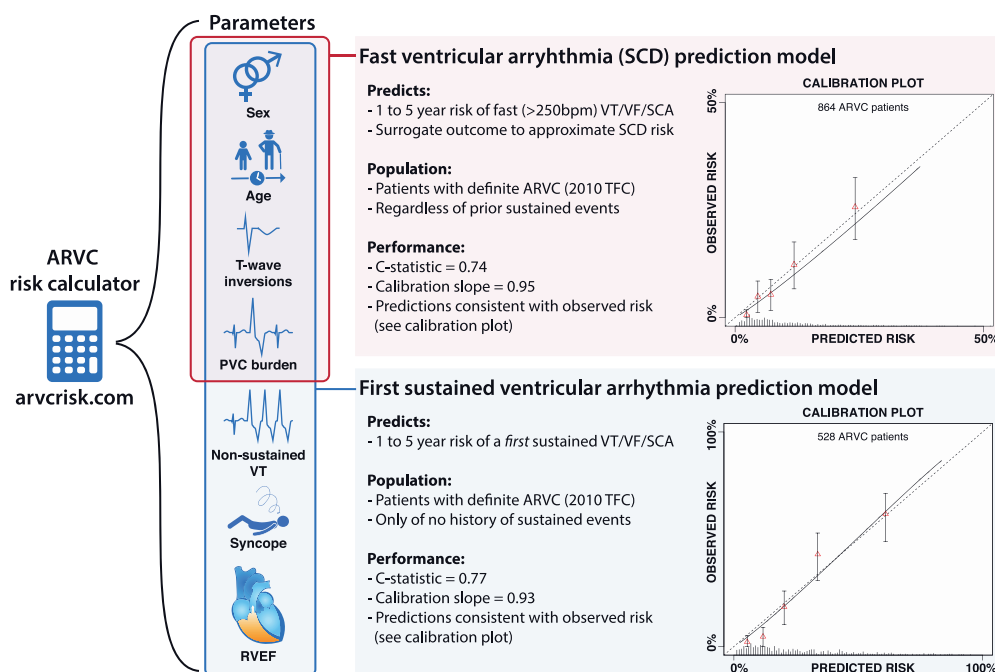


Figure 3. ARVC risk calculator.

The arrhythmogenic right ventricular cardiomyopathy (ARVC) risk calculator predicts ventricular arrhythmias in patients with ARVC by utilizing two prediction models. One to predict the risk of fast (>250bpm) ventricular tachycardia/fibrillation or sudden cardiac arrest (VT/VF/SCA) based on four risk parameters (red box), the other predicts the risk of any first sustained ventricular arrhythmia in those without a prior sustained event, using all seven risk parameters (blue box). The calibration plots of both prediction models are included (right side), plotting the predicted risk (X-axis) against the observed risk (Y-axis).^{38,39}

Abbreviations: PVC=premature ventricular complex; RVEF=right ventricular ejection fraction; SCD=sudden cardiac death; TFC=task force criteria

ARVC “risk calculator”

Traditional well-accepted univariable risk factors of arrhythmia in ARVC include prior VTs, RVEF and LVEF. However, multivariable models provide more accurate and quantitative estimations of arrhythmic risk. Two such models were recently developed in a large international cohort of ARVC patients: one to predict the first sustained ventricular arrhythmia in those without prior sustained events,³⁸ and one to predict fast (>250bpm) VT, ventricular fibrillation or sudden cardiac arrest/death (as SCD surrogate) in all patients.³⁹ Both models are available as “risk calculator” at www.arvcrisk.com (**Figure 3**). As of today, four studies tested the calculator’s accuracy. First, Aquaro et al. showed that the calculator outperformed both the 2015 international task force and 2019 HRS algorithms in a cohort of 140 ARVC patients.⁴⁰ Furthermore, studies by Aquaro et al. and Casella et al. confirmed excellent results in ARVC patients, but reported that arrhythmic risk was underestimated in non-classical subtypes with LV involvement, suggesting this as a limitation.^{41,42} Interestingly, while underestimation was expected in athletes as exercise is not included in the risk calculator, Gasperetti et al. found accurate predictions in 25 athletes with ARVC.⁴³ These results suggest a possible role for this risk calculator in clinical practice.

Clinical management

With no curative treatment options, clinical management is aimed at symptom reduction and prevention of disease progression and SCD. When an ICD is indicated as discussed above, both transvenous or subcutaneous are possible depending on preferences, vascular status, and the need for pacing options such as bradycardia or antitachycardia pacing.³⁷ Additional therapy options are discussed below.

Lifestyle

It is well appreciated that high-intensity or competitive exercise is associated with earlier disease onset, higher arrhythmic risk, and structural disease progression in ARVC patients and at-risk relatives.^{44,45} As such, exercise restriction is strongly recommended for both patients and at-risk relatives. Unfortunately, it remains unclear to what extent exercise should be reduced to prevent harmful effects, while maintaining the physical and mental health benefits. The ESC-guideline recommends a maximum of 150 minutes low-moderate intensity (3-6 metabolic equivalent) exercise per week in affected and at-risk subjects.⁴⁶

Medication

Since arrhythmias in ARVC typically occur during exertion and are sensitive to β -adrenergic stimulation,⁴⁷ beta-blockers are recommended as first-line pharmacologic agent. When unsuccessful, arrhythmic burden may be reduced using anti-arrhythmic drugs, of which sotalol and amiodarone are considered most effective.⁴⁸ Of note, none of these medications effectively reduce SCD risk. Pharmacologic management of heart failure involves regular heart failure drugs, including beta-blockers, ACE-inhibitors, and mineralocorticoid inhibitors, but there are no ARVC-specific controlled trials confirming the effectiveness of this approach. Although ARVC-specific therapies are currently lacking, new therapeutic strategies targeting the Wnt/ β and NF κ B pathways show disease regression in animal models, and may be promising in the future.⁴⁹

Cardiac catheter ablation and transplantation

In patients with frequent monomorphic VT, radiofrequency catheter ablation can be considered for symptom relief, but full resolution of ventricular arrhythmias is virtually impossible due to the progressive nature of disease. In addition, since arrhythmic substrates in ARVC are predominantly located on the epicardium, an epicardial approach is usually necessary. Indeed, several studies have shown significantly better results with an epicardial compared to endocardial approach.⁵⁰ In patients with untreatable ventricular arrhythmias or congestive heart failure refractory to therapy, cardiac transplantation can be considered as definitive solution.¹¹

Conclusions

ARVC is an inherited cardiomyopathy with high risk of ventricular arrhythmias which may lead to SCD at young age. Accurate early detection of disease is essential for SCD prevention, which was significantly advanced by genetic testing identifying those at risk at pre-clinical stages. However, clinicians are challenged by incomplete penetrance and highly variable disease expression among individuals. To overcome these challenges, the recent years has witnessed research into solutions that tailor clinical care to an individual level. To improve early disease detection, recent studies showed promising results using non-invasive tissue characterization and deformation imaging. To improve risk stratification, a multivariable prediction model for ventricular arrhythmias was developed. Furthermore, ARVC is now increasingly recognized as being part of a wider disease spectrum involving both ventricles: ACM. While uniform definitions are still lacking, subclassifying patients into similar, more uniform phenotypic groups may benefit future research and improve clinical management.

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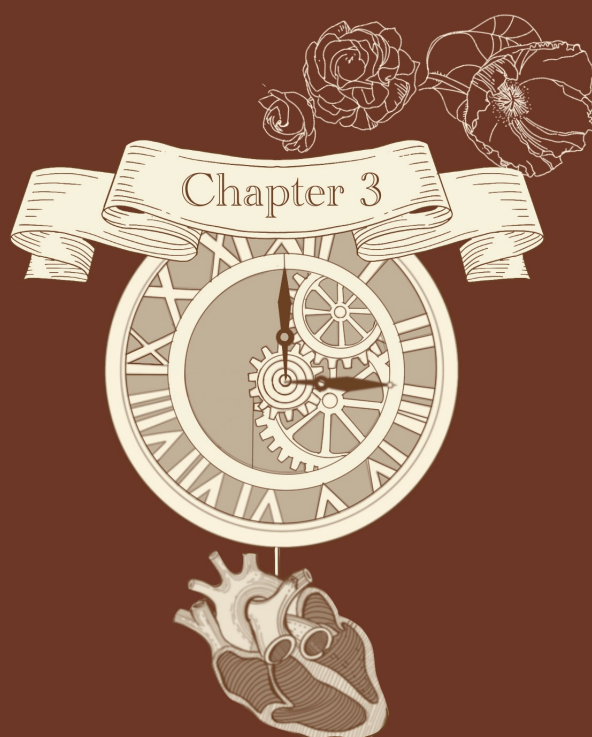
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Chapter 3

Predicting Arrhythmic Risk in Arrhythmogenic Right Ventricular Cardiomyopathy: A Systematic Review and Meta-Analysis

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Abstract

While many studies evaluate predictors for ventricular arrhythmias in Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), a systematic review consolidating this evidence is currently lacking. Therefore, we searched MEDLINE and Embase for studies analyzing predictors for ventricular arrhythmias (sustained ventricular tachycardia/fibrillation (VT/VF), appropriate implantable cardioverter-defibrillator therapy, or sudden cardiac death) in definite ARVC patients, borderline ARVC patients, and ARVC-associated mutation carriers. In case of multiple publications on the same cohort, the study with the largest population was included. This yielded 45 studies with a median cohort size of 70 (IQR 60) patients and 5.0 (IQR 3.5) years follow-up. The arrhythmic outcome was observed in 10.6%/year in definite ARVC patients, 10.0%/year in borderline ARVC patients, and 3.7%/year in mutation carriers. Predictors for ventricular arrhythmias were population-dependent: consistently predictive risk factors in definite ARVC patients were male sex, syncope, T-wave inversion >V3, right ventricular (RV) dysfunction, and prior (non)sustained VT/VF; in borderline ARVC patients, two additional predictors (inducibility at electrophysiology study and strenuous exercise) were identified; and in mutation carriers, all aforementioned predictors as well as ventricular ectopy, multiple ARVC-related pathogenic mutations, left ventricular dysfunction, and palpitations/pre-syncope determined arrhythmic risk. Most evidence originated from small observational cohort studies, with a moderate quality of evidence. In conclusion, the average risk of ventricular arrhythmia ranged from 3.7% to 10.6%/year depending on the ARVC population. Male sex, syncope, T-wave inversion >V3, RV dysfunction, and prior (non)sustained VT/VF consistently predict ventricular arrhythmias in all ARVC populations.

Introduction

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is an inherited cardiomyopathy with a high risk of ventricular arrhythmias, most notably in young individuals and athletes.¹ Identifying individuals at highest risk of arrhythmias is crucial to prevent sudden cardiac death (SCD) using an implantable cardioverter-defibrillator (ICD). Conversely, recognizing subjects at low arrhythmic risk is important since ICD placement bears a considerable risk of complications and inappropriate interventions.^{2,3} Since the clinical expression of ARVC is variable, reliable risk prediction is difficult, which presents a challenge to physicians and patients alike.

Over the years, many studies have described risk factors for ventricular arrhythmias in ARVC, including a consensus statement on ARVC treatment.⁴ Despite the wealth of data in the literature, most studies were non-randomized, included relatively small patient numbers, and did not account for differences in patient subgroups, leading to high variation in the reported associations. Indeed, while previous sustained ventricular arrhythmias and ventricular dysfunction are generally recognized as important predictors of arrhythmic events, the prognostic value of other risk factors remains unclear. To the best of our knowledge, a systematic review and meta-analysis summarizing the available evidence is currently lacking.

In light of these shortcomings, we systematically reviewed observational studies that assessed predictors for ventricular arrhythmias in ARVC. We evaluated the quality of evidence, quantified them using pooled analyses when appropriate, and performed sub-analyses on patient subgroups to obtain subgroup-specific risk estimates. The results of these analyses may aid clinical decision-making, counseling, and expectation management in this high-risk population.

Methods

This study was performed in accordance with the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)⁵ and Meta-analysis of Observational Studies in Epidemiology (MOOSE)⁶. We performed a systematic search of MEDLINE and Embase in January 2017 for clinical studies on risk factors for ventricular arrhythmias in patients with ARVC. A detailed description of our search strategy, selection and data extraction can be found in the Supplementary Methods.

Study Eligibility and Definitions

Any original study involving an ARVC population that investigated an association between ≥ 1 risk factor(s) and a predefined arrhythmic outcome was considered eligible for inclusion in this review.

The *study population of interest* included patients fulfilling diagnostic Task Force Criteria (TFC) for ARVC. Of note, these criteria were first described in 1994 and revised in 2010⁷. Since restricting the patient population to either one of these criteria would inevitably lead to selection bias, both were considered eligible for inclusion. The included studies were classified in three categories (i.e. patient domains) based on their inclusion criteria: (1) “definite ARVC” refers to cohorts in which all patients fulfilled diagnostic TFC, (2) “borderline ARVC” refers to cohorts in which patients had at least a borderline ARVC diagnosis (TFC score ≥ 3 , thus including definite ARVC patients), and (3) “mutation carriers” refers to cohorts of ARVC-associated mutation carriers regardless of phenotypic expression, thereby including both asymptomatic mutation-carrying relatives and a (small) proportion of definite ARVC patients. Since all three subgroups include definite ARVC patients, all were considered relevant for the purpose of our analyses. However, the patient domains were separately analyzed in this manuscript, since these differences in inclusion criteria is likely to affect the reported results.

The *outcome of interest* was potentially lethal ventricular arrhythmias. All studies that included spontaneous ventricular tachycardia (VT) or ventricular fibrillation (VF), sudden cardiac arrest, SCD, or appropriate ICD intervention for a ventricular arrhythmia were considered eligible for inclusion in this study. Non-sustained VT was excluded as an outcome in our analyses. Since almost all studies exclusively reported risk estimates for a combined arrhythmic outcome, we were obliged to consider all arrhythmic outcomes as equal, although we report outcome-specific risk estimates if available. Studies that included non-arrhythmic outcomes, such as heart failure, heart transplantation or overall mortality, were excluded unless subgroup analysis for arrhythmic outcome was provided or could be reconstructed.

Quality Assessment

To assess the individual study quality and risk of bias, we used the Quality In Prognostic Studies (QUIPS) tool developed by the Cochrane Collaboration.⁸ Details can be found in the Supplementary Methods. Study quality was assessed independently by two investigators (LPB and AZS); and a third (ASJMTR) in case of disagreement.

Statistical Analysis

Our analyses were divided in two components: (1) we presented a description of all studies that provided OR, risk ratios (RR), Kaplan Meier (KM) or Receiver Operator Characteristic (ROC), for every risk factor separately; (2) we pooled all studies that reported HRs in a meta-analysis, provided that the variable definitions were uniform. Only studies reporting HRs were considered for meta-analysis, as ORs can only reliably be pooled when follow-up time is equal. Furthermore, meta-analyses were only performed on crude (i.e. unadjusted) HRs within the same patient domain; studies selecting participants based on genotype were not pooled due to the expected high variation in phenotypic expression. All meta-analyses were conducted in Review Manager (RevMan 5.3, Copenhagen: The Cochrane Collaboration, 2014). Statistical heterogeneity between studies was assessed using the Chi-square homogeneity test, expressed by the I^2 index, where I^2 values indicated low(<25%), moderate(25-75%) and high(>75%) degree of heterogeneity. Study-specific crude HRs were combined using inverse variance-weighted averages of a random effects model. Sensitivity analyses were performed to assess the contribution of selection differences based on (1) TFC version and (2) primary prevention populations.

Results

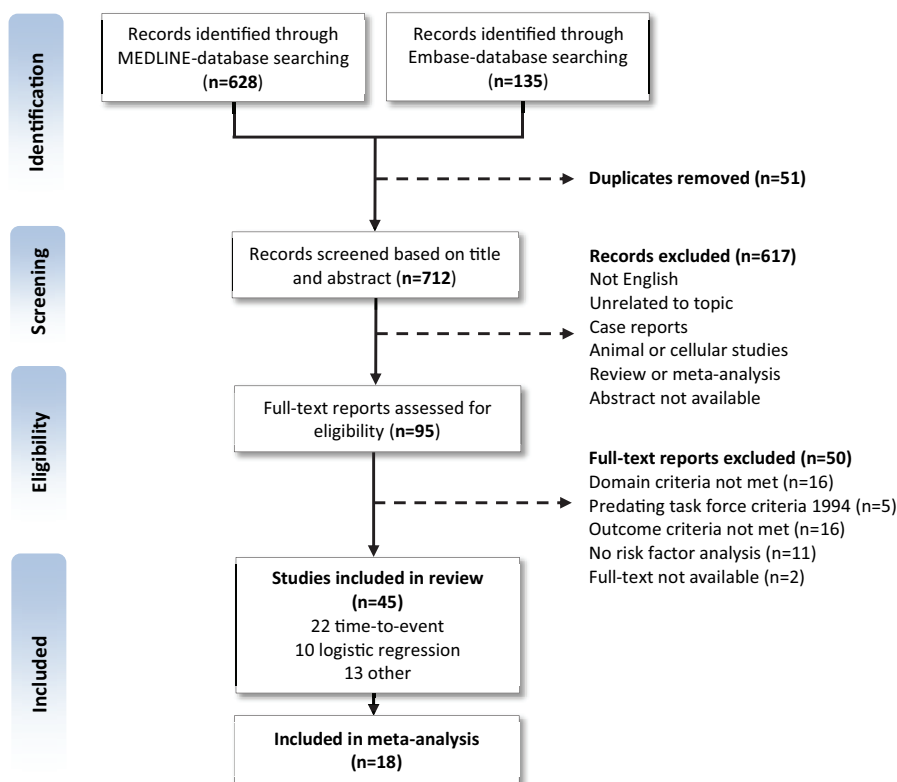


Figure 1. Flowchart of Search Results and Selection Process.

Search Results

Our search results and selection process are shown in **Figure 1**. Our literature search yielded 712 unique records, which were carefully screened based on title and abstract. Records (n=617) that did not report on prognostic factors for arrhythmic outcomes in the appropriate population were excluded. The remaining 95 candidate publications received a thorough full-text assessment, resulting in a total of 45 studies that met the inclusion criteria, see Supplementary Reference for a full reference list of the included studies. An overview of the excluded studies with reasons for exclusion can be found in **Supplementary Table 1**. Potential cohort overlap was excluded at the level of the individual risk factors by maintaining only the study with the largest population as disclosed in **Figure 2**.

Author, year	Design	Study population	Type of prevention	Size/ Events	Follow-up (yrs)	Endpoint	Risk factor type (n)	Statistic	Bias risk
Battipaglia, 2012 ¹⁴	RC	Definite TFC10	P	30/5	1.6±0.6	sVT, ATP/Shock, SCD	Clinical(4), Arrhythmic(13), ECG(5), Imaging(3), EPS(1)	HR	▲
Berruero, 2016 ¹⁵	PC	Definite TFC10	S	41/11	2.7±1.8	sVT, ATP/Shock	Clinical(1), Arrhythmic(1), Imaging(4), EPS(4)	HR	●
Bhonsale, 2011 ¹³	RC/PC	Definite/borderline TFC10, ICD	P	84/40	4.7±3.4	ATP/Shock	Clinical(6), Arrhythmic(3), ECG(3), EPS(1), Imaging(2), Genotype(1)	HR, KM	●
Bhonsale, 2013 ¹⁴	RC/PC	Mutation carriers	P/S	215/86	5.8†	sVT, ATP/Shock, SCD	Clinical(13), Arrhythmic(3), Imaging(1), ECG(2)	HR, KM, OR	▲
Bhonsale, 2015 ¹⁵	RC/PC	Mutation carriers	P/S	541/207	6.0±7.0	sVT, VF, ATP/Shock, SCD	Clinical(1), Genotype(2)	KM	▲
Canpolat, 2013 ¹⁶	RC	Definite TFC10	P/S	78/39	3.2±1.2	VT, VF, SCD	Clinical(8), Arrhythmic(2), ECG(2), Imaging(3)	HR	▲
Chan, 2015 ¹⁷	RC	Definite TFC10, RFA	P/S	59/14	2.5±1.7	VT, VF, ATP/Shock, SCD	ECG(1)	KM, OR	◆
Choudhary, 2016 ¹⁸	PC	Definite/borderline TFC10, ICD	P/S	101/19	3.0±1.8	ATP/Shock	Clinical(1)	HR, KM	▲
Chung, 2016 ¹⁹	PC	Definite/borderline TFC10	P/S	63/19	2.3±1.3	sVT, VF, SCD	Clinical(4), Arrhythmic(1), Imaging(4), ECG(3), EPS(1)	HR	●
Corrado, 2006 ¹¹⁰	RC	Definite TFC94, ICD	P/S	132/64	3.3±2.1	ATP/Shock on VF	Clinical(2), Arrhythmic(1), Imaging(2)	OR	▲
Corrado, 2010 ¹¹¹	RC	Definite TFC94, ICD	P	106/25	4.8±2.9	ATP/Shock	Clinical(4), Arrhythmic(1), ECG(2), Imaging(2), EPS(1)	HR	●
Dalal, 2006 ¹¹²	RC	Definite TFC94	P/S	48/28	5.0±4.0	ATP/Shock	Genetics(1)	KM	▲
Folino, 2002 ¹¹³	RC	Definite TFC94	P	46/8	10.8±1.9	sVT / VF	Clinical(2), Arrhythmic(6), Imaging(4)	OR, Means	◆
Greenewald, 2015 ¹¹⁴	RC	Definite TFC10	P/S	416/301	7[12]	sVT, VF, ATP/Shock	Genotype(1)	KM	▲
Hong, 2012 ¹¹⁵	RC	Definite TFC94, ICD	P/S	24/n.a.	3.3±1.7	ATP/Shock rate	Clinical(1), Biomarker(1)	OR, ROC	◆
James, 2013 ¹¹⁶	RC	Mutation carriers	P	87/39	8.4±6.7	sVT, VF	Exercise(1)	KM, OR	▲
Kikuchi, 2016 ¹¹⁷	RC	Definite TFC10	P/S	90/47	10.2±7.1	sVT, VF	TFC2010(12)	HR	▲
Liao, 2014 ¹¹⁸	PC	Definite TFC10	P/S	24/13	1.8±1.6	sVT, VF	Clinical(4), Imaging(5), ECG(5), Arrhythmic(1), Histology(1)	OR	▲
Lin, 2017 ¹¹⁹	RC	Definite TFC10, RFA	S	70/38	1.4±1.0	nsVT, sVT, VF	Clinical(5), Arrhythmic(1), ECG(2), Imaging(1), Histology(1), EPS(11)	HR	▲
Link, 2014 ¹²⁰	PC	Definite/borderline TFC94, ICD	P/S	108/48	3.3±1.7	ATP/Shock	Clinical(7), Arrhythmic(3), ECG(4), Imaging(2), EPS(1)	HR	●
Marcus, 2009 ¹²¹	PC	Definite TFC94, ICD	P/S	95/32	1.3±1.1	sVT, VF, ATP/Shock	Clinical(7), Arrhythmic(2), ECG(1), Imaging(2)	OR, Means	◆
Martin, 2016 ¹²²	PC	Definite TFC10, ICD	P/S	26/13	6.7[3.9-9.3]	ATP/Shock	Clinical(5), Arrhythmic(1), Imaging(1)	HR	●
Mast, 2015 ¹²³	PC	Definite TFC10	P/S	38/20	5.9±2.3	sVT, VF, ATP/Shock, SCD	Clinical(3), ECG(2), Arrhythmic(1), Imaging(11)	HR	●
Mazzanti, 2016 ¹²⁴	RC/PC	Definite TFC10	P/S	267/47	5.8[1.3-10.6]	sVT, VF, ATP/Shock, SCD	Clinical(6), Arrhythmic(4), Exercise(1), ECG(1)	HR	●
Migliore, 2013 ¹²⁵	PC	Definite TFC10	P/S	69/19	3.4[2.3-4.7]	sVT, VF, ATP/Shock, SCD	Clinical(4), Arrhythmic(2), Imaging(4), EPS(4)	HR	●
Peters, 2007 ¹²⁶	PC	Definite TFC94	P/S	313/26	8.5±3.9	SCD	Clinical(2), Imaging(1), ECG(5)	OR, PV	▲
Peters, 2012 ¹²⁷	RC	Definite TFC94	P/S	305/101	6.3±3.1	sVT, VF, ATP/Shock	Clinical(3), ECG(2), Arrhythmic(1), Imaging(2)	OR	▲
Pezawas, 2006 ¹²⁸	PC	Definite TFC94	S	34/12	6.5±2.4	sVT	ECG(1), Arrhythmic(1), Imaging(2), EPS(2)	HR, KM, PV	◆
Piccini, 2005 ¹²⁹	RC/PC	Definite/borderline TFC94, ICD	P/S	67/44	4.4±2.9	ATP/Shock	Clinical(5), Arrhythmic(1), ECG(3), Imaging(2), EPS(3)	OR, KM	▲
Protonotarios, 2016 ¹³⁰	PC	Mutation carriers	P/S	105/43	n.a.	sVT, SCD	Clinical(3), ECG(2), Imaging(2), Genotype(4)	HR, OR	●
Protonotarios, 2015 ¹³¹	PC	Definite TFC10	n.a.	86/53	9.0±7.0	sVT, SCD	ECG(1)	OR	◆
Rigato, 2013 ¹³²	RC/PC	Mutation carriers	P	134/22	n.a.	sVT, VF, ATP/Shock, SCD	Clinical(1), Genotype(5)	HR, KM	▲
Roguin, 2004 ¹³³	RC/PC	Definite TFC94, ICD	P/S	42/33	3.5±2.2	ATP/Shock	Clinical(6), Arrhythmic(3), ECG(4), Imaging(12), EPS(1)	OR, KM	●
Ruwaldo, 2015 ¹³⁴	RC	Definite/borderline TFC10	P	108/83	3.0±1.7	sVT, VF, SCD	Exercise(1), Histology(3)	HR	▲
Saguner, 2013 ¹³⁵	RC	Definite/borderline TFC10	P/S	62/30	9.8[4.4-12.7]	sVT, VF, SCD	Clinical(9), Arrhythmic(3), Imaging(2), EPS(22)	HR, OR, Means	●
Saguner, 2014 ¹³⁶	RC	Definite/borderline TFC10	P/S	106/51	4.6[1.9-10.0]	sVT, VF, SCD	ECG(14)	HR	●
Saguner, 2014 ¹³⁷	RC	Definite/borderline TFC10	P/S	70/37	5.3[1.8-9.8]	sVT, VF, SCD	Clinical(3), Imaging(19)	HR	●
Santangeli, 2012 ¹³⁸	RC	Definite TFC10, ICD	P	32/12	2.1±0.6	ATP/Shock	Clinical(4), Arrhythmic(2), Imaging(4), EPS(5)	HR	●
Sarvari, 2011 ¹³⁹	CC	Mutation carriers	n.a.	69/42	n.a.	sVT, VF	ECG(6), Imaging(9)	OR, Means	▲
Schuler, 2012 ¹⁴⁰	RC	Definite TFC94, ICD	P/S	26/12	10.0[2.7-37.0]	ATP/Shock	Clinical(7), Arrhythmic(5), ECG(2), Imaging(9)	OR	▲
Te Riele, 2011 ¹⁴¹	PC	Mutation carriers	P	69/11	5.8±4.4	sVT, ATP/Shock, SCD	Clinical(7), Arrhythmic(3), ECG(5), Imaging(16)	OR, KM, Means	▲
Te Riele, 2016 ¹⁴²	RC/PC	Definite TFC10, relatives	P/S	96/21	6.7±3.8	sVT, VF	Clinical(8), Arrhythmic(1), Genetics(1), ECG(8), Imaging(3)	OR, Means	▲
Turrini, 1999 ¹⁴³	CS	Definite TFC94	P/S	38/15	n.a.	sVT, VF	ECG(2), Imaging(1)	OR	▲
Wichter, 2004 ¹⁴⁴	PC	Definite TFC94, ICD	P/S	60/41	6.7±3.6	ATP/Shock	Imaging(3), EPS(1)	OR	▲
Zorzi, 2016 ¹⁴⁵	PC	Mutation carriers	P	116/10	8.5[5.0-12.0]	sVT, VF, ATP/Shock, SCD	Clinical(5), Arrhythmic(3), ECG(5), Imaging(3)	OR, KM, Means	▲

● = low, ▲ = moderate, ◆ = high

Figure 2. Study Characteristics of 45 Included Studies†.

For full references see supplementary material. Follow-up is in average±SD or median[IQR]. Abbreviations: ATP=anti-tachycardia pacing; CC=case-control study; CS=cross-sectional study; P=primary prevention; PC=prospective cohort; PV=predictive value; RC=retrospective cohort; RFA=radiofrequency ablation; S=secondary prevention; others: see text.

† There was potential overlap in 41 studies, in case of overlap, only results from the largest population were incorporated.

Study Characteristics

The 45 included studies were published between 1999 and 2017 and had a median cohort size of 70 patients (IQR 60; range 24-541), among whom a median of 31 patients (IQR 30; range 5-301) experienced arrhythmic events during a median follow-up of 5.0 years (IQR 3.5; range 3.2-7.6). The study population included definite ARVC patients in 28 studies, definite or borderline ARVC patients in 9 studies (median 76% fulfilling definite diagnosis [IQR 12; range 68-87%]), and ARVC-associated mutation carriers independent of phenotypic expression in the remaining 8 studies (median 60% fulfilling definite diagnosis [IQR 4; range 34-71%]). ARVC diagnosis was based on the original 1994 TFC in 15 (33.3%) studies and the modified 2010 TFC in 30 (66.7%) studies. While most studies did not differentiate between primary or secondary prevention, ten studies excluded patients who experienced a sustained arrhythmic

event prior to inclusion, and three studies included only secondary prevention patients. **Figure 2** summarizes the study characteristics.

Quality Assessment

Using the QUIPS tool⁸, the risk of bias was evaluated for six pre-defined areas important in observational prognostic research; (1) study participation, (2) study attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) study confounding, and (6) statistical analysis and reporting. As shown in **Figure 3**, the highest potential for bias was introduced by limited or absent adjustment for confounders using multivariable analysis (“study confounding”) and the use of statistical models not correcting for individual and group differences in follow-up time (“statistical analysis and reporting”). Additionally, bias due to selective loss to follow-up (“study attrition”) could not be ruled out for most studies as loss to follow-up was rarely addressed. Only studies that reported HRs were used in the meta-analysis, this subgroup of studies had a lower risk of bias given their use of the recommended statistical methods.

	Study participation	Study attrition	Risk factor measurement	Outcome measurement	Study confounding	Analysis and reporting	Risk of bias
Battipaglia, 2012 ⁵¹ †	▲	●	▲	●	▲	▲	▲
Berrueto, 2016 ⁵² †	▲	●	●	▲	●	●	●
Bhonsale, 2011 ⁵³ †	●	▲	●	●	●	●	●
Bhonsale, 2013 ⁵⁴	●	▲	●	●	▲	▲	▲
Bhonsale, 2015 ⁵⁵	●	▲	●	●	◆	▲	▲
Canpolat, 2013 ⁵⁶ †	▲	▲	▲	▲	●	▲	▲◆
Chan, 2015 ⁵⁷	▲	▲	●	●	◆	▲	▲◆
Choudhary, 2016 ⁵⁸ †	●	●	▲	●	◆	▲	▲
Chung, 2016 ⁵⁹ †	●	●	●	●	●	●	●
Corrado, 2003 ⁵¹⁰	●	▲	●	●	▲	◆	▲
Corrado, 2010 ⁵¹¹ †	●	▲	●	●	●	●	●
Dalal, 2006 ⁵¹²	●	▲	●	●	◆	▲	▲
Folino, 2002 ⁵¹³	▲	▲	●	▲	◆	◆	◆
Groeneweg, 2015 ⁵¹⁴	●	▲	●	●	◆	▲	▲
Hong, 2012 ⁵¹⁵	▲	●	▲	▲	◆	◆	▲◆
James, 2013 ⁵¹⁶	●	●	▲	●	▲	▲	▲
Kikuchi, 2016 ⁵¹⁷ †	●	▲	▲	●	▲	▲	▲
Liao, 2014 ⁵¹⁸	●	▲	●	●	▲	▲	▲
Lin, 2017 ⁵¹⁹ †	▲	▲	●	▲	●	●	▲
Link, 2014 ⁵²⁰	●	▲	●	●	●	▲	●
Marcus, 2009 ⁵²¹	●	▲	●	●	◆	◆	▲◆
Martin, 2016 ⁵²² †	▲	●	●	●	●	●	●
Mast, 2015 ⁵²³ †	●	●	▲	●	●	●	●
Mazzanti, 2016 ⁵²⁴ †	●	●	●	●	●	●	●
Migliore, 2013 ⁵²⁵ †	●	▲	●	●	●	●	●
Peters, 2007 ⁵²⁶	●	▲	●	●	▲	▲	▲
Peters, 2012 ⁵²⁷	●	▲	▲	●	▲	▲	▲
Pezawas, 2006 ⁵²⁸ †	●	●	▲	▲	▲	◆	▲◆
Piccini, 2005 ⁵²⁹	●	▲	●	●	▲	▲	▲
Protonotarios, 2016 ⁵³⁰	●	▲	●	●	●	▲	●
Protonotarios, 2015 ⁵³¹	●	▲	●	●	◆	◆	▲◆
Rigato, 2013 ⁵³²	●	●	▲	●	▲	▲	▲
Roguin, 2004 ⁵³³	▲	●	●	●	●	▲	●
Ruwald, 2015 ⁵³⁴	●	●	▲	●	◆	▲	▲
Saguner, 2013 ⁵³⁵ †	▲	●	●	▲	▲	●	●
Saguner, 2014 ⁵³⁶ †	●	●	●	▲	●	●	●
Saguner, 2014 ⁵³⁷ †	●	●	●	●	●	●	●
Santangeli, 2012 ⁵³⁸ †	▲	▲	●	●	●	●	●
Sarvari, 2011 ⁵³⁹	●	●	●	▲	◆	▲	▲
Schuler, 2012 ⁵⁴⁰	●	▲	●	●	◆	▲	▲
Te Riele, 2013 ⁵⁴¹	●	▲	●	●	◆	▲	▲
Te Riele, 2016 ⁵⁴²	●	▲	●	●	◆	▲	▲
Turrini, 1999 ⁵⁴³	●	●	●	▲	▲	◆	▲
Wichter, 2004 ⁵⁴⁴	●	▲	●	●	▲	▲	▲
Zorzi, 2016 ⁵⁴⁵	●	▲	●	●	◆	▲	▲
Overall	●	▲	●	●	▲●	▲●	▲
Meta-analysis studies	●	●	●	●	●	●	●

† = selected for meta-analysis

Risk of bias: ● = low, ▲ = moderate, ◆ = high

Figure 3. Quality Assessment of 45 Included Studies using the QUIPS tool

Arrhythmic Outcome

The proportion of patients in which the primary arrhythmic outcome was observed during follow-up ranged widely among studies; from 1.0%/year in a cohort of predominantly asymptomatic ARVC-associated mutation carriers, to 30.1%/year in a cohort of severely affected definite ARVC patients. The average proportion of arrhythmic events in studies with definite ARVC patients was 10.6%/year (range 3.0-30.1%), in studies with borderline ARVC patients 10.0%/year (range 6.3-13.1%), and in studies with pathogenic mutation carriers 3.7%/year (range 1.0-6.4%).

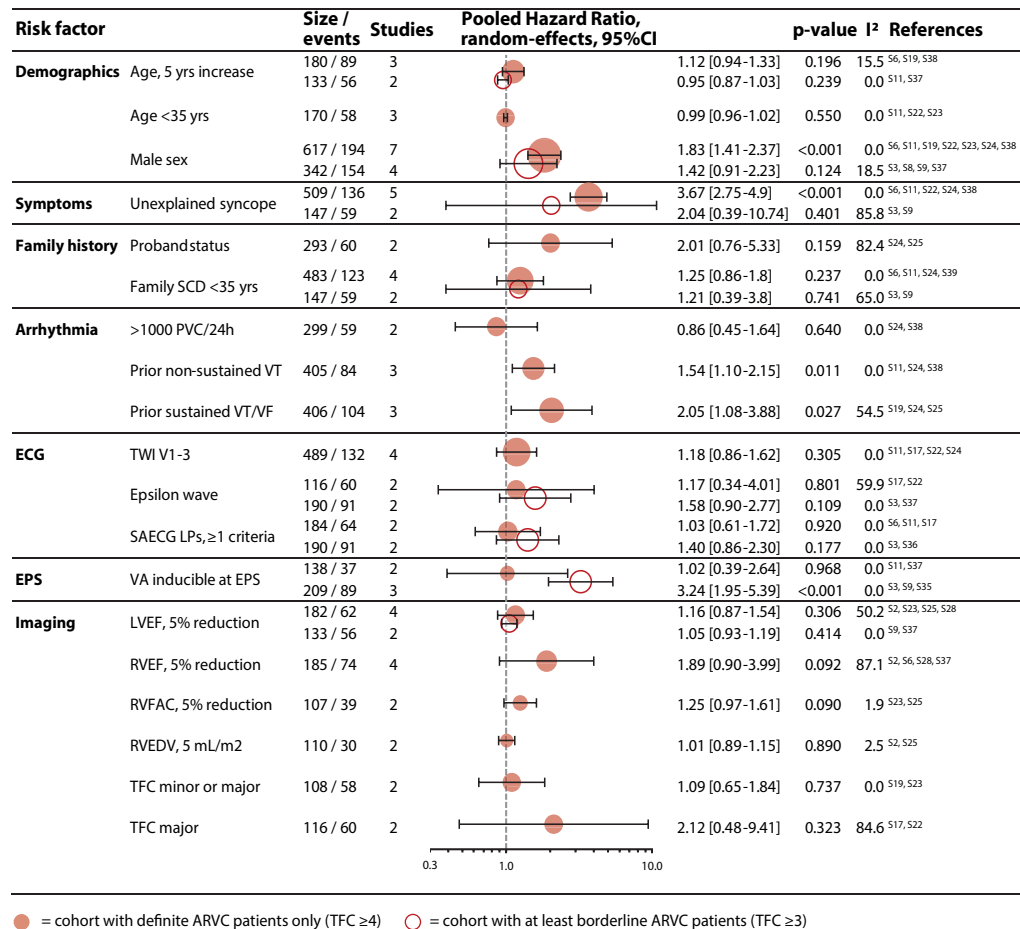


Figure 4. Summary of Meta-Analysis Results.

Pooled HR with 95%CI are plotted. Filled circles correspond to studies with definite ARVC patients, empty circles to studies with (at least) borderline ARVC subjects. Circles size is scaled to the number of events. I²=Chi-square test of heterogeneity (%). Abbreviations: see text.

Risk Factors for Ventricular Arrhythmia

The main risk factor associations are reported by category below; all extracted results are presented in **Supplementary Tables 2A-I**. The pooled HRs from all meta-analyses are summarized in **Figure 4**; the corresponding forest plots can be found in **Supplementary Figure 1**.

Demographics

Age · was investigated as a predictor of arrhythmic events by 23 studies. The vast majority (n=21/23) of these studies reported non-significant results. Only two studies, both with definite ARVC patients, reported a higher arrhythmic risk in younger patients: below 40 years (HR 2.90, 95%CI 1.51-5.58), or per year increase in age (OR 0.95, 95%CI 0.89-0.99)(**Supplementary Table 2A**). Meta-analysis of five studies using age as a continuous variable and three studies that used a cut-off value of 35 years did not yield significant results among definite and borderline ARVC subjects (**Figure 4**).

Male sex · was directed towards an increased risk of ventricular arrhythmias in 22 of 28 studies, although statistical significance was only reached in 6/16 studies with definite and 1/6 studies with borderline ARVC patients. In contrast, significant results were obtained in all six studies with mutation carriers (**Supplementary Table 2A**). Meta-analysis of seven studies with definite ARVC patients confirmed a higher risk in males, pooled HR 1.83 (95%CI 1.41-2.37). The pooled result from four studies with borderline patients was similar in direction, but did not reach statistical significance, pooled HR 1.42 (95%CI 0.91-2.23)(**Figure 4**).

Other · demographic and comorbidity risk factors were reported with no statistically significant results (**Supplementary Table 2A**).

Symptoms

Symptoms · including palpitations, chest pain, pre-syncope, and syncope were studied as predictors of arrhythmic events in 23 studies. Symptomatic participants (i.e. having any one of the abovementioned symptoms) were compared to asymptomatic participants in three studies (one with definite ARVC patients and two with mutation carriers), all reporting a significantly higher risk in the symptomatic group (**Supplementary Table 2B**).

Unexplained syncope · was investigated as risk factor for arrhythmic events in 19 studies. While most (n=15/19) studies were uniform in direction towards increased arrhythmic risk, statistical significance was only reached in 6/11 studies with definite ARVC patients, 1/5 studies with borderline ARVC patients, and 1/3 studies with mutation carriers (**Supplementary Table 2B**). Meta-analysis was feasible for five studies with definite ARVC patients and two

studies with borderline ARVC patients: pooled HR 3.67 (95%CI 2.75-4.90) and pooled HR 2.04 (95%CI 0.39-10.74), respectively (**Figure 4**).

Other · symptoms were also analyzed, for which results can be found in **Supplementary Table 2B**.

Physical Exercise

Physical exercise · has frequently been associated with ARVC, although it was analyzed as a risk factor for arrhythmic events by only three studies that used non-uniform definitions (**Supplementary Table 2C**). Regardless, exercise was significantly associated with arrhythmic risk in all three studies. One study with definite ARVC patients reported a HR of 2.90 (95%CI 1.14-7.38) comparing patients participating in strenuous exercise to inactive patients. Similar results were found in borderline ARVC patients, comparing competitive to recreational athletes (HR 1.99 [95%CI 1.21-3.28]). Likewise, a dose-related effect was found in mutation carriers who were endurance athletes, in whom reducing the level of exercise after presentation was protective of ventricular arrhythmias (OR 0.05 [95%CI 0.003-0.67]). Meta-analysis was not performed given the heterogeneity in patient domain and utilized statistics.

Family History and Genotype

Proband status · was analyzed as a risk factor by three studies, comparing the arrhythmic risk of the proband (i.e. first patient diagnosed with ARVC in a family) to family members. Although proband status was found to be associated with arrhythmic events in two of three studies in univariable analysis, this effect was lost after correcting for confounders (**Supplementary Table 2D**). Meta-analysis of three studies with definite ARVC patients yielded a non-significant result (pooled HR 2.01 [95%CI 0.39-10.74]) with large heterogeneity (I^2 82.4%, p 0.017) (**Figure 4**).

Family history · positive for premature SCD (defined as <35 years as per diagnostic TFC) was investigated as a risk factor by ten studies, most ($n=9/10$) of which reported non-significant results (**Supplementary Table 2D**). This non-significant predictive effect was confirmed in meta-analysis in definite ARVC patients (four studies, pooled HR 1.25 [95%CI 0.86-1.8]), and borderline ARVC patients (two studies, pooled HR 1.21 [95%CI 0.39-3.80]; **Figure 4**).

Pathogenic mutation · carriers were compared to patients without mutations by four studies. While two studies found that arrhythmias occurred at a younger age in mutation carriers, three studies compared the risk of arrhythmias from the age of presentation and

reported no significant difference (**Supplementary Table 2D**). Meta-analysis was not performed given the heterogeneity in patient domain and utilized statistics.

Multiple mutations · including compound heterogeneity and mutations in ≥ 1 ARVC-associated gene was investigated as a risk factor by two studies of which one reported an increased arrhythmic risk (HR 3.01 [95%CI 1.42-6.37]), and the other found a significantly younger age at time of the arrhythmic event (**Supplementary Table 2D**).

Other · reported risk factors defined by family history and genotype, including combinations of the two, can be found in **Supplementary Table 2D**.

Electrocardiography

T-wave inversion (TWI) · on a standard 12-lead ECG was investigated as a risk factor by 21 studies. Fulfilling a minor repolarization criterion (i.e. TWI in leads V1-2; V4, V5, V6; or V1-4 in presence of complete right bundle branch block) was not associated with arrhythmic events in most ($n=3/4$) studies regardless of patient domain. Fulfilling a major repolarization criterion (i.e. TWI in V1-3) had no predictive value in definite ARVC patients (five studies), while the results in borderline patients were conflicting (i.e. both significantly predictive and protective effects were reported; two studies), and analyses in mutation carriers reported a significant association with arrhythmic events (two studies). The remaining eight studies showed that a greater extent of TWI (i.e. $>V3$ or in inferior leads) is a significant risk factor in all patient domains (**Supplementary Table 2E**). Meta-analysis was only feasible for four studies reporting TWI V1-3 in definite ARVC patients; pooled HR 1.18 (95%CI 0.86-1.62)(**Figure 4**).

Epsilon waves · are defined as reproducible low-amplitude signals between the end of the QRS and the T-wave, separated from the QRS complex. Epsilon waves were investigated as a risk factor by ten studies, of which 4/10 reported a significantly predictive effect. Meta-analysis was feasible for two studies with definite ARVC patients (pooled HR 1.17 [95%CI 0.34-4.01]) and two studies with borderline ARVC patients (pooled HR 1.58 [95%CI 0.90-2.77]), both directed towards increased arrhythmic risk, although statistical significance was not reached (**Figure 4**).

Prolonged terminal activation duration (TAD) · is measured from the S-nadir to the end of all depolarization deflections, and defined as prolonged if ≥ 55 milliseconds in any of the leads V1-3. Prolonged TAD was investigated as a risk factor by four studies with non-consistent results: an association with ventricular arrhythmias was noted in 1/1 study with definite ARVC patients, 0/1 study with borderline ARVC patients, and 1/2 studies with mutation

carriers (**Supplementary Table 2E**). Meta-analysis was not feasible due to heterogeneity in patient domain and utilized statistics.

Late potentials · are defined as the presence of filtered QRS duration ≥ 114 ms, low-amplitude signal duration ≥ 38 ms, or root-mean square of terminal QRS ≤ 20 uV measured by signal-averaged ECG (SAECG). Late potentials were investigated as a risk factor by nine studies, which predominantly reported non-significant results (**Supplementary Table 2E**). Meta-analyses confirmed no predictive value of ≥ 1 late potential criterion in definite ARVC patients (six studies, pooled HR 1.03 [95%CI 0.61-1.72]), and borderline ARVC patients (three studies, pooled HR 1.4 [95%CI 0.86-2.3]; **Figure 4**).

QRS-fragmentation · is defined as additional deflections/notching at the beginning of QRS, on top of the R-wave, or in the nadir of the S-wave in either ≥ 1 right precordial lead or in >1 other leads. QRS-fragmentation was reported as a risk factor in three studies, which all reported significant results: HR 8.54 (95%CI 3.65-15.42) and OR 11.64 (95%CI 5.1-16.41) in definite ARVC patients, and HR 1.76 (95%CI 1.01-3.06) in borderline ARVC patients. Meta-analysis was not feasible due to heterogeneity in patient domain and utilized statistics.

Other · potential ECG-derived predictor variables were investigated for which the results can be found in **Supplementary Table 2E**.

Arrhythmias

Premature Ventricular Complexes (PVCs) · on continuous ECG monitoring were analyzed as a risk factor by 11 studies. Variability in definitions (e.g. total 24-hour PVC count vs. various cut-offs) limits comparability of results. Three studies, two with definite ARVC patients and one with mutation carriers, found an increased arrhythmic risk in patients with >500 PVCs/24hrs, whereas results in borderline ARVC patients were non-significant (**Supplementary Table 2F**). Meta-analysis was solely feasible for two studies analyzing >1000 PVCs/24hrs in definite ARVC patients: pooled HR 0.86 (95%CI 0.45-1.64)(**Figure 4**).

Non-sustained VT · is defined as ≥ 3 ventricular complexes at ≥ 100 beats/minute, and was analyzed as a predictor of sustained ventricular events in 11 studies. A significant association was reported in 1/5 studies with definite ARVC patients, 1/3 studies with borderline ARVC patients, and 2/3 studies in mutation carriers (**Supplementary Table 2F**). Meta-analysis was feasible for three studies with definite ARVC patients, yielding a significantly increased risk for patients who experienced non-sustained VT (pooled HR 1.43 [95%CI 1.10-2.15]; **Figure 4**).

Sustained VT/VF · is defined as a documented ventricular arrhythmia at ≥ 100 beats/minute, lasting ≥ 30 seconds or with hemodynamic compromise requiring termination. Prior sustained VT/VF was analyzed as a risk factor for recurring sustained ventricular arrhythmias by 17 studies. The majority of studies reported an increased risk of recurring events in definite ($n=8/13$ studies) and borderline ($n=3/4$ studies) patients (**Supplementary Table 2F**). Meta-analysis was feasible for three studies with definite ARVC patients, resulting in a significantly higher risk for patients with a prior sustained VT/VF (pooled HR 2.05 [95%CI 1.08-3.88]; **Figure 4**).

Other · reported risk factors are available in **Supplementary Table 2F**.

Electrophysiology Study

Inducibility of sustained ventricular arrhythmias · during EPS was evaluated as a predictor for spontaneous sustained ventricular arrhythmias by 15 studies. Despite the heterogeneity of stimulation protocols between studies, all ($n=5/5$) studies with borderline ARVC patients reported a significant association between inducibility and future arrhythmic events, whereas 9/10 studies with definite ARVC patients reported non-significant results (**Supplementary Table 2G**). The same trend was observed in meta-analysis of three studies with borderline ARVC patients (pooled HR 3.24 [95%CI 1.95-5.39]) and two studies with definite ARVC patients (pooled HR 1.02 [95%CI 0.39-2.64]; **Figure 4**).

Other · variables derived from EPS include low-voltage zones, epicardial voltage mapping, sub-specification of inducible ventricular arrhythmias, and fragmented electrograms, for which results are presented in **Supplementary Table 2G**.

Structural/Functional imaging

Reduced RV ejection fraction (RVEF) · was analyzed as a risk factor by 11 studies. While most ($n=8/11$) studies were directed towards increased arrhythmic risk with decreasing RVEF, statistical significance was only reached in 2/8 studies with definite ARVC patients, 0/2 studies with borderline ARVC patients, and 1/1 studies with mutation carriers (**Supplementary Table 2H**). Meta-analysis was feasible for four studies with definite ARVC patients resulting in a borderline significant increased risk per 5% RVEF reduction, pooled HR of 1.89 (95%CI 0.90-3.99)(**Figure 4**).

Reduced RV fractional area change (RVFAC) · was analyzed as a risk factor by five studies, most ($n=3/5$) of which reported a significantly increased arrhythmic risk with decreasing RVFAC: a significant association was observed in 1/3 studies with definite ARVC patients and 2/2 studies with borderline ARVC patients (**Supplementary Table 2H**). Meta-analysis was feasible for two studies with definite ARVC patients, resulting in a borderline significant increased risk per 5% RVFAC reduction, pooled HR 1.25 (95%CI 0.89-1.15)(**Figure 4**).

RV wall motion abnormalities · by qualitative assessment was analyzed as a risk factor by four studies. All studies in definite (n=2) and borderline (n=1) ARVC patients reported non-significant results (**Supplementary Table 2H**), whereas one study with mutation carriers found a significant association with arrhythmic risk (OR 70.59 [3.91-1273.69]). Of note, quantitative wall motion assessment using echocardiography-derived strain was associated with arrhythmic events in patients with definite or borderline ARVC (OR 1.25 [95%CI 1.08-1.44] per % strain reduction; **Supplementary Table 2H**). Meta-analysis for either qualitative or quantitative RV wall motion assessment was not feasible due to heterogeneity in patient domain, variable definitions, and utilized statistics.

Fulfillment of RV imaging criteria · as defined by the 2010 TFC was evaluated as a risk factor by ten studies. While studies in definite (n=5) and borderline (n=2) ARVC patients found no difference in arrhythmic risk, three studies with mutation carriers reported a higher arrhythmic risk for those fulfilling major imaging criteria (**Supplementary Table 2H**). Meta-analysis was feasible for four studies with definite ARVC patients, yielding non-significant results for fulfillment of any RV imaging criterion: pooled HR 1.09 (95%CI 0.65-1.84)(**Figure 4**).

Reduced LV ejection fraction (LVEF) · was analyzed as a risk factor by 17 studies. The majority of studies in definite ARVC patients (n=9/10) and borderline ARVC patients (n=4/5) reported no effect on arrhythmic risk, whereas all two studies in mutation carriers reported a significant association between reduced LVEF and arrhythmic events (**Supplementary Table 2H**). Meta-analysis in four studies with definite ARVC patients and two studies with borderline ARVC patients yielded non-significant results: pooled HR 1.16 (95%CI 0.87-1.54) and pooled HR 1.05 (95%CI 0.93-1.19), respectively, per 5% LVEF reduction (**Figure 4**).

Other · imaging parameters are reported in **Supplementary Table 2H**.

Sensitivity Analyses

Of the 18 studies included in our meta-analysis, two used the original 1994 TFC as opposed to the modified 2010 TFC, which remain the current gold standard for ARVC diagnosis. Furthermore, four studies reported on primary prevention patients only, while others included patients with prior sustained events. To analyze the effect of these selection differences, all analyses were repeated by excluding studies that (1) used the 1994 TFC, and (2) included secondary prevention patients. As shown in **Supplementary Table 3**, pooled estimates remained similar for all risk factors, except for prior non-sustained VT (in both analyses), and male sex (in primary prevention studies) which lost their statistical significance.

Discussion

This manuscript aimed to systematically review predictors for ventricular arrhythmias in ARVC, highlight the quality of evidence as well as its shortcomings, and determine promising risk factors per patient subgroup (i.e. definite ARVC patients, borderline ARVC patients, and mutation carriers). We have summarized our key findings and clinical recommendations in **Figure 5**.

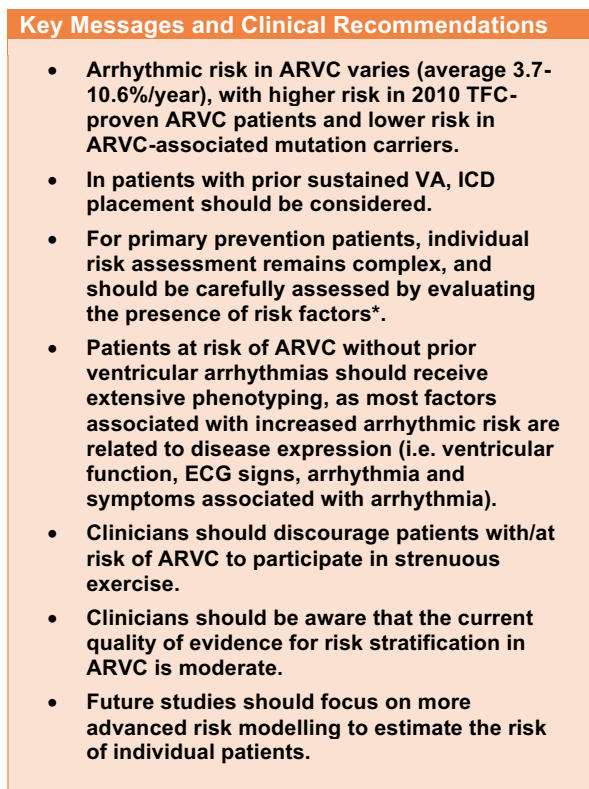


Figure 5. Key Messages and Clinical Recommendations.

Abbreviations: see text.

*Risk factors per patient population as shown in Figure 6.

Quality of Evidence

Although a relatively large number of studies investigated potential risk factors for ventricular arrhythmias in ARVC, the majority (n=43/45) of studies were conducted in observational cohorts (n=14 prospective, n=17 retrospective, n=12 pro- and retrospective), which are inherently (but not necessarily) limited in quality of evidence. Important sources of bias were differences in follow-up time, selective loss to follow-up, and selection towards patients presenting alive (left truncation bias). Correcting for these factors is essential for accuracy and generalizability of results, and fortunately many authors performed at least some level of adjustment. However, as ARVC studies are typically small, the potential for adequate adjustment is often limited by insufficient statistical power. This resulted in a variable risk of bias which is partly reflected by the inconsistency of reported results.

To compensate for the relatively small study populations, we attempted to pool results into a quantitative meta-analysis to obtain more evidence for the most commonly reported risk factors. Of note, pooling of results is only appropriate in the setting of uniform definitions. Since individual studies used variable predictor definitions and risk estimates, the number of studies satisfying this prerequisite was unfortunately limited.

Given both the limitations in individual study quality (as highlighted by the variable risk of bias) and our inability to pool all available results, we deem the overall quality of available evidence to be moderate. While this opens the path for future studies to specifically address these shortcomings, this should be taken into account when interpreting the main findings of this manuscript.

Main Findings

Overall Risk of Ventricular Arrhythmias in ARVC

We found that the proportion of patients experiencing sustained ventricular arrhythmias in ARVC was relatively high (up to 30.1%/year). It is important to note that the highest of these proportions were observed in cohorts with a high a priori risk (e.g. severely affected definite ARVC patients). Indeed, the proportion of arrhythmic events was strongly associated with overt disease expression and ranged from 10.6%/year in definite patients, to 10.0%/year in borderline patients, to 3.7%/year in mutation carriers.

Risk Factors for Ventricular Arrhythmias are Domain-Dependent

The patient domain (i.e. study population) is a fundamental principle of clinical research and dictates to whom the reported results apply. Given the variability in patient domain across studies, we classified the included studies in three pre-specified domains: studies with definite

ARVC patients only, studies with at least borderline ARVC patients (among whom a proportion had definite ARVC), and studies with ARVC-associated mutation carriers (among whom a [smaller] proportion had definite ARVC). Our separate analyses in these domains highlighted a pattern in the predictive value of risk factors based on the population. This is easily understandable in the context of their acquisition: most risk factors are related to disease expression, and therefore they typically overlap with diagnostic criteria. This is also in line with a recent publication suggesting that phenotypic expression is a prerequisite for arrhythmic events in desmosomal mutation carriers.⁹ As such, these risk factors correlate well with arrhythmic events when studied in a cohort of mutation carriers, but their potential to risk stratify patients with an established ARVC diagnosis is limited since the risk factor is present in most subjects. For example, T-wave inversions in V1-3 remained non-significant in definite patients, while conflicting results were obtained in borderline patients, and a strong association was reported among mutation carriers. We believe that the variability in patient domains explains at least some of the conflicting results that were pointed out by previous reviews and guidelines.^{4,10}

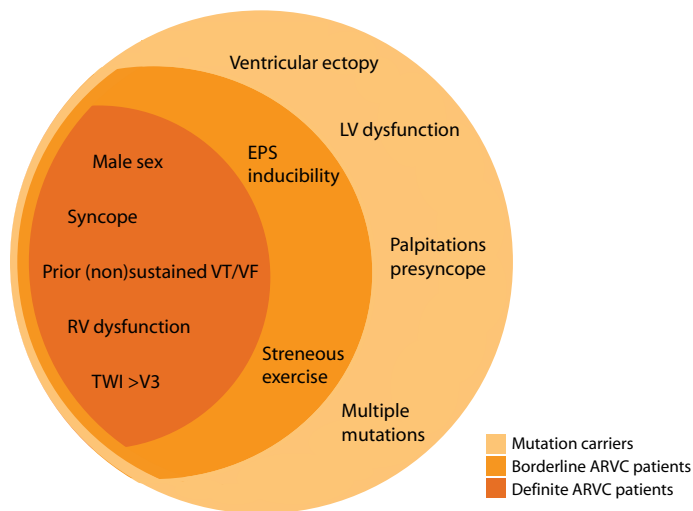


Figure 6. Predictors for Sustained VA Are Population-Dependent

Predictors are plotted by patient domain. The dark region (small circle) applies to definite ARVC patients; dark region plus lighter region (intermediate circle) applies to at least borderline ARVC patients; the full ellipse applies to mutation carriers. Abbreviations: see text.

Main Risk Factors for Ventricular Arrhythmias in ARVC

Figure 6 provides an overview of risk factors and their predictive potential specified by patient domain. In *definite ARVC patients*, consistently predictive risk factors included unexplained syncope, TWI extent, RV dysfunction, and previously registered (non-)sustained VT/VF. In addition, males were found to be at higher risk of ventricular arrhythmia than females. This is in line with a recently published study that reported an association between elevated testosterone levels and arrhythmic events in ARVC.¹¹

In *borderline ARVC patients*, additional risk factors were found to be significant. In addition to the risk factors observed in definite ARVC patients, substantial evidence indicated a predictive effect of strenuous exercise and inducibility at EPS.

In *ARVC-associated mutation carriers* (including asymptomatic patients), the list of predictors expanded even further, and also included the presence of symptoms (palpitations, pre-syncope and/or syncope), harboring multiple mutations, LV dysfunction, and ventricular ectopy.

Limitations and Future Directives

Given the nature of our study as a systematic review, our analyses are limited by the reported data in the original reports. Since almost all studies used a composite arrhythmic endpoint of sustained ventricular arrhythmias and/or ICD interventions, their outcomes may have included non-life-threatening arrhythmias. Future studies should specifically confirm whether the predictors highlighted in this review also remain significant for truly life-threatening (cycle length <240 milliseconds or VF) arrhythmias. The reported HRs from all 45 studies were cause-specific. As such, the results cannot directly be translated to event rates. Nonetheless, our study results remain meaningful for characterizing risk factors associated with arrhythmic events. Despite our efforts to analyze the three pre-defined domains separately, some level of heterogeneity in study population remains as some studies employed specific inclusion criteria, e.g. ICD carriers or secondary prevention populations. We accounted for this by fully disclosing the study populations, refraining from using these studies in our pooled analyses, and performing sensitivity analyses. Although meta-analysis potentially increases the power of pooled crude associations, it does not eliminate potential confounding, which is reflected by the severe heterogeneity of some pooled estimates in our study. Some of the included references only report adjusted values when significant in univariable analysis, which results in publication bias that cannot be corrected in our analyses. In addition, the design of this study as a systematic review limited our ability to analyze arrhythmic risk based on number of risk factors. Quantification of cumulative arrhythmic risk based on number of risk factors may

help guide risk/benefit considerations of ICD placement in the individual patient. These limitations can only be overcome by developing a comprehensive arrhythmia prediction model that incorporates multiple risk factors. Development of such a prediction model will require a multicenter collaborative effort to obtain survival data on a large group of ARVC patients, so that absolute risk estimations can be made based on individual patient characteristics.

Conclusion

This study aimed to systematically review current evidence on arrhythmic risk stratification in ARVC. The average annual risk of ventricular arrhythmia ranged from 3.7% to 10.6%/year depending on the ARVC population. Since many predictors for ventricular arrhythmias overlap with diagnostic criteria, the potential to risk stratify patients with an established ARVC diagnosis is limited. Regardless, consistently predictive risk factors for ventricular arrhythmias are male sex, unexplained syncope, TWI beyond V3, RV dysfunction and previously registered (non-)sustained VT/VF. Since most evidence originates from observational cohort studies in small patient cohorts, one has to be critical of the quality of evidence. Future studies in collaborative international registries should investigate the incremental value of multiple risk factors so that accurate risk predictions can be made for the individual patient.

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Supplementary Material

Supplementary Methods. Search strategy

We performed a systematic search of MEDLINE and Embase in January 2017 for clinical studies on risk factors for ventricular arrhythmias in patients with ARVC. Our search string consisted of three components which were simultaneously entered; (1) ARVC and synonyms; (2) ventricular arrhythmia or appropriate ICD therapy or sudden cardiac death, including synonyms; and (3) a previously validated string-based filter for prognostic research*, which was extended for the purpose of this review to minimize loss of eligible studies. We also searched through the reference lists of included articles and previously published reviews for additional relevant articles. Mendeley software (version 1.17.10, Elsevier, London, UK) was used to manage and de-duplicate all identified studies. The complete search string is presented in below.

* Haynes RB, McKibbin KA, Wilczynski NL, Walter SD, Werre SR, Hedges Team: Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ* 2005; 330:1179.

PubMed

Domain:	"arrhythmogenic cardiomyopathy"[Title/Abstract] OR "arrhythmogenic right ventricular cardiomyopathy"[Title/Abstract] OR "arrhythmogenic right ventricular cardiomyopathy/dysplasia"[Title/Abstract] OR "arrhythmogenic right ventricular dysplasia"[Title/Abstract] OR "arrhythmogenic right ventricular dysplasia/cardiomyopathy"[Title/Abstract] OR "arrhythmogenic right ventricular dysplasia cardiomyopathy"[Title/Abstract] OR "arrhythmogenic right ventricular cardiomyopathy dysplasia"[Title/Abstract] OR "arvc"[Title/Abstract] OR "arvc/d"[Title/Abstract] OR "arvc/arvd"[Title/Abstract] OR "arvd"[Title/Abstract] OR "arvd/arvc"[Title/Abstract] OR "arvd/c"[Title/Abstract] OR "arrhythmogenic right ventricular dysplasia"[MeSH Terms] OR "desmosomal mutation"[Title/Abstract] OR "desmosomal mutations"[Title/Abstract] OR "desmosome mutation"[Title/Abstract] OR "desmosome mutations"[Title/Abstract]
AND	
Outcome:	"arrhythmic outcome"[Title/Abstract] OR "arrhythmic risk"[Title/Abstract] OR "arrhythmic events"[Title/Abstract] OR "ventricular flutter"[MeSH Terms] OR "ventricular flutter"[Title/Abstract] OR "ventricular flutters"[Title/Abstract] OR "ventricular arrhythmia"[Title/Abstract] OR "sudden cardiac arrest"[Title/Abstract] OR "sudden cardiac death"[Title/Abstract] OR "scd"[Title/Abstract] OR "sca"[Title/Abstract] OR "death, sudden, cardiac"[MeSH Terms] OR "malignant arrhythmia"[Title/Abstract] OR "malignant arrhythmias"[Title/Abstract] OR "malignant arrhythmic event"[Title/Abstract] OR "malignant arrhythmic events"[Title/Abstract] OR "tachycardia, ventricular"[MeSH Terms] OR "ventricular tachycardia"[Title/Abstract] OR "ventricular fibrillation"[MeSH Terms] OR "ventricular fibrillation"[Title/Abstract] OR "appropriate icd activation"[Title/Abstract] OR "appropriate icd discharge"[Title/Abstract] OR "appropriate icd discharges"[Title/Abstract] OR "appropriate icd firing"[Title/Abstract] OR "appropriate icd

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AND

Filter: incidence [MeSH Terms] OR mortality[MeSH Terms] OR "follow up studies"[MeSH Terms] OR prognos*[Text Word] OR predict*[Text Word] OR course*[Text Word] OR cohort[Text Word] OR outcome*[Text Word] OR surviv*[Text Word]

Embase

Domain: 'heart right ventricle dysplasia'/exp OR 'arrhythmogenic cardiomyopathy':ab,ti OR 'arrhythmogenic right ventricular cardiomyopathy':ab,ti OR 'arrhythmogenic right ventricular cardiomyopathy/dysplasia':ab,ti OR 'arrhythmogenic right ventricular dysplasia':ab,ti OR 'arrhythmogenic right ventricular dysplasia/cardiomyopathy':ab,ti OR 'arrhythmogenic right ventricular dysplasia cardiomyopathy':ab,ti OR 'arrhythmogenic right ventricular cardiomyopathy dysplasia':ab,ti OR 'arvc':ab,ti OR 'arvc/d':ab,ti OR 'arvc/arvd':ab,ti OR 'arvd':ab,ti OR 'arvd/arvc':ab,ti OR 'arvd/c':ab,ti OR 'desmosomal mutation':ab,ti OR 'desmosomal mutations':ab,ti OR 'desmosome mutation':ab,ti OR 'desmosome mutations':ab,ti

AND

Outcome: 'heart ventricle flutter'/exp OR 'ventricular flutter':ab,ti OR 'ventricular flutters':ab,ti OR 'ventricular arrhythmia':ab,ti OR 'sudden cardiac arrest':ab,ti OR 'sudden cardiac death':ab,ti OR 'scd':ab,ti OR 'sca':ab,ti OR 'sudden cardiac death'/exp OR 'malignant arrhythmia':ab,ti OR 'malignant arrhythmias':ab,ti OR 'malignant arrhythmic event':ab,ti OR 'malignant arrhythmic events':ab,ti OR 'heart ventricle tachycardia'/exp OR 'ventricular tachycardia':ab,ti OR 'heart ventricle fibrillation'/exp OR 'ventricular fibrillation':ab,ti OR 'appropriate icd activation':ab,ti OR 'appropriate icd discharge':ab,ti OR 'appropriate icd discharges':ab,ti OR 'appropriate icd firing':ab,ti OR 'appropriate icd intervention':ab,ti OR 'appropriate icd interventions':ab,ti OR 'appropriate icd shock':ab,ti OR 'appropriate icd shock therapy':ab,ti OR 'appropriate icd shocks':ab,ti OR 'appropriate icd therapies':ab,ti OR 'appropriate icd therapy':ab,ti OR 'appropriate icd treatment':ab,ti OR 'appropriate icd treatments':ab,ti OR 'heart arrest'/exp OR 'heart arrest':ab,ti OR 'cardiac arrest':ab,ti OR 'wide complex tachycardia':ab,ti OR 'wide complex tachycardias':ab,ti OR 'wide complex ventricular':ab,ti OR 'wide complex ventricular tachycardia':ab,ti OR 'broad complex tachycardia':ab,ti OR 'broad complex tachycardias':ab,ti

AND

Filter: 'incidence'/exp OR 'mortality'/exp OR 'follow up'/exp OR prognos* OR predict* OR course* OR cohort OR outcome* OR surviv*

Supplementary Methods. Study Selection and Data Extraction

Eligibility of each study was assessed by two investigators independently (LPB and AS). In case of disagreement, consensus was obtained from a third investigator (ASJMTR). If a site-specific dataset had been published more than once, we compared the reported list of risk factors for overlap, in which case only the results obtained in the largest patient population was included. One investigator (LPB) extracted data using pre-specified forms detailing the following information: study design, study size, definition of patient population, baseline characteristics (age and sex), follow-up duration, outcome definitions, and covariate-specific risk estimates with 95% CI. Data extraction was checked for adequacy by another investigator (AS). Both crude and maximally adjusted risk estimates were collected.

Supplementary Methods. Quality in Prognostic Studies (QUIPS) tool

Domain	Risk of bias
1. Study participation	<p>High: The relationship between the PF and outcome is very likely to be different for participants and eligible nonparticipants</p> <p>Moderate: The relationship between the PF and outcome may be different for participants and eligible nonparticipants</p> <p>Low: The relationship between the PF and outcome is unlikely to be different for participants and eligible nonparticipants</p>
2. Study attrition	<p>High: The relationship between the PF and outcome is very likely to be different for completing and non-completing participants</p> <p>Moderate: The relationship between the PF and outcome may be different for completing and non-completing participants</p> <p>Low: The relationship between the PF and outcome is unlikely to be different for completing and non-completing participants</p>
3. Prognostic factor measurement	<p>High: The measurement of the PF is very likely to be different for different levels of the outcome of interest</p> <p>Moderate: The measurement of the PF may be different for different levels of the outcome of interest</p> <p>Low: The measurement of the PF is unlikely to be different for different levels of the outcome of interest</p>
4. Outcome measurement	<p>High: The measurement of the outcome is very likely to be different related to the baseline level of the PF</p> <p>Moderate: The measurement of the outcome may be different related to the baseline level of the PF</p> <p>Low: The measurement of the outcome is unlikely to be different related to the baseline level of the PF</p>
5. Study confounding	<p>High: The observed effect of the PF on the outcome is very likely to be distorted by another factor related to PF and outcome</p> <p>Moderate: The observed effect of the PF on outcome may be distorted by another factor related to PF and outcome</p> <p>Low: The observed effect of the PF on outcome is unlikely to be distorted by another factor related to PF and outcome</p>

6. Statistical analysis and reporting	a) Sufficient presentation of data to assess the adequacy of the analytic strategy	High: The reported results are very likely to be spurious or biased related to analysis or reporting
	b) Strategy for model building is appropriate and is based on a conceptual framework or model	Moderate: The reported results may be spurious or biased related to analysis or reporting
	c) The selected statistical model is adequate for the design of the study	Low: The reported results are unlikely to be spurious or biased related to analysis or reporting.
	d) There is no selective reporting of results	

Source: Hayden J a, Windt D a Van Der, Cartwright JL, Co P: Research and Reporting Methods Annals of Internal Medicine Assessing Bias in Studies of Prognostic Factors. Ann Intern Med 2013; 144:427–437.

Abbreviation: PF = prognostic factor

Supplementary References. 45 studies included in the review and meta-analysis.

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- S7.** Chan C-S, Lin Y-J, Chang S-L, Lo L-W, Hu Y-F, Chao T-F, Chung F-P, Liao J-N, Chen Y-J, Chen S-A: Early repolarization of surface ECG predicts fatal ventricular arrhythmias in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy and symptomatic ventricular arrhythmias. *Int J Cardiol* 2015; 197:300–305.
- S8.** Choudhary N, Tompkins C, Polonsky B, McNitt S, Calkins H, Mark Estes NA, Krahn AD, Link MS, Marcus FI, Towbin JA, Zareba W: Clinical Presentation and Outcomes by Sex in Arrhythmogenic Right Ventricular Cardiomyopathy: Findings from the North American ARVC Registry. *J Cardiovasc Electrophysiol* 2016; 27:555–562.
- S9.** Chung F-P, Lin Y-J, Chong E, Chang S-L, Lo L-W, Hu Y-F, Tuan T-C, Chao T-F, Liao J-N, Chen S-A: The Application of Ambulatory Electrocardiographically-Based T-Wave Alternans in Patients with Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. *Can J Cardiol* 2016; 32:1355.e15-1355.e22.
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- S11.** Corrado D, Calkins H, Link MS, et al.: Prophylactic Implantable Defibrillator in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia and No Prior Ventricular Fibrillation or Sustained Ventricular Tachycardia. *Circulation* 2010; 122:1144–1152.
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- S15.** Hong T-T, Cogswell R, James CA, et al.: Plasma BIN1 correlates with heart failure and predicts arrhythmia in patients with arrhythmogenic right ventricular cardiomyopathy. *Heart Rhythm* 2012; 9:961–967.
- S16.** James CA, Bhonsale A, Tichnell C, Murray B, Russell SD, Tandri H, Tedford RJ, Judge DP, Calkins H: Exercise Increases Age-Related Penetrance and Arrhythmic Risk in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy–Associated Desmosomal Mutation Carriers. *J Am Coll Cardiol* 2013; 62:1290–1297.
- S17.** Kikuchi N, Yumino D, Shiga T, Suzuki A, Hagiwara N: Long-Term Prognostic Role of the Diagnostic Criteria for Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia. *JACC Clin Electrophysiol* 2016; 2:107–115.
- S18.** Liao Y-C, Lin Y-J, Chung F-P, et al.: Risk stratification of arrhythmogenic right ventricular cardiomyopathy based on signal averaged electrocardiograms. *Int J Cardiol* 2014; 174:628–633.
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- S21.** Marcus GM, Glidden D V., Polonsky B, Zareba W, Smith LM, Cannom DS, Estes NAM, Marcus F, Scheinman MM: Efficacy of Antiarrhythmic Drugs in Arrhythmogenic Right Ventricular Cardiomyopathy. *J Am Coll Cardiol* 2009; 54:609–615.
- S22.** Martin A, Crawford J, Skinner JR, Smith W, Cardiac Inherited Diseases Group: High Arrhythmic Burden but Low Mortality during Long-term Follow-up in Arrhythmogenic Right Ventricular Cardiomyopathy. *Heart Lung Circ* 2016; 25:275–281.

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- S24.** Mazzanti A, Ng K, Faragli A, et al.: Arrhythmogenic Right Ventricular Cardiomyopathy: Clinical Course and Predictors of Arrhythmic Risk. *J Am Coll Cardiol* 2016; 68:2540–2550.
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- S26.** Peters S: Long-term follow-up and risk assessment of arrhythmogenic right ventricular dysplasia/cardiomyopathy: personal experience from different primary and tertiary centres. *J Cardiovasc Med* 2007; 8:521–526.
- S27.** Peters S, Truempel M, Koehler B: Prognostic value of QRS fragmentation in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. *J Cardiovasc Med* 2012; 13:295–298.
- S28.** Pezawas T, Stix G, Kastner J, Schneider B, Wolzt M, Schmidinger H: Ventricular tachycardia in arrhythmogenic right ventricular dysplasia/cardiomyopathy: Clinical presentation, risk stratification and results of long-term follow-up. *Int J Cardiol* 2006; 107:360–368.
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- S31.** Protonotarios A, Anastasakis A, Tsatsopoulou A, Antoniadis L, Prappa E, Syrris P, Tousoulis D, McKenna WJ, Protonotarios N: Clinical Significance of Epsilon Waves in Arrhythmogenic Cardiomyopathy. *J Cardiovasc Electrophysiol* 2015; 26:1204–1210.
- S32.** Rigato I, Bauce B, Rampazzo A, et al.: Compound and Digenic Heterozygosity Predicts Lifetime Arrhythmic Outcome and Sudden Cardiac Death in Desmosomal Gene-Related Arrhythmogenic Right Ventricular Cardiomyopathy. *Circ Cardiovasc Genet* 2013; 6:533–542.
- S33.** Roguin A, Bomma CS, Nasir K, Tandri H, Tichnell C, James C, Rutberg J, Crosson J, Spevak PJ, Berger RD, Halperin HR, Calkins H: Implantable Cardioverter-Defibrillators in patients with arrhythmogenic right ventricular Dysplasia/Cardiomyopathy. *J Am Coll Cardiol* 2004; 43:1843–1852.
- S34.** Ruwald A-C, Marcus F, Estes NAM, Link M, McNitt S, Polonsky B, Calkins H, Towbin JA, Moss AJ, Zareba W: Association of competitive and recreational sport participation with cardiac events in patients with arrhythmogenic right ventricular cardiomyopathy: results from the North American multidisciplinary study of arrhythmogenic right ventricular cardiomyopath. *Eur Heart J* 2015; 36:1735–1743.

- S35.** Saguner AM, Medeiros-Domingo A, Schwyzer M a, et al.: Usefulness of inducible ventricular tachycardia to predict long-term adverse outcomes in arrhythmogenic right ventricular cardiomyopathy. *Am J Cardiol* 2013; 111:250–257.
- S36.** Saguner AM, Ganahl S, Baldinger SH, et al.: Usefulness of electrocardiographic parameters for risk prediction in arrhythmogenic right ventricular dysplasia. *Am J Cardiol* 2014; 113:1728–1734.
- S37.** Saguner AM, Vecchiati A, Baldinger SH, et al.: Different Prognostic Value of Functional Right Ventricular Parameters in Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia. *Circ Cardiovasc Imaging* 2014; 7:230–239.
- S38.** Santangeli P, Dello Russo A, Pieroni M, et al.: Fragmented and delayed electrograms within fibrofatty scar predict arrhythmic events in arrhythmogenic right ventricular cardiomyopathy: Results from a prospective risk stratification study. *Heart Rhythm* 2012; 9:1200–1206.
- S39.** Sarvari SI, Haugaa KH, Anfinen O-G, Leren TP, Smiseth OA, Kongsgaard E, Amlie JP, Edvardsen T: Right ventricular mechanical dispersion is related to malignant arrhythmias: a study of patients with arrhythmogenic right ventricular cardiomyopathy and subclinical right ventricular dysfunction. *Eur Heart J* 2011; 32:1089–1096.
- S40.** Schuler PK, Haegeli LM, Saguner AM, Wolber T, Tanner FC, Jenni R, Corti N, Lüscher TF, Brunckhorst C, Duru F: Predictors of Appropriate ICD Therapy in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy: Long Term Experience of a Tertiary Care Center. Moretti C, ed: *PLoS One* 2012; 7:e39584.
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- S42.** te Riele ASJM, James CA, Groeneweg JA, et al.: Approach to family screening in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Eur Heart J* 2016; 37:755–763.
- S43.** Turrini P, Angelini A, Thiene G, Buja G, Daliento L, Rizzoli G, Nava A: Late potentials and ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy. *Am J Cardiol* 1999; 83:1214–1219.
- S44.** Wichter T: Implantable Cardioverter/Defibrillator Therapy in Arrhythmogenic Right Ventricular Cardiomyopathy: Single-Center Experience of Long-Term Follow-Up and Complications in 60 Patients. *Circulation* 2004; 109:1503–1508.
- S45.** Zorzi A, Rigato I, Pilichou K, et al.: Phenotypic expression is a prerequisite for malignant arrhythmic events and sudden cardiac death in arrhythmogenic right ventricular cardiomyopathy. *Europace* 2016; 18:1086–1094.

Supplementary Results Table 1. Excluded studies with reasons for exclusion

First author, year	Reference	Reason for exclusion
I-Ghamdi, 2014	Al-Ghamdi B, Shafquat A, Mallawi Y: Arrhythmogenic right ventricular cardiomyopathy/dysplasia in Saudi Arabia: A single-center experience with long-term follow-up. <i>Ann Saudi Med</i> , 2014; 34:415–426.	No risk factor analysis
Apiyasawat, 2014	Apiyasawat S, Sahasthas D, Ngarmukos T, Chandanamatttha P, Likittanasombat K: Fragmented QRS as a predictor of appropriate implantable cardioverter-defibrillator therapy. <i>Indian Pacing Electrophysiol J</i> , 2014; 14:4–11.	Domain criteria not met
Bauce, 2006	Bauce B, Daliento L, Frigo G, Russo G, Nava A: Pregnancy in women with arrhythmogenic right ventricular cardiomyopathy/dysplasia. <i>Eur J Obstet Gynecol Reprod Biol</i> , 2006; 127:186–189.	Domain criteria not met
Blomström-Lundqvist, 1989	Blomström-Lundqvist C, Olsson SB, Edvardsson N: Follow-up by repeated signal-averaged surface QRS in patients with the syndrome of arrhythmogenic right ventricular dysplasia. <i>Eur Heart J</i> , 1989; 10 Suppl D:54–60.	Study performed <1994 (first TFC)
Blomström-Lundqvist, 1987	Blomström-Lundqvist C, Sabel KG, Olsson SB: A long term follow up of 15 patients with arrhythmogenic right ventricular dysplasia. <i>Br Heart J</i> , 1987; 58:477–488.	Study performed <1994 (first TFC)
Camm, 2013	Camm CF, James CA, Tichnell C, Murray B, Bhonsale A, Te Riele ASJM, Judge DP, Tandri H, Calkins H: Prevalence of atrial arrhythmias in arrhythmogenic right ventricular dysplasia/cardiomyopathy. <i>Heart Rhythm</i> , 2013; 10:1661–1668.	Outcome criteria not met
Canu, 1993	Canu G, Atallah G, Claudel JP, Champagnac D, Desseigne D, Chevalier P, de Zuloaga C, Moncada E, Kirkorian G, Touboul P: [Prognosis and long-term development of arrhythmogenic dysplasia of the right ventricle]. <i>Arch Mal Coeur Vaiss</i> , 1993; 86:41–48.	Full-text not available
Chu, 2010	Chu AF, Zado E, Marchlinski FE: Atrial arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and ventricular tachycardia. <i>Am J Cardiol</i> , 2010; 106:720–722.	Outcome criteria not met
Chung, 2013	Chung FP, Li HR, Chong E, et al.: Seasonal variation in the frequency of sudden cardiac death and ventricular tachyarrhythmia in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy: The effect of meteorological factors. <i>Heart Rhythm</i> , 2013; 10:1859–1866.	No risk factor analysis
da Fonseca, 2007	da Fonseca SMS, Belo LG, Carvalho H, Araújo N, Munhoz C, Siqueira L, Maciel W, Andréa E, Atié J: Clinical follow-up of patients with implantable cardioverter-defibrillator. <i>Arq Bras Cardiol</i> , 2007; 88:8–16.	Domain criteria not met
Dalal, 2005	Dalal D, Nasir K, Bomma C, et al.: Arrhythmogenic right ventricular dysplasia: A United States experience. <i>Circulation</i> , 2005; 112:3823–3832.	No risk factor analysis
Deac, 2013	Deac M, Alpendurada F, Fanaie F, et al.: Prognostic value of cardiovascular magnetic resonance in patients with suspected arrhythmogenic right ventricular cardiomyopathy. <i>Int J Cardiol</i> , 2013; 168:3514–3521.	Domain criteria not met
Den Haan, 2009	Den Haan AD, Tan BY, Zikusoka MN, et al.: Comprehensive desmosome mutation analysis in North Americans with arrhythmogenic right ventricular dysplasia/cardiomyopathy. <i>Circ Cardiovasc Genet</i> , 2009; 2:428–435.	Outcome criteria not met
Fagundes, 2000	Fagundes ML, Maia IG, Cruz FE, Alves PA, Boghossian SH, Ribeiro JC, Sa R: Arrhythmogenic cardiomyopathy of the right ventricle. Predictive value of QT interval dispersion to assess arrhythmogenic risk and sudden death. <i>Arq Bras Cardiol</i> , 2000; 75:115–124.	Domain criteria not met
Furushima, 2012	Furushima H, Chinushi M, Iijima K, Hasegawa K, Sato A, Izumi D, Watanabe H, Aizawa Y: Is the coexistence of sustained ST-segment elevation and abnormal Q waves a risk factor for electrical storm in implanted cardioverter defibrillator patients with structural heart diseases? <i>Europace</i> , 2012; 14:675–681.	Domain criteria not met
Gallo, 2016	Gallo C, Blandino A, Giustetto C, Anselmino M, Castagno D, Richiardi E, Gaita F: Arrhythmogenic right ventricular cardiomyopathy: ECG progression over time and correlation with. <i>J Cardiovasc Med</i> , 2016; 17:418–424.	Outcome criteria not met
Hodgkinson, 2016	Hodgkinson KA, Howes AJ, Boland P, Shen XS, Stuckless S, Young T-L, Curtis F, Collier A, Parfrey PS, Connors SP: Long-Term Clinical Outcome of Arrhythmogenic Right Ventricular Cardiomyopathy in Individuals With a p.S358L Mutation in	Domain criteria not met

Hodgkinson, 2005	TMEM43 Following Implantable Cardioverter Defibrillator Therapy. <i>Circ Arrhythmia Electrophysiol</i> , 2016; 9:e003589. Hodgkinson KA, Parfrey PS, Bassett AS, Kupprion C, Drenckhahn J, Norman MW, Thierfelder L, Stuckless SN, Dicks EL, McKenna WJ, Connors SP: The impact of implantable cardioverter-defibrillator therapy on survival in autosomal-dominant arrhythmogenic right ventricular cardiomyopathy (ARVD5). <i>J Am Coll Cardiol</i> , 2005; 45:400–408.	Domain criteria not met
Hulot, 2004	Hulot JS, Jouven X, Empana JP, Frank R, Fontaine G: Natural History and Risk Stratification of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. <i>Circulation</i> , 2004; 110:1879–1884.	Outcome criteria not met
Inciardi, 2014	Inciardi RM, Maresi E, Coppola G, et al.: Anatomical features and clinical correlations in Caucasian patients with definite arrhythmogenic right ventricular dysplasia/cardiomyopathy. <i>Minerva Cardioangiol</i> , 2014; 62:369–378.	Full-text not available
Leclercq, 1993	Leclercq JF, Coumel P: Late potentials in arrhythmogenic right ventricular dysplasia. Prevalence, diagnostic and prognostic values. <i>Eur Heart J</i> , 1993; 14 Suppl E:80–83.	Study performed <1994 (first TFC)
Leclercq, 1989	Leclercq JF, Coumel P: Characteristics, prognosis and treatment of the ventricular arrhythmias of right ventricular dysplasia. <i>Eur Heart J</i> , 1989; 10 Suppl D:61–67.	Study performed <1994 (first TFC)
Lemery, 1989	Lemery R, Brugada P, Janssen J, Cheriex E, Dugernier T, Wellens HJ: Nonischemic sustained ventricular tachycardia: clinical outcome in 12 patients with arrhythmogenic right ventricular dysplasia. <i>J Am Coll Cardiol</i> , 1989; 14:96–105.	Study performed <1994 (first TFC)
Lemola, 2005	Lemola K, Bruckhorst C, Helfenstein U, Oechslin E, Jenni R, Duru F: Predictors of adverse outcome in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy: long term experience of a tertiary care centre. <i>Heart</i> , 2005; 91:1167–1172.	Outcome criteria not met
Li, 2012	Swope D, Cheng L, Gao E, Li J, Radice GL: Loss of cadherin-binding proteins beta-catenin and plakoglobin in the heart leads to gap junction remodeling and arrhythmogenesis. <i>Mol Cell Biol</i> , 2012; 32:1056–1067.	No risk factor analysis
Lopez, 2015	Lopez-Ayala JM, Pastor-Quirante F, Gonzalez-Carrillo J, Lopez-Cuenca D, Sanchez-Munoz JJ, Oliva-Sandoval MJ, Gimeno JR: Genetics of myocarditis in arrhythmogenic right ventricular dysplasia. <i>Heart Rhythm</i> , 2015; 12:766–773.	Domain criteria not met
Ma, 2012	Ma N, Cheng H, Lu M, Jiang S, Yin G, Zhao S: Cardiac magnetic resonance imaging in arrhythmogenic right ventricular cardiomyopathy: Correlation to the QRS dispersion. <i>Magn Reson Imaging</i> , 2012; 30:1454–1460.	Outcome criteria not met
Mast, 2016	Mast TP, Teske AJ, Te Riele AS, et al.: Prolonged Electromechanical Interval Unmasks Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy in the Subclinical Stage. <i>J Cardiovasc Electrophysiol</i> , 2016; 27:303–314.	Outcome criteria not met
Migliore, 2016	Migliore F, Silvano M, Zorzi A, Bertaglia E, Siciliano M, Leoni L, De Franceschi P, Iliceto S, Corrado D: Implantable cardioverter defibrillator therapy in young patients with cardiomyopathies and channelopathies. <i>J Cardiovasc Med</i> , 2016; 17:485–493.	Domain criteria not met
Neilan, 2015	Neilan TG, Farhad H, Mayrhofer T, et al.: Late gadolinium enhancement among survivors of sudden cardiac arrest. <i>JACC Cardiovasc Imaging</i> , 2015; 8:414–423.	Domain criteria not met
Ozben, 2008	Ozben B, Altun I, Sabri Hancer V, Bilge AK, Tanrikulu AM, Diz-Kucukkaya R, Fak AS, Yilmaz E, Adalet K: Angiotensin-converting enzyme gene polymorphism in arrhythmogenic right ventricular dysplasia: Is DD genotype helpful in predicting syncope risk? <i>JRAAS J Renin-Angiotensin-Aldosterone Syst</i> , 2008; 9:215–220.	No risk factor analysis
Peters, 2012	Peters S: QRS fragmentation in patients with arrhythmogenic right ventricular cardiomyopathy and complete right bundle branch block: a risk stratification. <i>Eur Hear J Acute Cardiovasc Care</i> , 2012; 1:236–239.	No risk factor analysis
Peters, 2008	Peters S: Arrhythmogenic right ventricular dysplasia-cardiomyopathy and provokable coved-type ST-segment elevation in right precordial leads: Clues from long-term follow-up. <i>Europace</i> , 2008; 10:816–820.	No risk factor analysis
Peters, 1999	Peters S, Peters H, Thierfelder L: Risk stratification of sudden cardiac death and malignant ventricular arrhythmias in right ventricular dysplasia-cardiomyopathy. <i>Int J Cardiol</i> , 1999; 71:243–250.	Outcome criteria not met
Pinamonti, 2011	Pinamonti B, Brun F, Mestroni L, Sinagra G: Arrhythmogenic right ventricular cardiomyopathy: From genetics to diagnostic and therapeutic challenges. <i>World J Cardiol</i> , 2014; 6:1234–1244.	Outcome criteria not met

Proclemer, 2009	Proclemer A, Ghidina M, Facchin D, Rebellato L, Corrado D, Gasparini M, Gregori D: Use of implantable cardioverter-defibrillator in inherited arrhythmogenic diseases: Data from Italian ICD registry for the years 2001-6. <i>PACE - Pacing Clin Electrophysiol</i> , 2009; 32:434–445.	No risk factor analysis
Quarta, 2010	Sen-Chowdhry S, Syrris P, Pantazis A, Quarta G, McKenna WJ, Chambers JC: Mutational heterogeneity, modifier genes, and environmental influences contribute to phenotypic diversity of arrhythmogenic cardiomyopathy. <i>Circ Cardiovasc Genet</i> , 2010; 3:323–330.	Outcome criteria not met
Sawant, 2016	Sawant AC, Te Riele ASJM, Tichnell C, Murray B, Bhonsale A, Tandri H, Judge DP, Calkins H, James CA: Safety of American Heart Association-recommended minimum exercise for desmosomal mutation carriers. <i>Heart Rhythm</i> , 2016; 13:199–207.	Domain criteria not met
Sawant, 2014	Sawant AC, Bhonsale A, te Riele ASJM, Tichnell C, Murray B, Russell SD, Tandri H, Tedford RJ, Judge DP, Calkins H, James CA: Exercise has a disproportionate role in the pathogenesis of arrhythmogenic right ventricular dysplasia/cardiomyopathy in patients without desmosomal mutations. <i>J Am Heart Assoc</i> , 2014; 3:e001471.	No risk factor analysis
Sen-Chowdhry, 2010	Sen-Chowdhry S, Syrris P, Pantazis A, Quarta G, McKenna WJ, Chambers JC: Mutational heterogeneity, modifier genes, and environmental influences contribute to phenotypic diversity of arrhythmogenic cardiomyopathy. <i>Circ Cardiovasc Genet</i> , 2010; 3:323–330.	No risk factor analysis
Tavernier, 2001	Tavernier R, Gevaert S, De Sutter J, De Clercq A, Rottiers H, Jordaens L, Fonteyne W: Long term results of cardioverter-defibrillator implantation in patients with right ventricular dysplasia and malignant ventricular tachyarrhythmias. <i>Heart</i> , 2001; 85:53–56.	No risk factor analysis
Te Riele, 2015	Te Riele ASJM, James CA, Sawant AC, et al.: Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy in the Pediatric Population Clinical Characterization and Comparison with Adult-Onset Disease. <i>JACC Clin Electrophysiol</i> , 2015; 1:551–560.	Pediatric population
Turrini, 2001	Turrini P, Corrado D, Basso C, Nava A, Bauce B, Thiene G: Dispersion of ventricular depolarization-repolarization: a noninvasive marker for risk stratification in arrhythmogenic right ventricular cardiomyopathy. <i>Circulation</i> , 2001; 103:3075–3080.	Outcome criteria not met
Van Rijsingen, 2014	Van Rijsingen IAW, Van Der Zwaag PA, Groeneweg JA, et al.: Outcome in phospholamban R14del carriers results of a large multicentre cohort study. <i>Circ Cardiovasc Genet</i> , 2014; 7:455–465.	Domain criteria not met
Vranic, 2013	Vranic I: Signaling prodromes of sudden cardiac death. <i>Bosn J Basic Med Sci</i> , 2013; 13:44–49.	Domain criteria not met
Watkins, 2009	Watkins DA, Hendricks N, Shaboodien G, et al.: Clinical features, survival experience, and profile of plakophilin-2 gene mutations in participants of the Arrhythmogenic Right Ventricular Cardiomyopathy Registry of South Africa. <i>Heart Rhythm</i> , 2009; 6:S10–S17.	Outcome criteria not met
Wijnmaalen, 2009	Wijnmaalen AP, Schaliij MJ, Bootsma M, Kies P, De Roos A, Putter H, Bax JJ, Zeppenfeld K: Patients with scar-related right ventricular tachycardia: Determinants of long-term outcome. <i>J Cardiovasc Electrophysiol</i> , 2009; 20:1119–1127.	Domain criteria not met
Wu, 2014	Wu L, Yao Y, Chen G, Fan X, Zheng L, Ding L, Zhang S: Intracardiac thrombosis in patients with arrhythmogenic right ventricular cardiomyopathy. <i>J Cardiovasc Electrophysiol</i> , 2014; 25:1359–1362.	Outcome criteria not met
Zorzi, 2013	Zorzi A, Migliore F, Elmaghawry M, et al.: Electrocardiographic predictors of electroanatomic scar size in arrhythmogenic right ventricular cardiomyopathy: Implications for arrhythmic risk stratification. <i>J Cardiovasc Electrophysiol</i> , 2013; 24:1321–1327.	Outcome criteria not met
Brun, 2016	Brun F, Groeneweg JA, Gear K, Sinagra G, van der Heijden J, Mestroni L, Hauer RN, Borgstrom M, Hughes T, Marcus FI: Risk Stratification in Arrhythmic Right Ventricular Cardiomyopathy Without Implantable Cardioverter-Defibrillators. <i>JACC Clin Electrophysiol</i> , 2016; 2:558–564.	Outcome criteria not met

Supplementary Table 2. Risk factor estimates; Demographics

Demographics							
Risk factor	Author, year	Size (events)	Statistic	Crude [95%CI]	p-value	Adjusted [95%CI]	p-value
Definite ARVC diagnosis							
Age	Santangeli, 2012	32 (12)	HR	1.02 [0.98-1.06]	0.300		
	Canpolat, 2013	78 (39)	HR	1.34 [0.77-1.54]	0.350		
	Migliore, 2013	69 (19)	HR	1 [1-1]	0.730		
	Lin, 2017	70 (38)	HR	1.02 [0.98-1.07]	0.287		
	Corrado, 2003	132 (64)	OR		n.a.	0.95 [0.89-0.99]	0.007
	Peters, 2012	305 (101)	OR	1.34 [0.34-3.45]	0.500		
	Liao, 2014	32 (13)	OR	0.99 [0.94-1.04]	0.642		
	Folino, 2002	46 (8)	Means		n.s.		
	Roguin, 2004	42 (33)	Means		0.860		
	Marcus, 2009	95 (32)	Means		0.620		
	Battipaglia, 2012	30 (5)	Means		0.390		
	te Riele, 2016	96 (21)	Means		0.652		
Age <20 vs. >40 years	Mazzanti, 2016	267 (47)	HR	0.7 [0.23-2.14]	0.530		
Age <35 years	Corrado, 2010	106 (25)	HR	1.36 [0.91-3.13]	0.070	1.22 [0.72-2.56]	0.470
	Mast, 2015	38 (20)	HR	0.99 [0.96-1.02]	0.538		n.s.
	Martin, 2016	28 (13)	HR	0.9 [0.75-1.6]	1.000		
Age <40	Mazzanti, 2016	267 (47)	HR	2.91 [1.51-5.58]	0.001		
Age at ablation	Berruezo, 2016	41 (11)	HR	1.05 [0.99-1.12]	0.064	1.03 [0.98-1.09]	0.218
Age at diagnosis	Schuler, 2012	26 (12)	OR	1 [0.94-1.06]	0.968		
Male sex	Corrado, 2010	106 (25)	HR	1.37 [0.65-3.94]	0.240		
	Santangeli, 2012	32 (12)	HR	1.66 [0.49-5.55]	0.410		
	Canpolat, 2013	78 (39)	HR	1.35 [0.95-2.56]	0.440		
	Migliore, 2013	69 (19)	HR	1.1 [0.4-3.3]	0.780		
	Mast, 2015	38 (20)	HR	1.36 [0.56-3.33]	0.501		n.s.
	Martin, 2016	26 (13)	HR	1.9 [1.1-3.1]	0.010	1.6 [1.5-2.7]	0.010
	Mazzanti, 2016	267 (47)	HR	2.76 [1.37-5.56]	0.005	2.49 [1.22-5.07]	0.012
	Lin, 2017	70 (38)	HR	3.27 [1.55-6.9]	0.002	2.41 [1.09-5.37]	0.031
	Folino, 2002	46 (8)	OR	2.43 [0.43-13.61]	0.313		
	Roguin, 2004	42 (33)	OR	5.38 [0.96-30.06]	0.040	2.64 [0.8-8.71]	0.110
	Marcus, 2009	95 (32)	OR	1.28 [0.53-3.06]	0.630		
	Battipaglia, 2012	30 (5)	OR	1.18 [0.17-8.33]	0.869		
	Peters, 2012	305 (101)	OR	2.65 [1.36-5.61]	<0.05		
	Schuler, 2012	26 (12)	OR	4.4 [0.42-46.3]	0.217		
	Liao, 2014	32 (13)	OR	0.8 [0.17-3.82]	0.783		
	te Riele, 2016	96 (21)	OR	2.83 [1.05-7.64]	0.036		
Alcohol	Canpolat, 2013	78 (39)	HR	0.85 [0.44-2.11]	0.730		
Body Mass Index	Canpolat, 2013	78 (39)	HR	1.21 [0.89-1.63]	0.080		
	Marcus, 2009	95 (32)	Means		0.530		
Diabetes mellitus	Lin, 2017	70 (38)	HR	2.53 [0.59-10.78]	0.200		
Dyslipidemia	Canpolat, 2013	78 (39)	HR	0.84 [0.55-1.23]	0.630		
Hypertension	Lin, 2017	70 (38)	HR	1.62 [0.75-3.5]	0.219		
Maori ethnicity	Martin, 2016	26 (13)	HR	2 [0.44-9.1]	0.640		
Race	Marcus, 2009	95 (32)	OR		0.580		
Smoking	Canpolat, 2013	78 (39)	HR	1.13 [0.84-2.12]	0.160		
Diagnosis independent of family history	te Riele, 2016	96 (21)	OR	90.39 [5.26-1554.6]	<0.001		
Definite or borderline ARVC diagnosis							
Age	Saguner, 2014	70 (37)	HR	0.99 [0.97-1.01]	0.430		
	Chung, 2016	63 (19)	HR	0.99 [0.96-1.02]	0.650		
	Piccini, 2005	67 (44)	Means		0.300		
Age <30 years	Bhonsale, 2011	84 (40)	HR	0.96 [0.52-1.79]	0.906		
Age at earliest symptom	Link, 2014	108 (48)	HR		0.609		
Age at enrolment	Link, 2014	108 (48)	HR		0.413		
Male sex	Bhonsale, 2011	84 (40)	HR	0.95 [0.51-1.79]	0.878		
	Link, 2014	108 (48)	HR		0.218		
	Saguner, 2014	70 (37)	HR	1.3 [0.64-2.63]	0.470		
	Choudary, 2016	101 (19)	HR	2.44 [0.9-6.62]	0.066		
	Chung, 2016	63 (19)	HR	2.47 [0.82-7.46]	0.110		
	Piccini, 2005	67 (44)	OR	0.77 [0.28-2.12]	0.610		
Definite ARVC TFC10	Bhonsale, 2011	84 (40)	HR	0.58 [0.26-1.26]	0.167		
	Saguner, 2014	70 (37)	HR	1.04 [0.47-2.27]	0.930		
	Saguner, 2013	62 (30)	OR	1.25 [0.42-3.76]	0.783		
Definite ARVC TFC94	Link, 2014	108 (48)	HR		0.013		
	Piccini, 2005	67 (44)	KM		0.027		
	Piccini, 2005	67 (44)	OR	5.33 [1.4-20.35]	0.010		
Diagnostic score TFC94	Link, 2014	108 (48)	HR		0.840		
ARVC associated mutation carriers							
Male sex	Bhonsale, 2013	215 (86)	HR		n.a.	1.8 [1.2-2.8]	0.004
	Rigato, 2013	134 (22)	HR	2.24 [0.92-5.46]	0.070	2.76 [1.19-6.41]	0.020
	Protonoratos, 2016	105 (43)	HR	2.66 [1.38-5.12]	0.003	3.26 [1.63-6.51]	0.001
	te Riele, 2013	69 (11)	OR	4.7 [1.12-19.65]	0.024		
	Zorzi, 2016	116 (10)	OR	4.65 [0.94-10.2]	0.050		
	Bhonsale, 2015	541 (207)	KM		<0.001		
				356.18 [21.57-5880.14]			
Definite ARVC TFC10	Bhonsale, 2013	215 (86)	OR		<0.001		
	Protonoratos, 2016	105 (43)	OR	81.65 [4.81-1385.19]	<0.001		
	Zorzi, 2016	116 (10)	KM		0.002		

Supplementary Table 3. Risk factor estimates; Symptoms

Symptoms							
Risk factor	Author, year	Size (events)	Statistic	Crude [95%CI]	p-value	Adjusted [95%CI]	p-value
Definite ARVC diagnosis							
Symptomatic at presentation	te Riele, 2016	96 (21)	OR	6.33 [2.21-18.11]	<0.001		
Palpitations	Roguin, 2004	42 (33)	OR	1.56 [0.32-7.73]	0.580		
Presyncope	Roguin, 2004	42 (33)	OR	0.96 [0.22-4.23]	0.970		
Syncope / presyncope	Liao, 2014	32 (13)	OR	2.2 [0.52-9.3]	0.284		
Syncope	Martin, 2016	26 (13)	HR	0.5 [0.05-4.9]	1.000		
	Mazzanti, 2016	267 (47)	HR	4.54 [2.48-8.34]	<0.001	3.36 [1.71-6.6]	<0.001
	Canpolat, 2013	78 (39)	HR	3.45 [2.33-6.2]	<0.001	3.12 [2.65-5.33]	0.001
	Battipaglia, 2012	30 (5)	HR		n.a.	16.1 [1.15-226]	0.039
	Santangel, 2012	32 (12)	HR	3.2 [1.01-10.13]	0.048	1.77 [0.46-6.78]	0.400
	Corrado, 2010	106 (25)	HR	3.82 [2.15-5.72]	0.008	2.94 [1.83-4.67]	0.013
	Schuler, 2012	26 (12)	OR	0.11 [0.02-0.7]	0.020		
	Marcus, 2009	95 (32)	OR	1.75 [0.67-4.59]	0.270		
	Peters, 2007	313 (26)	OR	3.49 [1.35-7.63]	0.020		
	Roguin, 2004	42 (33)	OR	1.33 [0.3-5.84]	0.330		
	Corrado, 2003	132 (64)	OR		n.a.	7.5 [0.84-18.1]	0.070
Syncope or cardiac arrest	Migliore, 2013	69 (19)	HR	3.4 [1.4-8.8]	0.030	2.4 [0.8-6.2]	0.110
Chest pain	Roguin, 2004	42 (33)	OR	0.52 [0.12-2.3]	0.430		
Heart failure	Peters, 2012	305 (101)	OR	3.15 [2.02-5.16]	<0.01		
	Schuler, 2012	26 (12)	OR	0.28 [0.01-7.67]	0.480		
NYHA functional class	Marcus, 2009	95 (32)	OR		0.380		
Definite or borderline ARVC diagnosis							
Palpitations	Saguner, 2013	62 (30)	OR	1.47 [0.54-4]	0.612		
Presyncope	Saguner, 2013	62 (30)	OR	1.5 [0.5-4.52]	0.579		
Syncope	Chung, 2016	63 (19)	HR	4.97 [1.77-13.92]	0.002	1.63 [0.52-5.14]	0.400
	Link, 2014	108 (48)	HR		0.492		
	Bhonsale, 2011	84 (40)	HR	0.91 [0.45-1.87]	0.799		
	Piccini, 2005	67 (44)	OR	0.41 [0.14-1.15]	0.080		
	Saguner, 2013	62 (30)	OR	2.88 [1.03-8.07]	0.074		
Chest pain	Saguner, 2013	62 (30)	OR	1.53 [0.49-4.81]	0.566		
Dyspnea	Saguner, 2013	62 (30)	OR	0.83 [0.2-3.44]	1.000		
Peripheral edema	Saguner, 2013	62 (30)	OR	0.34 [0.01-8.78]	1.000		
Heart failure	Saguner, 2013	62 (30)	HR	2.25 [1.04-4.87]	0.038		
ARVC associated mutation carriers							
Symptomatic at presentation	Bhonsale, 2013	215 (86)	OR	23.7 [11.44-49.12]	<0.001		
	te Riele, 2013	69 (11)	OR	5.02 [1.29-19.58]	0.014		
Palpitations	Bhonsale, 2013	215 (86)	OR	16.25 [8.23-32.09]	<0.001		
	te Riele, 2013	69 (11)	OR	5.76 [1.47-22.63]	0.007		
Presyncope	Bhonsale, 2013	215 (86)	OR	8.13 [3.99-16.58]	<0.001		
	te Riele, 2013	69 (11)	OR	3 [0.48-18.86]	0.241		
Syncope	Zorzi, 2016	116 (10)	OR	5.05 [0.84-35.23]	0.100		
	Bhonsale, 2013	215 (86)	OR	5.75 [2.69-12.3]	<0.001		
	te Riele, 2013	69 (11)	OR	1.62 [0.29-9.06]	0.584		
Chest pain	Bhonsale, 2013	215 (86)	OR	1.96 [0.77-4.94]	0.156		
	te Riele, 2013	69 (11)	OR	2.8 [0.23-33.87]	0.418		
Heart failure	Bhonsale, 2013	215 (86)	OR	3.01 [1.07-8.47]	0.037		

Supplementary Table 4. Risk factor estimates; Exercise

Physical exercise							
Risk factor	Author, year	Size (events)	Statistic	Crude [95%CI]	p-value	Adjusted [95%CI]	p-value
Definite ARVC diagnosis							
Strenuous exercise after Dx	Mazzanti, 2016	267 (47)	HR	2.9 [1.14-7.38]	0.026	2.98 [1.12-7.9]	0.028
Definite or borderline ARVC diagnosis							
History competitive high-dynamic vs. recreational high dynamic	Ruwald, 2015	108 (83)	HR	1.89 [1.03-3.48]	0.041		
History competitive sport vs. inactive	Ruwald, 2015	108 (83)	HR	2.05 [1.07-3.91]	0.030		
History competitive sport vs. recreational	Ruwald, 2015	108 (83)	HR	1.99 [1.21-3.28]	0.007		
History recreational high-dynamic vs. inactive	Ruwald, 2015	108 (83)	HR	0.93 [0.45-1.9]	0.835		
History recreational sport vs. Inactive	Ruwald, 2015	108 (83)	HR	1.03 [0.54-1.97]	0.930		
Competitive before and after Dx	Ruwald, 2015	108 (83)	HR	1.77 [0.59-5.29]	0.307		
Competitive before, rec/inactive after Dx	Ruwald, 2015	108 (83)	HR	0.98 [0.45-2.1]	0.950		
ARVC associated mutation carriers							
Endurance athletes (high dynamic, >50h/y)	James, 2013	87 (39)	KM		0.013		
Exercise >516h/yr before presentation	James, 2013	61 (13)	KM		0.036		
Exercise >425h/yr after presentation	James, 2013	61 (13)	KM		0.005		
Presentation >516h/yr: <425h/yr after presentation	James, 2013	16 (7)	OR	0.05 [0-0.66]	0.041		
Presentation <516h/yr: >425h/yr after presentation	James, 2013	45 (6)	OR	3.4 [0.49-23.65]	0.230		

Supplementary Table 5. Risk factor estimates; Family history and genetics

Family history and genotype							
Risk factor	Author, year	Size (events)	Statistic	Crude [95%CI]	p-value	Adjusted [95%CI]	p-value
Definite ARVC diagnosis							
Proband status	Martin, 2016	26 (13)	HR	1.3 [0.97-1.8]	0.220		
	Mazzanti, 2016	267 (47)	HR	3.54 [1.65-7.59]	0.001		n.s.
Family history SCD <35y	Mazzanti, 2016	267 (47)	HR	0.95 [0.52-1.73]	0.872		
	Canpolat, 2013	78 (39)	HR	1.58 [1.35-2.77]	0.003		
	Migliore, 2013	69 (19)	HR	1.1 [0.4-3]	0.880		
	Santangeli, 2012	32 (12)	HR	1.03 [0.28-3.84]	0.960		
	Corrado, 2010	106 (25)	HR	1.43 [0.76-4.12]	0.140	0.9 [0.35-5.9]	0.820
	Marcus, 2009	95 (32)	OR	1.05 [0.41-2.66]	0.920		
	Peters, 2007	313 (26)	OR	1.07 [0.93-3.46]	0.150		
Family history of ARVC	Battipaglia, 2012	30 (5)	OR	0.64 [0.06-6.8]	0.714		
	Schuler, 2012	26 (12)	OR	0.33 [0.03-3.72]	0.372		
Family history of ARVC or SCD <35y	Roguin, 2004	42 (33)	OR	0.75 [0.15-3.65]	0.570		
Family history SCD or HTx	Liao, 2014	32 (13)	OR	1.5 [0.09-26.36]	0.782		
Family history or pathogenic mutation (TFC10)	te Riele, 2016	96 (21)	OR	0.59 [0.19-1.79]	0.347		
	Lin, 2017	70 (38)	HR	2.41 [1.28-4.53]	0.070	1.94 [0.98-2.99]	0.059
	Mast, 2015	38 (20)	HR	0.88 [0.32-2.42]	0.803		n.s.
Family history TFC10 major	Kikuchi, 2016	90 (47)	HR	0.05 [0.00-45]	0.514		
Family history TFC10 minor	Kikuchi, 2016	90 (47)	HR	1.02 [0.02-3.3]	0.972		
Pathogenic mutation	te Riele, 2016	96 (21)	OR	3.22 [0.69-15.14]	0.121		
Pathogenic mutation (probands)	Groeneweg, 2015	416 (301)	OR	1.17 [0.75-1.81]	0.565		
	Groeneweg, 2015	416 (301)	KM		0.001		
Pathogenic mutation (family members)	Groeneweg, 2015	208 (66)	KM		0.027		
PKP2 gene mutation	Dalal, 2006	58 (n.a.)	KM		<0.05		
Definite or borderline ARVC diagnosis							
Proband status	Bhonsale, 2011	84 (40)	HR	6.48 [2.3-18.23]	<0.001	1.62 [0.3-8.59]	0.574
Family history SCD <35y	Chung, 2016	63 (19)	HR	2.25 [0.8-6.34]	0.130		
	Link, 2014	108 (48)	HR		0.960		
	Bhonsale, 2011	84 (40)	HR	0.7 [0.29-1.66]	0.417		
Family history of ARVC or SCD <35y	Piccini, 2005	67 (44)	OR	0.51 [0.16-1.64]	0.250		
Pathogenic mutation	Bhonsale, 2011	84 (40)	HR	0.59 [0.29-1.16]	0.125	0.44 [0.14-1.4]	0.165
ARVC associated mutation carriers							
Proband status	Bhonsale, 2013	215 (86)	HR		n.a.	7.7 [2.8-22.5]	<0.001
	Protonoratos, 2016	105 (43)	OR	10.77 [1.51-7.81]	<0.001		
	Zorzi, 2016	116 (10)	OR	3.61 [0.96-8.82]	0.060		
	te Riele, 2013	69 (11)	OR	19.43 [4.15-91.02]	0.000		
	Zorzi, 2016	116 (10)	KM		0.070		
PKP2 vs. Other mutation	Protonoratos, 2016	105 (43)	HR	1.24 [0.67-2.29]	0.490		1
JUP vs. Other mutation	Protonoratos, 2016	105 (43)	HR	1.74 [0.94-3.25]	0.080	1.42 [0.71-2.82]	0.320
DSC2 vs. Other mutation	Protonoratos, 2016	105 (43)	HR	0.32 [0.13-0.75]	0.009	0.33 [0.12-0.86]	0.023
DSP vs. Other mutation	Protonoratos, 2016	105 (43)	HR	1.46 [0.52-4.13]	0.480	2.01 [0.65-6.21]	0.220
DSP vs. PKP2	Rigato, 2013	134 (22)	HR	1.41 [0.28-3.05]	0.890		
DSG2 vs. PKP2	Rigato, 2013	134 (22)	HR	1.53 [0.38-6.15]	0.380		
Missense vs. Splice site vs. Truncating	Bhonsale, 2015	541 (207)	KM		0.137		
Non-missense vs. Missense	Rigato, 2013	134 (22)	HR	1.53 [0.53-4.42]	0.432		
Multiple mutations	Bhonsale, 2015	541 (207)	KM		0.037		
	Rigato, 2013	134 (22)	HR	3.01 [1.42-6.37]	0.004	3.71 [1.54-8.92]	0.003

Supplementary Table 6. Risk factor estimates; Electrocardiogram

Electrocardiogram							
Risk factor	Author, year	Size (events)	Statistic	Crude [95%CI]	p-value	Adjusted [95%CI]	p-value
Definite ARVC diagnosis							
TWI V1-V2 / V4-V6 / V1-V4 with CRBBB	Kikuchi, 2016	90 (47)	HR	2.72 [1.42-5.2]	0.002		
	te Riele, 2016	96 (21)	OR	0.62 [0.19-2]	0.424		
TWI V1-V3	Kikuchi, 2016	90 (47)	HR	0.78 [0.33-1.84]	0.565		
	Martin, 2016	26 (13)	HR	1.1 [0.7-1.8]	1.000		
	Mazzanti, 2016	267 (47)	HR	1.62 [0.88-2.99]	0.121		
	Corrado, 2010	106 (25)	HR	1.2 [0.42-2.13]	0.330		
TWI >V3	te Riele, 2016	96 (21)	OR	1.58 [0.59-4.26]	0.506		
	Battipaglia, 2012	30 (5)	OR	1.31 [0.12-15.03]	0.827		
	Peters, 2007	313 (26)	OR	2.61 [1.14-5.96]	<0.025		
Repolarization abnormalities (TFC10)	Lin, 2017	70 (38)	HR	1.36 [0.84-2.21]	0.214		
	Mast, 2015	38 (20)	HR	0.92 [0.31-2.77]	0.884		
	Liao, 2014	32 (13)	OR	5.31 [0.84-33.54]	0.076	13.75 [1-188.38]	n.s.
Repolarization abnormalities (TFC94)	Roguin, 2004	42 (33)	OR	0.7 [0.07-6.89]	0.360		
Epsilon wave	Kikuchi, 2016	90 (47)	HR	1.86 [1.03-3.34]	0.039		
	Martin, 2016	26 (13)	HR	0.5 [0.11-2.3]	0.640		
	te Riele, 2016	96 (21)	OR	4.18 [0.95-18.41]	0.066		
	Protonoratos, 2015	86 (38)	OR	4.05 [1.5-10.92]	0.004		
	Peters, 2007	313 (26)	OR	4.71 [2.07-10.73]	<0.001		
	Roguin, 2004	42 (33)	OR	2.15 [0.23-20.24]	0.550		
TAD >55ms	te Riele, 2016	96 (21)	OR	2.83 [1.05-7.63]	0.035		
Late potentials on SAECG	Canpolat, 2013	78 (39)	HR	1.09 [0.56-1.78]	0.780		
	Corrado, 2010	106 (25)	HR	0.82 [0.37-3.48]	0.230		
	te Riele, 2016	96 (21)	OR	2.1 [0.62-7.12]	0.253		
	Liao, 2014	32 (13)	OR	2.54 [0.42-15.21]	0.308		
	Battipaglia, 2012	30 (5)	OR	1.38 [0.2-9.77]	0.744		
	Roguin, 2004	42 (33)	OR	3.11 [0.47-20.65]	0.230		
						45.04 [4.59-92.21]	
Late potentials on SAECG, 2-3 criteria	Pezawas, 2006	34 (12)	HR	23.7 [2.96-68.8]	<0.001	92.21	0.002
Late potentials on SAECG, 2-3 criteria	Turrini, 1999	38 (15)	OR	3.75 [0.95-14.82]	0.054	3.75 n.a.	0.059
						11.06 [1.3-93.89]	
Late potentials on SAECG, all 3 criteria	Liao, 2014	32 (13)	OR	4.88 [1.06-22.38]	0.042	n.a.	0.028
SAECG terminal 40ms RMS, uV	Turrini, 1999	38 (15)	OR			0.96 [0.94-0.99]	0.025
Late potentials on SAECG or TAD >55ms	Kikuchi, 2016	90 (47)	HR	1.66 [0.4-6.93]	0.484		
Depolarization abnormalities (TFC10)	Lin, 2017	70 (38)	HR	1.44 [0.64-3.22]	0.376		
	Mast, 2015	38 (20)	HR	1.39 [0.47-4.18]	0.554		n.s.
Depolarization abnormalities other than SAECG (TFC10)	Liao, 2014	32 (13)	OR	1.35 [0.31-5.94]	0.688		
Abnormal ECG (TFC10)	te Riele, 2016	96 (21)	OR	1.38 [0.36-5.33]	0.642		
AV-block, PR >200ms	Schuler, 2012	26 (12)	OR	2.36 [0.31-17.8]	0.410		
QRS duration, ms	Battipaglia, 2012	30 (5)	Means		0.750		
	Marcus, 2009	95 (32)	Means		0.770		
QRS duration >120ms	Schuler, 2012	26 (12)	OR	4.67 [0.77-28.5]	0.100		
Right bundle branch block	Roguin, 2004	42 (33)	OR	2.56 [0.28-23.72]	0.670		
QRS dispersion precordial >30ms	Peters, 2007	313 (26)	OR	1.26 [0.53-3]	0.602		
QRS fragmentation	Canpolat, 2013	78 (39)	HR	8.54 [3.65-15.42]	<0.001	6.52 [3.42-12.5]	<0.001
						10.46 [4.88-15.51]	
Early repolarisation (other than V1-V3)	Peters, 2012	305 (101)	OR	11.64 [5.1-16.41]	<0.001		<0.001
ST elevation V1-V3	Chan, 2015	59 (14)	KM		0.020		
J-T interval	Peters, 2007	313 (26)	OR	4.15 [1.83-9.42]	<0.005		
	Battipaglia, 2012	30 (5)	Means		1.000		
				10.41 [3.36-15.45]		9.67 [2.21-14.56]	<0.001
Left precordial J-T prolongation >20ms	Peters, 2012	305 (101)	OR		<0.001		
				11.47 [3.36-39.08]			
Left precordial J-T prolongation >30ms	Peters, 2007	313 (26)	OR		<0.001		
QTc (ms)	Battipaglia, 2012	30 (5)	Means		0.870		
Definite or borderline ARVC diagnosis							
TWI V1-V3	Bhonsale, 2011	84 (40)	HR	1.12 [0.54-2.32]	0.758		
	Piccini, 2005	67 (44)	OR	4.82 [1.08-21.55]	0.030		
TWI >3 precordial leads (vs. 3 or less)	Saguner, 2014	106 (51)	HR	1.88 [1.07-3.31]	0.029		
TWI II, III, aVF	Link, 2014	108 (48)	HR		<0.001		
TWI ≥2 inferior leads	Saguner, 2014	106 (51)	HR	1.73 [0.98-3.06]	0.058	2.44 [1.15-5.18]	0.020
Repolarization abnormalities (TFC10)	Chung, 2016	63 (19)	HR	0.97 [0.39-2.42]	0.950		
	Saguner, 2014	106 (51)	HR	2.4 [1.22-4.73]	0.011		
Epsilon wave	Saguner, 2014	106 (51)	HR	1.61 [0.86-3.03]	0.140		
	Bhonsale, 2011	84 (40)	HR	1.48 [0.43-5.14]	0.533		
TAD >55ms	Saguner, 2014	106 (51)	HR	1.07 [0.57-1.99]	0.830		
Late potentials on SAECG	Saguner, 2014	106 (51)	HR	1.63 [0.89-3.01]	0.110		
	Bhonsale, 2011	84 (40)	HR	1.06 [0.46-2.45]	0.896		
	Piccini, 2005	67 (44)	OR	2.05 [0.72-5.82]	0.120		
Late potentials on SAECG, 2-3 criteria	Sarvari, 2011	69 (42)	OR	4.01 [1.28-12.5]	0.020	2.27 [0.53-9.79]	0.270
SAECG iQRS duration, per ms	Link, 2014	108 (48)	Means		0.020		
SAECG iQRS duration, >120 ms	Link, 2014	108 (48)	HR		0.011		
SAECG Terminal QRS <40uV duration, ms	Sarvari, 2011	69 (42)	Means		0.080		
SAECG terminal 40ms RMS, uV	Sarvari, 2011	69 (42)	Means		0.090		
Depolarization abnormalities (TFC10)	Chung, 2016	63 (19)	HR	0.86 [0.35-2.12]	0.750		
QRS duration in V2, ms	Link, 2014	108 (48)	HR		0.055		
QRS duration, ms	Sarvari, 2011	69 (42)	Means		0.010		
Right bundle branch block	Piccini, 2005	67 (44)	OR	1.06 [0.28-3.96]	0.900		
Bundle branch block (cLBBB, cRBBB, LAfB, iRBBB)	Saguner, 2014	106 (51)	HR	0.7 [0.38-1.32]	0.270		
Parietal block (QRS V1-3 >25ms longer than V6)	Saguner, 2014	106 (51)	HR	1.07 [0.57-1.99]	0.830		
QRS precordial amplitude ratio <0.48	Saguner, 2014	106 (51)	HR	2.31 [1.13-4.74]	0.022	2.92 [1.39-6.15]	0.005
QRS fragmentation	Saguner, 2014	106 (51)	HR	1.76 [1.01-3.06]	0.047	2.65 [1.1-6.34]	0.029
QTc (ms)	Sarvari, 2011	69 (42)	Means		0.020		
Tpeak-Tend dispersion >20ms	Saguner, 2014	106 (51)	HR	1.36 [0.69-2.67]	0.380		
Tpeak-Tend duration >100ms	Saguner, 2014	106 (51)	HR	1.47 [0.83-2.61]	0.190		
Maximal T-wave alternans	Chung, 2016	63 (19)	HR	1.07 [1.04-1.1]	<0.001	1.06 [1.03-1.1]	<0.001

Peripheral low voltage	Saguner, 2014	106 (51)	HR	1.29 [0.63-2.66]	0.480		
ARVC associated mutation carriers							
TWI V1-V2	te Riele, 2013	69 (11)	OR	0.87 [0.09-8]	0.900		
TWI V1-V2 / V4-V6 / V1-V4 with CRBBB	Zorzi, 2016	116 (10)	OR	0.55 [0.03-10.26]	1.000		
				10.73 [2.67-			
TWI V1-V3	Zorzi, 2016	116 (10)	OR	15.12]	0.001		
TWI V1-V3 (or beyond)	te Riele, 2013	69 (11)	OR	9.24 [1.81-47.02]	0.002		
TWI ≥3 precordial leads	Bhonsale, 2013	215 (86)	HR		n.a.	4.2 [1.2-14.5]	0.035
	Protonoratos,						
Repolarization abnormalities (TFC10)	2016	105 (43)	OR	6.41 [2.61-15.72]	<0.001		
Epsilon wave	Zorzi, 2016	116 (10)	OR	6.38 [1.01-44.47]	0.049		
				16.71 [0.64-			
	te Riele, 2013	69 (11)	OR	438.63]	0.091		
				11.14 [2.23-			
TAD >55ms	Zorzi, 2016	116 (10)	OR	23.69]	<0.001		
	te Riele, 2013	69 (11)	OR	3.11 [0.75-12.86]	0.117		
	Protonoratos,						
Depolarization abnormalities (TFC10)	2016	105 (43)	OR	4.76 [2.45-17.35]	0.001		
Abnormal ECG (TFC10)	te Riele, 2013	69 (11)	OR	10 [1.2-83.24]	0.012		
Composite ECG characteristics	Bhonsale, 2013	215 (86)	KM		<0.001		

Supplementary Table 7. Risk factor estimates; Arrhythmia

Arrhythmia							
Risk factor	Author, year	Size (events)	Statistic	Crude [95%CI]	p-value	Adjusted [95%CI]	p-value
Definite ARVC diagnosis							
PVC >10/h	Battipaglia, 2012	30 (5)	OR	0.23 [0.02-2.37]	0.217		
PVC >500/24h	Canpolat, 2013	78 (39)	HR	2.6 [1.12-6.25]	0.026		
	te Riele, 2016	96 (21)	OR	8.78 [1.09-70.71]	0.017		
PVC >1000/24h	Mazzanti, 2016	267 (47)	HR	1.01 [0.47-2.18]	0.984		
	Santangeli, 2012	32 (12)	HR	0.57 [0.17-1.9]	0.360		
PVC count	te Riele, 2016	96 (21)	Means		0.001		
	Battipaglia, 2012	30 (5)	Means		0.990		
	Folino, 2002	46 (8)	Means		0.001		
Non-sustained VT	Mazzanti, 2016	267 (47)	HR	1.4 [0.78-2.51]	0.256		
	Migliore, 2013	69 (19)	HR	1.8 [0.3-5.7]	0.720		
	Santangeli, 2012	32 (12)	HR	0.87 [0.26-2.9]	0.830		
	Corrado, 2010	106 (25)	HR	1.74 [1.35-3.19]	0.030	1.62 [0.96-4.62]	0.068
	Battipaglia, 2012	30 (5)	OR	1 [0.09-11.03]	1.000		
Sustained or non-sustained VT	Mast, 2015	38 (20)	HR	22.34 [0.01-83633.53]	0.459		n.s.
	Roguin, 2004	42 (33)	OR	18.4 [2.02-167.31]	0.001		
Sustained or non-sustained VT, non-PKP2 subgroup	Dalal, 2006	48 (25)	KM		<0.05		
Sustained or non-sustained VT, PKP2 subgroup	Dalal, 2006	48 (25)	KM		0.120		
Sustained or non-sustained VT, stable	Canpolat, 2013	78 (39)	HR	1.72 [1.28-3.32]	0.004		
Sustained or non-sustained VT, symptomatic	Martin, 2016	26 (13)	HR	1.4 [0.8-2.6]	0.410		
Sustained or non-sustained VT	Schuler, 2012	26 (12)	OR	2.22 [0.33-15.18]	0.415		
		305					<0.001
Sustained or non-sustained VT or VF	Peters, 2012	(101)	OR	5.84 [2.93-10.23]	<0.001	5.33 [2.8-9.87]	1
Sustained VT, aborted SCD or syncope	Marcus, 2009	95 (32)	OR	5.54 [1.19-25.75]	0.022		
Sustained VT	Migliore, 2013	69 (19)	HR	1.1 [0.4-2.5]	0.900		
	Mazzanti, 2016	267 (47)	HR	3.37 [1.87-6.07]	<0.001	2.19 [1.12-4.32]	0.023
	Lin, 2017	70 (38)	HR	1.86 [0.87-3.97]	0.111		
						12.62 [1.55-102.98]	0.018
	Liao, 2014	32 (13)	OR	7.22 [1.44-36.22]	0.016	14 [1.7-21.1]	0.015
Sustained VT or aborted SCD	Corrado, 2003	132 (64)	OR		n.a.		
Aborted SCD	Marcus, 2009	95 (32)	OR	3.02 [0.93-9.82]	0.073		
	Schuler, 2012	26 (12)	OR	4 [0.36-45.1]	0.262		<0.001
						79 [6.8-90.6]	1
Arrhythmia TFC10 minor	Corrado, 2003	132 (64)	OR		n.a.		
Arrhythmia TFC10 major	Kikuchi, 2016	90 (47)	HR	1.84 [0.71-4.76]	0.210		
Fast VT/VF vs. Slow VT or non-sustained	Kikuchi, 2016	90 (47)	HR	3.29 [1.02-10.61]	0.046		
VT cycle length, ms	Pezawas, 2006	34 (12)	KM		<0.001		
VT cycle length, ms	Bernués, 2016	41 (11)	HR	0.99 [0.98-1.01]	0.432		
Atrial fibrillation	Mazzanti, 2016	267 (47)	HR	3.51 [1.38-8.93]	0.008	4.38 [1.7-11.29]	0.002
Atrial fibrillation / flutter	Schuler, 2012	26 (12)	OR	0.6 [0.05-7.63]	0.694		
HRV: RR interval, ms	Battipaglia, 2012	30 (5)	Means		0.450		
HRV: RR interval SD (SDNN), ms	Battipaglia, 2012	30 (5)	Means		0.004		
HRV: RR interval SD (SDNN), ms	Folino, 2002	46 (8)	Means		n.s.		
HRV: RR interval SD daylight (SDNNd), ms	Folino, 2002	46 (8)	Means		n.s.		
HRV: amplitude RR interval oscillations <0.04 Hz, ms							
HRV: low-frequency amplitude, ms	Battipaglia, 2012	30 (5)	Means		0.003		
HRV: Low frequency (0.04-0.15 Hz), ms	Battipaglia, 2012	30 (5)	HR		n.a.	0.88 [0.78-0.99]	0.047
HRV: High frequency (0.15-0.49 Hz), ms	Battipaglia, 2012	30 (5)	Means		0.002		
HRV: LF/HF ratio	Battipaglia, 2012	30 (5)	Means		0.005		
HRV: Mean heart rate in 24h, bpm	Battipaglia, 2012	30 (5)	Means		0.320		
HRV: Mean heart rate daytime, bpm	Folino, 2002	46 (8)	Means		0.019		
HRV: Mean heart rate nighttime, bpm	Folino, 2002	46 (8)	Means		0.039		
	Folino, 2002	46 (8)	Means		n.s.		
Definite or borderline ARVC diagnosis							
PVC >1000/24h	Link, 2014	108 (48)	HR		0.553		
	Bhonsale, 2011	84 (40)	HR	3.12 [1.16-8.35]	0.024	3.48 [0.72-16.98]	0.123
	Piccini, 2005	67 (44)	OR	2.22 [0.55-8.94]	0.260		
PVC seen on ECG	Saguner, 2014	106 (51)	HR	1.2 [0.61-2.35]	0.600		
Non-sustained VT	Bhonsale, 2011	84 (40)	HR	3.83 [1.92-7.61]	<0.001	10.54 [2.4-46.19]	0.002
	Saguner, 2013	62 (30)	OR	2.31 [0.67-7.94]	0.230		
	Piccini, 2005	67 (44)	OR	0.63 [0.19-2.1]	0.452	6.29 [0.99-40.02]	0.051
Sustained VT, stable	Chung, 2016	63 (19)	HR	4.1 [0.93-18.07]	0.060		
Sustained VT, stable	Saguner, 2013	62 (30)	OR	0.61 [0.21-1.79]	0.432		
Sustained VT/VF	Link, 2014	108 (48)	HR		<0.001		
	Saguner, 2013	62 (30)	OR	3.43 [1.17-10.04]	0.036		
	Piccini, 2005	67 (44)	OR	8.5 [2.68-26.95]	0.000	11.4 [1.61-81.22]	0.015
	Piccini, 2005	67 (44)	KM		0.001		
Aborted SCD	Saguner, 2013	62 (30)	OR	1.49 [0.3-7.28]	0.703		
Inappropriate ICD shock	Bhonsale, 2011	84 (40)	HR	0.86 [0.42-1.77]	0.686		
ARVC associated mutation carriers							
PVC >500/24h	te Riele, 2013	69 (11)	OR	17.78 [1.77-178.67]	0.002		
PVC >500/24h or nsVT	te Riele, 2013	69 (11)	OR	15.6 [1.57-155.42]	0.004		
Non-sustained VT	Zorzi, 2016	116 (10)	OR	5.05 [0.84-35.23]	0.100		
	Bhonsale, 2013	215 (86)	OR	19.43 [9.66-39.08]	<0.001		
	te Riele, 2013	69 (11)	OR	10.75 [1.48-78.07]	0.006		
PVC count	Bhonsale, 2013	215 (86)	Means		<0.001		
Aborted SCD	Bhonsale, 2013	215 (86)	OR	20.91 [1.16-376.26]	0.039		
Arrhythmia TFC10 minor	Zorzi, 2016	116 (10)	OR	5.73 [1.49-22.08]	0.010		
Arrhythmia TFC10 major	Zorzi, 2016	116 (10)	OR	10.14 [0.19-537.92]	0.253		

Supplementary Table 8. Risk factor estimates; Electrophysiology study

Electrophysiology study							
Risk factor	Author, year	Size (events)	Statistic	Crude [95%CI]	p-value	Adjusted [95%CI]	p-value
Definite ARVC diagnosis							
Inducible sustained VT/VF	Migliore, 2013	69 (19)	HR	1.4 [0.5-5]	0.440		
	Battipaglia, 2012	30 (5)	HR		n.a.	0.35 [0.02-5]	0.440
	Corrado, 2010	106 (25)	HR	1.03 [0.23-3.61]	0.980		
	Battipaglia, 2012	30 (5)	OR	11 [1.27-95.18]	0.060		
	Roguin, 2004	42 (33)	OR	5.63 [1.15-27.44]	0.024	11.2 [1.23-101.24]	0.031
	Wichter, 2004	60 (41)	OR		n.a.	2.16 [0.94-5]	0.069
Inducible sustained VT/VF, non-PKP2 subgroup	Dalal, 2006	48 (25)	KM		<0.01		
Inducible sustained VT/VF, PKP2 subgroup	Dalal, 2006	48 (25)	KM		0.800		
				PPV 63% NPV 93%			
Inducible sustained VT	Pezawas, 2006	34 (12)					
Inducible monomorphic sustained VT	Santangeli, 2012	32 (12)	HR	1.01 [0.27-3.76]	0.990		
Inducible VT, post-procedure	Berruezo, 2016	41 (11)	HR	0.04 [0.01-47.8]	0.366		
Fragmented electrograms (>3 deflections, amplitude <1.5mV, >100ms)	Santangeli, 2012	32 (12)	HR	20.96 [2.68-163.7]	0.004	21.22 [1.79-251.83]	0.015
Fragmented electrograms (>3 deflections, amplitude <1.5mV, >70ms)	Migliore, 2013	69 (19)	HR	1.2 [0.7-3.1]	0.320		
Endocardial bipolar area <1.5mV, per 5%	Lin, 2017	70 (38)	HR	1.05 [0.86-1.22]	0.793		
Endocardial bipolar area <1.5mV, cm2	Berruezo, 2016	41 (11)	HR	0.99 [0.97-1.02]	0.946		
Endocardial bipolar area <1.5mV, cm2	Santangeli, 2012	32 (12)	HR	1.01 [0.98-1.03]	0.680		
					<0.00		<0.00
Endocardial bipolar area <1.5mV, per 5%	Migliore, 2013	69 (19)	HR	1.7 [1.5-2]	1	1.6 [1.2-1.9]	1
Endocardial RV mean bipolar mV	Lin, 2017	70 (38)	HR	0.84 [0.65-1.07]	0.157		
Endocardial RV mean unipolar mV	Lin, 2017	70 (38)	HR	0.87 [0.72-1.06]	0.159		
Endocardial unipolar area <6mV, per 5%	Migliore, 2013	69 (19)	HR	1.3 [0.6-4.3]	0.310		
Epicardial bipolar area <1.5 mV, cm2	Berruezo, 2016	41 (11)	HR	0.99 [0.98-1.01]	0.304		
Epicardial bipolar area <1.5mV, %	Lin, 2017	70 (38)	HR	0.99 [0.97-1.02]	0.464		
Epicardial RV mean bipolar mV	Lin, 2017	70 (38)	HR	0.99 [0.99-1.01]	0.615		
Epicardial RV mean unipolar mV	Lin, 2017	70 (38)	HR	1.02 [0.78-1.33]	0.900		
Epicardial unipolar area <5.5mV, %	Lin, 2017	70 (38)	HR	1.01 [0.97-1.04]	0.706		
Endocardial late potentials, >20ms from electrogram	Santangeli, 2012	32 (12)	HR	5.59 [1.5-20.79]	0.010	0.77 [0.14-4.13]	0.760
Endocardial very late potentials, >100ms after QRS V1	Santangeli, 2012	32 (12)	HR	3.79 [1.13-12.67]	0.030	1.04 [0.28-3.91]	0.950
					<0.00		
Endocarial area with LPs, %	Lin, 2017	70 (38)	HR	1.36 [1.16-1.58]	1	1.07 [1.01-1.13]	0.024
Epicardial area with LPs, %	Lin, 2017	70 (38)	HR	1.04 [0.96-1.13]	0.298		
Number of electrograms with delayed component (late potential >2 consecutive)	Berruezo, 2016	41 (11)	HR	0.73 [0.98-1.01]	0.732		
Endocardial activation time, ms	Lin, 2017	70 (38)	HR	1 [0.98-1.01]	0.101		
Epicardial activation time, per ms	Lin, 2017	70 (38)	HR	1 [0.99-1]	0.247		
Definite or borderline ARVC diagnosis							
Inducible sustained VT/VF	Chung, 2016	63 (19)	HR	3.72 [1.44-9.61]	0.007	1.16 [0.41-3.28]	0.780
	Link, 2014	108 (48)	HR		0.050		
	Bhonsale, 2011	84 (40)	HR	3.13 [1.41-6.91]	0.005	4.52 [1.37-14.96]	0.013
Inducible sustained VT/VF, Definite vs. Probable ARVC	Piccini, 2005	67 (44)	KM		0.011		
Inducible polymorphic sustained VT/VF	Piccini, 2005	67 (44)	OR	1.4 [0.39-5.07]	0.509		
Inducible VF	Saguner, 2013	62 (30)	OR	0.91 [0.28-2.93]	1.000		
Inducible sustained VT	Saguner, 2013	62 (30)	OR	2.9 [0.97-8.66]	0.067		
Inducible monomorphic sustained VT	Saguner, 2013	62 (30)	HR	2.99 [1.23-7.72]	0.016	2.52 [1.03-6.16]	0.043
	Piccini, 2005	67 (44)	OR	5.48 [1.79-16.79]	0.003		
Inducible monomorphic non-sustained VT	Saguner, 2013	62 (30)	OR	1.53 [0.49-4.81]	0.566		
Inducible polymorphic non-sustained VT	Saguner, 2013	62 (30)	OR	0.1 [0.01-0.91]	0.077		
Inducible VT ≥2 morphologies	Saguner, 2013	62 (30)	OR	1.7 [0.59-4.93]	0.423		
Inducible VT LBBB morphology	Saguner, 2013	62 (30)	OR	0.75 [0.16-3.44]	0.722		
Inducible VT LBBB morphology, inferior axis	Saguner, 2013	62 (30)	OR	0.64 [0.2-2.07]	0.553		
Inducible VT LBBB morphology, superior axis	Saguner, 2013	62 (30)	OR	0.8 [0.25-2.58]	0.766		
Inducible VT origin (5 RV, 1 LV)	Saguner, 2013	62 (30)	OR		n.s.		
Inducible supraventricular tachycardia	Saguner, 2013	62 (30)	OR	0.44 [0.13-1.49]	0.240		
Dual AVn physiology	Saguner, 2013	62 (30)	OR	0.67 [0.17-2.64]	0.733		
Normal AVn physiology	Saguner, 2013	62 (30)	OR	0.9 [0.32-2.5]	1.000		
HV conduction prolonged	Saguner, 2013	62 (30)	OR	3 [0.54-16.81]	0.249		
HV conduction, ms	Saguner, 2013	62 (30)	Means		0.715		
AH conduction, ms	Saguner, 2013	62 (30)	Means		0.669		

Supplementary Table 9. Risk factor estimates; Imaging

Structural/functional imaging							
Risk factor	Author, year	Size (events)	Statistic	Crude [95%CI]	p-value	Adjusted [95%CI]	p-value
Definite ARVC diagnosis							
RVEF, % decrease	Pezawas, 2006	34 (12)	HR	1.1 [1.09-1.19]	0.016		
	Berruezo, 2016	41 (11)	HR	1.02 [0.91-1.16]	0.991		
	Canpolat, 2013	78 (39)	HR	3.24 [1.98-5.23]	0.001	3.76 [2.45-6.24]	<0.001
	Santangeli, 2012	32 (12)	HR	1.01 [0.93-1.1]	0.800		
	Liao, 2014	32 (13)	OR	0.99 [0.93-1.05]	0.749		
	Folino, 2002	46 (8)	Means		n.s.		
	Marcus, 2009	95 (32)	Means		0.730		
	Turmini, 1999	38 (15)	OR		0.000	4.66 [0-0]	0.020
RVEF <50%	Liao, 2014	32 (13)	OR	0.93 [0.22-4]	0.926		
RVEF <40%	Mast, 2015	38 (20)	HR	1.06 [1-1.13]	0.044		
RVFAC, per % decrease	Migliore, 2013	69 (19)	HR	1 [0.91-1.11]	0.520		n.s.
	Schuler, 2012	26 (12)	OR	1.07 [0.97-1.17]	0.173		
RVFAC <24%	Schuler, 2012	26 (12)	OR	0.16 [0.02-1.66]	0.125		
TAPSE, per mm decrease	Mast, 2015	38 (20)	HR	1.08 [0.95-1.23]	0.264		n.s.
	Schuler, 2012	26 (12)	OR	0.91 [0.76-1.09]	0.326		
RVOT PSAX, per mm/m2 increase	Mast, 2015	38 (20)	HR	1.21 [1.08-1.36]	0.001	1.2 [1.1-1.3]	<0.05
RVEDV, ml/m2	Migliore, 2013	69 (19)	HR	1.1 [0.9-1.3]	0.810		
	Folino, 2002	46 (8)	Means		n.s.		
RVEDV, per ml increase	Berruezo, 2016	41 (11)	HR	1 [0.98-1.01]	0.991		
RVEDA, per cm2 increase	Schuler, 2012	26 (12)	OR	1.1 [0.95-1.28]	0.189		
RVEDD, per mm increase	Canpolat, 2013	78 (39)	HR	2.27 [1.45-4.15]	0.002	1.12 [0.77-1.45]	0.452
RV dilatation	Schuler, 2012	26 (12)	OR	3.94 [0.72-21.59]	0.114		
RV dilatation (on echo)	Roguin, 2004	42 (33)	OR	3.91 [0.84-18.17]	0.070		
RV dilatation (on MRI)	Roguin, 2004	42 (33)	OR	1.57 [0.32-7.75]	0.660		
RV dilatation, moderate/severe	Roguin, 2004	42 (33)	OR	12.51 [0.67-233.31]	0.013		
RV dilatation (none vs. mild vs. moderate-severe)	Roguin, 2004	42 (33)	OR	3.91 [0.84-18.17]	0.070	3.41 [0.88-14.21]	0.070
RV aneurysm	Schuler, 2012	26 (12)	OR	0.31 [0.01-4.62]	0.651		
RV wall motion abnormalities	Roguin, 2004	42 (33)	OR	5.89 [0.66-52.7]	0.080		
	Liao, 2014	32 (13)	OR	1.16 [0.28-4.92]	0.837		
	Roguin, 2004	42 (33)	OR	2.33 [0.4-13.61]	0.920		
RV dysfunction	Battipaglia, 2012	30 (5)	OR	1.42 [0.2-10.23]	0.730		
	Roguin, 2004	42 (33)	OR	4.75 [0.85-26.43]	0.270		
	Peters, 2012	305 (101)	OR	1.36 [0.41-3.46]	0.500		
	Roguin, 2004	42 (33)	OR	2.53 [0.26-24.51]	0.440		
RV dysfunction, severe (≥2 WMA or RVEF<45%)	Wichter, 2004	60 (41)	OR		n.a.	2.09 [1.03-4.24]	0.041
	Corrado, 2010	106 (25)	HR	1.07 [0.52-3.19]	0.350		
RV disease regional vs diffuse, non-PKP2 subgroup	Dalal, 2006	48 (25)	KM		<0.05		
RV disease regional vs diffuse, PKP2 subgroup	Dalal, 2006	48 (25)	KM		0.780		
RV fatty infiltration	Santangeli, 2012	32 (12)	HR	0.71 [0.23-2.2]	0.550		
	Roguin, 2004	42 (33)	OR	1.15 [0.25-5.33]	0.860		
RV delayed enhancement	Santangeli, 2012	32 (12)	HR	0.77 [0.24-2.46]	0.660		
TFC10 imaging minor	Kikuchi, 2016	90 (47)	HR	0.24 [0.07-0.77]	0.017		
	te Riele, 2016	96 (21)	OR	1.6 [0.53-4.82]	0.532		
TFC10 imaging minor/major	Lin, 2017	70 (38)	HR	1.07 [0.63-1.8]	0.802		
				27.48 [0.14-53874.21]	0.219		n.s.
TFC10 imaging major	Mast, 2015	38 (20)	HR		0.006		
	Kikuchi, 2016	90 (47)	HR	5.12 [1.59-16.48]	0.006		
	Martin, 2016	26 (13)	HR	1.1 [0.93-1.3]	1.000		
	te Riele, 2016	96 (21)	OR	4.82 [1.71-13.56]	0.002		
LVEF, % decrease	Battipaglia, 2012	30 (5)	Means		0.270		
	Folino, 2002	46 (8)	Means		n.s.		
	Marcus, 2009	95 (32)	Means		0.960		
	Pezawas, 2006	34 (12)	HR	1.01 [0.91-1.11]	0.920	1.2 [1.04-1.38]	0.011
	Mast, 2015	38 (20)	HR	1.1 [1.03-1.16]	0.002		n.s.
	Migliore, 2013	69 (19)	HR	1 [0.91-1.11]	0.960		
	Corrado, 2003	132 (64)	OR		n.a.	1.06 [1.05-1.12]	0.037
	Berruezo, 2016	41 (11)	HR	0.99 [0.93-1.06]	0.675		
LVEF <55%	Corrado, 2010	106 (25)	HR	1.21 [0.87-4.73]	0.100	1.13 [0.64-3.46]	0.590
					<0.00		
LVEF <50%	Mast, 2015	38 (20)	HR	9.52 [3.01-30.15]	1		n.s.
	Liao, 2014	32 (13)	OR	3.84 n.a.	1.000		
LVEDV, ml/m2	Migliore, 2013	69 (19)	HR	0.9 [0.9-1]	1.000		
	Folino, 2002	46 (8)	Means		n.s.		
LV wall motion abnormalities	Mast, 2015	38 (20)	HR	4.67 [1.8-12.09]	0.002		n.s.
LV abnormal deformation imaging	Mast, 2015	38 (20)	HR	4.34 [1.77-10.64]	0.001	4.9 [1.7-14.2]	0.010
LV systolic peak strain, per % decrease	Mast, 2015	38 (20)	HR	1.19 [1.08-1.32]	0.001		n.s.
LV delayed enhancement	Santangeli, 2012	32 (12)	HR	1.6 [0.42-6.05]	0.490		
LV dysfunction	Peters, 2007	313 (26)	OR	14.68 [2.67-49.68]	0.002	14.8 [2.37-53.47]	0.001
	Wichter, 2004	60 (41)	OR		n.a.	1.94 [0.93-4.05]	0.078
					<0.00		
	Canpolat, 2013	78 (39)	HR	4.32 [2.55-6.72]	1	2.88 [2.12-5.34]	0.001
	Battipaglia, 2012	30 (5)	OR	0.58 [0.03-13.06]	0.735		
	Peters, 2012	305 (101)	OR	7.61 [2.48-12.32]	<0.00		
					1		
					<0.00		n.s.
	Mast, 2015	38 (20)	HR	10.45 [3.23-33.84]	1		
	Schuler, 2012	26 (12)	OR	5 [0.94-26.53]	0.059		
LV abnormal diastolic function	Mast, 2015	38 (20)	HR	1.03 [0.4-2.68]	0.955		
Predominant LV involvement	Berruezo, 2016	41 (11)	HR	3.41 [1.03-11.25]	0.044	3.28 [1-10.78]	0.050
RA dilatation	Schuler, 2012	26 (12)	OR	0.86 [0.16-4.47]	0.855		
LA dilatation	Schuler, 2012	26 (12)	OR	1 [0.15-6.53]	0.990		
Definite or borderline ARVC diagnosis							
RVEF, per % decrease	Link, 2014	108 (48)	HR		0.334		
	Chung, 2016	63 (19)	HR	0.98 [0.93-1.03]	0.500		
					<0.00		<0.00
RVFAC, per % decrease	Saguner, 2014	70 (37)	HR	1.08 [1.04-1.12]	1	1.08 [1.04-1.12]	1
	Sarvari, 2011	69 (42)	OR	1.18 [1.08-1.3]	0.001	1.17 [1.01-1.35]	0.040
RVFAC <33%	Saguner, 2014	70 (37)	HR	3.12 [1.42-6.87]	0.005		

	Saguner, 2013	62 (30)	OR	1.91 [0.7-5.25]	0.390 <0.00		
RVFAC <23%	Saguner, 2014	70 (37)	HR	4.49 [2.25-8.97]	1		
TAPSE, per mm decrease	Saguner, 2014	70 (37)	HR	1.05 [0.99-1.12]	0.090	1.01 [0.94-1.08]	0.730
TAPSE, per mm/m2 decrease	Saguner, 2014	70 (37)	HR	1.09 [0.98-1.2]	0.120		
TAPSE <17mm	Saguner, 2014	70 (37)	HR	2.15 [1.1-4.17]	0.020		
RVOT PSAX, mm	Sarvari, 2011	69 (42)	Means		<0.01		
RVEDA, cm2	Sarvari, 2011	69 (42)	Means		<0.01		
RVEDA, per cm2 increase	Saguner, 2014	70 (37)	HR	1.05 [1.02-1.09]	1	1.05 [1.01-1.08]	0.004
RVEDA, per cm2/m2 increase	Saguner, 2014	70 (37)	HR	1.08 [1.03-1.14]	0.002		
RVEDA ≥28cm2	Saguner, 2014	70 (37)	HR	2.96 [1.48-5.91]	0.002		
RVESA, cm2	Sarvari, 2011	69 (42)	Means		<0.01		
RV contraction duration dispersion, per 10ms	Sarvari, 2011	69 (42)	OR	1.71 [1.22-2.39]	0.002	1.66 [1.06-2.58]	0.030
RV wall motion abnormalities	Saguner, 2014	70 (37)	HR	1.56 [0.48-1.96]	0.380		
RV wall motion abnormalities, ≥2 regions	Saguner, 2014	70 (37)	HR	2.08 [0.93-4.55]	0.080		
RV strain, per % decrease	Sarvari, 2011	69 (42)	OR	1.25 [1.08-1.44]	0.003	0.98 [0.76-1.26]	0.850
RV global dysfunction	Piccini, 2005	67 (44)	OR	3.1 [1.03-9.35]	0.040		
RV delayed enhancement	Chung, 2016	63 (19)	HR	0.67 [0.25-1.77]	0.420		
Moderate/severe T1	Saguner, 2014	70 (37)	HR	1.99 [0.71-5.55]	0.190		
TFC10 imaging minor/major	Chung, 2016	63 (19)	HR	0.91 [0.37-2.26]	0.850		
TFC10 imaging major	Bhonsale, 2011	84 (40)	HR	0.87 [0.25-3.07]	0.826		
LVEF, per % decrease	Saguner, 2014	70 (37)	HR	1.01 [0.98-1.04]	0.540		
	Sarvari, 2011	69 (42)	OR	1.06 [0.99-1.12]	0.090	1.03 [0.93-1.14]	0.600
	Link, 2014	108 (48)	HR		0.009		
	Chung, 2016	63 (19)	HR	1.01 [0.97-1.05]	0.530		
LVEF <55%	Bhonsale, 2011	84 (40)	HR	1.28 [0.57-2.9]	0.552		
LVEF <50%	Saguner, 2013	62 (30)	OR	1.86 [0.57-6.06]	0.379		
LV global longitudinal strain, per % decrease	Sarvari, 2011	69 (42)	OR	1.41 [1.12-1.76]	0.003	1.22 [0.89-1.67]	0.220
LV contraction duration dispersion, ms	Sarvari, 2011	69 (42)	Means		<0.01		
LV dysfunction	Piccini, 2005	67 (44)	OR	0.46 [0.12-1.8]	0.260		
RA short axis, mm, per unit increase	Saguner, 2014	70 (37)	HR	1.04 [1.01-1.07]	0.010	1.03 [1-1.06]	0.037
RA short axis, mm/m2, per unit increase	Saguner, 2014	70 (37)	HR	1.06 [1.01-1.12]	0.020		
RA short axis ≥25mm/m2	Saguner, 2014	70 (37)	HR	2.03 [1.03-3.99]	0.040		
RA long axis, mm, per unit increase	Saguner, 2014	70 (37)	HR	1.03 [1-1.06]	0.060		
LA, mm/m2, per unit increase	Saguner, 2014	70 (37)	HR	1.03 [0.95-1.12]	0.460		
LA ≥23mm/m2	Saguner, 2014	70 (37)	HR	1.93 [0.88-4.25]	0.100		
ARVC associated mutation carriers							
RVeF, %	te Riele, 2013	69 (11)	Means		<0.00		
					1		
RVeF, %					<0.00		
RVeF, %					1		
RVeF, %					<0.00		
RV wall motion abnormalities	te Riele, 2013	69 (11)	OR	70.59 [3.91-1273.69]	1		
RV fatty infiltration	te Riele, 2013	69 (11)	OR	1.62 [0.29-9.08]	0.584		
RV delayed enhancement	te Riele, 2013	69 (11)	OR	35 [1.53-801.65]	0.001		
TFC10 imaging minor	Zorzi, 2016	116 (10)	OR	0.88 [0.05-17.03]	1.000		
	te Riele, 2013	69 (11)	OR	0.53 [0.03-10.47]	0.674		
	Protonorati, 2016	105 (43)	OR	6.44 [2.67-15.56]	<0.00		
TFC10 imaging minor/major					1		
					<0.00		
TFC10 imaging major	Zorzi, 2016	116 (10)	OR	15.33 [3.54-66.34]	1		
				185.77 [9.76-3536.64]	<0.00		
	te Riele, 2013	69 (11)	OR		1		
					<0.00		
LVEF, %	te Riele, 2013	69 (11)	Means		1		
LVEF <55%	Bhonsale, 2013	215 (86)	OR	5.07 [1.58-16.29]	0.006		
LVEDV, ml/m2	te Riele, 2013	69 (11)	Means		n.s.		
LV wall motion abnormalities	te Riele, 2013	69 (11)	OR	3 [0.48-18.86]	0.241		
LV fatty infiltration	te Riele, 2013	69 (11)	OR	8.74 [2.1-36.38]	0.001		
LV delayed enhancement	te Riele, 2013	69 (11)	OR	2.69 [0.43-16.61]	0.288		
	Protonorati, 2016	105 (43)	OR	7.5 [2.79-20.14]	<0.00		
LV involvement					1		
Dysfunction (RVFAC<24%/RVEF<40%/LVEF<45%)	Zorzi, 2016	116 (10)	OR	47.13 [9.3-223.7]	0.001		
					<0.00		
Biventricular involvement	te Riele, 2013	69 (11)	OR	10.94 [2.6-46.05]	1		
LV involvement only	te Riele, 2013	69 (11)	OR	0.69 [0.03-14.28]	0.810		
RV involvement only	te Riele, 2013	69 (11)	OR	3.57 [0.85-15.04]	0.083		

Supplementary Table 10. Risk factor estimates; Tissue histology

Tissue characterisation							
Risk factor	Author, year	Size (events)	Statistic	Crude [95%CI]	p-value	Adjusted [95%CI]	p-value
Definite ARVC diagnosis							
TFC10 Tissue characterization minor	Kikuchi, 2016	90 (47)	HR	1.1 [0.6-2.02]	0.760		
TFC10 Tissue characterization major	Kikuchi, 2016	90 (47)	HR	0.91 [0.49-1.67]	0.760		
TFC10 Tissue characterization minor/major	Lin, 2017	70 (38)	HR	1.23 [0.79-1.91]	0.359		
RV biopsy: fibro-fatty replacement	Liao, 2014	32 (13)	OR	0.69 [0.17-2.92]	0.618		
RV biopsy: fat	Roguin, 2004	42 (33)	OR	0.14 [0.01-2.07]	0.280		
RV biopsy: fibrosis	Roguin, 2004	42 (33)	OR	0.25 [0.01-5.72]	0.530		
RV biopsy: hypertrophy	Roguin, 2004	42 (33)	OR	0.5 [0.04-6.86]	0.910		

Supplementary Table 11. Sensitivity analysis

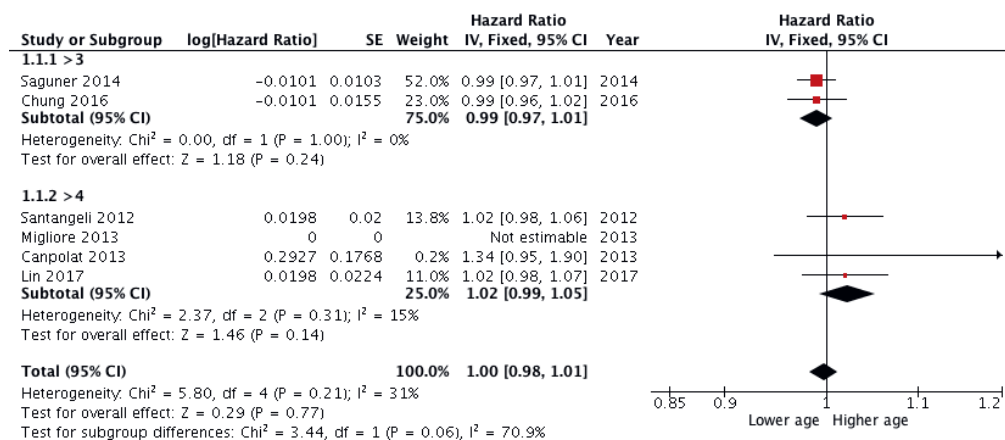
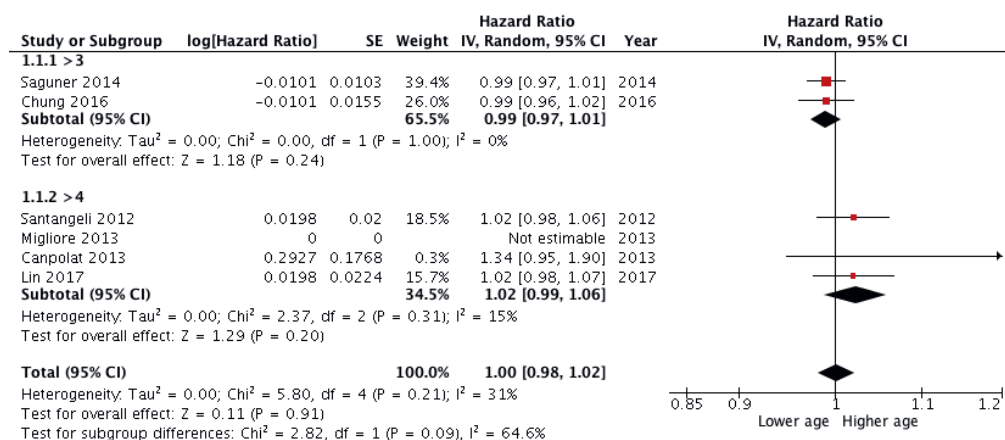
Risk factor	Domain	Overall studies		TFC 2010 only studies		Primary prevention only studies	
		(n)	HR (95%CI)	(n)	HR (95%CI)	(n)	HR (95%CI)
Age, per year increase	TFC ≥ 4	2	1.02 (0.97-1.01)	2	(=)	1	1.02 (0.98-1.06)
	TFC ≥ 3	4	0.99 (0.99-1.06)	4	(=)	0	
	TFC ≥ 4	3	0.99 (0.96-1.02)	2	(=)	1	1.36 (0.73-2.52)
Age <35yrs	TFC ≥ 3	0		0		0	
	TFC ≥ 4	7	1.83 (1.41-2.37)	6	1.89 (1.42-2.53)	2	1.47 (0.71-3.02)*
	TFC ≥ 3	4	1.42 (0.91-2.23)	4	(=)	1	0.95 (0.51-1.79)
Unexplained syncope	TFC ≥ 4	5	3.67 (2.75-4.90)	4	3.55 (2.35-5.36)	2	3.72 (2.37-5.83)
	TFC ≥ 3	2	2.04 (0.39-10.74)	2	(=)	1	0.91 (0.45-1.86)
	TFC ≥ 4	2	2.01 (0.76-5.33)	2	(=)	0	
Proband status	TFC ≥ 3	1	6.48 (2.30-18.24)	1	(=)	1	(=)
	TFC ≥ 4	4	1.25 (0.86-1.8)	3	1.22 (0.83-1.81)	2	1.26 (0.55-2.87)
	TFC ≥ 3	2	1.21 (0.39-3.8)	2	(=)	1	0.70 (0.29-1.67)
>1000 PVCs / 24h	TFC ≥ 4	2	0.86 (0.45-1.64)	2	(=)	1	0.57 (0.17-1.91)
	TFC ≥ 3	1	3.12 (1.16-8.37)	1	(=)	1	(=)
	TFC ≥ 4	3	1.54 (1.10-2.15)	2	1.28 (0.76-2.16)*	2	1.56 (0.95-2.56)*
Prior non-sustained VA	TFC ≥ 3	1	3.83 (1.92-7.63)	1	(=)	1	(=)
	TFC ≥ 4	3	2.05 (1.08-3.88)	3	(=)	n.a.	
	TFC ≥ 3	1	4.10 (0.93-18.07)	1	(=)	n.a.	
Prior sustained VA	TFC ≥ 4	4	1.18 (0.86-1.62)	3	1.18 (0.83-1.66)	1	1.20 (0.53-2.70)
	TFC ≥ 3	1	1.12 (0.54-2.32)	1	(=)	1	(=)
	TFC ≥ 4	2	1.17 (0.34-4.01)	2	(=)	1	1.48 (0.43-5.12)
Epsilon-wave	TFC ≥ 3	2	1.58 (0.90-2.77)	2	(=)	0	
	TFC ≥ 4	2	1.03 (0.61-1.72)	1	1.09 (0.64-1.94)	1	0.82 (0.27-2.51)
	TFC ≥ 3	2	1.40 (0.86-2.30)	2	(=)	1	1.06 (0.46-2.45)
SAECG, potentials	TFC ≥ 4	2	1.02 (0.39-2.64)	1	1.01 (0.27-3.77)	1	1.03 (0.26-4.08)
	TFC ≥ 3	3	3.24 (1.95-5.39)	3	(=)	1	3.13 (1.41-6.93)
	TFC ≥ 4	4	1.03 (0.97-1.09)	3	1.03 (0.96-1.11)	0	
VA inducible at EPS	TFC ≥ 3	2	1.01 (0.99-1.03)	2	(=)	0	
	TFC ≥ 4	4	1.14 (0.98-1.32)	3	1.28 (0.95-1.71)	1	1.01 (0.93-1.10)
	TFC ≥ 3	1	0.98 (0.93-1.03)	1	(=)	0	
LVEF, per % decrease	TFC ≥ 4	2	1.05 (0.99-1.10)	2	(=)	0	
	TFC ≥ 3	1	1.08 (1.04-1.12)	1	(=)	0	
	TFC ≥ 4	2	1.00 (0.98-1.03)	2	(=)	0	
RVEF, per % decrease	TFC ≥ 3	0		0		0	
	TFC ≥ 4	2	1.00 (0.98-1.03)	2	(=)	0	
	TFC ≥ 3	0		0		0	
RVFAC, per % decrease	TFC ≥ 4	2	1.00 (0.98-1.03)	2	(=)	0	
	TFC ≥ 3	0		0		0	
	TFC ≥ 4	2	1.00 (0.98-1.03)	2	(=)	0	
RVEDV, mL/m2	TFC ≥ 3	0		0		0	

Imaging TFC, any	TFC ≥ 4	2	1.09 (0.65-1.84)	2	(=)	0	
	TFC ≥ 3	1	0.91 (0.37-2.25)	1	(=)	0	
Imaging TFC, major	TFC ≥ 4	2	2.12 (0.48-9.41)	2	(=)	0	
	TFC ≥ 3	1	0.87 (0.25-3.04)	1	(=)	1	(=)

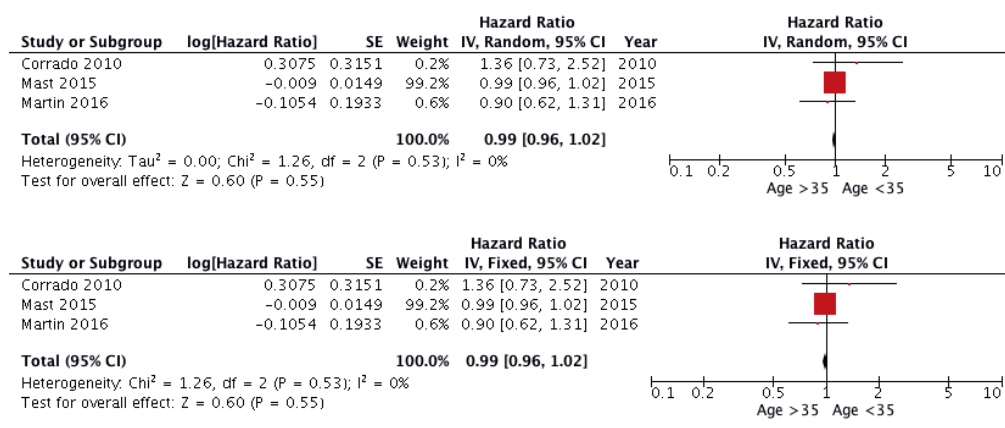
Supplementary Table 11. Sensitivity analysis for different selection criteria in studies. The results in the "Overall" column represent the main results as presented in Figure 2 in the main manuscript. The results in the "TFC 2010 only" column are the results when studies that based selection on the original 1994 criteria were excluded. The results in the "Primary prevention only" are from studies solely selecting patients that did not have sustained ventricular arrhythmias prior to inclusion. * = results that lost their significance compared to the main result. (=) = results are identical to the main result. Abbreviations: SCD = sudden cardiac death, PVC = premature ventricular complex, VT = ventricular tachycardia, VF = ventricular fibrillation, VA = ventricular arrhythmia, TWI = T-wave inversion, (SA)ECG = (signal-averaged) electrocardiogram, LP = late potential, EPS = electrophysiological study, LVEF = left ventricular ejection fraction, RVEF = right ventricular ejection fraction, RVEDV = right ventricular end-diastolic volume, TFC = task force criteria 2010.

Supplementary Figure 1. Individual meta-analyses

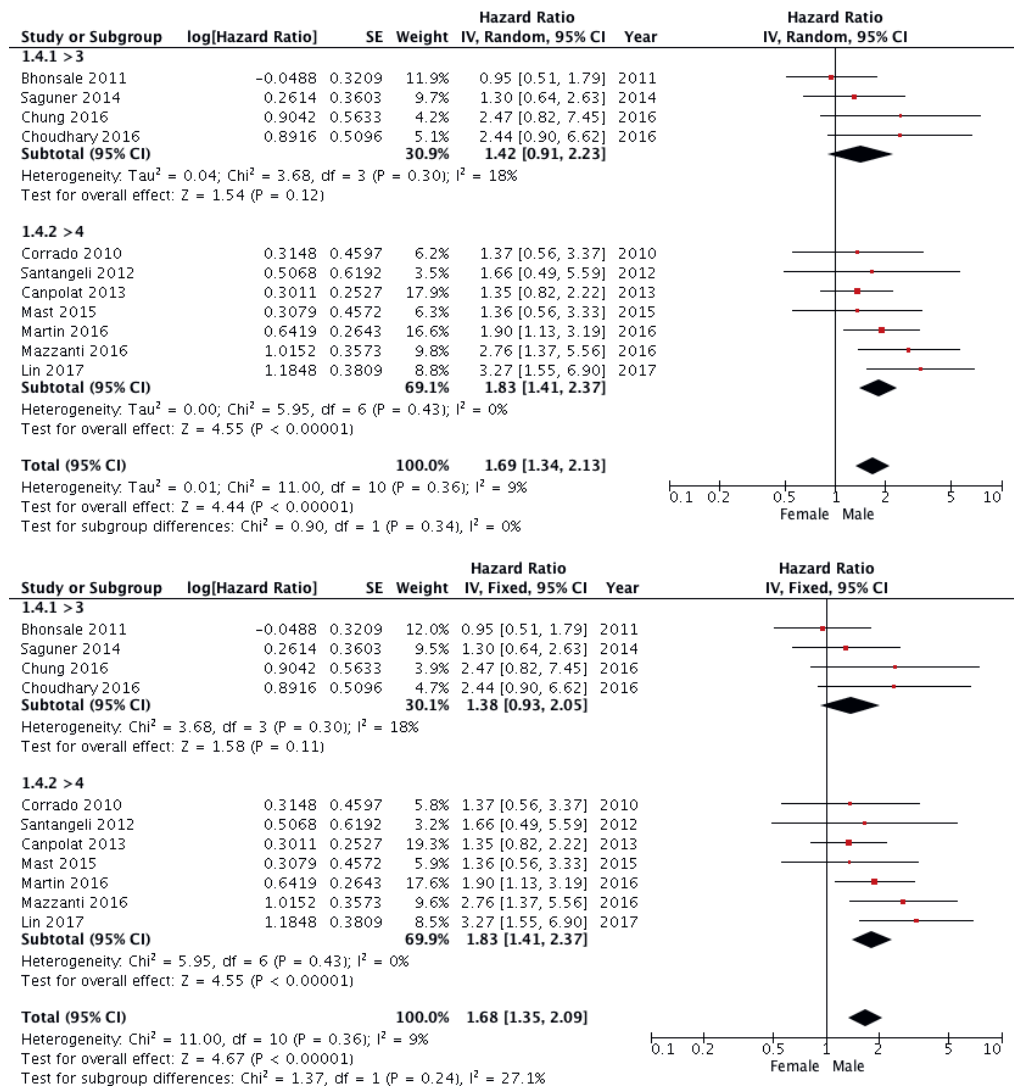
Age, per year increase



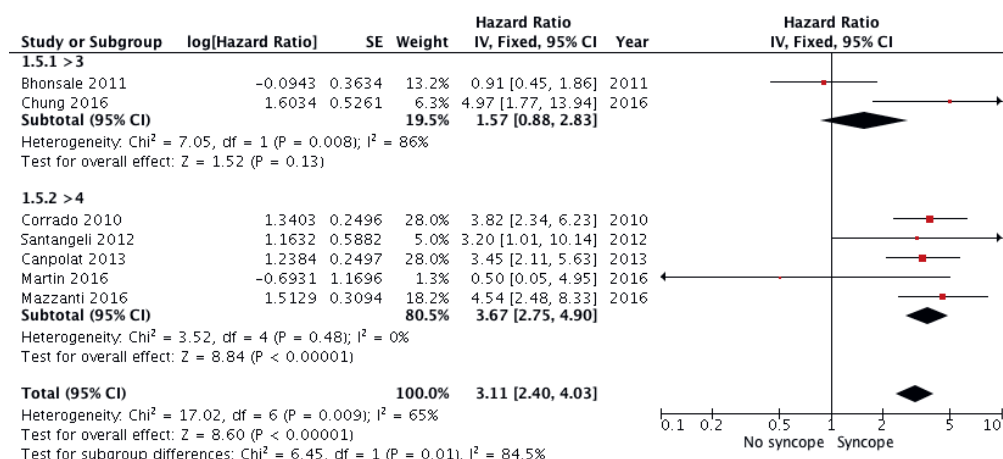
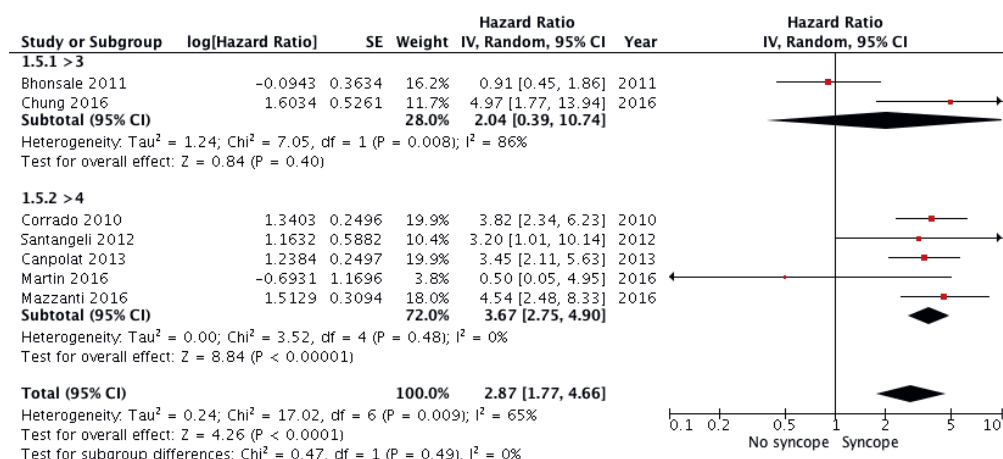
Age <35 years



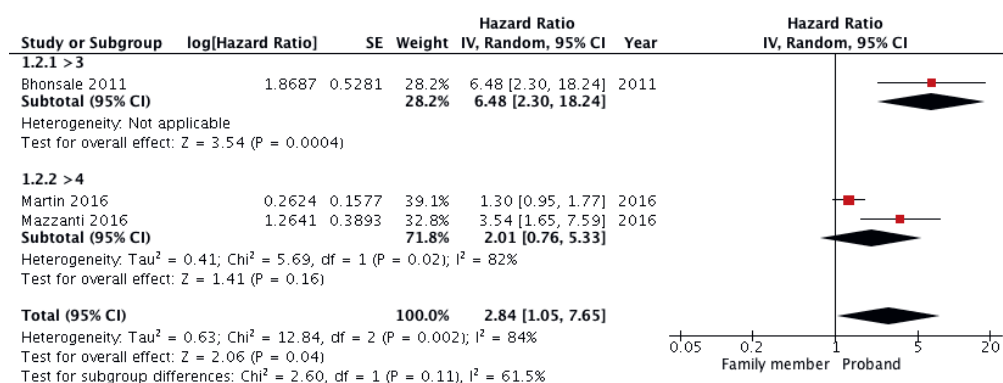
Male sex

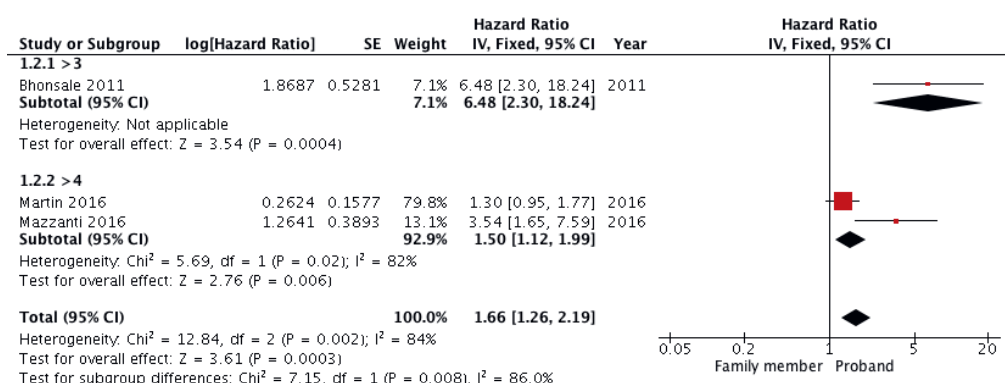


Unexplained syncope

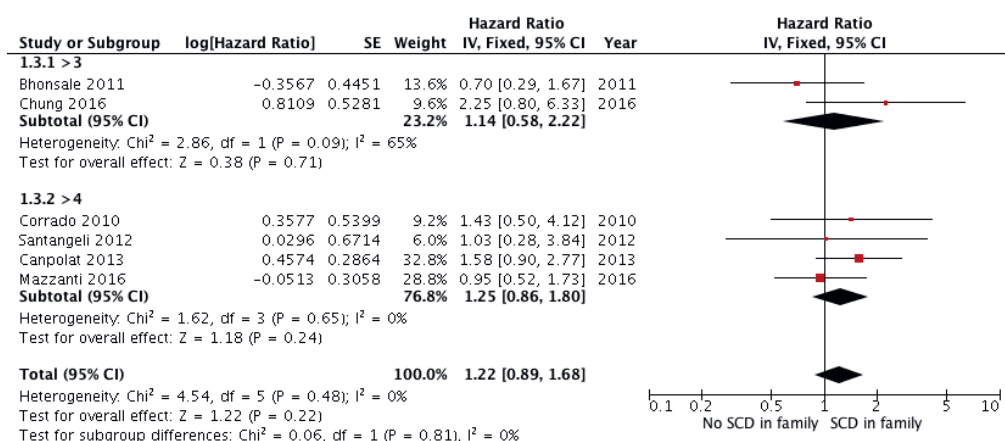
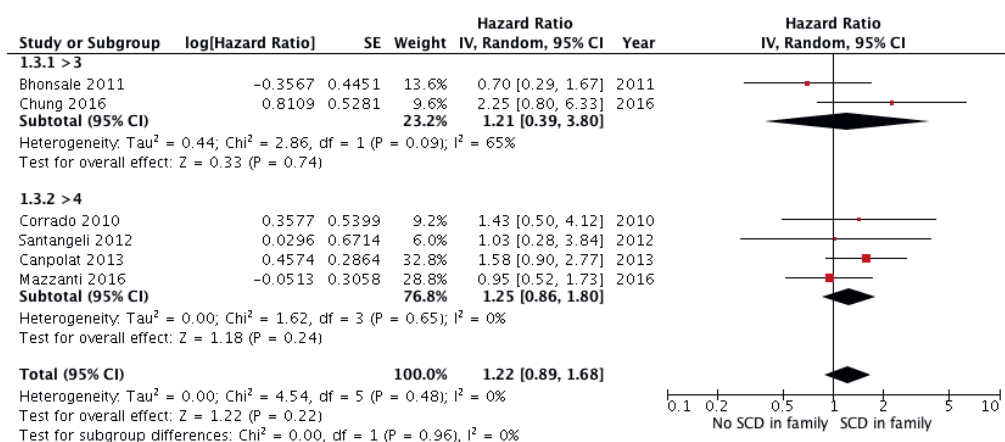


Proband status

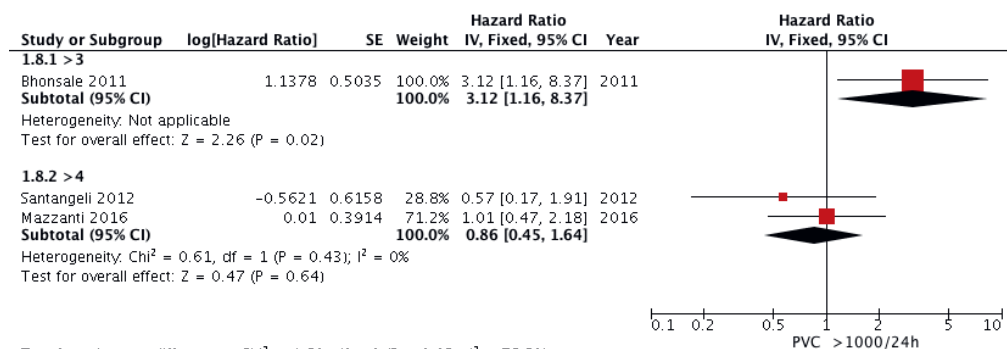
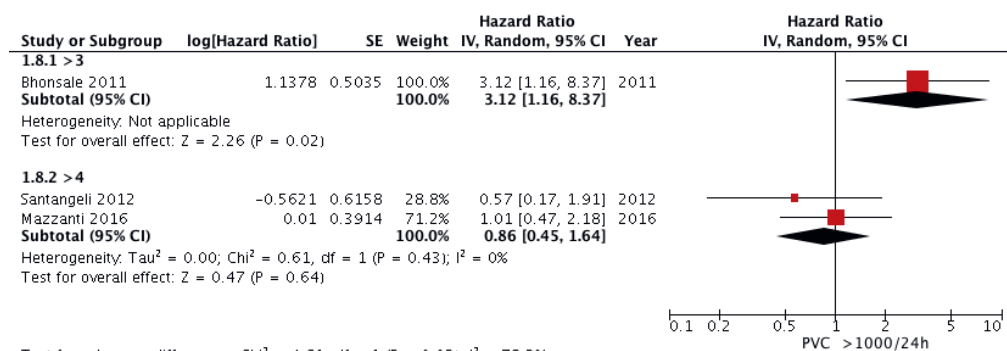




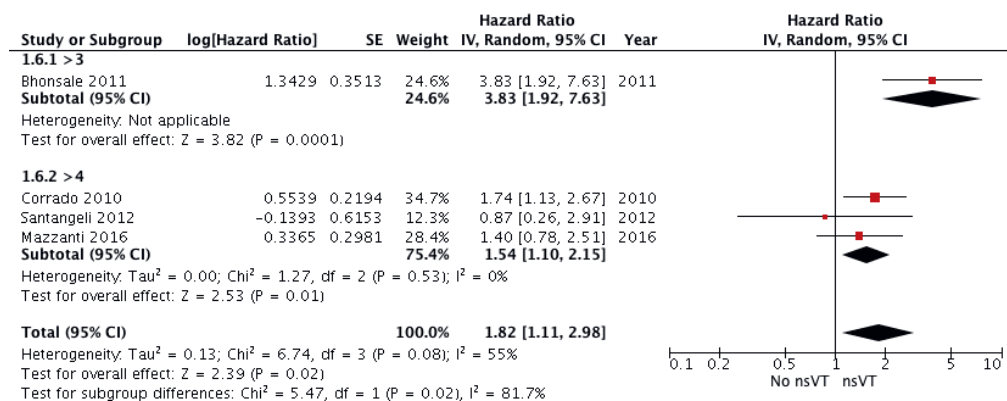
Family history of SCD <35 yrs

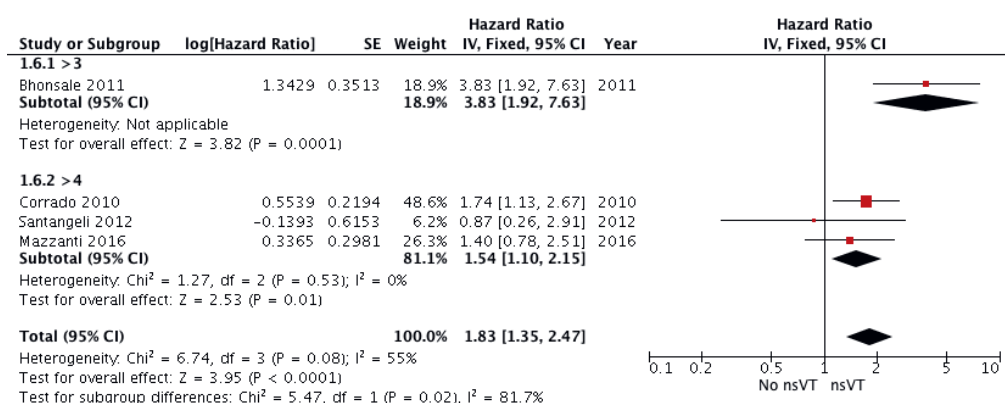


>1000 PVCs per 24h

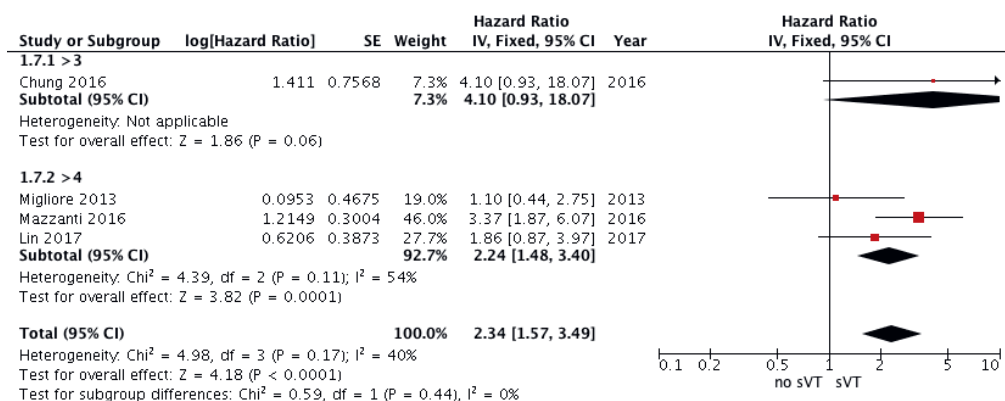
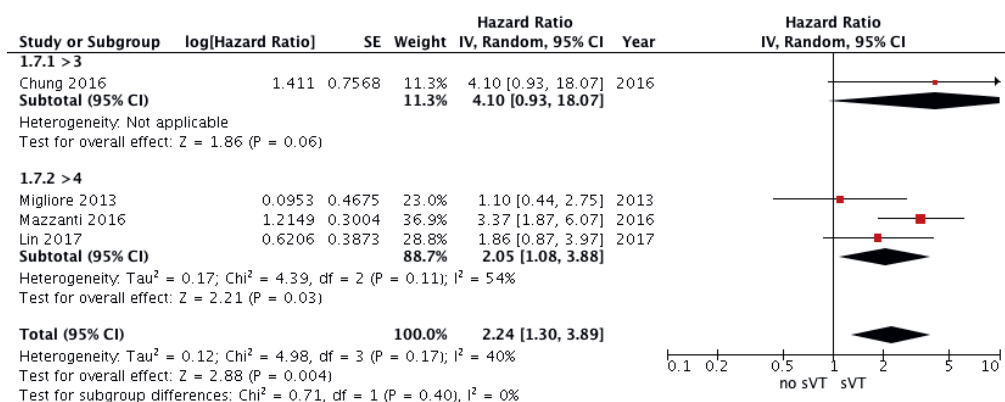


Prior non-sustained VT

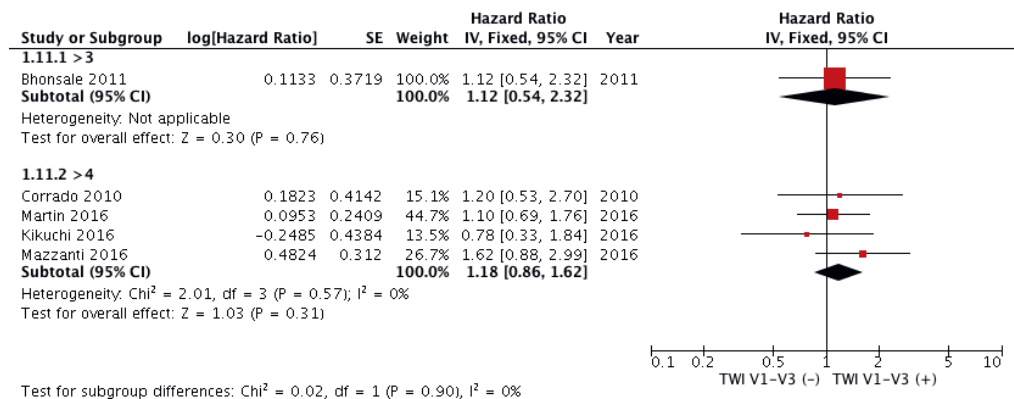
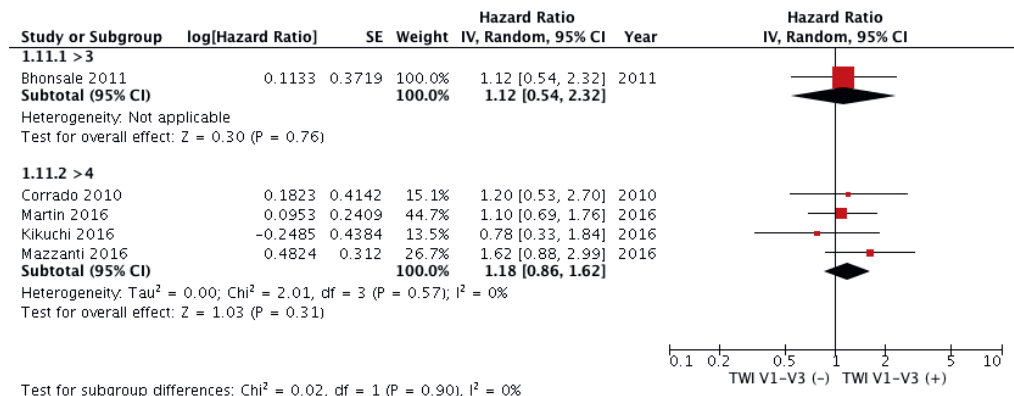




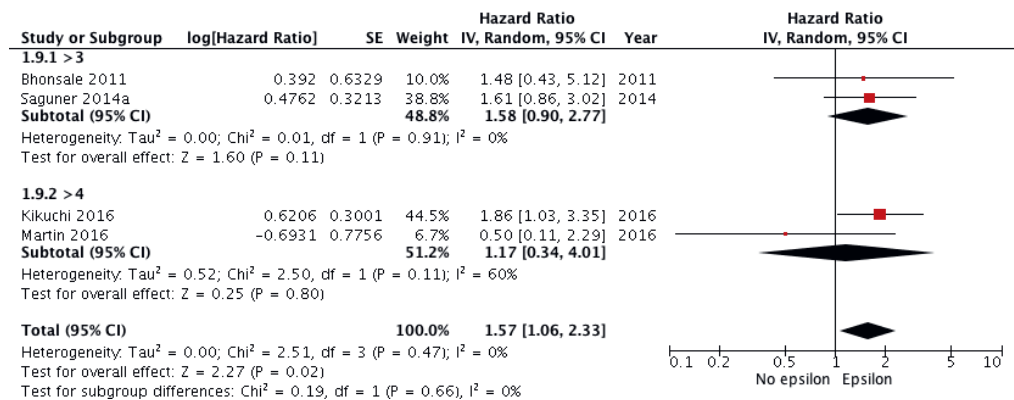
Prior sustained VT/VF

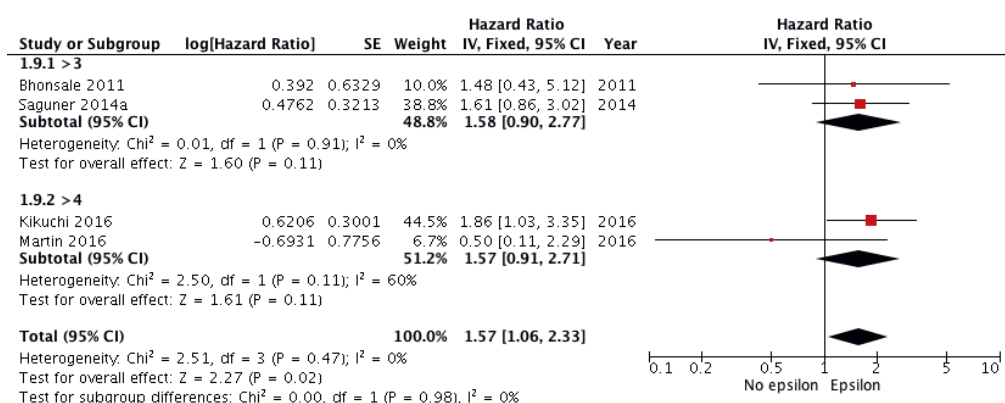


TWI V1-3

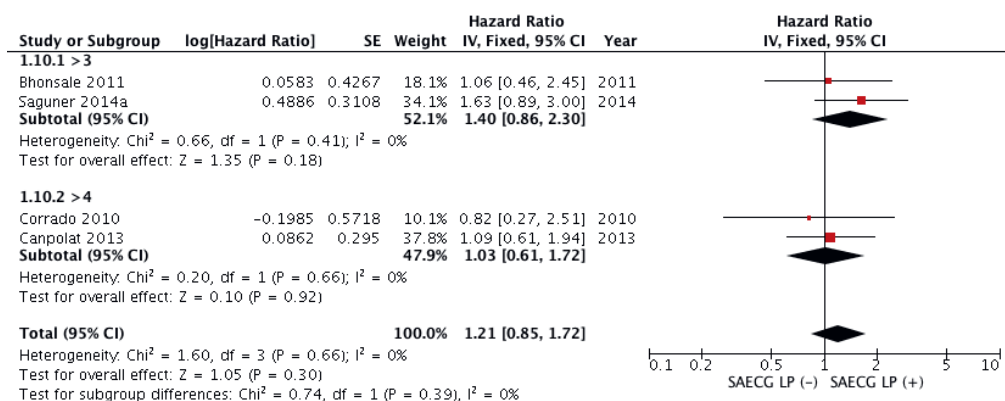
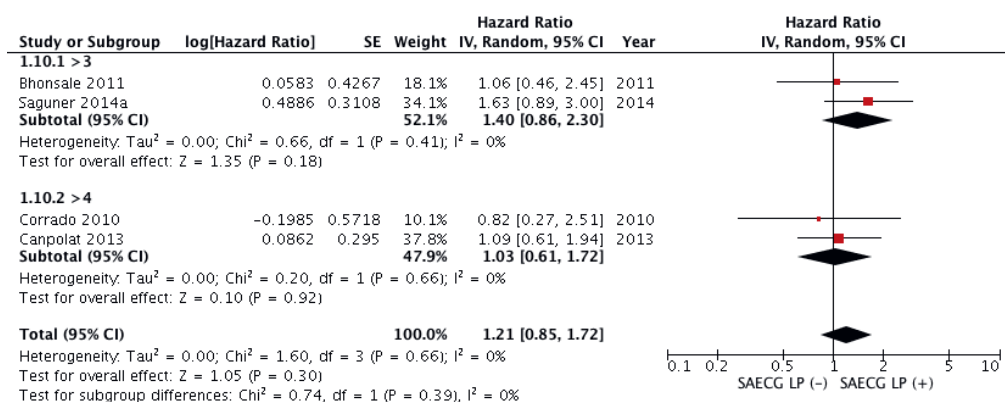


Epsilon wave

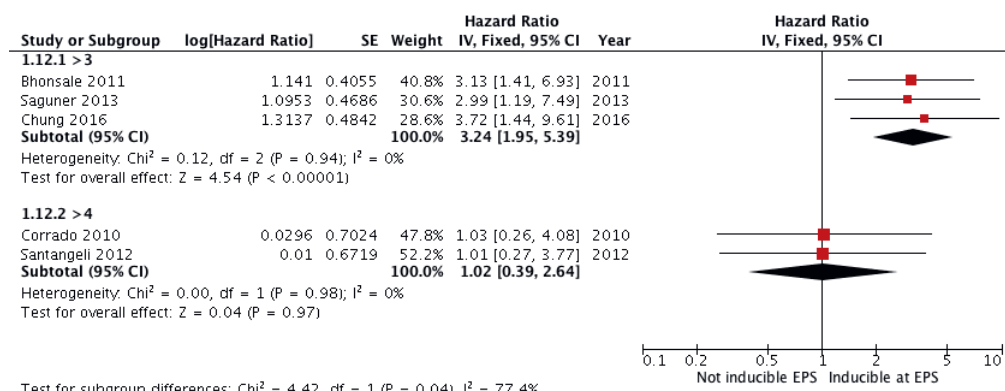
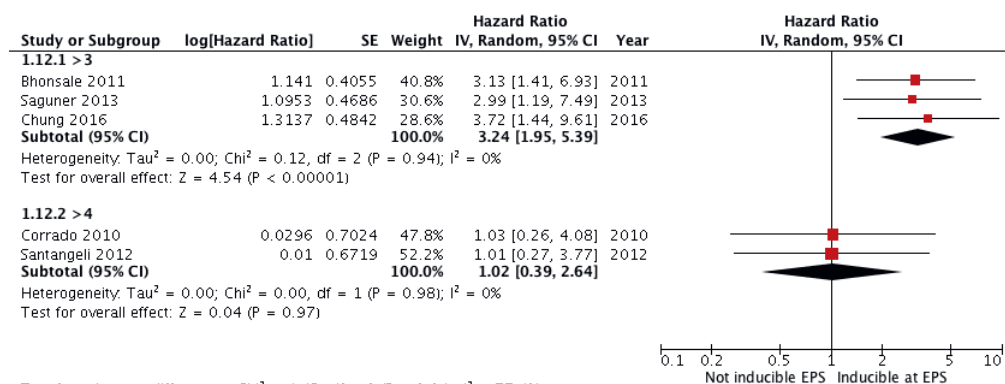




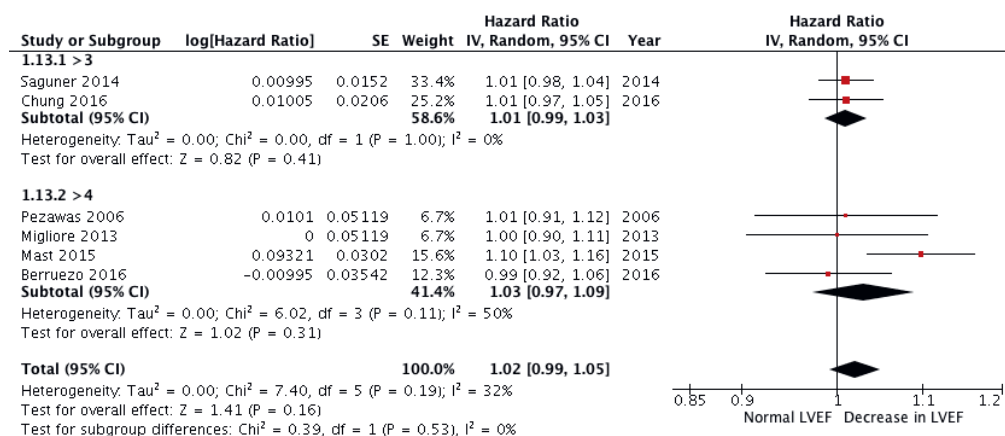
SAECC Late potentials

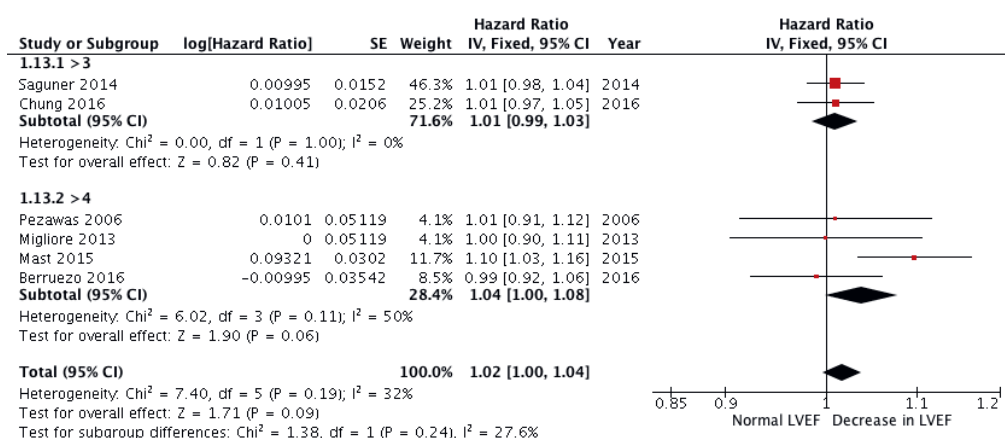


Inducibility at EPS

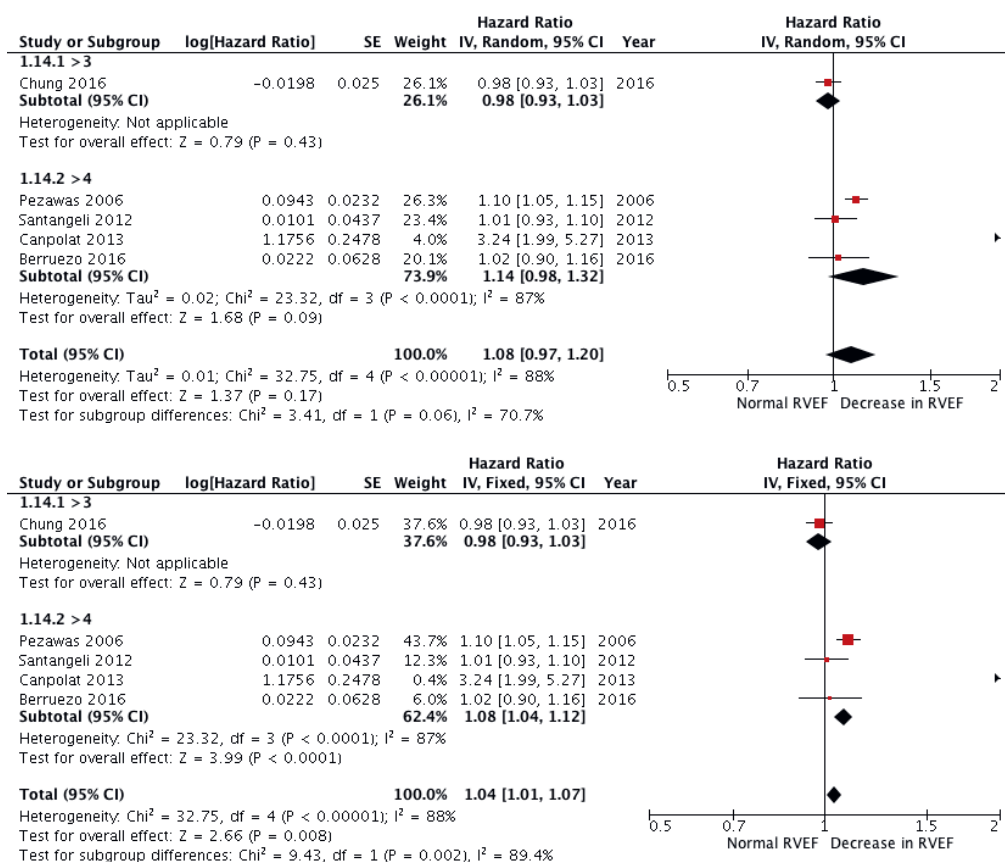


LVEF per % reduction

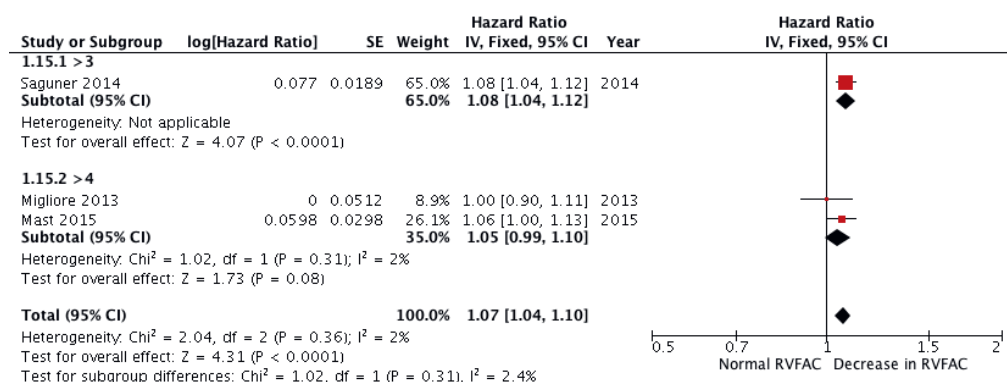
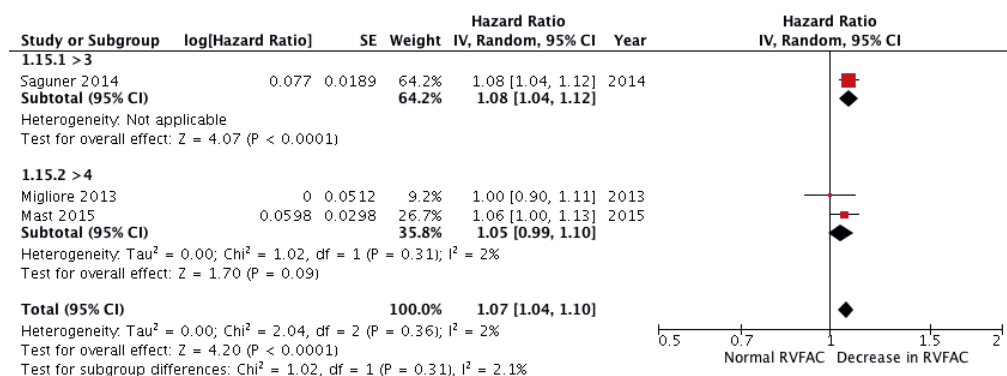




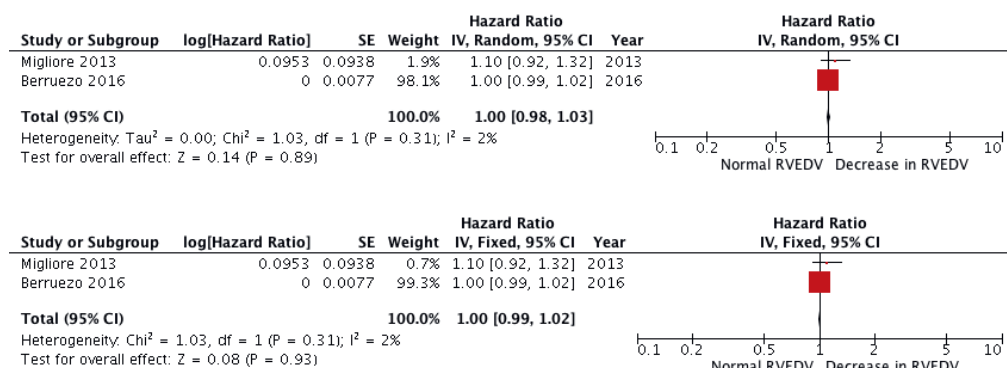
RVEF per % reduction



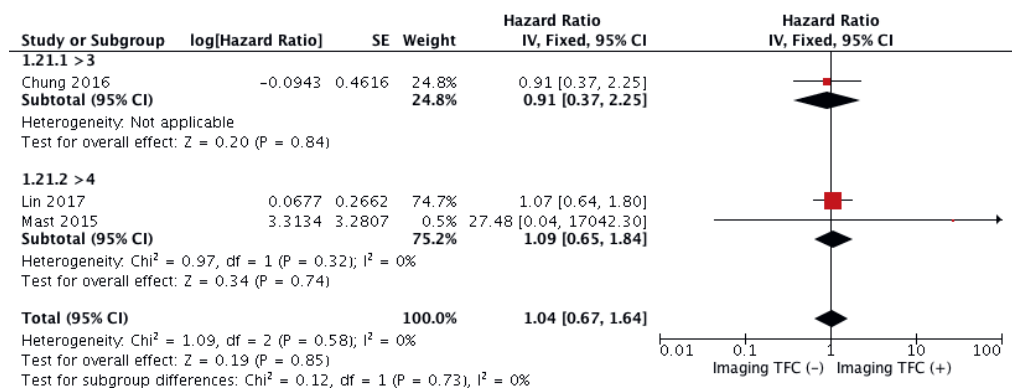
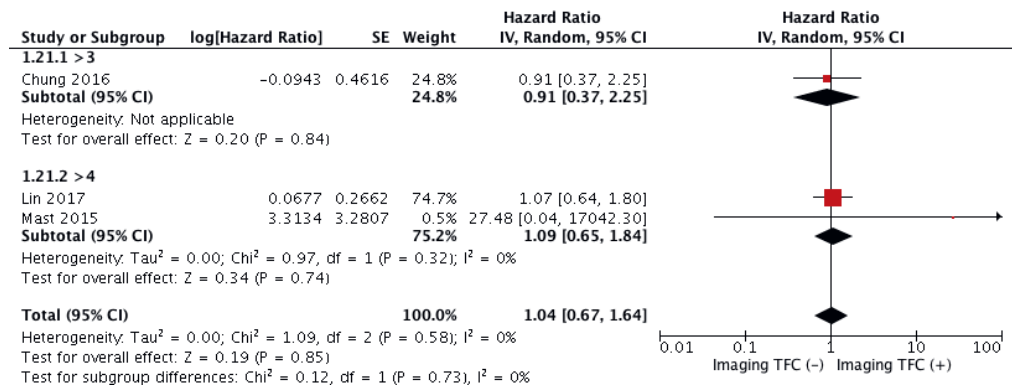
RVFAC per % reduction



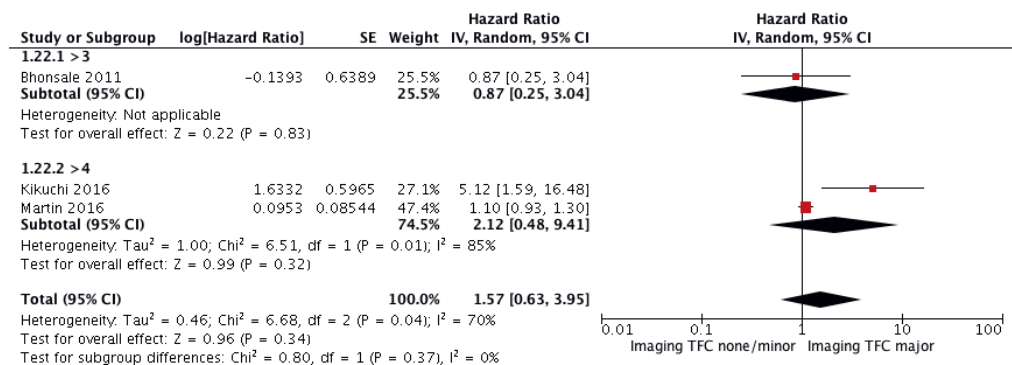
RVEDV per ml/m2 increase

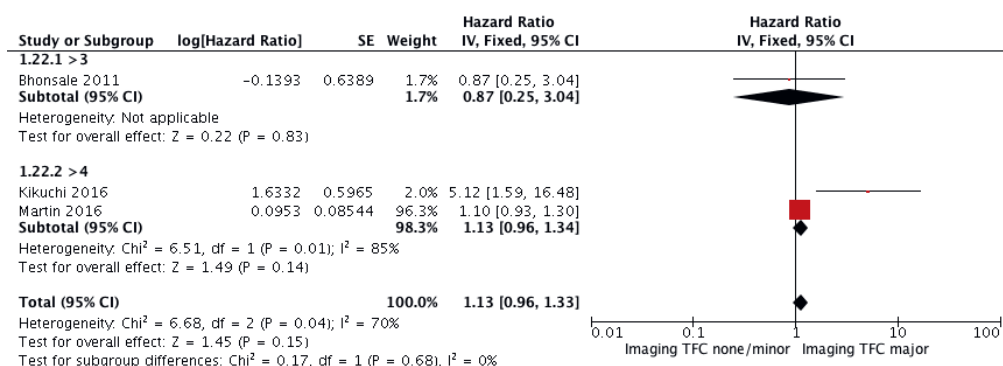


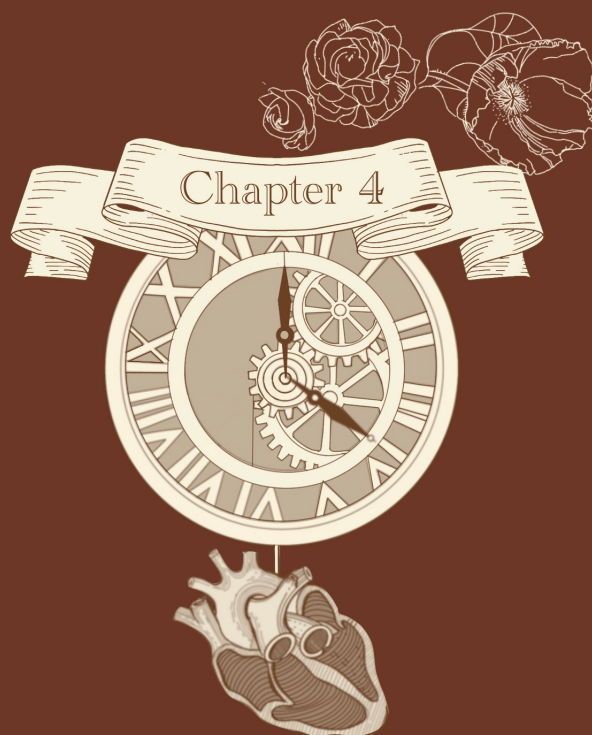
Imaging TFC minor or major



Imaging TFC major







Chapter 4

The Netherlands Arrhythmogenic Cardiomyopathy Registry: Design and Status Update

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Abstract

Background - Clinical research on arrhythmogenic cardiomyopathy (ACM) is typically limited by small patient numbers, retrospective study designs, and inconsistent definitions.

Aim To create a large national ACM patient cohort with a vast amount of uniformly collected high-quality data that is readily available for future research.

Methods - This is a multicentre, longitudinal, observational cohort study that includes (1) patients with a definite ACM diagnosis, (2) at-risk relatives of ACM patients, and (3) ACM-associated mutation carriers. At baseline and every follow-up visit, a medical history as well information regarding (non-)invasive tests is collected (e.g. electrocardiograms, Holter recordings, imaging and electrophysiological studies, pathology reports, etc.). Outcome data include (non-)sustained ventricular and atrial arrhythmias, heart failure, and (cardiac) death. Data are collected on a research electronic data capture (REDCap) platform in which every participating centre has its own restricted data access group, thus empowering local studies while facilitating data sharing.

Discussion - The Netherlands ACM Registry is a national observational cohort study of ACM patients and relatives. Prospective and retrospective data are obtained at multiple time points, enabling both cross-sectional and longitudinal research in a hypothesis-generating approach that extends beyond one specific research question. In so doing, this registry aims to (1) increase the scientific knowledge base on disease mechanisms, genetics, and novel diagnostic and treatment strategies of ACM; and (2) provide education for physicians and patients concerning ACM, e.g. through our website (www.acmregistry.nl) and patient conferences.

Introduction

Arrhythmogenic cardiomyopathy (ACM), including its major subform arrhythmogenic right ventricular cardiomyopathy, is a relatively rare heart muscle disease that affects approximately 1:1000-5000 people^{1, 2}. It is characterised by an increased risk of ventricular arrhythmias, sudden cardiac death, and progressively deteriorating ventricular function due to intercalated disk remodelling and fibro-fatty myocardial replacement³. ACM can present both in isolated and in familial forms and is consistent with an autosomal dominant inheritance pattern with incomplete penetrance and variable expressivity.

ACM was first described by Marcus et al. in 1982⁴. Since then, considerable advancements have been made that have improved our knowledge of this clinical entity. Nonetheless, management of ACM is complex due to the clinical heterogeneity of the disease, and optimal treatment protocols including risk stratification are still under development⁵⁻⁸. Studies on ACM often suffer from limitations secondary to the low prevalence and slow progression of the disease, i.e. many studies have insufficient statistical power and are restricted to retrospective follow-up since development of disease and (arrhythmic) endpoints is slow⁹. Additionally, the lack of uniform definitions complicates comparison of results among studies¹⁰.

In order to overcome these limitations, we designed a national registry to include all Dutch ACM patients, first-degree relatives and/or carriers of ACM-associated pathogenic mutations. Observational clinical data are systematically collected (both retrospectively and prospectively) from first visit to last follow-up using uniform data collection instruments. In so doing, we aim to create a large national ACM patient cohort with a vast amount of uniformly collected high-quality data that is readily available for future research. The goals of this registry are to (1) increase the scientific knowledge base on disease mechanisms, genetics, and novel diagnostic and treatment strategies of ACM; and (2) use this platform to provide education for physicians and patients concerning ACM.

Methods

Design

The Netherlands ACM Registry is a national, multicentre observational cohort that is coordinated by the Netherlands Heart Institute (NHI, Utrecht, The Netherlands). The registry follows the Code of Conduct and the Use of Data in Health Research and the national inclusion

of patients is exempt from the Medical Research Involving Human Subjects Act (WMO) as per judgement of the Medical Ethics Committee (METC 18-126/C, Utrecht, The Netherlands). The ACM Registry is registered at the Netherlands Trial Registry, project 7097 (www.trialregister.nl).

Objectives

The ACM Registry aims to (1) facilitate research on ACM disease mechanisms, genetics, diagnosis, prognosis, and treatment strategies; and (2) provide education for physicians and patients concerning ACM, e.g. through our website (www.acmregistry.nl) and patient conferences.

Study population

Eligible for inclusion in the ACM Registry are: (1) index patients with a definite ACM diagnosis according to the diagnostic Task Force Criteria (TFC)¹¹ and in whom alternative diagnoses are excluded; (2) all first-degree relatives of ACM patients regardless of the index patient's genetic testing results, which also includes relatives who are asymptomatic, who refuse genetic or cardiac testing, or those who are known to be mutation-negative (i.e. serve as control subjects); and (3) all carriers of pathogenic mutations in genes associated with ACM, regardless of their phenotype. After inclusion, a unique study ID is assigned to each registry enrollee by the NHI study coordinator to ensure the enrollee's privacy. The study ID can be traced back to the enrollee only by the NHI coordinator and the local coordinator from the medical centre at which the enrollee is recruited. Currently, patients are recruited through all eight academic medical centres in the Netherlands.

Data collection

Patient data are collected by researchers in the study centres using standardised data collection instruments hosted in REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA)¹². **Supplementary Table 1** shows an overview of the collected clinical data with their definitions. In short, a comprehensive medical history is obtained, including demographics, symptoms, medication use, family history, molecular genetic analysis, pregnancy, and exercise history. Test results are ascertained at first presentation and at every follow-up visit, including laboratory values, (signal averaged) electrocardiograms, Holter recordings, exercise testing, electrophysiological studies, cardiac imaging, ventricular/coronary cine-angiograms, and cardiac tissue from biopsy or surgery. When available, raw data such as electrocardiogram tracings and de-identified images from cardiac imaging are stored through the Extensible Neuroimaging Archive Toolkit (XNAT,

Washington University School of Medicine, St. Louis, MO, USA) software application for validation purposes and retrospective collection of newly identified relevant parameters. In addition, all interventions such as implantable cardioverter-defibrillator (ICD) placement and endocardial/epicardial ablations are recorded. As the registry design is observational, management and follow-up intervals remain at the discretion of the participant's own cardiologist. Outcome data that are collected include (non-)sustained ventricular arrhythmias, ICD interventions, atrial arrhythmias, heart failure symptoms, hospitalisations, and (cardiac) death. The complete data dictionary and data collection instruments are available for download upon request.

Data quality assurance

Data are acquired from routine clinical care in multiple academic centres that are all members of the Dutch Heritable Cardiomyopathy working group. Within this working group, clinical protocols regarding the diagnosis, genetic analysis and clinical care of cardiomyopathy patients are harmonised, which enhances the uniformity and quality of the data in this observational cohort. Uniform data collection is ensured by standardised data collection instruments built in REDCap accompanied by a detailed standard operating procedure document. Data entry fields are provided with entry instructions and are pre-programmed to accept values only within a possible range. The status of every data collection instrument is recorded: the default setting of 'incomplete' may be upgraded to 'unverified' when data are entered but not yet verified, and to 'complete' when data verification has been performed by an experienced researcher (rights are pre-specified in the researcher's user account). All data access, entries and changes are recorded in a detailed audit trail by REDCap. The diagnostic criteria for ACM¹¹, dilated cardiomyopathy¹³ and non-compaction cardiomyopathy^{14, 15} are calculated by pre-programmed algorithms. Fulfilment of these criteria is thereby automatically determined in real time while entering the data to ensure accurate phenotyping.

Data sharing and logistics

The Redcaps database is hosted by the NHI. Security, data protection, and IT support are provided by the NHI Durrer Centre. Access to the ACM database is restricted to specific data access groups corresponding to the participating centres (**Figure 1**) to ensure that researchers can access data only from patients known in their own centre. Only NHI research coordinators have access to the full database for quality assurance, database support, prevention of duplicate entries, and coordination of family linkage. Local coordinators are appointed in every centre to supervise data access and entry by local researchers. Together with the NHI coordinators, these local coordinators form the ACM Registry working group,

which is tasked with discussing and coordinating data requests for multicentre studies. Prior to data release, the study protocol with research question, inclusion criteria, required data, and list of potential co-authors is approved by all collaborators to ensure scientific integrity. Researchers are free to use patient data within their data access group for local studies, provided that the ACM Registry and REDCap database are acknowledged.

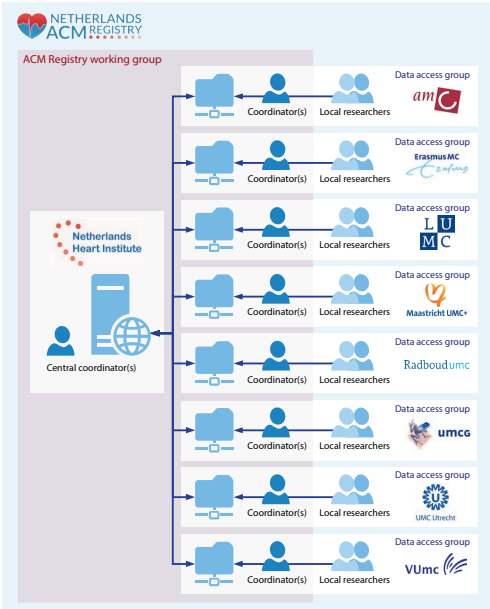


Figure 1. Graphic representation of the Netherlands ACM Registry: data access, logistics and sharing

The ACM Registry is hosted on a central server at the Netherlands Heart Institute. The database is divided in 8 data-access groups, managed by local coordinators of each participating centre. The central coordinators have access to the complete database for quality control and coordination of collaboration. The central coordinators together with the local coordinators form the ACM Registry working group.

Results

As of 1 February 2018, the ACM Registry contains 850 individual patient records. Among these, 228 (27%) are ACM index patients and 622 (73%) are at-risk relatives, among whom 114 (18%) fulfil a definite ACM diagnosis. Pathogenic mutations are found in 69% of index patients (most commonly in plakophilin-2; 52%). An overview of the clinical characteristics is provided in **Table 1**.

Follow-up information is currently available for 384 (45%) patients, among whom 210 (92%) are index patients and 174 (28%) relatives. Median follow-up is 9.5 years (interquartile range 4.6-16.2). The available clinical tests are outlined in **Table 1**. At least one electrocardiogram is available for almost all index patients ($n=215$, 94%) and most relatives ($n=459$, 74%), while Holter monitoring is available in the majority of both groups ($n=166$, 73% and $n=329$, 53%, respectively). An electrophysiological study is available in 133 (58%) index patients and 36 (6%) family members. Almost all index patients ($n=210$, 92%) and most family members ($n=366$, 59%) underwent at least one modality of cardiac imaging, with echocardiography being the most common ($n=206$, 90% and $n=344$, 55%, respectively), followed by cardiac magnetic resonance ($n=170$, 75% and $n=219$, 35%, respectively), and angiography ($n=150$, 66% and $n=43$, 7%, respectively).

Table 1. Clinical characteristics and available tests of 850 patients included in the Netherlands ACM registry

as of February 1st, 2018.

Patient characteristics	All	Index patients	Family members
Number	850 (100.0%)	228 (26.8%)	622 (73.2%)
Age at presentation (years)	38 [24-50]	39 [27-46]	38 [21-52]
Male sex	443 (52.1%)	161 (70.6%)	282 (45.3%)
ACM diagnosis [*]			
- <i>Definite</i>	342 (40.2%)	228 (100%)	114 (18.3%)
- <i>Borderline</i>	90 (10.6%)	n.a.	90 (14.5%)
Genetic testing performed	702 (82.6%)	226 (99.1%)	476 (76.5%)
Pathogenic mutation	458 (65.2%)	157 (69.5%)	301 (63.2%)
- <i>PKP2</i>	361 (51.4%)	118 (52.2%)	243 (51.1%)
- <i>DSP</i>	7 (1.0%)	4 (1.8%)	3 (0.6%)
- <i>JUP</i>	0 (0.0%)	0 (0.0%)	0 (0.0%)
- <i>DSG2</i>	14 (2.0%)	6 (2.7%)	8 (1.7%)
- <i>DSC2</i>	11 (1.6%)	5 (2.2%)	6 (1.3%)
- <i>PLN</i>	63 (9.0%)	24 (10.6%)	39 (8.2%)
- <i>Other</i>	12 (1.7%)	5 (2.2%)	7 (1.5%)
- <i>Multiple</i> [†]	9 (1.3%)	4 (1.8%)	5 (1.1%)
Test results available (≥1)			
ECG	674 (79.3%)	215 (94.3%)	459 (73.8%)
SAECG	88 (10.4%)	50 (21.9%)	38 (6.1%)
ETT	397 (46.7%)	166 (72.8%)	231 (37.1%)
Holter monitoring	495 (58.2%)	166 (72.8%)	329 (52.9%)
Imaging	576 (67.8%)	210 (92.1%)	366 (58.8%)

- <i>Echo</i>	550 (64.7%)	206 (90.4%)	344 (55.3%)
- <i>MRI</i>	389 (45.8%)	170 (74.6%)	219 (35.2%)
- <i>Angiogram</i>	193 (22.7%)	150 (65.8%)	43 (6.9%)
EPS	169 (19.9%)	133 (58.3%)	36 (5.8%)
Tissue biopsy	115 (13.5%)	89 (39.0%)	26 (4.2%)

Follow-up			
Follow-up available	384 (45.2%)	210 (92.1%)	174 (28%)
- <i>Duration (years)</i>	9.5 [4.6-16.2]	12.2 [5.1-20.0]	7.6 [3.3-12.1]
ICD implanted	235 (27.6%)	165 (72.4%)	70 (11.3%)
Sustained VA	196 (23.1%)	163 (71.5%)	33 (5.3%)
Heart transplantation	7 (0.8%)	5 (2.2%)	2 (0.3%)
Death	53 (6.2%)	36 (15.8%)	17 (2.7%)

Abbreviations: ACM = arrhythmogenic cardiomyopathy; *DSC2* = desmocollin-2; *DSG2* = desmoglein-2; *DSP* = desmoplakin; ECG = electrocardiogram; EPS = electrophysiologic study; ETT = exercise treadmill test; ICD = implantable cardioverter-defibrillator; *JUP* = junction plakoglobin; MRI = magnetic resonance imaging; *PKP2* = plakophilin-2; *PLN* = phospholamban; SAEKG = signal-averaged electrocardiogram; TFC = task force criteria; VA = ventricular arrhythmia.

*Definite ACM is defined as modified TFC score ≥ 4 , borderline ACM is defined as modified TFC score 3.

†Digenic or compound heterozygous.

Discussion

Clinical research on ACM is often limited by (1) small patient numbers; (2) retrospective study designs; and (3) inconsistent data definitions, leading to inability to compare results across studies¹⁰. To overcome these limitations, collaboration and sharing of expertise is paramount.

In the past, collaborative ACM research using multinational transatlantic databases has provided strong evidence on several clinically relevant problems including diagnosis, genotype-phenotype correlations and family screening^{11, 16-18}. While Dutch ACM patients have previously been enrolled in these studies, data collection was largely cross-sectional and hypothesis-driven, hence only applicable to one specific study. This, as well as the introduction of new data collection guidelines (e.g. standardised case record forms and audit trails), demanded a new platform. With the Netherlands ACM Registry, we designed a platform to create and maintain a large observational longitudinal patient cohort that continues and expands our prior database to a user-friendly and sustainable ACM Registry.

In the Netherlands ACM Registry, we use standardised protocols to ensure uniform, high-quality data. All these data are readily available to facilitate collaborative ACM research. A wide range of demographic and clinical data are collected including disease phenotype, genotype, treatment, and outcomes at multiple time points, enabling both cross-sectional and longitudinal studies in a hypothesis-generating approach. Data validation occurs through several automated validation processes (e.g. real-time calculation of diagnostic TFC) which undergo an additional manual check by experts (e.g. electrocardiogram over-read by trained electrophysiologists). Final ACM diagnosis is manually confirmed by experts. The phenotype algorithms aid long-term sustainability of the database, as they can easily be altered if the diagnostic guidelines are modified. In addition, data validity and sustainability are assured by storing raw data such as de-identified cardiac magnetic resonance images, which can be re-evaluated if new insights are gained.

One limitation of our registry is the observational nature, in which we do not impose standard clinical evaluation intervals or interfere with diagnostic and/or treatment strategies. This may introduce centre-specific differences, which should be accounted for in every study separately depending on the research question. Furthermore, our registry is phenotype-based, meaning that inclusion of patients and relatives is restricted to families in which at least one relative has a definite diagnosis of ACM¹¹ and ACM-related mutation carriers. Although we consider this to be a strength to minimise distortion of results by inclusion of non-ACM patients, this also introduces limitations: at the present time, our registry cannot be used to study the differentiation of ACM with disease-mimicking entities.

Future perspectives

We aim to improve this registry continuously. Future perspectives include the expansion of the population to borderline/possible ACM patients. We also plan to collaborate with existing biobanks for cardiac tissue, DNA and plasma to facilitate additional research on disease penetrance and the pathophysiological mechanisms of ACM. The Netherlands ACM Registry aims to stimulate existing and future (inter-)national collaboration and transparency in ACM research, not only among researchers but also between researchers and patients. In the future, we intend to use this registry as a tool to enable physician and patient education by means of patient conferences as well as to provide interested readers with the possibility to receive updates on current and future research in newsletters.

Conclusion

The Netherlands ACM Registry is a national observational cohort of ACM patients and at-risk relatives. Data collection is performed both prospectively and retrospectively using a secure online platform that includes demographic, genetic, and clinical characteristics at multiple time points, enabling both cross-sectional and longitudinal research. By using uniform variable definitions and automatic data verification, a user-friendly and sustainable platform is generated. The final aim of this registry is to (1) increase the scientific knowledge base of ACM by strong national collaboration, as well as facilitating potential international collaborations; and (2) provide education for physicians and patients concerning ACM.

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Supplementary material

Supplementary Table 1. ACM Registry data dictionary

Demographics		
Country	Free text	<i>Country of residence</i>
Centre	Free text	<i>Centre of enrolment</i>
Year of birth	YYYY	<i>Year in which the patient was born</i>
Sex	<ul style="list-style-type: none"> Female Male 	<i>Sex of the patient</i>
Pedigree	<ul style="list-style-type: none"> Proband Family member 	<i>Proband ('index patient') is defined as the first affected family member seeking medical attention for ACM-related complaints in whom the diagnosis was confirmed (i.e. an individual ascertained independently of family history).</i>
Ethnicity	<ul style="list-style-type: none"> Caucasian Asian African (-American) Hispanic Mixed 	<i>Ethnicity of the patient</i>
Presentation & symptoms		
Date of presentation	DD/MM/YYYY	
Type of presentation	<ul style="list-style-type: none"> Sudden cardiac death Symptomatic and living Resuscitated sudden cardiac arrest Abnormal test Family history 	<i>Symptomatic is defined as having symptoms attributed to ACM (syncope, pre-syncope, palpitations, chest pain).</i>
Ventricular arrhythmia	Duration; morphology; cycle length.	
Symptoms	<ul style="list-style-type: none"> Cardiac syncope Presyncope Palpitations Dyspnoea Chest pain 	<i>Cardiac syncope is defined as transient loss of consciousness and postural tone with spontaneous recovery with a likely arrhythmic mechanism.</i>
NYHA class	I - IV	<i>Functional classification as defined by the New York Heart Association.</i>
Comorbidities	<ul style="list-style-type: none"> Hypertension Diabetes Mellitus Dyslipidaemia Myocardial infarction Peripheral vascular disease Cerebrovascular accident / Transient ischemic attack COPD Sarcoidosis 	
Family history		
Date of ascertainment of family history	DD/MM/YYYY	
Degree of relatedness to the index patient	<ul style="list-style-type: none"> First degree Second degree 	<i>First degree is defined as family members with 50% relatedness (i.e. parents, siblings and children). Second degree is defined as family members with 25% relatedness (i.e. grandparents, grandchildren, aunts, uncles, nephews, nieces, etc.)</i>
Family history of heart disease	<ul style="list-style-type: none"> ACM/ARVC <ul style="list-style-type: none"> Task force diagnosis Autopsy diagnosis Assumed diagnosis DCM HCM Other (specify) 	<i>Assumed diagnosis is defined as diagnosis not confirmed by Task Force criteria or autopsy</i>
Genetics		
Date of genetic testing	DD/MM/YYYY	
Type of analysis	<ul style="list-style-type: none"> Sanger sequencing 	

	<ul style="list-style-type: none"> Gene panel(s) CNV detection software Multiplex ligation-dependent probe amplification 	
Gene tested	<ul style="list-style-type: none"> Plakophilin-2 (<i>PKP2</i>) Desmoplakin (<i>DSP</i>) Junctional plakoglobin (<i>JUP</i>) Desmoglein-2 (<i>DSG2</i>) Desmocollin-2 (<i>DSC2</i>) Transmembrane protein 43 (<i>TMEM43</i>) Transforming growth factor β3 (<i>TGFβ3</i>) Phospholamban (<i>PLN</i>) Titin (<i>TTN</i>) Desmin (<i>DES</i>) Lamin A/C (<i>LMNA</i>) Ryanodine receptor 2 (<i>RYR2</i>) Voltage-gated sodium channel α-subunit 5 (<i>SCN5A</i>) N-cadherin (<i>CDH2</i>) Catenin α3 (<i>CTNNA3</i>) Other variants found (specify) 	
If variant found:	<ul style="list-style-type: none"> Reference sequence number Nucleotide variant Amino acid change Homozygous, heterozygous, compound heterozygous Pathogenicity classification 	<p><i>Pathogenicity classification as per ACMG guidelines. 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 (ESP) was $\leq 0.05\%$, (NHLBI 6500 Exome data sets; EVS; http://evs.gs.washington.edu/EVS/) and 2) in silico prediction programs predicted the variant to affect protein function by score < 0.02 (SIFT) and > 0.900 (Polyphen2).</i></p>

Exercise history		
Endurance athlete	Yes/no	Defined as Bethesda class C (High dynamic component $>70\%$ max O_2)
Types of sport	Free text	E.g. Soccer, tennis, basketball, etc.
Activity level	Low	
	Moderate	
	High	
Competitive athlete	Yes/no	

Medication		
Date of medication log	DD/MM/YYYY	
Beta-blockers	<ul style="list-style-type: none"> Yes (specify name + dose) No 	
Anti-arrhythmic drugs	<ul style="list-style-type: none"> Class 1A (specify name + dose) Class 1B (specify name + dose) Class 1C (specify name + dose) Class 3 (specify name + dose) Class 4 (specify name + dose) 	NB Sotalol classified as class 3 anti-arrhythmic drug irrespective of dose
Diuretics	<ul style="list-style-type: none"> Yes (specify name + dose) No 	
ACE-inhibitors / ARBs	<ul style="list-style-type: none"> Yes (specify name + dose) No 	

Electrocardiogram			
Date of ECG	DD/MM/YYYY		
Upload anonymized ECG	Upload button		Anonymization facilitated by automatic redaction tool
Medication recording	used	during	Free text
Rhythm	<ul style="list-style-type: none"> Sinus rhythm Atrial pacing 		

	<ul style="list-style-type: none"> • (Atrial-)ventricular pacing • Other (free text) 	
Heart rate frequency	(bpm)	Allowed range 10 - 400
QRS duration	(ms)	Maximal QRS duration on ECG Allowed range 20-400
R-axis	(degrees)	Allowed range -90 - 270
PQ duration	(ms)	Allowed range 20-400
QT interval	(ms)	Allowed range 100-700
Bundle branch block	<ul style="list-style-type: none"> • Complete RBBB • Atypical complete RBBB • Complete LBBB • Non-specific intraventricular conduction delay 	Criteria for typical right and left bundle branch block criteria as per WHO criteria
Terminal activation duration	<ul style="list-style-type: none"> • >55 ms (Yes/No) • Absolute duration (ms) 	TAD is defined as the longest duration in V1-3, from the nadir of the S wave to the end of all depolarization deflections including R', in the absence of typical complete right bundle-branch block
Epsilon wave	<ul style="list-style-type: none"> • Yes • No 	Distinct waves of small amplitude within the ST segment in the right precordial leads (V1-3) which are distinct from the QRS complex.
T-wave inversion	<ul style="list-style-type: none"> • V1 • V2 • V3 • V4 • V5 • V6 • II • III • aVF 	Inverted T-waves are recorded per lead. T-waves are considered inverted if amplitude ≥ 1 mV.
Presence of PVC(s)	Yes/No; number; morphology.	
Low QRS voltage	<ul style="list-style-type: none"> • Leads I, II and III all <0.5 mV • Leads I+II+III <1.5 mV • Leads V1-6 all <1.0 mV • Other (free text) 	

Signal-averaged Electrocardiogram (SAECG)

Date of SAECG	DD/MM/YYYY	
Upload anonymized SAECG	Upload button	Anonymization facilitated by automatic redaction tool
Filtered QRS duration	(ms)	Allowed range 60-300
Duration of terminal QRS <40mV	(ms)	Allowed range 0-100
Root mean square voltage of terminal 40ms	(mV)	Allowed range 0-100

Holter monitoring

Date of Holter monitor	DD/MM/YYYY	
Upload copy of Holter monitor report	Upload button	Anonymization facilitated by automatic redaction tool
Use of cardiac medication during recording	Free text	
Monitoring time	hours	Allowed range 12-50
Total PVC count	number	Allowed range 0-200000
Ventricular arrhythmia	Duration; morphology; cycle length.	

Exercise tolerance test

Date of exercise tolerance test	DD/MM/YYYY	
Upload anonymized exercise tolerance test	Upload button	Anonymization facilitated by automatic redaction tool
Cardiac medication during test	Free text	
Baseline blood pressure	(mmHg)	Allowed range 40-250 / 20-180
Maximum blood pressure	(mmHg)	Allowed range 40-250 / 20-180
Ventricular tachycardia	Duration; morphology; cycle length.	
PVC(s)	Presence; morphology.	
Other arrhythmia(s)	Free text	

Electrophysiology study (EPS)

Date of EPS	DD/MM/YYYY	
Upload copy of EPS report	Upload button	Anonymization facilitated by automatic redaction tool

Cardiac medication during	Free text	
EPS		
Ventricular arrhythmia induced at stimulation	Duration; morphology; cycle length.	
Induction method	<ul style="list-style-type: none"> Programmed ventricular stimulation Isoproterenol infusion 	
Late potentials	<ul style="list-style-type: none"> Yes No 	Considered positive if potentials are recorded on intracardiac electrogram after the end of the QRS-complex on the surface ECG.
Ablation performed	<ul style="list-style-type: none"> Yes No 	
	If yes:	
	<ul style="list-style-type: none"> Endocardial location(s) Epicardial location(s) Both endo- and epicardial location(s) 	

Magnetic resonance imaging (MRI)		
Date of MRI	DD/MM/YYYY	
Upload copy of MRI report	Upload button	Anonymization facilitated by automatic redaction tool
Body surface area at time of test	(m ²)	As calculated by DuBois formula (height ^{0.725})*(length ^{0.425})*0.007184
Global RV dilatation	<ul style="list-style-type: none"> Mild Moderate Severe 	Qualitative assessment
		Mild: RV diameter < LV diameter
		Moderate: RV diameter = LV diameter
		Severe: RV diameter > LV diameter
Global RV dysfunction	<ul style="list-style-type: none"> Mild Moderate Severe 	Qualitative assessment
Regional RV wall motion abnormalities	<ul style="list-style-type: none"> Hypokinesia (specify region) Akinesia (specify region) Dyskinesia (specify region) Aneurysm (specify region) 	Qualitative assessment
RV measurements	<ul style="list-style-type: none"> End-diastolic volume (mL) End-systolic volume (mL) Ejection fraction (%) 	
Global LV dilatation	<ul style="list-style-type: none"> Mild Moderate Severe 	Qualitative assessment
Global LV dysfunction	<ul style="list-style-type: none"> Mild Moderate Severe 	Qualitative assessment
Regional LV wall motion abnormalities	<ul style="list-style-type: none"> Hypokinesia (specify region) Akinesia (specify region) Dyskinesia (specify region) Aneurysm (specify region) 	Qualitative assessment
LV measurements	<ul style="list-style-type: none"> End-diastolic volume (mL) End-systolic volume (mL) Ejection fraction (%) 	
Dyssynchronous movement	<ul style="list-style-type: none"> Dyssynchronous contraction Dyssynchronous relaxation 	Qualitative assessment
Fatty infiltration	<ul style="list-style-type: none"> Yes (specify region) No 	Qualitative assessment
Late gadolinium enhancement	<ul style="list-style-type: none"> Yes (specify region) No 	Qualitative assessment
Atrial dilatation	<ul style="list-style-type: none"> Left Right Both 	Qualitative assessment
Abnormal feature tracking	<ul style="list-style-type: none"> Yes (specify region) No 	
T1 mapping performed	<ul style="list-style-type: none"> Yes No 	
Signs of non-compaction	<ul style="list-style-type: none"> RV LV 	

<ul style="list-style-type: none"> Both 		
--	--	--

Echocardiogram		
Date of echocardiogram	DD/MM/YYYY	
Upload copy of echocardiogram report	Upload button	Anonymization facilitated by automatic redaction tool
Body surface area at time of test (m ²)		Calculated by DuBois formula (height ^{0.725})*(length ^{0.425})*0.007184
Global RV dilatation	<ul style="list-style-type: none"> Mild Moderate Severe 	Qualitative assessment
		Mild: RV diameter < LV diameter
		Moderate: RV diameter = LV diameter
		Severe: RV diameter > LV diameter
Global RV dysfunction	<ul style="list-style-type: none"> Mild Moderate Severe 	Qualitative assessment of RV function
Regional RV wall motion abnormalities	<ul style="list-style-type: none"> Hypokinesia (specify region) Akinesia (specify region) Dyskinesia (specify region) Aneurysm (specify region) 	Qualitative assessment
RV measurements	<ul style="list-style-type: none"> Fractional area change (%) Tricuspid annular plane systolic excursion (mm) Outflow tract (PLAX)(mm) Outflow tract (PSAX)(mm) 	
Global LV dilatation	<ul style="list-style-type: none"> Mild Moderate Severe 	Qualitative assessment
Global LV dysfunction	<ul style="list-style-type: none"> Mild Moderate Severe 	Qualitative assessment
LV measurements	<ul style="list-style-type: none"> Ejection fraction (%) Fractional shortening (%) End-diastolic volume (mL) 	
Abnormal deformation imaging	<ul style="list-style-type: none"> Yes (specify region) No 	
Atrial dilatation	<ul style="list-style-type: none"> Left Right Both 	
Signs of non-compaction	<ul style="list-style-type: none"> RV LV Both 	

Angiogram		
Date of angiogram	DD/MM/YYYY	
Upload copy of angiogram report	Upload button	Anonymization facilitated by automatic redaction tool
Global RV dilatation	<ul style="list-style-type: none"> Yes No 	Qualitative assessment
Regional RV regional wall motion abnormalities	<ul style="list-style-type: none"> Akinesia, dyskinesia or aneurysm (specify region) Hypokinesia (specify region) No 	Qualitative assessment
Global LV dilatation	<ul style="list-style-type: none"> Yes No 	Qualitative assessment
Regional LV regional wall motion abnormalities	<ul style="list-style-type: none"> Akinesia, dyskinesia or aneurysm (specify region) Hypokinesia (specify region) No 	Qualitative assessment
Coronary artery disease	<ul style="list-style-type: none"> Yes No 	Defined as >=75% stenosis in a major epicardial coronary artery

Tissue histology		
Date that specimen is obtained	DD/MM/YYYY	
Upload copy of pathology report	Upload button	Anonymization facilitated by automatic redaction tool
Source of tissue	<ul style="list-style-type: none"> Biopsy Autopsy 	

	<ul style="list-style-type: none"> • Transplantation • Other 	
Fulfilment of Arrhythmogenic Cardiomyopathy diagnostic criteria	<ul style="list-style-type: none"> • Major • Minor • None 	<p><i>As defined by the 2010 TFC: Major if < 60% residual myocytes by morphometric analysis (or < 50% if estimated), with fibrous replacement of the</i></p> <p><i>RV free wall myocardium >=1 sample, with or without fatty replacement of tissue on</i></p> <p><i>endomyocardial biopsy; Minor if 60% to 75% residual myocytes by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in >=1 sample, with or without fatty replacement of tissue on endomyocardial biopsy.</i></p>

Device implantation		
Date of implantation	DD/MM/YYYY	
Copy of device readouts / settings summary	Upload button	<i>Anonymization facilitated by automatic redaction tool</i>
Type of device	<ul style="list-style-type: none"> • ICD: Single chamber • ICD: Dual chamber or CRT-D • S-ICD • Pacemaker: single chamber • Pacemaker: dual chamber • Pacemaker: leadless • Other (specify) 	<i>RV lead only = single chamber. RV and RA lead = dual chamber. RA, RV and LV lead = CRT-(D), subcutaneous ICD = S-ICD.</i>
Type of implantation	<ul style="list-style-type: none"> • New implantation • Generator replacement • Lead revision • Other (specify) 	
Defibrillator indication	<ul style="list-style-type: none"> • Primary prevention • Secondary prevention 	<i>Secondary prevention if previously documented sustained VT/VF. If the ICD indication is based on syncope without registration of a ventricular arrhythmia it is regarded as primary prevention.</i>
Defibrillator settings	<ul style="list-style-type: none"> • Rate cut-off for anti-tachycardia pacing or shock • Rate cut-off for monitoring window 	<p><i>For anti-tachycardia pacing or shock, note lowest rate at which device provides therapy.</i></p> <p><i>For rate cut-off specify cycle lengths in ms.</i></p>

Arrhythmic event / ICD intervention		
Date of arrhythmic event	DD/MM/YYYY	
Upload copy of event registration	Upload button	<i>Anonymization facilitated by automatic redaction tool</i>
Documentation type	<ul style="list-style-type: none"> • ECG recording • ICD recording • Other (specify) 	
Cardiac medication at time of event	Free text	
Event type	<ul style="list-style-type: none"> • Spontaneous VT/VF • Appropriate ICD intervention (anti-tachycardia pacing or shock) • VT-storm / electrical storm • Aborted SCD 	<i>VT storm is defined by >2 sustained arrhythmias (or appropriate ICD interventions) within 24h.</i>
Ventricular tachycardia or ICD intervention	Duration; morphology; cycle length	<i>Ventricular tachycardia is considered sustained if lasting 30 seconds or more, or less than 30 seconds when terminated electrically or pharmacologically</i>
Type of ICD intervention	<ul style="list-style-type: none"> • Anti-tachy-pacing (ATP) • Shock 	
Circumstances event	<ul style="list-style-type: none"> • Routine activity • Rest • Sleep • Exercise 	

Inappropriate ICD intervention		
Date of inappropriate ICD intervention	DD/MM/YYYY	
Upload copy of event registration	Upload button	<i>Anonymization facilitated by automatic redaction tool</i>
Type of intervention	<ul style="list-style-type: none"> • Anti-tachycardia pacing (ATP) • Shock 	
Cause	<ul style="list-style-type: none"> • Atrial arrhythmia • Sinus tachycardia • Lead or device malfunction • Other (specify) 	

Atrial arrhythmia		
Date of atrial arrhythmia	DD/MM/YYYY	
Upload copy of event registration	Upload button	<i>Anonymization facilitated by automatic redaction tool</i>
Type	<ul style="list-style-type: none"> • Atrial fibrillation • Atrial flutter • Other (specify) 	
Documentation type	<ul style="list-style-type: none"> • ECG recording • ICD recording • Holter recording • Exercise test • Other (specify) 	

Pregnancy		
Number of pregnancies	Number; date of delivery	
Cardiac complications associated with pregnancy	<ul style="list-style-type: none"> • Yes (specify) • No • Unknown 	<i>E.g. symptoms of heart failure or arrhythmia in the mother, obstetric complications in the child</i>

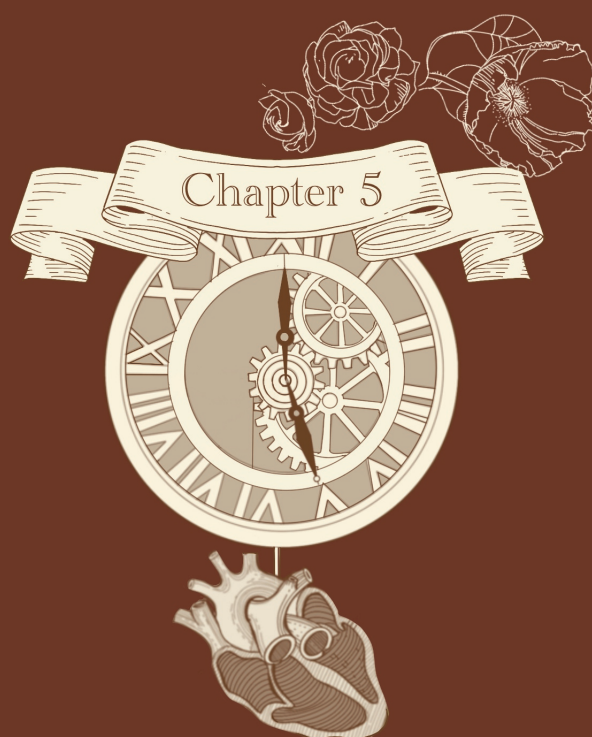
Heart failure		
Date of onset heart failure	DD/MM/YYYY	<i>Defined as a clinical syndrome with symptoms as dyspnoea, fatigue, limited exercise tolerance, and/or fluid retention caused by a structural and/or functional cardiac abnormality. (Definitions from: ACCF/AHA 2013, ESC 2016).</i>
Date of first hospitalization for heart failure	DD/MM/YYYY	

Heart transplantation / ventricular assist device		
Date of transplantation / VAD implantation	DD/MM/YYYY	
Type	<ul style="list-style-type: none"> • Heart transplantation • LVAD • RVAD • BiVAD • Other 	
Indication	<ul style="list-style-type: none"> • Incessant ventricular arrhythmia • RV failure • LV failure • Biventricular failure • Other (specify) 	

Death		
Date of death	DD/MM/YYYY	
Cause	<ul style="list-style-type: none"> • Cardiovascular <ul style="list-style-type: none"> ◦ Sudden cardiac death ◦ Heart failure / shock ◦ Other (specify) • Non-cardiovascular (specify) 	

Diagnostic criteria		
Fulfilment of criteria for ARVC	Total TFC score; automatically calculated by software based on previous entry sheets	<i>Definite diagnosis ≥ 4 TFC criteria</i> <i>Borderline diagnosis: 3 TFC criteria</i> <i>Possible diagnosis: 2 TFC criteria</i>
Fulfilment of criteria for ARVC; by category	<ul style="list-style-type: none"> • Family history / genetics • Depolarization 	

	<ul style="list-style-type: none"> • Repolarization • Arrhythmia • Structural (imaging) • Tissue 	
	Automatically calculated by software based on previous entry sheets	
Fulfilment of criteria for DCM	Automatically calculated by software based on previous entry sheets	<i>If LVEDD>117% of the predicted value, and a reduced LV function (EF< 45% or FS< 35%)</i>
Coronary artery disease	Automatically calculated by software based on previous entry sheets	<i>If CTA calcium score >10 and/or CAG stenosis >= 75%</i>
Fulfilment of criteria for non-compaction	Automatically calculated by software based on previous entry sheets	<i>If non-compacted / compacted layer ratio on MRI is >2.3, or the end systolic non-compacted / compacted layer ratio in echocardiogram is >2.0</i>



Chapter 5

A New Prediction Model for Ventricular Arrhythmias in Arrhythmogenic Right Ventricular Cardiomyopathy

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Abstract

Aims: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by ventricular arrhythmias (VA) and sudden cardiac death (SCD). We aimed to develop a model for individualized prediction of incident VA/SCD in ARVC patients.

Methods and Results: 528 patients with a definite diagnosis and no history of sustained VA/SCD at baseline, aged 38.2 ± 15.5 years, 44.7% male, were enrolled from five registries in North America and Europe. Over 4.83 (IQR 2.44-9.33) years of follow-up, 146 (27.7%) experienced sustained VA, defined as SCD, aborted SCD, sustained ventricular tachycardia, or appropriate implantable cardioverter-defibrillator (ICD) therapy. A prediction model estimating annual VA risk was developed using Cox regression with internal validation. Eight potential predictors were pre-specified: age, sex, cardiac syncope in the prior 6 months, non-sustained ventricular tachycardia, number of premature ventricular complexes in 24 hours, number of leads with T-wave inversion, and right and left ventricular ejection fractions (LVEF). All except LVEF were retained in the final model. The model accurately distinguished patients with and without events, with an optimism corrected C-index of 0.77 [95% CI 0.73-0.81] and minimal over-optimism (calibration slope of 0.93 [95% CI 0.92-0.95]). By decision curve analysis, the clinical benefit of the model was superior to a current consensus-based ICD placement algorithm with a 20.6% reduction of ICD placements with the same proportion of protected patients ($p < 0.001$).

Conclusion: Using the largest cohort of patients with ARVC and no prior VA, a prediction model using readily available clinical parameters was devised to estimate VA risk and guide decisions regarding primary prevention ICDs.

Introduction

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by progressive fibrofatty replacement of the myocardium which predisposes patients to ventricular arrhythmias (VA) and sudden cardiac death (SCD). Once the diagnosis is established, a primary goal of management is prevention of SCD, for which implantable cardioverter-defibrillators (ICD) are a common consideration. There is agreement that most ARVC patients with a prior history of sustained ventricular arrhythmia (VA) or resuscitated sudden cardiac arrest (SCA) benefit from secondary prevention ICDs.¹ However, for the primary prevention population, there is no established risk stratification scheme.

Over the past two decades, multiple attempts have been made to identify factors associated with VA in this clinically challenging population.²⁻⁴ While these studies have significantly contributed to our understanding of clinical, demographic, and behavioural factors associated with arrhythmic risk, the relatively small patient populations provided insufficient statistical power to assess the independent predictive value of potentially correlated risk factors.⁵

To overcome this important limitation, we assembled a large cohort of patients with ARVC from 5 registries (Johns Hopkins, Dutch, Nordic, Swiss, Canadian) without a history of sustained VAs at baseline. Our aim was 1) to develop a model for individualized prediction of incident VA in patients with ARVC using readily available clinical variables; and 2) to compare this new model to a current consensus-based ICD placement algorithm.

Methods

Study Design

We conducted an observational, retrospective, longitudinal cohort study in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement.⁶

Study Population

The study population was drawn from 5 ARVC registries encompassing 14 academic centres (**Supplementary Table 1**) in 6 countries. Each registry is itself a longitudinal cohort study. From each registry, we included all patients who 1) were diagnosed with definite ARVC by the current Task Force Criteria (TFC)⁷ and 2) had not experienced spontaneous sustained VA or

SCA at diagnosis. The study conforms to the Helsinki declaration and was approved by local ethics and/or institutional review boards.

Study Outcomes

The primary study outcome was the first sustained VA following diagnosis by the TFC. Sustained VA was defined as a composite of the occurrence of SCD, SCA, spontaneous sustained ventricular tachycardia (VT) (VT lasting ≥ 30 seconds at ≥ 100 bpm or with hemodynamic compromise requiring cardioversion), ventricular fibrillation/flutter (VF), or appropriate ICD intervention. The first episode of a rapid sustained VA (defined as SCD, SCA, VF, or VT > 250 bpm), heart transplantation, cardiovascular mortality, and all-cause mortality were also recorded.

Predictors

Potential predictors were pre-specified based on clinical experience and current literature on arrhythmic risk stratification in ARVC including 1) a recent systematic review and meta-analysis⁵ and 2) the International Task Force Consensus (ITFC) Statement for Treatment of ARVD/C¹ and a recent analysis of the performance of its risk stratification algorithm.⁸ Variables considered were: sex, age, recent (< 6 months) cardiac syncope, non-sustained VT (NSVT), number of premature ventricular complexes (PVC) on 24-hour Holter monitoring, extent of T-wave inversion (TWI) on anterior and inferior leads, and right (RVEF) and left ventricular ejection fractions (LVEF). Each predictor variable was determined at the time of diagnosis, defined as one year before to one year after the date of diagnosis by TFC, but always prior to occurrence of the primary outcome. Definitions of predictor variables are provided in **Supplementary Table 2**. In **Supplementary Table 3** we describe the rationale for selecting each predictor, as well as the rationale for excluding other variables.

Data Collection

Data were collected independently by each registry according to standard operating procedures (**Supplementary Table 4**). Outcomes were adjudicated at each centre via review of electrocardiogram (ECG) tracings, ICD interrogation tracings, as well as medical and death records. ECGs were interpreted through an ECG core laboratory by two cardiologists-electrophysiologists (JCT and RT) blinded to the rest of the data and outcomes. Genetic variants were adjudicated according to the American College of Medical Genetics and Genomics guidelines by consensus of specialists in cardiac genetics (BM, JDHJ, JPVt, CAJ).⁹

Statistical Analysis

Analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina) and RStudio version 1.1.414 (Boston, Massachusetts). Categorical variables were summarized as frequencies (percentages) and compared using Chi-Square or Fisher's exact tests, as appropriate. Continuous variables were presented as mean \pm standard deviation (SD) or median (interquartile range [IQR]), and compared using the independent sample t-test or Mann-Whitney U test. Follow-up duration was calculated from the date of diagnosis to the date of reaching the endpoint or censoring, which was defined as death from any other cause, heart transplantation, or the most recent follow-up visit at which the endpoint could be ascertained. The overall probability of survival free from sustained VA was estimated using the Kaplan-Meier method.

Missing Data

Potential bias from missing data was evaluated by comparing characteristics of patients with one or more missing predictor variables to patients with complete data. Missing quantitative values for RVEF and LVEF were imputed manually when qualitative assessment was present (as detailed in **Supplementary Table 4**). Other missing data were assumed to be missing at random and imputed using multiple imputation with chained equations.¹⁰ The multiple imputation model included all pre-specified predictors as well as proband status, QRS duration, right ventricular volume, ICD carrier status, together with the outcome and a cumulative baseline hazard estimation.¹¹ A total of 25 imputed datasets were generated and the final inference estimations were combined using Rubin's rules.¹² A complete case analysis and an analysis without manual imputation of RVEF and LVEF were conducted as sensitivity analyses.

Model Development and Validation

The association between the pre-specified predictors and the primary outcome was assessed using Cox regression. Proportional-hazard assumptions were verified as well as linearity of the association for continuous predictors. The final model was fitted using stepwise backward selection based on Akaike's Information Criterion.⁶ The discriminative performance of the model was measured using Harrell's C-statistic.

The model was validated using 200 bootstrap samples. The degree of optimism was estimated by the average calibration slope of the bootstrap samples.¹³ Agreement between predicted and observed outcomes was evaluated graphically using calibration plots that incorporated grouped Kaplan-Meier estimates and the continuous hazard regression function.¹⁴ Calibration analyses were repeated for patient subgroups including genotype and

ICD status.

Model Presentation

For an individual patient, the risk of sustained VA was calculated using the following equation:

$$P(\text{VA at time } t) = 1 - S_0(t)^{\exp(\text{PI})}$$

Where $S_0(t)$ is the baseline survival probability at time t (i.e. at 5 years), and PI (prognostic index) is the sum of the products of the predictors and associated coefficients for a given patient.

Clinical Utility

To assess the implications of our model in clinical practice, we compared performance of our model to that of the consensus-based algorithm for ICD placement published in the ITFC Statement for Treatment of ARVD/C.¹ First, we explored the clinical impact of potential thresholds for ICD implantation by evaluating the proportions of appropriate and inappropriate treatment at each of these thresholds. Second, we performed a decision curve analysis to evaluate the clinical benefit of our model. In this analysis, the clinical benefit was assessed by the “net benefit”; a weighted measure of the balance between appropriate and inappropriate ICD implantations.¹⁵ A value of 0 indicates no benefit, while higher values indicate greater benefit.

Results

Study Population

The study population consisted of 528 patients with definite ARVC and no history of sustained VA or SCA at time of diagnosis. Almost half ($n=236$, 44.7%) of the population was male with an average age at diagnosis of 38.2 ± 15.5 years. Probands ($n=263$, 49.8%) and family members ($n=265$, 50.2%) were equally represented. Two-thirds ($n=340$, 64.4%) of patients had a pathogenic or likely pathogenic variant (eg. mutation) in an ARVC-associated gene. Other clinical and demographic characteristics are summarized in **Table 1**. The study population had balanced representation from North America ($n=259$, 49.1%) and Europe ($n=269$, 50.9%). Characteristics of patients contributed by each registry are shown in **Supplementary Table 5**.

Table 1. Baseline clinical characteristics

	Overall	Patients without sustained VA	Patients with sustained VA	p-value
Total	528 (100.0)	382 (72.3)	146 (27.7)	
Demographics				
Male sex	236 (44.7)	155 (40.6)	81 (55.5)	0.003
Age at diagnosis (years)	38.16 ± 15.47	39.73 ± 15.84	34.05 ± 13.67	<0.001
Caucasian ethnicity (n=498)	485 (91.9)	348 (91.1)	137 (93.8)	0.064
Proband status	263 (49.8)	151 (39.5)	112 (76.7)	<0.001
Pathogenic mutation (n=504)	340 (64.4)	248 (64.9)	92 (63.0)	0.599
<i>PKP2</i>	258 (48.9)	185 (48.4)	73 (50.0)	0.582
<i>DSP</i>	23 (4.4)	18 (4.7)	5 (3.4)	
<i>DSG2</i>	17 (3.2)	15 (3.9)	2 (1.4)	
<i>PLN</i>	26 (4.9)	19 (5.0)	7 (4.8)	
Multiple mutations	6 (1.1)	4 (1.0)	2 (1.4)	
Other	10 (1.9)	7 (1.8)	3 (2.1)	
History				
Symptoms	307 (58.1)	190 (49.7)	117 (80.1)	<0.001
Cardiac syncope	107 (20.3)	59 (15.4)	48 (32.9)	<0.001
Recent cardiac syncope (n=519)	48 (9.1)	23 (6.0)	25 (17.1)	<0.001
ECG / continuous ECG monitoring				
TWI in ≥3 precordial leads (n=517)	298 (56.4)	193 (50.5)	105 (71.9)	<0.001
TWI in ≥2 inferior leads (n=506)	85 (16.1)	53 (13.9)	32 (21.9)	0.021
NSVT (n=470)	231 (43.8)	145 (38.0)	86 (58.9)	<0.001
24h PVC count (n=425)	1007 [278, 3731]	833 [125, 2768]	2782 [992, 5918]	<0.001
Imaging				
RVEF (%) (n=510)	43.80 ± 10.40	45.40 ± 9.55	39.33 ± 11.37	<0.001
LVEF (%) (n=515)	57.66 ± 8.42	58.16 ± 8.00	56.34 ± 9.34	0.029
Treatment at baseline				
ICD	218 (41.3)	136 (35.6)	82 (56.2)	<0.001
Beta blockers (n=511)	200 (37.9)	142 (37.2)	58 (39.7)	0.343
Anti-arrhythmic drugs (n=510)	82 (3.4)	50 (13.1)	32 (21.9)	0.019

Variables are expressed as frequency (%), mean±SD or median [IQR]. *PKP2*=Plakophilin-2; *DSP*=desmoplakin; *DSG2*=desmoglein-2; *PLN*=phospholamban; ICD=implantable cardioverter defibrillator; IQR, interquartile range. Other abbreviations as per Table 1. Total number of patients for a given variable mentioned if missing data.

Overall, 390 (73.8%) patients had complete data for the pre-specified predictors. Missing data occurred for 6 of the 8 predictors: recent cardiac syncope (n=9, 1.7%), NSVT (n=58, 11.0%), PVC count (n=103, 19.5%), sum of TWI in anterior and inferior leads (n=22, 4.2%), RVEF (n=19, 3.6%) and LVEF (n=13, 2.5%).

Outcomes

During a median follow-up of 4.83 (IQR 2.44-9.33) years, 146 (27.7%) patients experienced the composite outcome, with a corresponding annual event rate of 5.6% (95% confidence interval [CI] 4.7-6.6). **Figure 1** shows the cumulative survival free from first sustained VA. As shown in the figure, events occurred throughout follow-up, with a cumulative event-free survival at 5 years of 73.6% (95% CI 69.4-78.0%). The most common first sustained VA was appropriate ICD therapy (n=102, 70.0%), followed by spontaneous sustained VT (n=35, 23.9%), SCA (n=6, 4.1%), and SCD (n=3, 2.0%). Rapid sustained VAs (VT with cycle length <240ms, SCA, or SCD) were experienced by 53 (10.0%) patients at an annual event rate of 1.7% (95% CI 1.3-2.2). At last follow-up, 18 (3.4%) patients had died and 14 (2.7%) had undergone heart transplantation.

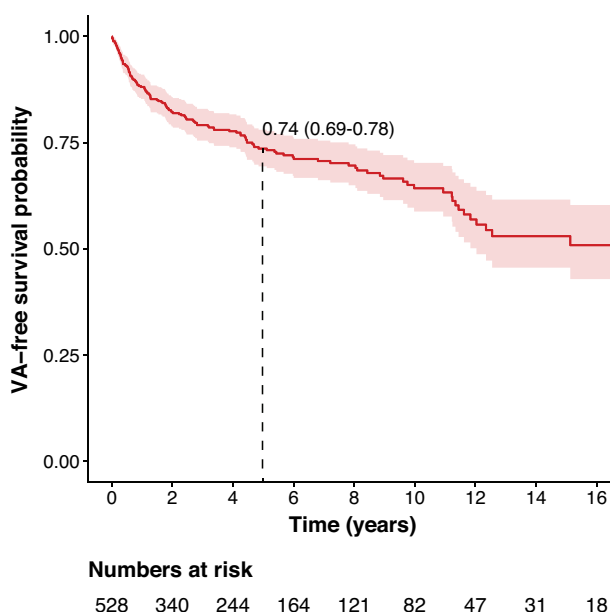


Figure 1. Cumulative survival free from sustained ventricular arrhythmia.

Plotted is the cumulative event-free survival for any ventricular arrhythmia (VA) with 95% confidence intervals (shaded area). Dotted line represents cumulative 5-year survival.

Model Development

Table 1 shows baseline characteristics of patients with and without sustained VA during follow-up. **Table 2** summarizes development of the risk prediction model. As shown in these tables, each pre-specified predictor had a significant ($p < 0.05$) univariable linear or log-linear relationship with the primary outcome. All predictors were, therefore, fitted into a multivariable model, after which stepwise backward selection was performed leading to the removal of LVEF from the final model. As a sensitivity analysis, we repeated this process 1) for patients with complete data and 2) without manual imputation for RVEF. As can be appreciated from **Supplementary Table 6**, this resulted in inclusion of the same predictor variables (i.e. excluding LVEF) with only small changes to the coefficients in the resulting model.

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

$$P(\text{VA at 5 years}) = 1 - 0.801^{\exp(\text{PI})}$$

Where:

$$\text{PI} = 0.488 * \text{sex} - 0.022 * \text{age} + 0.657 * \text{history of recent cardiac syncope} + 0.811 * \text{history of NSVT} + 0.170 * \ln(24 \text{ hour PVC count}) + 0.113 * \text{Sum of anterior and inferior leads with TWI} - 0.025 * \text{RVEF}.$$

Supplementary Table 7 provides the probability of survival ($S_0(t)$) at 1, 2, 3, and 4 years to facilitate calculating risk for shorter time durations. **Supplementary Table 8** illustrates the use of this risk calculator in 3 patients from our cohort. Instructions for accessing a preliminary version of a planned online application are provided below the table.

Table 2: Ventricular Arrhythmia Risk Prediction Model

	Univariable model		Multivariable (final model)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Male sex	1.74 (1.26-2.42)	< 0.001	1.63 (1.17-2.29)	0.005
Age (per year increase)	0.98 (0.97-0.99)	0.001	0.98 (0.97-0.99)	< 0.001
Recent cardiac syncope	2.57 (1.66-3.97)	< 0.001	1.93 (1.20-3.11)	0.007
Prior NSVT	3.15 (2.12-4.68)	< 0.001	2.25 (1.47-3.44)	< 0.001
24 h. PVC count (ln)*	1.32 (1.17-1.48)	< 0.001	1.19 (1.05-1.34)	0.013
Leads with TWI anterior + inferior	1.20 (1.12-1.29)	< 0.001	1.12 (1.02-1.23)	0.014
RVEF (per % decrease)	1.05 (1.03-1.06)	< 0.001	1.03 (1.01-1.04)	0.002
LVEF (per % decrease)	1.02 (1.01-1.04)	0.011	<i>(Not included in the final model)</i>	

*PVC count had a log-linear relationship

Abbreviations as per table 1

Model Validation

The optimism-corrected C-statistic of the predictive model was 0.77 (95% CI 0.73-0.81). Internal validation with bootstrapping revealed a calibration slope of 0.93 (95% CI 0.92-0.95), reflecting a small degree of over-optimism. **Figure 2** presents a graphical representation of calibration, showing good overall agreement between the predicted and observed 5-year risk. Calibration plots showing similarly good agreement for shorter follow-up durations can be found in **Supplementary Figure 1**. Additional calibration plots for patients stratified by ICD carrier status and genotype are presented in **Supplementary Figure 2**. As can be appreciated from this figure, predicted and observed 5-year risk remained concordant in these patient subgroups.

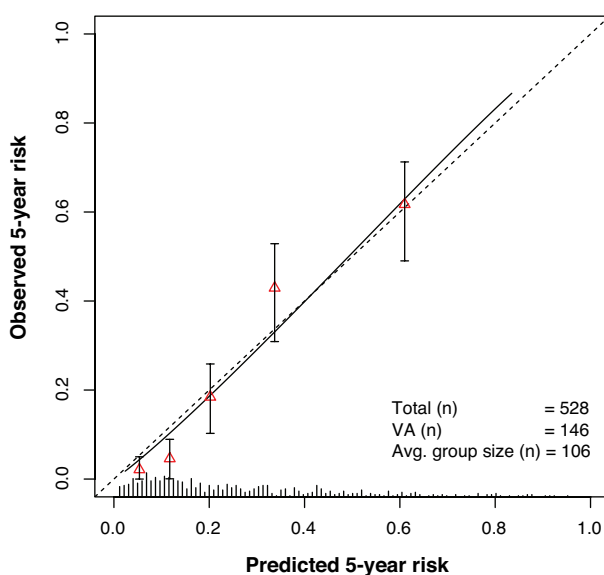


Figure 2. Calibration plot showing the agreement between predicted (X-axis) and observed (Y-axis) 5-year risk of the primary outcome.

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. Abbreviations: Ventricular arrhythmia = VA.

Clinical Utility

To assess the implications of our model in clinical practice, we explored the impact of potential 5-year VA risk thresholds for ICD implantation in our model vs. the ITFC consensus algorithm (i.e. ICD implantation in those with an ITFC class I/IIa indication).¹ This is laid out in **Figure 3**. As can be appreciated from **Supplementary Table 9**, applying the ITFC algorithm would have

resulted in treating 355 (67.2%) patients and protecting 131 (89.9%) of those who subsequently developed VA. In comparison, to provide the same level of protection (89.9%), our model would result in the implantation of 282 (53.4%) ICDs, thereby reducing the total number of ICD implants by 20.6% ($p<0.001$).

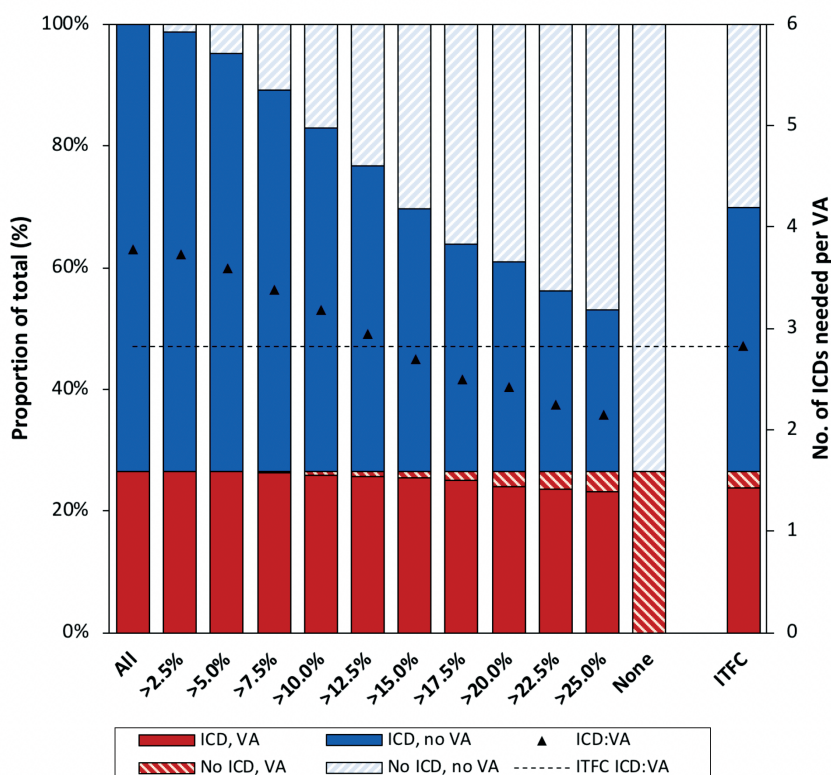


Figure 3. Outcomes of patients associated with model-based ICD implantation thresholds.

The implications of implanting an ICD in all (left bar) or none (second-to-right bar) of the patients are shown, as well as the implications of treating all patients as per ITFC (far right bar). The rest of the bars show the impact of using different ICD placement thresholds based on the risk calculated by our model. Each bar represents the complete cohort ($n=528$) and colour coding represents the proportion of patients experiencing sustained VA (red) or absence thereof (blue) as well as the placement (solid colours) versus the non-placement (striped colours) of an ICD. The black triangles represent the number of ICDs needed to protect one patient developing VA, with a horizontal dotted line for the reference value (i.e. treatment as per ITFC). Left Y-axis denotes proportion of patients (corresponding to the colour coding); right Y axis denotes the number of ICDs needed to protect one patient (corresponding to the black triangles).

Abbreviations: ICD = implantable cardioverter-defibrillator; ICD:VA = ratio of ICD placements required to protect one patient developing ventricular arrhythmia (VA); ITFC = International Task Force Consensus Statement.

We subsequently compared the clinical performance of our model to the ITFC algorithm using decision curve analysis. As shown in **Figure 4**, our proposed model was associated with the highest net benefit within the entire range of potential treatment thresholds for ICD placement. This suggests superiority in clinical practice regardless of implantation threshold.

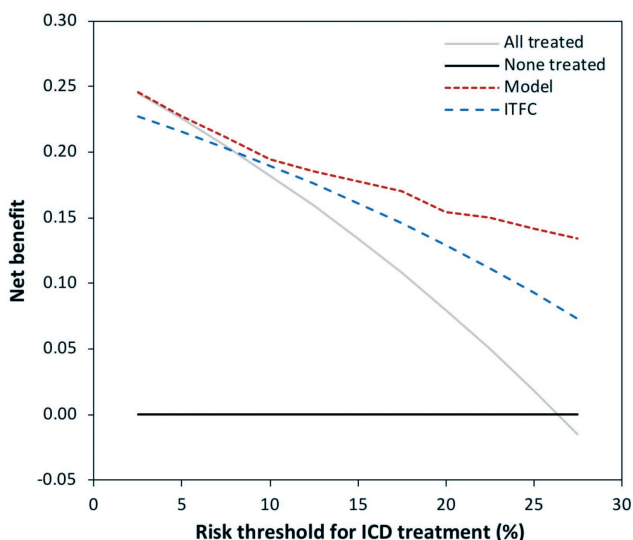


Figure 4: Decision curve analysis comparing the clinical utility of our model (red dotted line) to the ITFC algorithm (blue dotted line).

The clinical utility of both treatment strategies is compared by plotting the net benefit (Y-axis) for a range of potential ICD placement thresholds based on the 5-year risk of VA (X-axis). Our model showed the highest net benefit for all potential thresholds (ranging from 2.5% to 27.5%). This indicates that our model would result in the highest weighted balance of appropriate vs. inappropriate ICD placements, regardless of the clinically preferred risk threshold. Abbreviations as in Figure 3.

Discussion

Main Findings

We developed and internally validated the first prediction model to generate individualized risk estimates for sustained VA in patients with ARVC. This model accurately distinguished patients who had sustained VA during follow-up from those who did not using seven non-invasive parameters that are readily available to the clinician. Predicted and observed risks were concordant both in the overall population and in key patient subgroups. In addition, the model compared favourably to a clinically available treatment algorithm, suggesting greater utility in everyday clinical practice.

Prior Studies

This work builds upon numerous efforts in the ARVC community directed towards optimization of arrhythmic risk stratification. Indeed, selection of pre-specified predictors was based on a meta-analysis that included 45 studies examining the association of clinical and demographic characteristics with ventricular arrhythmias.⁵ Despite this wealth of data, a lack of systematically analysed results complicates their translation to clinical care. Interpretation of the results of prior studies has been significantly hampered by limited sample sizes and heterogeneous study populations.⁵ In addition, none of the prior studies were designed to derive a prediction model that can be applied to clinical care. The 2015 ITFC Statement for Treatment of ARVD/C was a major step forward in consolidating the literature and proposing an algorithm for ICD placement.¹ Nevertheless, the ITFC recommendations were based on expert opinion and provided only risk strata with a crude estimate of risk. Opportunities for improvement were subsequently raised.⁸ Therefore, to the present day, there is no uniformly accepted risk stratification algorithm for ARVC.

Model Development and Validation

In order to be widely applicable, a risk stratification algorithm should be derived from a broad population, simple, and easy to use. As such, we assembled the largest cohort to date of ARVC patients from multinational transatlantic registries, and measured seven easily available clinical parameters. Our model showed good discrimination between those with vs. without sustained VA (as indicated by the C-statistic), and good agreement between observed and predicted sustained VA risk (as determined by the calibration plots). In addition, sensitivity analyses revealed that the relationships between predictors and outcome were comparable in key patient subgroups.

The Need for Accurate VA Risk Prediction in ARVC

Our study quantifies the high rate of VA events in ARVC patients without a pre-existing history of sustained VA (5.6% per year). While this event rate is significantly higher than for other types of non-ischemic cardiomyopathies, it is comparable to previous studies in primary prevention ARVC populations, which reported annual event rates of 2-10%.^{2, 16} Faced with this high event rate, many clinicians would agree that the majority of patients with definite ARVC benefit from ICD placement. However, ICD placement has significant drawbacks in this usually young and active population, including a considerable risk of complications and inappropriate interventions.¹⁷ Appropriate patient selection is thus of paramount importance.

Clinical Utility

The greatest clinical utility of our model lies in the accurate individualized quantification of arrhythmic risk. By treating VA risk as a continuum instead of dividing patients into high-, intermediate- and low-risk strata, we provide prognostic information that can aid clinical decision-making for prophylactic ICD placement. Importantly in this high-risk population, our model can help the clinician identify those who would fare well without an ICD. Of note, our study does not aim to prescribe ICD placement for a given patient. Instead, we seek to provide the clinician and patient with the necessary data to facilitate well-informed shared clinical decision-making.

While the acceptable risk threshold is undefined, our model performed better than the current consensus-based algorithm¹ at any risk threshold. Importantly, our model results in a 20.6% reduction of ICD placement compared to the ITFC consensus algorithm while protecting as many patients with VA events. Therefore, we believe that the model has the potential to set the standard for everyday clinical decision-making for primary prevention ICDs in patients with ARVC. To facilitate this, we anticipate making our model available online as a “risk calculator”. Such a tool has had considerable clinical utility for arrhythmic risk prediction in hypertrophic cardiomyopathy.^{18, 19} It is important to recognize that ARVC is a progressive condition. Thus, patients should be periodically re-stratified. We provided values to facilitate shorter-term prediction and calibration plots establishing concordance between predicted and observed events over shorter timeframes (**Supplementary Figure 1**).

Limitations and Future Directions

Our study population was drawn from academic centres across Northern Europe and North America. Consistent with this, patients were predominantly Caucasian and pathogenic variants were primarily identified in *PKP2*. Results should consequently be extrapolated with caution to patients of other ethnic background or genotypes. Our ascertainment from tertiary care settings may have created a referral bias that could lead to overestimation of VA risk in a community-derived population. These limitations highlight the importance of external validation studies that include patients from community settings and with a diversity of ethnic backgrounds and genotypes. As in similar studies, we used a surrogate composite endpoint that included appropriate ICD therapy to infer risk of SCD. While most clinicians agree that ICD-treated VA represents a severe event, ICD therapies are an imperfect substitute for SCD.²⁰ To address these limitations, we stratified the population by prophylactic ICD placement and demonstrated the model performed similarly well (**Supplementary Figure 2**).

Conclusion

Based on the largest cohort to date of ARVC patients with no sustained VA history at diagnosis, we present a new prediction model to generate individualized estimates of the risk of incident VA. This model, based on readily available clinical parameters, performs better than the current consensus guideline and has the potential to set the standard for prophylactic ICD placement in ARVC.

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Supplementary Material

Supplementary Table 1: Included registries and associated hospitals

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

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 ≥ 100 bpm, 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

Predictors included		Rationale
Sex		<ul style="list-style-type: none"> Predictor in definite ARVC patients, as shown in prior meta-analysis(1)
Age		<ul style="list-style-type: none"> Predictor in definite ARVC in prior studies(2, 3)
Cardiac syncope and recent cardiac syncope		<ul style="list-style-type: none"> 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 tachycardia	ventricular	<ul style="list-style-type: none"> Predictor in definite ARVC patients, as shown in prior meta-analysis(1)
No. of premature complexes on 24h Holter	ventricular	<ul style="list-style-type: none"> Predictor in definite ARVC primary prevention population(1, 4, 5)
Extent of leads with T-wave inversion (sum of ante		<ul style="list-style-type: none"> Predictor in definite ARVC patients, as shown in prior meta-analysis(1)
Right ventricular ejection fraction		<ul style="list-style-type: none"> Predictor in definite ARVC patients, as shown in prior meta-analysis(1)
Left ventricular ejection fraction		<ul style="list-style-type: none"> 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 excluded		Rationale
History of strenuous physical activity		<ul style="list-style-type: none"> Not a predictor in patients with definite ARVC in prior meta-analysis (1) Heterogeneity in reporting among different centers and countries limit reliability
Inducibility on electrophysiology (EP) study		<ul style="list-style-type: none"> Not a predictor in patients with definite ARVC in prior meta-analysis(1) Invasiveness and availability limit widespread use
Symptoms including pre-syncope		<ul style="list-style-type: none"> Not a predictor in patients with definite ARVC in prior meta-analysis(1) Heterogeneity in reporting by patients and physicians limit reliability
Epsilon wave		<ul style="list-style-type: none"> Not a predictor in patients with definite ARVC in prior meta-analysis(1) Not unambiguously defined(7)
Genotype		<ul style="list-style-type: none"> 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		<ul style="list-style-type: none"> Not a predictor in patients with definite ARVC in prior meta-analysis (1) Present in a minimal number of patients
Right ventricular volume		<ul style="list-style-type: none"> 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
Patient characteristics	
Site	Site of enrolment
Age at diagnosis	Days since birth
Sex	Gender of patient
Pedigree	Proband or 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	Race of the patient
Pathogenic mutation	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 $\leq 0.05\%$, 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.
Gene	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) 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)
Amino acid	Amino acid change(s)
DNA change	Nucleotide change(s)
Genetic remarks	Free text
Genotype	Text: Gene with mutation and base pair chain (c.DNA genotype)
Secondary prevention	Definition: sustained event at any time before or at date of diagnosis
Variables at diagnosis	
Prior to one year after diagnosis or first sustained event	
SymptomsDx	Presence of symptoms associated with ARVC at diagnosis as reported in the medical notes
CardiacSyncopeDx	Definition: Transient loss of consciousness and postural tone with spontaneous recovery with arrhythmic mechanism likely at diagnosis. This thus excludes syncope of vasovagal etiology.
DateCardiacSyncopeDx	Age at syncope (days)
ECGDx	ECG performed at diagnosis
QRSdurationDx	Maximal QRS duration on ECG in milliseconds. Select ECG picked for "DateECG", if not on class 1 anti-arrhythmics or amiodarone. If on these medication on that ECG, select another one without medication that is closest from diagnosis if possible.
TAD_Dx	Terminal activation duration of QRS measured from the nadir of the S
BBBDx	wave to the end of the QRS, including R', in V1, V2, or V3, in the absence of complete right bundle-branch block. Presence of bundle branch block (on ECG selected for "DateECG") 0=No 1=Right Bundle branch block (RBBB): <ul style="list-style-type: none"> 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 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 S wave of greater duration than R wave or greater than 40 ms in leads I and V6 in adults 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):

	<ul style="list-style-type: none"> • 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. • 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. • 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 • 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 <p><i>Definitions from: AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram 2009(8)</i></p>
NumLeads_Tinversion_antDx	Number of precordial leads with T-wave inversion (V1 through V6). (on ECG selected for "DateECG")
NumLeads_Tinversion_infDx	<p>Definition: T-waves are considered inverted if amplitude ≥ 1 mV (1 mm).</p> <p>Number of inferior leads with T-wave inversion II, III and AVF. (on ECG selected for "DateECG")</p>
ECG_Comments	Definition: T-waves are considered inverted if amplitude ≥ 1 mV (1 mm).
HolterDx	Free text
MaxHolterPVCcountDx	Holter performed at diagnosis
EchoDx	Maximum PVC count on a 24 hrs Holter
EchodilatationRV	Transthoracic echocardiogram performed at diagnosis
ECHOdilatationPLAXDx	Qualitative global assessment of RV volume on ECHO
ECHOdilatationPSAXDx	Measure of right ventricular outflow tract (RVOT) in parasternal long axis on transthoracic echocardiogram (mm)
MRI_Dx	Mesure of RVOT in parasternal short axis on transthoracic echocardiogram (mm)
BSA	Magnetic resonance imaging (MRI) performed at diagnosis
MRIRVvolumeDx	Body mass area (m ²)
AngioDx	Right ventricular end-diastolic volume (RVEDV) on MRI
RVEF	RV angiogram performed at diagnosis
	Best available estimate of right ventricular ejection fraction (%):
	<ul style="list-style-type: none"> • RVEF on CMR is preferred for RVEF assessment • 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) • For patient with ultrasound-only assessed RV function, the median value calculated in step 2 will be assigned for the primary analysis • 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 • For patients with both FAC and RVEF by MRI, a conversion factor will be determined • Patients who only have RV function assessment by FAC will be assigned a RVEF with the method described in 5. • 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
RVEFMRI_Dx	RV ejection fraction as measurement for RV dysfunction on MRI
RV_FAC_Dx	Right ventricular (RV) fractional area change on transthoracic echocardiogram
LVEF	Best available estimate of left ventricular ejection fraction (%):
	<ul style="list-style-type: none"> • LVEF on CMR is preferred for LVEF assessment. • If LVEF on CMR is not available, quantitative assessment by cardiac ultrasound will be used • 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) • 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
LVEFMRI_Dx	LV ejection fraction as measurement for LV dysfunction on MRI
LVEFAngio_Dx	LV ejection fraction as measurement for LV dysfunction on RV angiogram
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	Code the highest/most severe result regardless of delay before diagnosis and up to one year after diagnosis / prior to the first event
ECHOTFCDx	<p>0=None</p> <p>1=Minor criteria</p> <ul style="list-style-type: none"> Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): PLAX RVOT ≥ 29 to $\leq 40\%$ <p>2=Major criteria</p> <ul style="list-style-type: none"> 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 $\leq 33\%$
MRITFCDx	<p>0=None</p> <p>1=Minor criteria</p> <ul style="list-style-type: none"> 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 to 40% to $\leq 45\%$. <p>2=Major criteria</p> <ul style="list-style-type: none"> 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 $\leq 40\%$
RVangiogramTFCDx	<p>0=None</p> <p>2=Major criteria</p> <ul style="list-style-type: none"> Regional RV akinesia, dyskinesia, or aneurysm (no 1 because no minor criteria)
TissueTFCDx	<p>0=None</p> <p>1=Minor criteria</p> <p>2=Major criteria</p> <ul style="list-style-type: none"> 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 (if >14 y old, no BBB)
NegTV1-2Dx	Negative T wave in leads V1 and 2, minor criterion
NMinor5Dx	Negative T wave in V1 to 4 in presence of complete RBBB, minor criterion
NMinor4Dx	Negative T wave in leads V4, V5 or 6, minor criterion
NMajor6Dx	Epsilon wave in leads V1, V2 or V3, major criterion. Definition: Defined as waves of small amplitude within the ST segment in V1-3 that are distinct from the QRS complex.
NMajor7Dx	Prolonged TAD in one of leads V1, V2 or V3 (≥ 55 ms), minor criterion Definition: longest value in V1-3 from the nadir of S to all depolarization deflections, in the absence of CRBBB (WHO definition).
NMinor6Dx	Late potentials (SAECG), minor criterion. Definition: Abnormal SAECG defined as ≥ 1 abnormal parameter on SAECG.

	<ul style="list-style-type: none"> Filtered QRS duration ≥ 14 ms Duration of terminal QRS <40 uV low-amplitude signal ≥ 38 ms Root mean square voltage of terminal 40 ms ≤ 20 uV
NMajor7Dx	LBBB VT (sustained or non sustained) with superior axis, definition: -30 to -150 degree axis, major criterion
NMinor8Dx	LBBB VT (sustained or non sustained) with inferior or unknown axis, minor criterion
NMinor9Dx	>500 ventricular premature ventricular complexes (PVC)/ 24 hour by Holter, minor criterion
NMajor8DxorFU	ARVD/C confirmed in first-degree relative who meets 2010 TFC, major criterion
NMajor9DxorFU	ARVD/C confirmed pathologically at autopsy/surgery in first-degree relative, major criterion
NMajor10DxorFU	Pathogenic mutation associated with ARVD/C detected per TFC (before end of follow-up or last outcome event coded)
NMinor11DxorFU	Premature sudden death (<35 years) due to suspected ARVD/C in a first-degree relative, minor criterion
NMinor10DxorFU	History of ARVD/C in first degree relative not possible or practical to determine whether family member meets 2010 TFC, minor criterion
NMinor12DxorFU	ARVC (confirmed pathologically or by TFC) in second degree relative

ICD history and programming

ICD	ICD implanted at any time
AgeatICDimplantation	Date of first ICD implantation
ICD_MinotorZoneimplant	Cycle length of the Monitor zone at implant
ICD_TxzoneImplant	Cycle length of the lowest therapy zone at implant
ICD_MonitorZone_AryorEnd	Cycle length of the monitor zone at first LTVA or last programing available at follow-up
ICD_Therapy_AryorEnd	Cycle length of the lowest therapy zone at first LTVA or last programing available at follow-up

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)
BetablockersEvent	Betablockers (excluding sotalol) taken at time of first event or censoring

Outcomes

LTVAafterDx	0 = no VT
	1 = Spontaneous sustained VT. Definition: VT lasting ≥ 30 secs or with hemodynamic compromise at ≥ 100 bpm 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
AgeatfirstLTVA	Age of 1st composite outcome of first life threatening ventricular arrhythmia
LTVAafterDx_CL	Cycle length of ventricular arrhythmia coded for primary outcome
SevereLTVAAfterDx	0 = no severe LTVA
	1 = spontaneous sustained VT $CL \leq 240$ ms (≥ 250 bpm). Definition: VT ($CL \leq 240$ ms (≥ 250 bpm) lasting ≥ 30 secs or with hemodynamic compromise at ≥ 100 bpm or terminated by electrical cardioversion
	2 = ICD intervention for VT $CL \leq 240$ 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
Age at 1st severe VA (VT with CL≤ 240 ms(≥250 bpm) or FV, SCD or resuscitated SCD)

AgeSevereLTVAfterDx

SevereLTVAfterDx_CL

Transplant

Age_Transplant

Death

Age at death

CauseDeath_text

CauseDeath_cat

Cycle length of severe VA

Cardiac transplant at follow-up

Age at cardiac transplant

Death during follow-up

Age at death

Free text, cause of death

1=SCD, 2=heart failure, 3=arrhythmic and heart failure (eg. heart failure largely caused by arrhythmias, 4= non-cardiac

VTAblation

AgeVTAblation

AgeLFU

Endocardial or epicardial VT ablation performed at any time before last coded event

Age of first ablation

Age at last clinical follow-up allowing assertion of outcomes

Supplementary Table 5: Baseine 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)
<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)
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 cases

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)	0.009	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)	0.001	0.97 (0.96-0.99)	0.001	0.98 (0.97-0.99)	< 0.001
Recent syncope	1.97(1.23-4.22)	0.008	2.07 (1.10-3.87)	0.001	1.92 (1.20-3.11)	0.007
Prior NSVT	2.31(1.48-3.62)	0.001	1.90 (1.16-3.11)	0.001	2.25 (1.47-3.44)	< 0.001
24 h. PVC count (ln)*	1.16(1.03-1.30)	0.013	1.19 (1.04-1.36)	0.001	1.19 (1.05-1.34)	0.013
Leads with TWI anterior + inferior (per lead increase)	1.12 (1.03-1.22)	0.012	1.13 (1.02-1.26)	0.002	1.12 (1.02-1.23)	0.014
RVEF (per % decrease)	1.02(1.01-1.04)	0.002	1.02 (1.01-1.05)	0.005	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	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

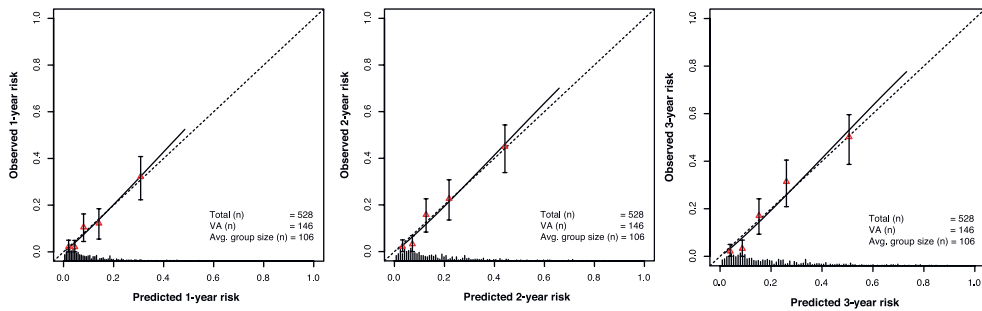
Patient 1: Low risk										Patient 2: Medium risk										Patient 3: High risk									
Demographics: 48 year-old female, Genetics/Pedigree: family history of ARVC in daughter, no pathogenic mutation. History of recent syncope: Absent Arrhythmia: No NSVT 24 hour PVC count is 1 ECG: TWI in V1-V4 RV function: RVEF: 55%										Demographics: 50 year-old male, Genetics/Pedigree: Family history of ARVC. Pathogenic mutation 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 mutation 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 prognostic index (PI)										Calculation of 5-year risk									

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 thresholds for ICD implantation at 5 years with Kaplan-Meier corrected estimates

	All	>2.5%	>5.0%	>7.5%	>10.0%	>15.0%	>20.0%	>22.5%	ITFC
VA, ICD	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%)
VA, No ICD	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)	3 (0.5%)	5 (1%)	12 (2.4%)	14 (2.6%)	14 (2.6%)
No VA, ICD	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%)
No VA, No ICD	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%)
ICD, total	528 (100%)	521 (98.7%)	502 (95.1%)	470 (89%)	434 (82.2%)	362 (68.6%)	309 (58.5%)	282 (53.4%)	355 (67.2%)
ICD:VA ratio	3.8	3.7	3.6	3.4	3.2	2.7	2.4	2.3	2.8
Protection rate (%)	100.0%	100.0%	100.0%	99.3%	97.8%	96.4%	91.4%	89.9%	89.9%

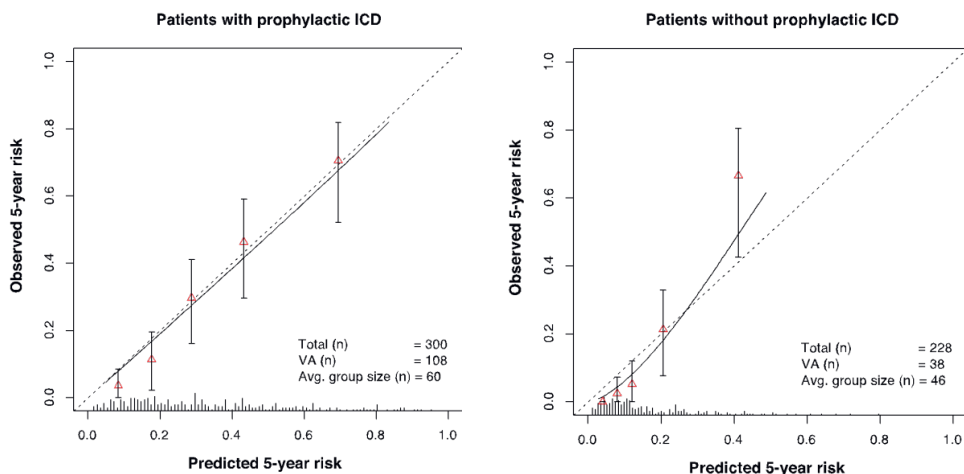
Abbreviations as per Table 2. ITFC designates the Treatment of Arrhythmogenic Right Ventricular Cardiomyopathy: An International Task Force Consensus Statement published in 2015(6)



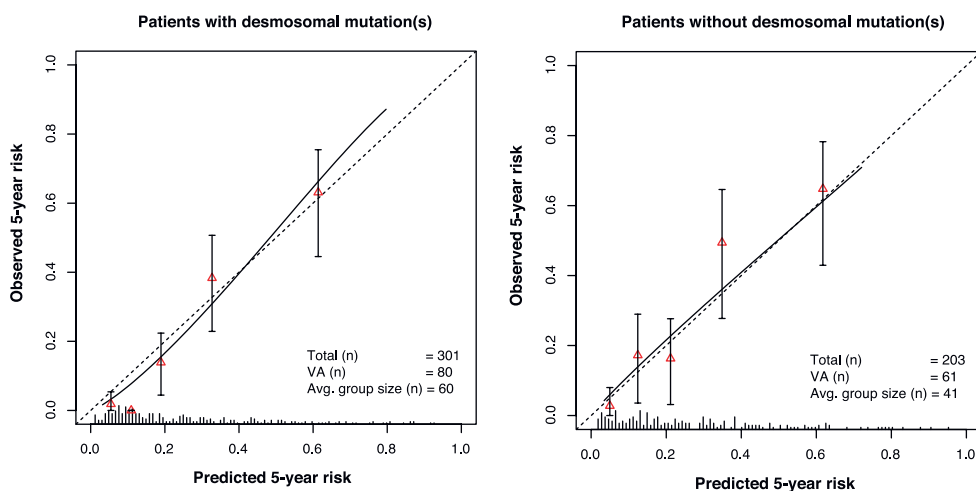
Supplementary Figure 1: Calibration plot showing the agreement between predicted (X-axis) and observed (Y-axis) 1, 2 and 3-year risk of developing any ventricular arrhythmia in different subgroups.

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.

A)



B)

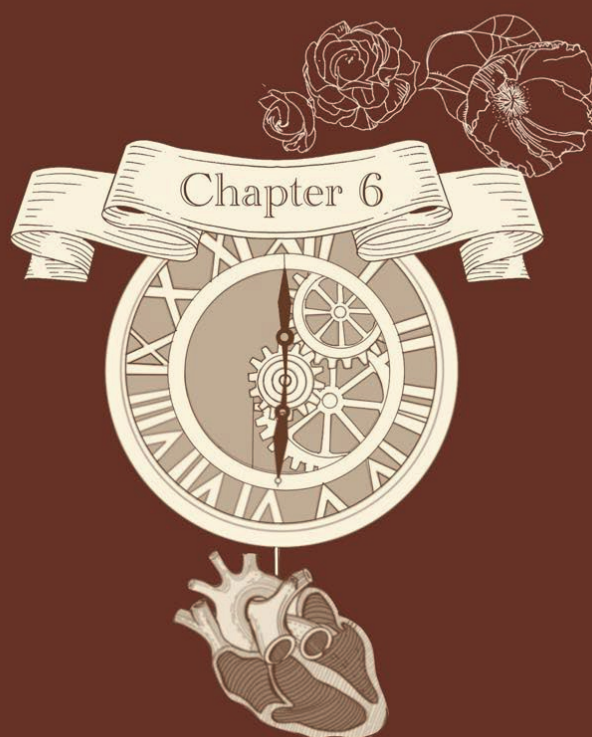


Supplementary Figure 2: Calibration plot showing the agreement between predicted (X-axis) and observed (Y-axis) 5-year risk of developing any ventricular arrhythmia in different subgroups.

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.

References for supplemental material

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Chapter 6

Integrating Exercise into Personalized Ventricular Arrhythmia Risk Prediction in Arrhythmogenic Right Ventricular Cardiomyopathy

Submitted

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Abstract

Background: Exercise is associated with sustained ventricular arrhythmias (VA) in Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), but is not included in the ARVC risk calculator (arvcrisk.com). The objective of this study is to quantify the influence of exercise at diagnosis on incident VA risk, and evaluate whether the risk calculator needs adjustment for exercise.

Methods: We interviewed ARVC patients without sustained VA at diagnosis about their exercise history. The relationship between exercise-dose three years preceding diagnosis (average MET-hours/week) and incident VA during follow up was analyzed with time-to-event analysis. The incremental prognostic value of exercise to the risk calculator was evaluated by Cox-models.

Results: We included 176 patients (male 43.2%, age 37.6 ± 16.1) from three ARVC-centers, of which 53 (30.1%) developed sustained VA during 5.4 [2.7-9.7] years follow-up. Exercise at diagnosis showed a dose-dependent non-linear relationship with VA, with no significant risk increase <15-30 METh/week. Athlete status, using three definitions from literature (>18, >24, and >36 MET-h/week), was significantly associated with VA (hazard ratios 2.53-2.91), but was also correlated with risk factors currently in the risk calculator model. Thus, adding athlete status to the model did not change the C-index of 0.77 (0.71-0.84) and showed no significant improvement (Akaike's information criterion change <2).

Conclusions: Exercise at diagnosis was dose-dependently associated with risk of sustained VA in ARVC patients, but only above 15-30 METh/week. Exercise does not appear to have incremental prognostic value over the risk calculator. The ARVC risk calculator can be used accurately in athletic patients without modification.

Introduction

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is an inherited heart disease characterized by fibrofatty replacement of the myocardial wall, frequent life-threatening ventricular arrhythmias (VA) and a higher risk of sudden cardiac death (SCD).¹ In approximately two-thirds of the patients, a disease-causing mutation is identified,² most commonly in genes encoding desmosomal-proteins, impairing both electrical and mechanical myocardial function.

Exercise promotes development of ARVC in at-risk individuals and is associated with earlier disease onset, higher risk of arrhythmias, and worse structural disease in patients. Most clinicians now advise exercise restriction, as this was recently suggested to be effective in VA-risk reduction.^{3,4} However, it is well established that exercise is beneficial for physical and mental health, reducing the risk of other cardiovascular diseases, osteoporosis, type-2 diabetes mellitus, anxiety and depression.⁵ Unfortunately, it remains uncertain to what extent exercise should be restricted, and if there is a level of exercise safe for ARVC patients that allows the general physical and mental health benefits of exercise to remain. Several studies have posited that low intensity or non-competitive activities may be safer for ARVC patients^{6,7} but these had limited statistical power or did not precisely define type or intensity of exercise.

We recently developed a risk calculator for incident sustained VA in patients newly diagnosed with ARVC without prior sustained VA (arvcrisk.com).⁸ By design, this did not include the quantity of exercise exposure in generating risk estimates, as the aim was to develop a prediction model using risk factors that were consistently collected in participating centers and readily available in clinical practice. Nonetheless, not integrating exercise raises valid concerns about the accuracy of predictions in athletes.⁹

To address these important clinical queries, we designed a study combining exercise data collected by interview from three large ARVC registries to: 1) better quantify the dose-dependent relationship of exercise at diagnosis and risk of incident sustained VA, and 2) evaluate the incremental value of adding exercise to the risk calculator model and test whether it can be accurately used in athletic patients or requires modification.

Methods

Study design and population

This is a retrospective, observational, longitudinal multicenter cohort study. Patients eligible for inclusion were 1) definite ARVC patients per 2010 Task Force Criteria without sustained

VA prior to their diagnosis who 2) participated in a detailed exercise interview in one of the three participating ARVC centers: Johns Hopkins Hospital (Baltimore, USA), Oslo University Hospital (Oslo, Norway), and the University Medical Center Utrecht (Utrecht, The Netherlands). All participants provided written informed consent and the study protocols were approved by local IRB / Ethics boards.

Data collection

Demographic and clinical data were collected as previously described in detail in the manuscript describing development of the ARVC risk calculator.⁸ Briefly, data was collected independently by each center following standard operating procedures. All electrocardiogram (ECG) data and genetic variants were additionally reviewed by an electrophysiology team and genetic specialist team respectively for validity. The outcome of the first sustained VA was defined as the occurrence of either (aborted) SCD, ventricular fibrillation (VF), spontaneous sustained ventricular tachycardia (VT) (lasting >30s at >100bpm or with hemodynamic instability requiring cardioversion), or appropriate implantable cardioverter-defibrillator (ICD) intervention. Time to event was defined as the time from inclusion at the time of diagnosis by 2010 Task Force Criteria to first incident sustained VA, or censoring by death, heart transplantation or last clinical follow-up.

Exercise history

The exercise history of all included patients was obtained through a structured telephone or in-person interview according to previously published protocols.^{6,10} Exercise data included in this analysis included all exercise, recreational or competitive, done on a regular basis during the three years prior to diagnosis. For each exercise activity, we determined the intensity in metabolic equivalents (METs) based on the 2011 Compendium of Physical Activities.¹¹ Only activities requiring at least 3 METs were considered as exercise in this study. The exercise dose was calculated by first multiplying the MET of each individual activity by the reported duration (METH), then combining these values and averaging per week (METH/week).

To evaluate the association of exercise dose with the predefined outcome, first we considered exercise as a continuous value expressed as METH/week. Second, we divided exercise dose into five categories based on multiples of the American Heart Association recommended minimum of 7.5 METH/week,⁵ i.e. below minimum (<1x, 0-7.5 METH/week), $\geq 1x$ (7.5-15 METH/week), $\geq 2x$ (15-30 METH/week), $\geq 4x$ (30-60 METH/week), and $\geq 8x$ the minimum (≥ 60 METH/week). Furthermore, we estimated the prognostic value of "athlete status" using three definitions shown to be significantly associated with higher arrhythmia risk in prior ARVC studies: >18 METH/week^{3,12}, >24 METH/week¹³, and >36 METH/week.¹⁴

Data analysis

Statistical analysis was performed in RStudio version 1.1.414 (Boston, MA, USA). Continuous variables were expressed as mean \pm standard deviation or median [first quartile – third quartile], and compared using the t-test or Mann-Whitney U test as appropriate. Categorical variables were compared using the χ^2 or Fisher's exact test. Two-tailed p-values of <0.05 were considered statistically significant. Survival analysis was performed using the Kaplan-Meier method and the Cox-Proportional Hazard model. Multiple testing was corrected with the Benjamini & Hochberg method. In total 7% of data was missing, and as described previously assumed to be at random and imputed using multiple imputation by chained equations.⁸ The Cox model linearity assumption of continuous variables was evaluated using martingale residuals. Possible interactions of exercise with sex, age, and genetic variants were tested. Model performance of the risk calculator with and without the addition of exercise was calculated by Harrel's C-statistic. Akaike's Information Criterion (AIC) as relative estimator of prediction error was used for model selection, for which difference of >2 was considered significant.

Results

Population characteristics

In total, 176 patients were included (**Table 1**). Almost half (76, 43.2%) were male, with an average age of 37.6 ± 16.1 years at the time of diagnosis. The majority (134, 76.1%) of patients had a pathogenic or likely-pathogenic variant (e.g. mutation), most frequently in the *PKP2* gene (105, 59.7%). During 5.4 [2.7-9.7] years of follow-up, 53 (30.1%) developed the composite outcome of sustained VA.

Most patients were enrolled at the Johns Hopkins Hospital (105, 59.7%) and the Oslo University Hospital (47, 26.7%)(**Supplementary Table 1**). Most had been included (164, 93.2%) in the original risk calculator development cohort, the remainder were patients with new diagnoses at our centers.

Based on the demographics, clinical characteristics and outcomes during follow-up, this cohort with exercise interviews was similar to the overall risk calculator cohort (**Table 1**). The only significant difference was a higher proportion of pathogenic/likely pathogenic variant carriers in the study cohort (76.1 vs. 64.4%, $p=0.001$).

Table 1. Population characteristics

	Risk calculator cohort	Study cohort	p
Total	528	176	
Male sex	236 (44.7)	76 (43.2)	0.793
Age at diagnosis (years)	38.2±15.5	37.6±16.1	0.660
Proband	263 (49.8)	77 (43.8)	0.191
Pathogenic variant (mutation)	340 (64.4)	134 (76.1)	0.001
<i>PKP2</i>	258 (48.9)	105 (59.7)	0.018
<i>DSP</i>	23 (4.4)	11 (6.2)	
<i>DSG2</i>	17 (3.2)	3 (1.7)	
<i>PLN</i>	26 (4.9)	5 (2.8)	
Multiple	6 (1.1)	4 (2.3)	
Other	10 (1.9)	6 (3.4)	
Symptomatic	307 (58.1)	96 (54.5)	0.584
Recent cardiac syncope	48 (9.1)	15 (8.5)	0.844
24h PVC count	1076 [300-3798]	847 [231-3008]	0.299
Non-sustained VT	231 (43.8)	66 (37.5)	0.302
Leads with TWI (II, III, aVF and V1-6)	3 [2-5]	3 [2-5]	0.880
RVEF (%)	48 [38-51]	48 [38-55]	0.086
Follow-up (years)	4.8 [2.4-9.3]	5.4 [2.7-9.7]	0.496
Sustained VA	146 (27.7)	53 (30.1)	0.595
Sustained VT	35 (6.6)	11 (6.2)	0.754
Appropriate ICD intervention	102 (19.3)	40 (22.7)	
VF/aborted SCD	6 (1.1)	2 (1.1)	
SCD	3 (0.6)	0 (0.0)	

Abbreviations: PVC=premature ventricular complex; ICD=implantable cardioverter-defibrillator; RVEF=Right ventricular ejection fraction; SCD=sudden cardiac death; TWI=T-wave inversions; VA=ventricular arrhythmia; VF=ventricular fibrillation; VT=ventricular tachycardia.

Exercise dose and incidence of ventricular arrhythmia

Overall, the median exercise dose at diagnosis was 2.4 [10.7-52.6] METh/week. This was significantly higher in patients who experienced sustained VA during follow-up (16.8 [9.0-38.9] vs. 7.4 [4.5-10.9], $p<0.001$)(**Supplementary Figure 1**). The association between exercise dose as a continuous variable and the risk of sustained VA was plotted for visual analysis, revealing a non-linear relationship which appeared to fit an S-shaped curve (**Supplementary Figure 2**). As this violates the linearity assumption of the Cox regression model for continuous variables, we treated exercise dose categorically using multiples of the AHA recommended minimum of 7.5 METh/week. Kaplan-Meier curves for incident sustained VA among patients fitting in these five exercise dose categories are plotted in **Figure 1**. Notably, the survival

curves of the first three categories ($<1x$, $\geq 1x$, and $\geq 2x$ AHA minimum) showed considerable overlap, and only the patients exercising $\geq 4x$ ($p=0.003$) and $\geq 8x$ ($p<0.001$) the recommended AHA minimum had significantly higher incidence of sustained VA compared to the lower three categories.

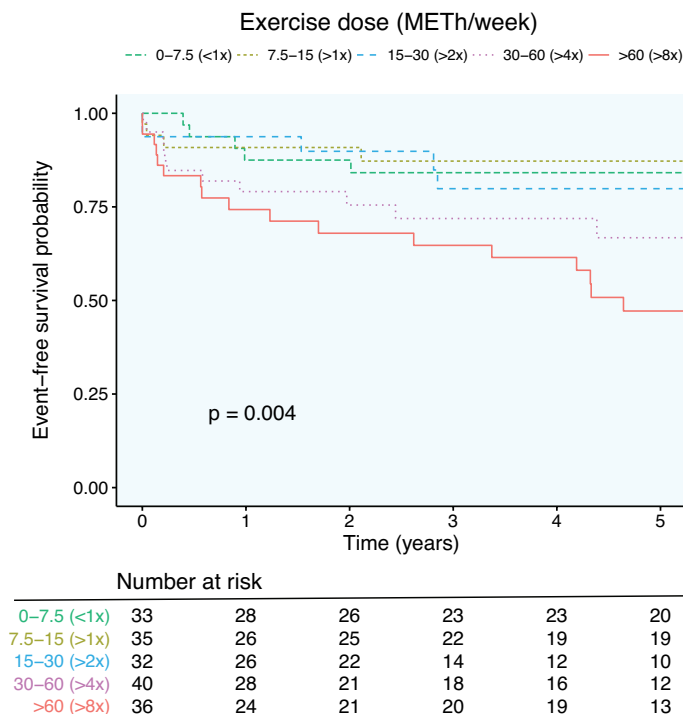


Figure 1. Exercise dose and sustained VA free survival

Kaplan-Meier plot showing the sustained VA free survival of the cohort divided into five categories of exercise dose, based on multiples of the AHA recommended minimum of 7.5 METh/week.

Consistent with this, relative to exercising below 7.5 METh/week (**Figure 2**), there was no clear difference in sustained VA risk at exercising between 7.5–15 METh/week (HR 0.99, 95%CI 0.32–3.06, $p=0.981$) or 15–30 METh/week (HR 1.37, 95%CI 0.44–4.29, $p=0.579$), with the first significant increase at >30 METh/week (HR 3.00, 95%CI 1.17–7.68, $p=0.022$). Similar results were found when adjusting for sex and age (**Supplementary Figure 3**). Additionally, no significant interaction was found between any category of exercise and sex ($p>0.220$), age ($p>0.182$), carriers of a pathogenic variant ($p>0.475$), nor carriers of a *PKP2* pathogenic variant specifically ($p>0.266$).

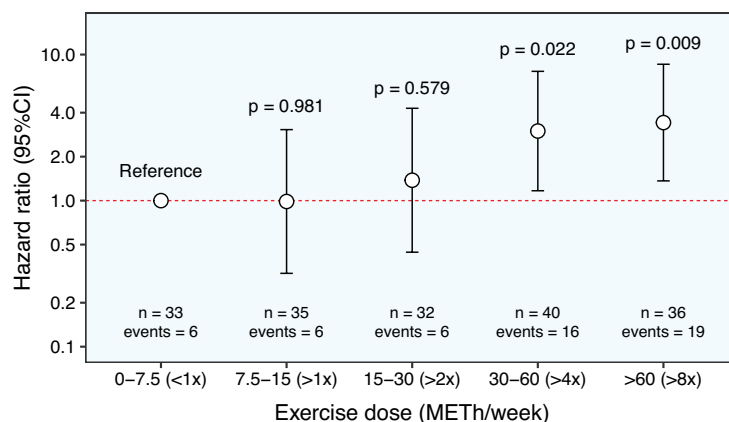


Figure 2. Dose-dependent association of exercise dose and sustained VA risk

Plot of the hazard ratios (Y-axis) per exercise dose (X-axis) with the 0-7.5 METH/week group as reference. Error bars are 95% confidence intervals.

Athlete status has been shown to be a significant predictor for risk of sustained VA in ARVC in prior studies using three “athlete” definitions (i.e. >18 METH/week, >24 METH/week, and >36METH/week). In this cohort, all three definitions of athlete status at diagnosis were significantly associated with an increased risk of incident VA in univariable analysis. As shown in **Figure 3**, the HR ranged from 2.53 (95%CI 1.40-4.55, $p=0.002$) for >18 METH/week, to 2.91 (95%CI 1.68-5.03, $p<0.001$) for >36 METH/week.

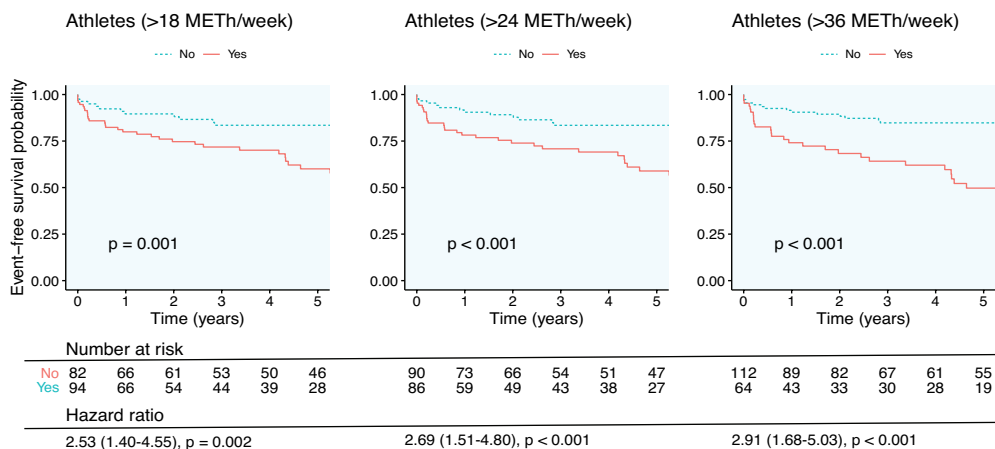


Figure 3. Athlete status as sustained VA risk predictor

For each exercise-dose cut-off value defining athletes, a Kaplan-Meier plot for event-free survival is shown stratified by athletes (red lines) and non-athletes (blue dotted lines), as well as the univariable hazard ratio for incident sustained VA.

Exercise history in personalized risk prediction

To assess whether exercise at diagnosis could further refine personalized risk prediction we first tested the performance of the current ARVC risk calculator model for personalized risk prediction of incident sustained VA in this cohort. Without modification, it showed a C-statistic of 0.77 (95%CI 0.71-0.84) consistent with prior results.⁸

Table 2. Personalized risk prediction

	Adjusted HR (95%CI)	p	C-statistic (95%CI)	AIC
Risk calculator model	-	-	0.77 (0.71-0.84)	411.7
+ Athlete if >18 METH/week	1.31 (0.69-2.49)	0.412	0.77 (0.71-0.84)	+1.3
+ Athlete if >24 METH/week	1.43 (0.75-2.70)	0.270	0.78 (0.71-0.84)	+0.8
+ Athlete if >36 METH/week	1.67 (0.93-3.02)	0.088	0.78 (0.71-0.84)	-0.9

Abbreviations: as in text.

Athlete status was added to the model using each of the three definitions for “athlete” previously used in the ARVC literature. The resulting adjusted HR was 1.31 (95%CI 0.69-2.49, $p=0.412$) for the >18 METH/week definition, 1.43 (95%CI 0.76-2.70, $p=0.270$) for the >24 METH/week definition, and 1.67 (95%CI 0.93-3.02, $p=0.088$) for the >36 METH/week definition

(**Table 2**). The C-statistic remained similar to the original risk calculator model, and none of the definitions reduced the model AIC by >2 indicating no significant improvement. As a visual confirmation, we plotted the risk calculator predictions stratified by athletes (triangles) and non-athletes (circles), and superimposed the actual observed risk of sustained VA (red crosses) in **Figure 4**, showing that the risk calculator derived predictions are within range of the observed risks in this cohort.

In addition, all three definitions of athlete status showed significant or borderline significant associations with at least five of the predictors in the current risk model (**Supplementary Table 2**). This suggests the increased risk of incident VA for athletes is already accounted for by variables in the risk calculator. Specifically, we found athletes to have a younger age, higher 24h PVC count, a higher proportion with non-sustained VT, more T-wave inversions (TWI) on ECG, and a lower right ventricular ejection fraction (RVEF), all associated with a higher risk of sustained VA.

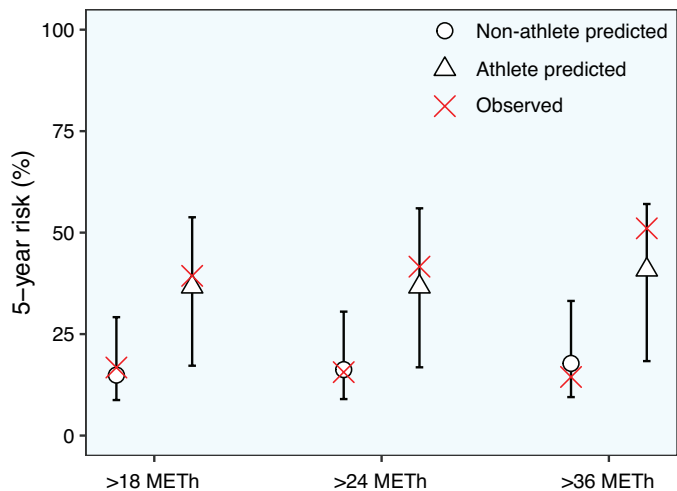


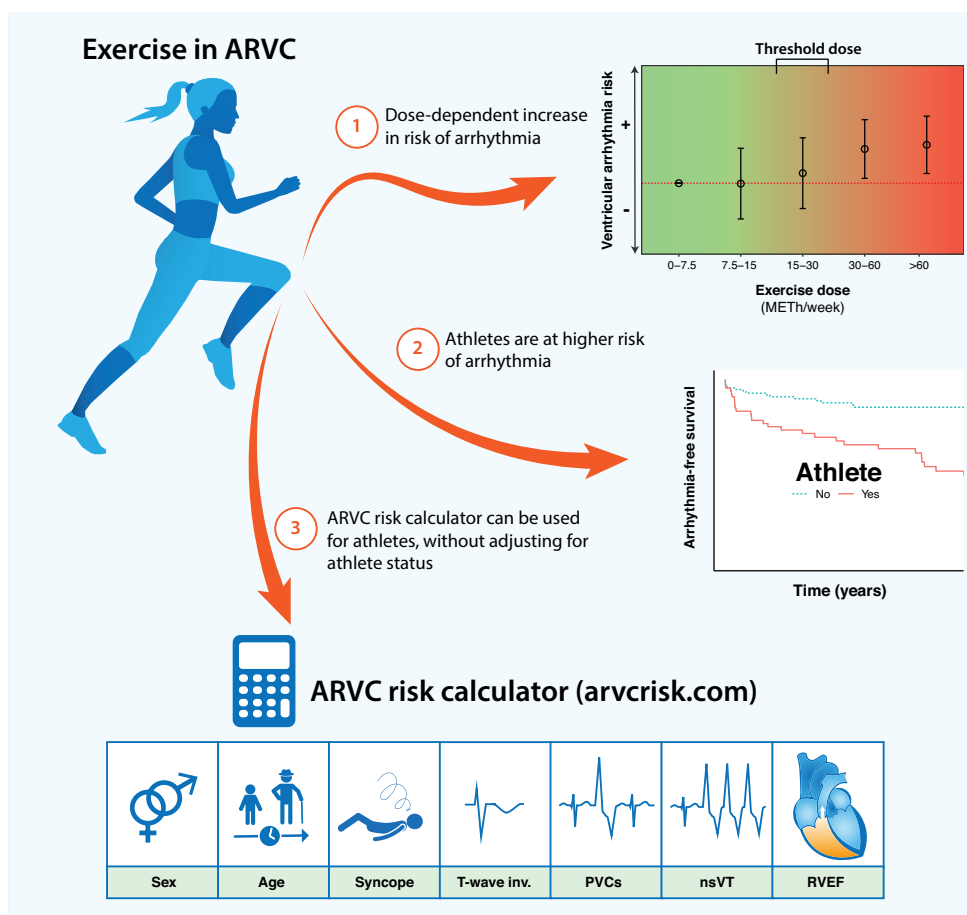
Figure 4. Observed vs. predicted risk in athletes

Plot of the observed 5-year sustained VA risk with 95%CI (black) stratified by athlete (triangles) and non-athlete (circles) status, for all three definitions of athlete. Superimposed is the predicted risk from the 5-year ARVC sustained VA risk calculator (red crosses).

Discussion

In this study, we aimed to refine understanding of the influence of exercise in arrhythmic risk prediction in newly diagnosed ARVC patients. Although prior studies have established that exercise is associated with risk of sustained VA, it remains uncertain how best to integrate exercise into personalized risk prediction and provide more quantifiable estimates of the amount of exercise associated with increased VA risk. These limitations are caused by a deficit in statistical power in prior studies, lack of granularity in exercise data, or both.^{6,7,10,12,13,15} Our current study includes the largest cohort to date of newly diagnosed ARVC patients with detailed exercise history at a similar stage of disease (definite diagnosis, no history of sustained VA).

Our study has several interesting results that will inform both current clinical care and future research (**Central Illustration**). First, the association between exercise at diagnosis and risk of incident sustained VA appears to be non-linear and dose-dependent. Exercise limited to 15-30 METh/week (2-4x the AHA-recommended minimum for healthy adults) appeared not to elevate VA risk beyond the natural ARVC development, hinting at a threshold model for safe exercise for future research. Second, while athletic patients had a higher risk of VA, this higher risk was accurately predicted by the risk calculator. Therefore, the current risk calculator (arvcrisk.com) can be applied without alterations to athletes newly diagnosed with ARVC.



Central Illustration

Exercise at ARVC diagnosis is associated with increase in sustained VA risk in a dose-dependent non-linear manner showing a threshold at 15-30 METh/week (arrow 1). Athletes are at significant higher risk of incident ventricular arrhythmia (arrow 2). Nonetheless, predictions from the 5-year sustained VA risk calculator are accurate in athletes and adding athlete status to the model did not result in a significantly improvement (arrow 3).

Quantifying the relationship between exercise and risk of incident sustained VA

Prior studies have provided indisputable evidence of the relationship between exercise and risk of sustained VA in ARVC patients and family members.^{6,7,10,12,13,15} The effect of exercise dose on arrhythmic risk was demonstrated using predefined definitions of athlete status, competitive vs. recreational exercise, or a single cut-off value based on quantiles or ROC-analysis. Recently, a study by Wang et al. provided data hinting at dose-dependency (in a cohort of family members with pathogenic variants), showing that the proportions of patients with VA increased with increasing exercise dose.⁴ However, no definite conclusions can be

drawn as this result was derived from cross-sectional analysis with limited statistical power. In the current study, we evaluated the association of exercise dose with incident sustained VA using a longitudinal analysis. Our results provide the first detailed, quantified, description suggesting a non-linear dose-dependent relationship of exercise with VA outcomes, indicating that there may be a threshold below which exercise causes little to no increase in risk of incident sustained VA.

Towards a safe exercise threshold

Exercise is important for health in the general population, and the AHA recommends at least 7.5 METh/week.⁵ However, it is uncertain to which extent ARVC patients can enjoy the health benefits from exercising without increasing their arrhythmic risk, which is a major concern for many patients who are often young and likely active. Defining a safe exercise threshold, if any, is therefore a highly sought-after topic of scientific debate.¹⁶ The ESC recently published a guideline in which ARVC patients are advised to practice up to 150 minutes of low-moderate intensity (3-6 MET) exercise per week, equivalent to approximately 15 METh/week.¹⁷ An example of this dose would be 2.5 hours of light running (at 4mph). Of note, this recommendation has a weak level of evidence C (expert opinion).

Prior studies have hinted at a safe levels of exercise, for example, Ruwald et al. showed that recreational sport does not increase risk, but no threshold quantification was provided.⁷ Similarly, Lie et al. showed that those participating only in low intensity (3-6 MET) exercise at presentation had the lowest proportion with VA, but the analysis was cross-sectional and not suitable to define a quantifiable threshold.⁶ Sawant et al., observed that *PKP2* mutation carriers restricting exercise below the upper bound of the recommended AHA minimum (<12.5 METh/week) did not develop sustained VA.¹⁸ While suggestive for a potential safe threshold, this result was derived from a small cohort of 28 subjects only.

In our study, participation in up to 15-30 METh/week of exercise at diagnosis was not associated with a higher risk of incident sustained VA in follow-up. While this is in line with the suggested threshold of 12.5 METh/week by Sawant et al, as well as the ESC threshold of exercise up to 15 METh/week, our findings, of course, refer to the exercise dose at diagnosis only. Whether continuing exercise at this level after diagnosis is similarly relatively safe needs prospective study. It is standard in our programs to recommend that newly diagnosed patients avoid competitive or frequent high-intensity endurance exercise consistent with professional guidelines, and most patients do their best to comply.

Exercise in personalized risk prediction

ARVC patients with a substantial exercise participation history (i.e. “athletes”) are at higher risk of sustained VA.^{6,7,10} But, the risk calculator for incident sustained VA (arvcrisk.com) does not specifically include an exercise metric.⁸ This possible limitation has raised concerns about the validity of its predictions in athletes.⁹ Reassuringly, Gasperetti et al. recently validated the risk calculator in a cohort of 25 Italian athletes (defined as those practicing >6 hours per week of >6 MET activities during the past 3 years) showing the risk calculator predictions to be accurate.¹⁴ However, these results were inconclusive due to the small sample size and the absence of non-athletes.

Our results confirm and extend this finding. We evaluated the incremental value of exercise dose and athlete status to the risk calculator estimate, using the three athlete definitions used in prior ARVC studies (>18 METh, >24METh, and >36 METh per week). Our results confirm that while indeed patients with an athletic history have a higher risk of sustained VA, this effect is rendered non-significant when corrected for the predicted risk generated by the risk calculator (**Table 2**). This is further confirmed by the reassuring agreement observed between the observed risk of sustained VA and the predictions from the risk calculator, regardless of exercise history (**Figure 4**). Furthermore, we found a possible explanation why athlete status did not improve the risk calculator estimate: we observed higher levels of exercise to correlate with a younger age, higher 24h PVC count, higher proportion with non-sustained VT, more TWI on ECG, and a lower RVEF, all parameters already included in the risk calculator. Thus, our results suggest that risk predictions generated by the ARVC risk calculator are accurate for both athletes and non-athletes.

Clinical implications

This study shows that while athletes diagnosed with ARVC have a higher risk of incident sustained VA than non-athletes, the risk calculator (arvcrisk.com) provides accurate predictions for both. The risk calculator can be used by clinicians and newly diagnosed athletic or sedentary ARVC patients alike to estimate risk of developing a first sustained VA and use this information in shared decision-making regarding ICD implantation and other management options. As is true for the general ARVC risk calculator, risk calculator estimates for any VA are only accurate for patients who have not yet had a documented sustained VA.

The current study revealed a non-linear dose-dependent effect of exercise history and the risk of sustained VA in patients diagnosed with ARVC without prior sustained VA, with no significant increase in risk below 15-30 METh/week. This is a promising result advancing both our understanding of the relationship between exercise and VA and our search to specify a

safe threshold. While our results specifically investigate only the influence of exercise at diagnosis on risk prediction, they do help establish what may be a reasonable exercise threshold for further study.

Study limitations

Most of our study participants had pathogenic/likely pathogenic variants (76.1%), primarily of the *PKP2* gene (59.7%). Generalization to highly arrhythmogenic genetic variants (e.g. males with *TMEM43* S358L) or populations in which the association of exercise with arrhythmic risk remains understudied (e.g. *DSP*) should be met with caution. As exercise data was collected retrospectively through interviews, recall bias might have influenced the results. Finally, this analysis captures exercise at the time of diagnosis. Patients in our centers are currently recommended to limit exercise when diagnosed and nearly all comply. Thus, the safety of exercise into the future for this progressive condition remains uncertain and will require longitudinal prospective studies of exercise. It is also worth noting that while this study provides insight into exercise relative to incident VA, data suggest that exercise also promotes structural progression.^{6,10} This current study was not designed to assess whether the exercise necessary to accelerate structural progression is the same as for VA-risk and there is as yet no risk calculator for structural progression in ARVC.

Conclusion

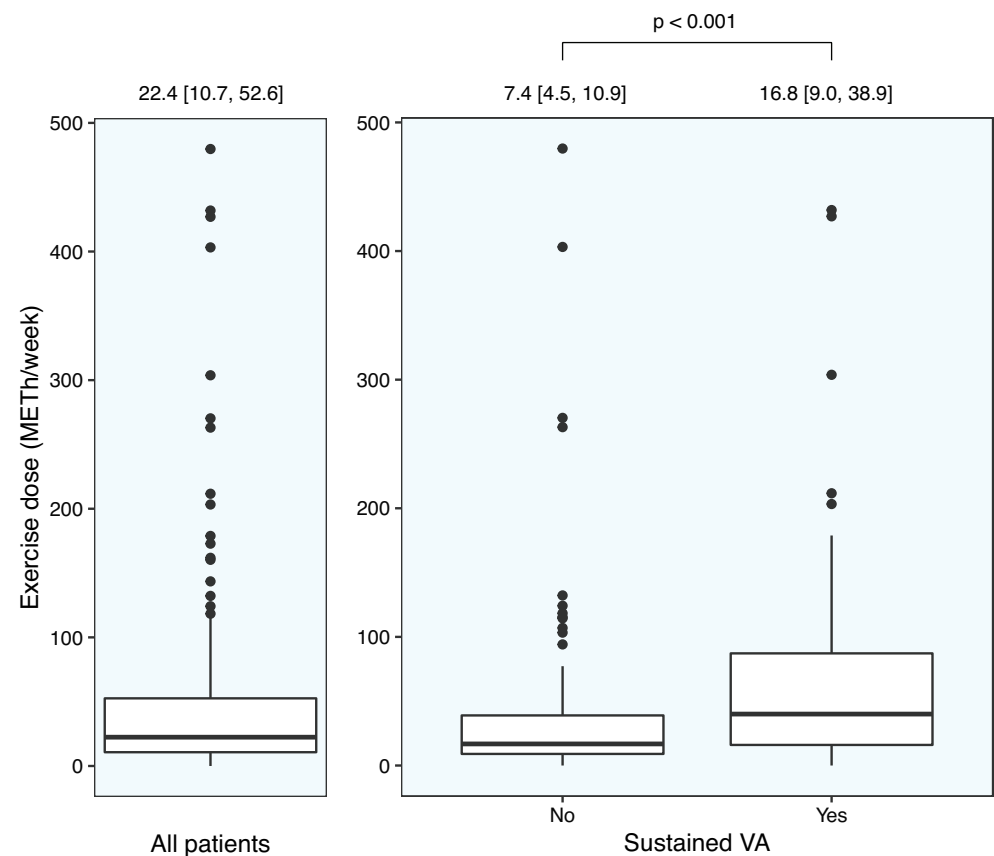
Exercise in patients with ARVC is associated with a significant increase in risk of sustained VA in a dose-dependent manner. However, our study revealed this relationship to be non-linear, with no significant risk increase in ARVC patients exercising below 15-30 METh/week at diagnosis. Future research is required to confirm this as a safe threshold for exercise continuation after diagnosis. Furthermore, while athletes have a 2.5-2.9 times higher risk of sustained VA, this increase is largely already indirectly incorporated in the risk score from the ARVC risk calculator (arvcrisk.com). Adding athlete status to the prediction model showed no significant improvement, and the risk calculator provided accurate predictions for athletes with ARVC. The ARVC risk calculator can be used without modification for newly diagnosed athletes and non-athletes alike to estimate risk of incident VA.

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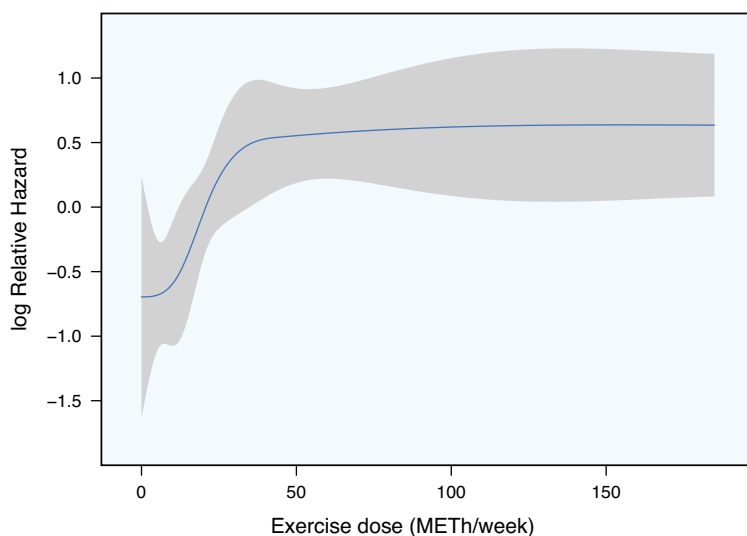
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Supplementary material



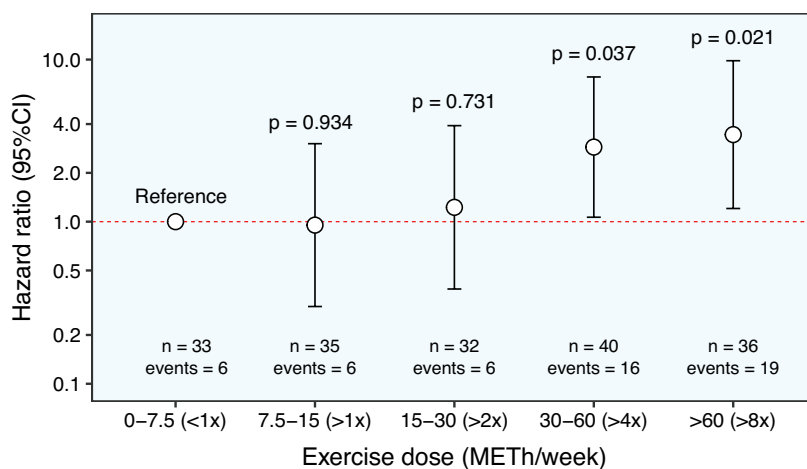
Supplementary Figure 1. Exercise dose distribution

Boxplots of exercise dose (METh/week) distrubution of the study cohort overall (left), and stratified by sustained ventricular arrhythmia outcome (right).



Supplementary Figure 2. Relationship exercise dose and sustained VA

Continuous log relative hazard (blue line) plot for relationship between exercise dose and sustained VA outcome in a Cox-PH model. Grey area represents 95% confidence interval. There is a non-linear S-shaped relationship indicating a potential threshold before risk elevation, moreover, at higher exercise levels the effect on risk plateaus.



Supplementary Figure 3. Dose-dependent association of exercise dose and sustained VA risk adjusted for sex and age

Plot of the hazard ratios (Y-axis) per exercise dose (X-axis) with the 0-7.5 METh/week group as reference. Error bars are 95% confidence intervals.

Supplementary Table 1. Study exercise interview cohort characteristics per center

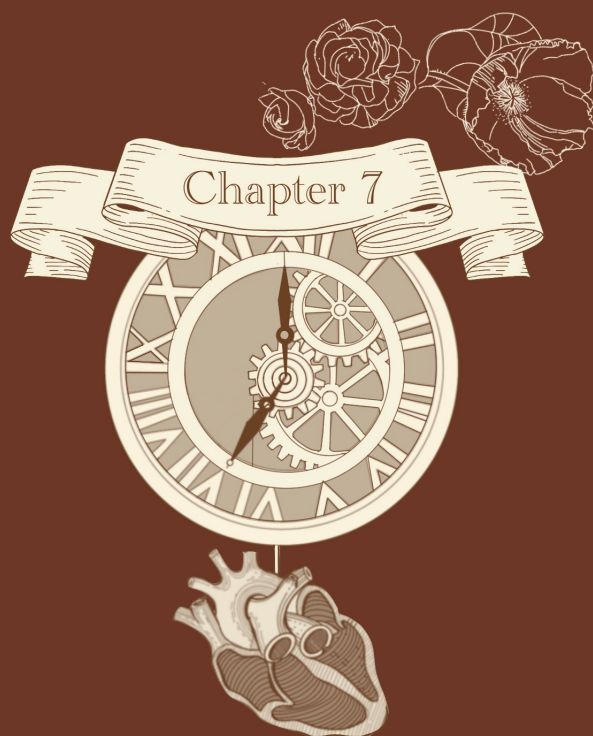
	JOHNS HOPKINS HOSPITAL	OSLO UNIVERSITY HOSPITAL	UNIVERSITY MEDICAL CENTER UTRECHT
TOTAL	105	47	24
MALE SEX	39 (37.1)	27 (57.4)	10 (41.7)
AGE AT DIAGNOSIS (YEARS)	34.8±15.0	42.8±18.1	39.6±14.5
PROBAND	47 (44.8)	22 (46.8)	8 (33.3)
PATHOGENIC VARIANT	77 (73.3)	36 (76.6)	21 (87.5)
SYMPTOMATIC	67 (63.8)	13 (27.7)	16 (66.7)
RECENT CARDIAC SYNCOPE	10 (9.5)	4 (8.5)	1 (4.2)
24H PVC COUNT	1222 [345-3656]	388 [44-1337]	978 [610-1528]
NON-SUSTAINED VT	48 (45.7)	8 (17.0)	10 (41.7)
LEADS WITH TWI (II, III, AVF AND V1-6)	3 [2-5]	2 [1-3]	3 [1-4]
RVEF (%)	48 [39-55]	44 [35-55]	44 [42-50]
EXERCISE DURATION (H/WEEK)	4.6 [2.3-10.6]	2.0 [2.0-5.0]	1.5 [0.9-3.6]
EXERCISE DOSE (METH/WEEK)	31.3 [14.5-81.4]	14.0 [11.0-36.8]	9.3 [4.7-17.9]
FOLLOW-UP (YEARS)	4.6 [1.9-9.5]	7.2 [3.9-10.3]	5.7 [4.3-9.5]
SUSTAINED VA AT FOLLOW-UP (%)	35 (33.3)	14 (29.8)	4 (16.7)

Abbreviations: PVC=premature ventricular complex; RVEF=Right ventricular ejection fraction; TWI=T-wave inversions; VA=ventricular arrhythmia; VT=ventricular tachycardia.

Supplementary Table 2. Risk calculator predictors' association with athlete status

	ATHLETE IF >18 METH/WEEK			ATHLETE IF >24 METH/WEEK			ATHLETE IF >36 METH/WEEK		
	No	Yes	p	No	Yes	p	No	Yes	p
TOTAL	82	94		90	86		112	64	
MALE SEX	34 (41.5)	42 (44.7)	0.782	38 (42.2)	38 (44.2)	0.912	48 (42.9)	28 (43.8)	1
AGE AT DIAGNOSIS (YEARS)	43.9±16.6	32.0±13.5	<0.001	43.5±16.3	31.4±13.4	<0.001	42.3±16.2	29.2±12.1	<0.001
RECENT SYNCOPE	4 (4.9)	11 (11.7)	0.104	4 (4.4)	11 (12.8)	0.14	6 (5.4)	9 (14.1)	0.124
24H PVC COUNT	572 [116-2160]	1281 [528-3584]	0.018	668 [125-2487]	1281 [496-3513]	0.051	697 [127-2624]	1300 [576-3963]	0.044
NON-SUSTAINED VT LEADS WITH TWI (II, III, AVF AND V1-6)	26 (31.7)	40 (42.6)	0.02	32 (35.6)	34 (39.5)	0.035	41 (36.6)	25 (39.1)	0.469
RVEF (%)	3 [1-4]	3 [2-5]	0.003	3 [1-4]	3 [3, 5]	0.001	3 [1-4]	4 [3-5]	<0.001
EXERCISE DOSE (METH/WE EK)	50 [41-55]	45 [36-55]	0.067	50 [41-55]	45 [36, 54]	0.042	48 [40-55]	45 [36-55]	0.146
	10.0 [3.0-13.7]	49.1 [31.4-93.7]	<0.001	10.9 [3.1, 14.6]	53.2 [36.1-105.3]	<0.001	12.0 [5.8-20.1]	68.0 [47.7-119.8]	<0.001

Abbreviations: PVC=premature ventricular complex; RVEF=right ventricular ejection fraction; TWI=T-wave inversion; VT=ventricular tachycardia.



Chapter 7

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

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Abstract

Background

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

Methods

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

Results

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

Conclusion

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

Introduction

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

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

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

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

Methods

Study Design

The design of this international observational cohort study is similar to what has previously been described². In brief, our cohort combines longitudinal observational data from 5 registries encompassing 6 countries (**supplementary table 1**). This study is in accordance with the current international guidelines for prognostic research,⁶ conforms to the declaration of Helsinki, and was approved by local ethics and/or institutional review boards.

Study Population

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

Study Outcomes

With the aim of predicting potentially fatal VA and SCD, the primary study outcome was the time to first life-threatening VA (LTVA) during follow-up, defined by a composite of SCD, aborted SCD, ventricular fibrillation (VF), and rapid ventricular tachycardia (VT; >250 bpm) that was either sustained (lasting ≥ 30 seconds) or terminated by ICD. The choice of 250 bpm as a cut-off for rapid VT was pre-specified based on the widespread use of this threshold for VF therapy in many ICD studies since the PAINFREE trial in 2001^{8,9} and in clinical practice. This cut-off for life-threatening events is also consistent with prior ARVC arrhythmic risk prediction literature.¹⁰⁻¹² In addition, we recorded outcomes of any sustained VA, heart transplantation, cardiovascular- and all-cause mortality.

Predictors

Based on clinical experience and the current literature, particularly a recent published meta-analysis¹³ and a prognostic model for predicting incident sustained VA in patients with ARVC,² eight potential predictors were pre-selected and recorded at the time of diagnosis.^{2, 11-15} These were: sex, age at diagnosis, recent (<6 months) cardiac syncope, number of premature ventricular complexes (PVCs) on 24-hour Holter monitoring, prior sustained VA events, number of anterior and inferior leads with T wave inversion (TWI), and left and right ventricular ejection fraction (LVEF, RVEF). The definitions for these predictor variables are presented in **supplementary table 2**. In addition, the relationship between the type of prior sustained VA event (only stable VT, as opposed to LTVA or unstable VT/VF) was studied (definitions in **supplementary table 2**). Each predictor variable was determined at the time of definite diagnosis, defined as one year before to one year after the date of diagnosis per TFC, but always prior to occurrence of the primary outcome.

Data Collection

Data were collected according to previously published standard operating procedures². All ECG tracings were reviewed by a core laboratory consisting of two cardiac electrophysiologists (JCT and RT) blinded to the outcome data. Adjudication of reported genetic variants was performed by consensus of a team of specialists in cardiac genetics (BM, JDHJ, JPVt, CAJ) according to the American College of Medical Genetics and Genomics guidelines as previously described.^{2, 16}

Statistical Analysis

Analyses were performed using R version 3.5.1 (R Foundation, Vienna, Austria). Categorical variables are presented as frequencies (percentages) and were compared using Fisher's exact tests. Continuous variables were presented as mean \pm standard deviation (SD) or median (interquartile range [IQR]) and compared using independent sample t-tests or Mann-Whitney U tests, as appropriate. The follow-up duration was calculated as the time interval from diagnosis to the outcome of interest or censoring. Censoring occurred at the most recent available clinical assessment, death from any other cause or heart transplantation. Event-free survival probabilities were estimated using the Kaplan-Meier method and Cox Proportional Hazard regression analysis.

Missing Data

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

Model Development

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

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

In which $S_0(t)$ represents the estimated baseline survival probability at time t and the linear

predictor (LP) is the sum of the predictor variables in the model multiplied by their estimated coefficient.

Model Validation and Calibration

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

Sensitivity Analyses

We assessed whether the predictions of LTVA were consistent in patients with and without a prior history of LTVA or unstable VT (according to the **supplementary table 2** definition) by performing a sensitivity analysis excluding patients who had already suffered these events.

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

Results

A cohort of 864 patients with definite ARVC was assembled from 15 centers in 6 countries in North America and Europe, including the 528 patients from the previously published cohort². The average age at diagnosis was 39.5 ± 15.5 years and 53.4% (n=461) were male. More than half were probands (57.8%, n=499). Two-thirds (65.0%, n=539) had a (likely)pathogenic variant identified, predominantly a single heterozygous variant in Plakophilin 2 (*PKP2*) (77.6%, n=418/539). Overall, 38.8% (n=335) of patients had a history of sustained VA at the time of diagnosis including 129 (14.9%, average age 39.7 ± 15.5 years, 64% male, 57% with a (likely)pathogenic variant) with a prior history of LTVA or unstable VT. Other clinical characteristics are summarized in **table 1**. The study population was evenly distributed between North America (433) and Europe (431) (**supplementary table 3**).

Table 1. Baseline Clinical Characteristics

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

Treatment at baseline					
ICD		450(52.1)	391(50.7)	59(63.4)	0.027
Beta blockers (n=817)		394(48.2)	352(48.2)	42(48.3)	1
Anti-arrhythmic (n=816)	drugs	252(27.0)	225(27.3)	27(24.1)	0.522
VT ablation		152(17.6)	142(18.4)	10(10.8)	0.091

Variables are expressed as frequency (%), mean±SD or median [IQR]. Total number of patients for a given variable mentioned if missing data. *DSC2=desmocollin-2; DSG2=desmoglein-2; DSP=desmoplakin; ECG=electrocardiogram; ICD=implantable cardioverter-defibrillator; IQR=interquartile range; LVEF=left ventricular ejection fraction; NSVT=non-sustained ventricular tachycardia; PKP2=plakophilin-2; PLN= phospholamban; PVC=premature ventricular complex; RVEF=right ventricular ejection fraction; TMEM43=Transmembrane protein 43; TWI=T-wave inversion; VA=ventricular arrhythmia; VT=ventricular tachycardia.*

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

Outcomes

Over a median follow-up of 5.75 years [IQR 2.77, 10.58], 93 (10.8%) patients experienced a LTVA event, representing an event rate of 1.56%/year (95% CI 1.26-1.91). This included 15 patients (1.7%) with SCD or aborted SCD. Overall, 375 (43.4%) patients experienced any sustained VA event during follow-up. Over the course of follow-up, 42 (4.9%) patients died and 35 (4.1%) had cardiac transplantation. The median cycle length of LTVA classified VT events was 224 ms [210-230] while non-LTVA VT events had a median cycle length of 310 ms [280-350].

As depicted on **Figure 1 panel A**, history of a sustained VA prior to diagnosis was not associated with survival free from LTVA during follow-up ($p=0.43$). In contrast, prior sustained VA predicted recurrence of sustained VA ($p<0.0001$; **Figure 1, panel B**). However, no significant difference was found regarding the severity of the prior VA event, i.e., unstable or life-threatening, including aborted SCD, versus stable, on the risk of sustained VA recurrence ($p=0.15$).

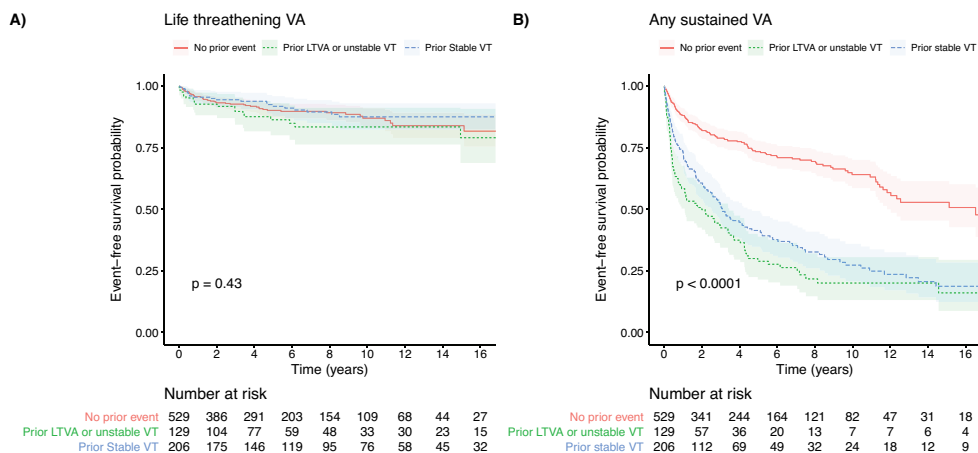


Figure 1. Survival free from life-threatening ventricular arrhythmia (LTVA) (panel A) and any sustained ventricular arrhythmia (panel B).

The cumulative event-free survival for life-threatening ventricular arrhythmia (LTVA) is plotted in Panel A. LTVA events occurred in follow-up in 52 patients with no prior sustained VA event at baseline, 19 with prior LTVA/unstable VT a and 23 with prior stable VT. The cumulative event-free survival for any ventricular arrhythmia (VA) is plotted in Panel B. Sustained VA events occurred in follow-up in 147 patients with no prior sustained VA event at baseline, 91 with prior LTVA/unstable VT a and 137 with prior stable VT. For both panels, 95% confidence intervals are provided (shaded area). VT, ventricular tachycardia.

Model Development

Baseline characteristics of patients with and without LTVA during follow-up are shown in **table 1**. The univariable and multivariable predictors of LTVA are presented in **table 2**. All predictors except prior sustained VA, LVEF and RVEF either had a significant ($p < 0.05$) or borderline significant univariable linear (or log-linear) relationship with the outcome. Subsequently, all variables were fitted into a multivariable model. Only 4 predictors were independently associated with the outcome: male sex ($p = 0.0021$), younger age at diagnosis ($p < 0.0001$), the 24-hour PVC count (log-linear relationship; $p = 0.010$) and the total number of leads with TWI ($p = 0.024$). The following formula allows for the calculation of the 5-year risk of LTVA:

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

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

Table 2. Life-threatening Ventricular Arrhythmia (LTVA) Risk Prediction Model

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

Abbreviations as per table 1. *PVC count had a log-linear relationship.

Supplementary table 4 provides the probability of survival ($S_0(t)$) at 1, 2, 3, and 4 years allowing calculation of risk for shorter time durations. An online version of this new risk prediction model combined with the published sustained VA risk calculation model can be found at www.ARVCrisk.com.

Model Validation

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

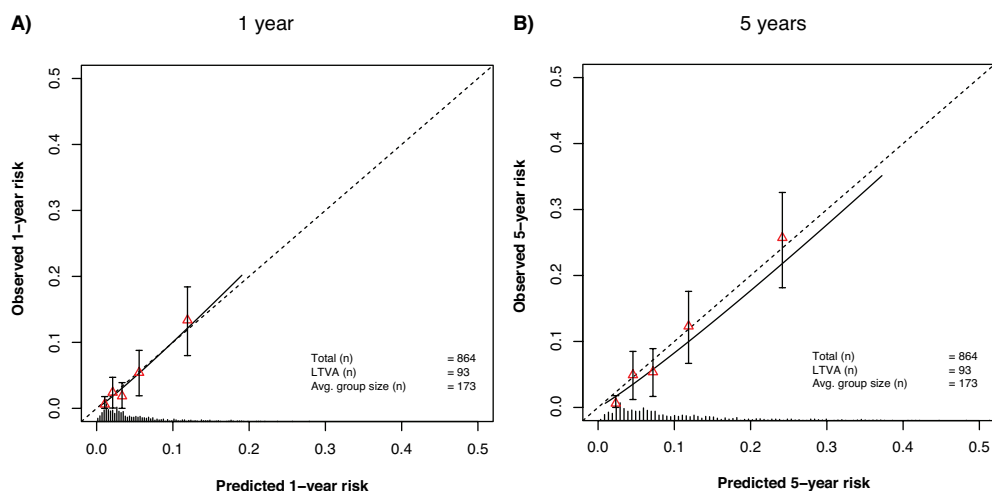


Figure 2. Calibration plot showing the agreement between predicted (X-axis) and observed (Y-axis) 5-year risk of the primary outcome of life-threatening ventricular arrhythmia (LTVA).

Triangles represent binned Kaplan-Meier estimates with 95% 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.

Clinical Utility

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

(protection rate 73.3%, 63 patients with LTVA protected by an ICD/ a total of 86 patients with LTVA at 5 years).

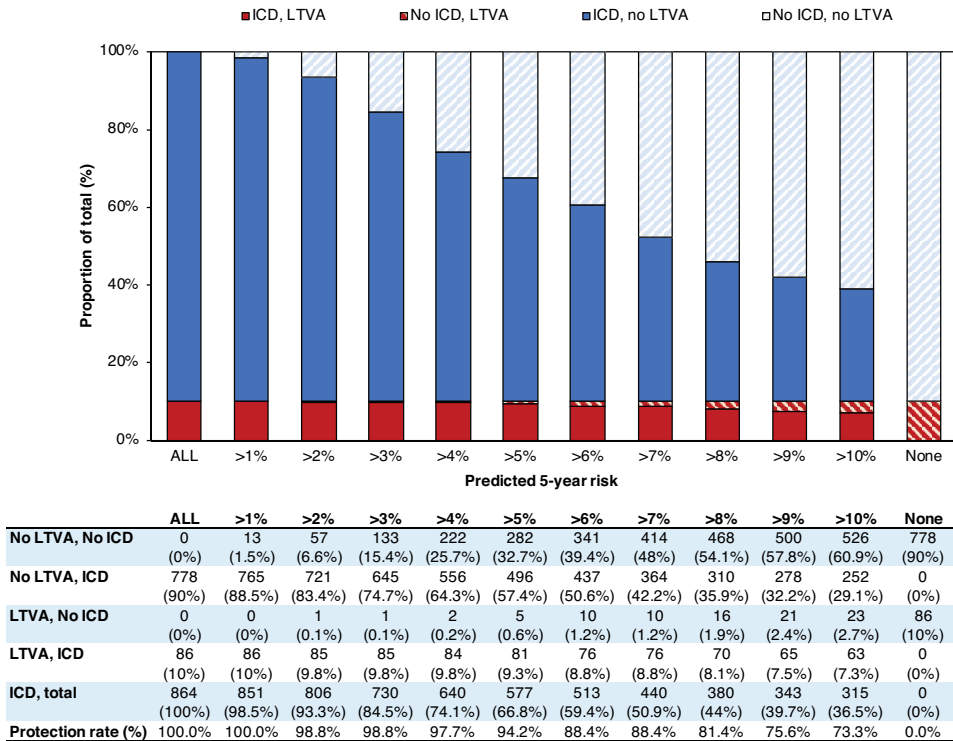


Figure 3. Outcomes of patients associated with model-based implantable cardioverter-defibrillator use thresholds.

The implications of using implantable cardioverter-defibrillators (ICD) in all (left bar) or none (right bar) of the patients are shown. The bars show the impact of using different ICD placement thresholds based on the 5-year risk calculated by our model. Each bar represents the complete cohort (n=864) and color coding represents the proportion of patients experiencing LTVA (red) or absence thereof (blue) as well as the placement (solid colors) versus the non-placement (striped colors) of an ICD. The number of patients in each of the four categories is presented in the table below.

Sensitivity Analyses

LTVA Prediction in Patients with no Prior History of LTVA or Unstable VT

We performed a sensitivity analysis excluding patients with a prior history of unstable or life-threatening VA to ensure that our predictors remain consistent in predicting incident LTVA. Patients presenting with aborted SCD or unstable and/or rapid VT would likely undergo ICD placement such that it is imperative for the model to perform well in the remaining subset. Overall, 735 patients did not have such prior events and had similar characteristics as the

complete cohort (supplementary table 5). Over a median follow-up of 5.64 years [2.66-10.47] 75 of these patients experienced a LTVA including 12 SCD/aborted SCDs. The same predictors as for primary analysis, were fitted into a multivariable model. As shown in supplementary table 6, the same 4 predictors with similar weights remained in the model. This model performed well with an optimism-corrected C-statistic of 0.75 (95%CI 0.69-0.80) and a calibration slope of 0.95 (95%CI 0.93-0.97).

Comparison of the performance of the model in PKP2 variant carriers vs non-carriers

We performed another sensitivity analysis to assess the potential differences in the performance of our model in patients with and without a PKP2 (likely)pathogenic variant. First, adding PKP2 variant status to our model caused almost no shift in the predictive effect of any of the included variables (**supplementary table 7**). Second, we evaluated separately the performance of our model in those with and without a PKP2 (likely)pathogenic variants. The calibration curves showed equally good performance in both groups (**supplementary figure 2**).

Discussion

Main Findings

In this paper, we used a large cohort of multinational ARVC patients to specifically assess LTVA in ARVC as a surrogate marker that more closely approximates SCD. This effort had two aims. First, we sought to get a better understanding of the specific determinants of potentially fatal arrhythmias in an adequately powered ARVC population, with the underlying rationale that these might differ from those for stable sustained VT. Second, we intended to refine the prediction of these events by providing a distinct prediction model for LTVA that can be used in all newly diagnosed ARVC patients in addition to the published incident sustained VA prediction model.²

The three main findings are as follows: First, prior history of any VA or LTVA/unstable VT did not predict subsequent LTVA. This finding differs from the outcome “any sustained VA” which, as expected, was predicted by prior sustained VA events. Second, after evaluating several predefined clinical and demographic predictors, only 4 remained independently associated with LTVA: younger age, male sex, PVC count and the number of leads with TWI. Notably, the severity of functional alteration (i.e. RVEF, LVEF) was not associated with LTVA in multivariable analyses. Third, LTVA events can be predicted with reasonable accuracy by

a risk prediction model that has adequate discrimination (C-statistic of 0.74) and consistency through internal validation (calibration slope of 0.95).

LTVA as a Closer Surrogate for SCD in ARVC

With the appropriate recognition of the significant risk of VA in ARVC and subsequent widespread use of ICDs, SCD has fortunately become a rare occurrence after the diagnosis of ARVC is established. Conducting a randomized controlled trial of ICD use would no longer be ethical such that surrogate outcomes are required in studies designed to inform decision-making for ICD placement. The most widely used surrogate is a composite of any sustained or ICD treated ventricular arrhythmia, as used in the recently published risk prediction model for incident VA.² While the underlying risk of SCD is known to be overestimated when using ICD treated events as a surrogate³, the extent of this overestimation might be particularly important in ARVC as the difference between the rate of VA events and underlying rate of SCD is higher than what is found in other conditions such as in hypertrophic cardiomyopathy, reflecting the higher rate of scar-related hemodynamically stable monomorphic VT in ARVC.²¹ In the cohort used to develop the initial arrhythmic risk calculator for incident VA, only 36% of events (53/146 sustained VA events) were LTVA.² We thus believe that restricting the outcome to LTVA, while not replacing the more comprehensive outcome of any sustained VA, could provide incremental information on the risk of SCD. More closely targeting potentially lethal arrhythmias can be of particular interest in resource-limited settings where event rates must be higher to justify ICDs. This model may also provide new information for a more comprehensive approach to the shared decision-making for ICD implantation. The LTVA model might be of particular importance in patients with borderline indications, in those who are reluctant to accept this therapy, and in cases where the risk of ICD-related complications is deemed higher.

Identified Predictors and Prior Studies

While any sustained VA has been the most commonly used outcome in ARVC risk prediction research, only a few studies have specifically reported on the prediction of LTVA using a similar definition as in the present study.^{11, 12, 14, 15} Given the limited sample size in each cohort and lower frequency of LTVA events, interpretation is uniformly hampered by insufficient power to discern the independent effect of individual predictors. Similarly to our study, identified predictors of LTVA have included younger age at presentation,^{12, 14} male sex¹⁵ and higher PVC burden.¹² Our results thus further support the importance of male sex²² and younger age as predictors and highlight the importance of PVC count as an easily measured indicator of electrical activity and instability of the disease. On the other hand, prior sustained

VA was interestingly not predictive of LTVA events in the present study. This may be surprising at first glance. Yet, the predictive value of prior sustained events for incident LTVA has been inconsistent in the literature. Two studies reported no association between prior VT^{11, 14} and subsequent unstable VA, with only 1% of patients with VT subsequently developing VF¹¹ in one study. Conversely, a recent large series reported hemodynamically stable VT to be a predictor of subsequent lethal VA²³ but the endpoint was substantially different as it excluded rapid VT and included electrical storm. LV dysfunction²⁴ was associated with SCD in one study and syncope¹⁰ with LTVA in another. RV dysfunction has not been associated specifically with LTVA in prior literature nor in this study despite being a good predictor of any sustained VA outcomes^{2,13}, illustrating that unstable arrhythmias might occur before scar burden negatively affects RVEF.

The Specific Determinants of LTVA and Mechanistic Rationale

Interestingly, we found that the predictors of LTVA differ from those associated with any sustained VA by not being predicted by the extent of functional impairment (RVEF, LVEF), nor by prior sustained VA or syncope events. These findings are consistent with the long-recognized notion that an early electrical phase of the disease predisposes to rapid unstable ventricular arrhythmia and is independent from the severity of the underlying substrate. This concept is now further supported by accumulating clinical⁴ and experimental evidence^{5, 25-27}. More data now link desmosomes to other components of the intercalated disk including the sodium channel and gap junction.²⁵⁻²⁷ More recently, conduction delays and electrogram fractionation developing before detectable cardiac imaging and histological abnormalities have also been reported in human and murine desmoplakin mutation carriers.⁵

Furthermore, inflammatory infiltration has long been recognized as a histopathological feature of ARVC,²⁸ and ARVC patients have elevated levels of circulating inflammatory cytokines.^{29, 30} More recent work in a murine model and in induced pluripotent stem cells (iPSC) demonstrated that myocytes produce and secrete potent inflammatory cytokines.³¹ Thus, inflammatory signaling in ARVC may act as both intrinsic and extrinsic contributors in aberrant electrophysiology and histopathological remodeling early in disease pathogenesis. While the clinical correlations of these phases and mechanisms of disease with arrhythmic outcomes have yet to be elucidated, they could explain why identified predictors do not depend on the burden of scar as a substrate for re-entry and do not include prior sustained or non-sustained ventricular arrhythmia. Rather, this form of disease instability could perhaps be better explained by interactions between desmosomes and other electrical cellular components as well as inflammatory signals.

Clinical Utility of a Prediction Model for LTVA

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

Another concern stemming from the fact that these two outcomes, LTVA and any sustained VA, have a different set of predictors is that the sustained VA prediction model might disproportionally under-estimate the risk of LTVA in a certain profile of patients. Reassuringly however, patients with the lowest calculated risk of sustained VA as per the published sustained VA risk model, also experience a low LTVA event rate while patients who experienced a LTVA event were at significantly higher calculated risk of any sustained VA than patients who did not suffer these events (**supplementary figure 3**).

Finally and importantly, despite not being independent predictors of LTVA, prior sustained events are powerful predictors of recurrent sustained VA events with more than 50% of patients suffering recurrences at 5 years (**figure 1, panel B**). We thus do not suggest that our findings should impact the usually recommended approach of ICD implantation in secondary prevention for patients with structural heart disease.

Limitations

Our cohort is drawn from North-European and North American academic centers with a population predominantly of Caucasian descent with a high rate of pathogenic *PKP2* variants. Caution should thus be exerted when extrapolating our results to different populations. While the model performed equally well in patients with and without pathogenic *PKP2* variants,

external validation of our model will be an important additional step in the future. In particular, the model may underperform in cohorts with genotypes poorly represented in this study for instance Naxos disease patients or patients with a *TMEM43* founder variant. Importantly, we only included patients with a definite diagnosis of ARVC thus excluding patients in the “concealed phase” of the disease, patients with a possible or borderline ARVC diagnosis or with non-ARVC forms of ACM in which our results cannot be applied. Although a widely used measure of RV function, RVEF might lack sensitivity in detecting subtle changes in early structural disease^{32, 33} that could potentially be valuable predictors of LTVA.

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

Conclusion

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

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Supplementary Material

Supplementary Table 1: Included registries and associated hospitals

Registry	Director	Included hospitals
Johns Hopkins ARVD Registry	Dr Hugh Calkins	Johns Hopkins Hospital, Baltimore, USA
Netherlands ACM Registry	Dr Richard Hauer	University Medical Center, Utrecht
	Dr Peter van Tintelen	University Medical Center, Groningen
	Dr Anneline te Riele	Leiden University Medical Center, Leiden
		Academic Medical Center, Amsterdam
Swiss ARVC Registry		Vrije Universiteit Medical Center, Amsterdam
		Erasmus Medical Center, Rotterdam
	Dr Firat Duru	University Heart Center, Zurich
		University Hospital Bern
Nordic ARVC Registry sites	Dr Kristina H. Haugaa	Triemli Hospital Zurich
		University Hospital, Rikshospitalet, Oslo, Norway
	Dr Pyotr Platonov	Skane University Hospital, Lund, Sweden
	Dr Anneli Svensson	Linköping University, Linköping, Sweden
Canada,	Dr Mario Talajic	Cardiovascular Genetics Center, Montreal Heart Institute
Montreal Registry	Dr Andrew Krahn	
Vancouver Registry		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
Recent cardiac syncope	Transient loss of consciousness and postural tone with spontaneous recovery with likely arrhythmic mechanism, excluding vasovagal etiology, <6 months before diagnosis
Prior sustained VA	Any sustained arrhythmic event prior to the time of diagnosis according to Task Force Criteria 2010 including sustained VT (≥ 100 bpm, for ≥ 30 sec or hemodynamically unstable, or terminated by ICD intervention) or SCA.
Prior LTVA / unstable VT [‡]	Sustained arrhythmic event prior to the time of diagnosis that is either: <ul style="list-style-type: none"> • LTVA defined as a composite of SCD, aborted SCD, ventricular fibrillation/flutter (VF), rapid ventricular tachycardia (VT) (lasting ≥ 30 seconds at > 250 bpm), sustained or terminated by ICD intervention • Hemodynamically unstable ventricular tachycardia defined as VT with loss of consciousness or pre-syncope
Prior sustained stable VT [‡]	Sustained arrhythmic event prior to the time of diagnosis that is VT lasting ≥ 30 secs at ≥ 100 bpm or terminated by electrical cardioversion in the absence of LTVA or Unstable VT events as defined above.
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

[‡] Patients who both had prior LTVA or Unstable VT and Sustained stable VT will be considered as having had prior LTVA or Unstable VT.

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: Baseline characteristics according to registry/country

	Hopkins	Netherlands	Canadian	Zurich	Nordic
Total	362	255	71	46	130
Demographics					
Male sex	175 (48.3)	142 (55.7)	42 (59.2)	24 (52.2)	78 (60.0)
Age at diagnosis (years)	35.6(14.13)	42.15 (15.01)	41.42 (17.10)	38.54 (15.75)	44.31 (16.83)
Caucasian ethnicity	345 (95.8)	253 (99.2)	14 (77.8)	45 (97.8)	127 (97.7)
Proband status	214 (59.1)	133 (52.2)	41 (57.7)	40 (87.0)	71 (54.6)
Pathogenic variant	227 (63.9)	197 (77.3)	26 (39.4)	11 (36.7)	78 (63.4)
<i>PKP2</i>	180 (50.7)	150 (58.8)	16 (24.2)	6 (20.0)	66 (53.7)
<i>DSP</i>	16 (4.5)	1 (0.4)	2 (3.0)	3 (10.0)	6 (4.9)
<i>DSG2</i>	14 (3.9)	4 (1.6)	4 (6.1)	1 (3.3)	5 (4.1)
<i>PLN</i>	3 (0.8)	37 (14.5)	1 (1.5)	0 (0.0)	0 (0.0)
Other	14(4)	5 (2)	3 (4.5)	1 (3.3)	1 (0.8)

History					
Symptoms	278 (77.0)	203 (79.6)	47 (66.2)	36 (78.3)	62 (47.7)
Cardiac syncope	93 (25.7)	68 (26.7)	20 (28.2)	12 (26.1)	39 (30.0)
Recent syncope (n=)	135 (37.3)	108 (42.4)	38 (53.5)	0 (0.0)	54 (41.5)
Prior history of Sustained VA					
	46 (12.7)	33 (12.9)	27 (38.0)	0 (0.0)	23 (17.7)
Prior LTVA and unstable VA					
ECG / continuous ECG monitoring					
	227 (66.6)	133 (53.0)	39 (54.9)	32 (71.1)	66 (51.2)
TWI in ≥3 precordial leads	66 (20.5)	46 (18.3)	10 (14.3)	3 (6.7)	29 (22.5)
TWI in ≥2 inferior leads					
Non-sustained VT	156 (54.9)	116 (55.2)	28 (44.4)	24 (58.5)	24 (23.5)
24h PVC count	1404 [366, 4996]	1107 [535, 3559]	637 [24 3900]	1005 [475, 3641]	544 [56, 1562]
Imaging					
RVEF (%)	42.22 (10.75)	44.22 (8.35)	40.88 (11.25)	40.46 (10.44)	41.54 (11.73)
LVEF (%)	58.51 (8.11)	57.51 (7.13)	57.22 (8.23)	54.40 (10.82)	55.59 (9.18)
Treatment at baseline					
ICD	223 (61.6)	102 (40.0)	48 (67.6)	18 (39.1)	59 (45.4)
Beta blockers	161 (47.1)	76 (30.0)	25 (36.2)	20 (43.5)	53 (40.8)
Anti-arrhythmic drugs	81 (25.3)	98 (39.0)	22 (31.4)	9 (19.6)	43 (33.3)
Follow-up (years)	4.61 [1.83, 9.67]	8.21 [4.66, 13.02]	3.52 [2.15, 6.65]	4.04 [2.46, 10.28]	7.37 [3.61, 10.31]

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

Supplementary Table 4: Probability of survival for different time duration.

Duration	Probability of Survival ($S_0(t)$)
1 year	0.966
2 years	0.953
3 years	0.948
4 years	0.940
5 years	0.927

Supplementary Table 5: Baseline characteristics of patients without a prior history of unstable or life-threatening ventricular arrhythmia

	Overall	Without LTVA	With LTVA	
	(n=735)	(n=660)	(n=75)	P-value
Demographics				
Male sex	378 (51.4)	330 (50.0)	48 (64.0)	0.029
Age at diagnosis (years)	39.48 (15.53)	40.46 (15.50)	30.79 (13.00)	<0.001
Caucasian ethnicity (n=707)	681 (97.0)	613 (97.0)	68 (97.1)	0.327
Proband status	414 (56.3)	350 (53.0)	64 (85.3)	<0.001
Pathogenic variant (%) (n=705)	466 (66.3)	412 (65.4)	54 (74.0)	0.181
Pathogenic variant (n=705)				0.006
<i>PKP2</i>	361 (51.4)	312 (49.5)	49 (67.1)	
<i>DSP</i>	26 (3.7)	23 (3.7)	3 (4.1)	
<i>DSG2</i>	25 (3.6)	24 (3.8)	1 (1.4)	
<i>JUP</i>	3 (0.4)	3 (0.5)	0 (0.0)	
<i>TMEM43</i>	1 (0.1)	0 (0.0)	1 (1.4)	
<i>PLN</i>	35 (5.0)	35 (5.6)	0 (0.0)	
Multiple mutations	8 (1.1)	8 (1.3)	0 (0.0)	
Other	7 (1.0)	7 (1.1)	0 (0.0)	
History				
Symptoms (%) (n=734)	506 (68.9)	442 (67.1)	64 (85.3)	0.002
Cardiac syncope (%)	155 (21.1)	133 (20.2)	22 (29.3)	0.090
Recent (%) (n=720)	67 (9.3)	53 (8.2)	14 (18.7)	0.006
ECG/Continuous ECG monitoring				
TWI ≥3 precordial (n=718)	417 (58.3)	364 (56.6)	53 (73.6)	0.008
TWI ≥2 inferior (n=700)	125 (18.0)	106 (17.0)	19 (26.8)	0.061
NSVTdx (%)	437 (64.5)	384 (62.8)	53 (80.3)	0.007
24h PVC count (n=503)	1044 [287, 3725]	983 [249, 3511]	2726 [772, 5123]	0.005
Imaging				
RVEF (%) (n=687)	42.90 (10.31)	43.16 (10.27)	40.51 (10.53)	0.045
LVEF (%) (n=704)	57.57 (8.33)	57.69 (8.27)	56.49 (8.86)	0.246
Treatment at baseline				
ICD (%) (n=733)	349 (47.5)	305 (46.2)	44 (58.7)	0.054
Beta blockers (%) (n=719)	284 (39.8)	256 (39.8)	28 (40.0)	1.000
Anti-arrhythmic drugs (%) (n=699)	174 (24.4)	181 (24.7)	16 (23.1)	0.569

Variables are expressed as frequency(%), mean±SD or median [IQR]. Total number of patients for a given variable mentioned if missing data. Abbreviations as per Supplementary Table 3.

Supplementary Table 6: LTVA Risk Prediction in patients without prior LTVA or unstable VA

	Univariable model		Multivariable (final model)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Male sex	1.59(0.99-2.55)	0.0532	1.80 (1.12-2.91)	0.0156
Age (per year increase)	0.96(0.94-0.98)	<0.0001	0.96 (0.94-0.97)	<0.0001
Recent cardiac syncope	2.27(1.27-4.08)	0.00469		
Prior sustained VA	0.79(0.47-1.31)	0.356		
24 h. PVC count (ln)*	1.20(1.03-1.40)	0.0066	1.18 (1.01-1.38)	0.0395
Leads TWI anterior + inferior	1.15(1.04-1.27)	0.00767	1.13 (1.01-1.27)	0.0339
RVEF (per % decrease)	0.98(0.96-1.01)	0.0584		
LVEF (per % decrease)	0.98(0.96-1.01)	0.144		

*PVC count had a log-linear relationship

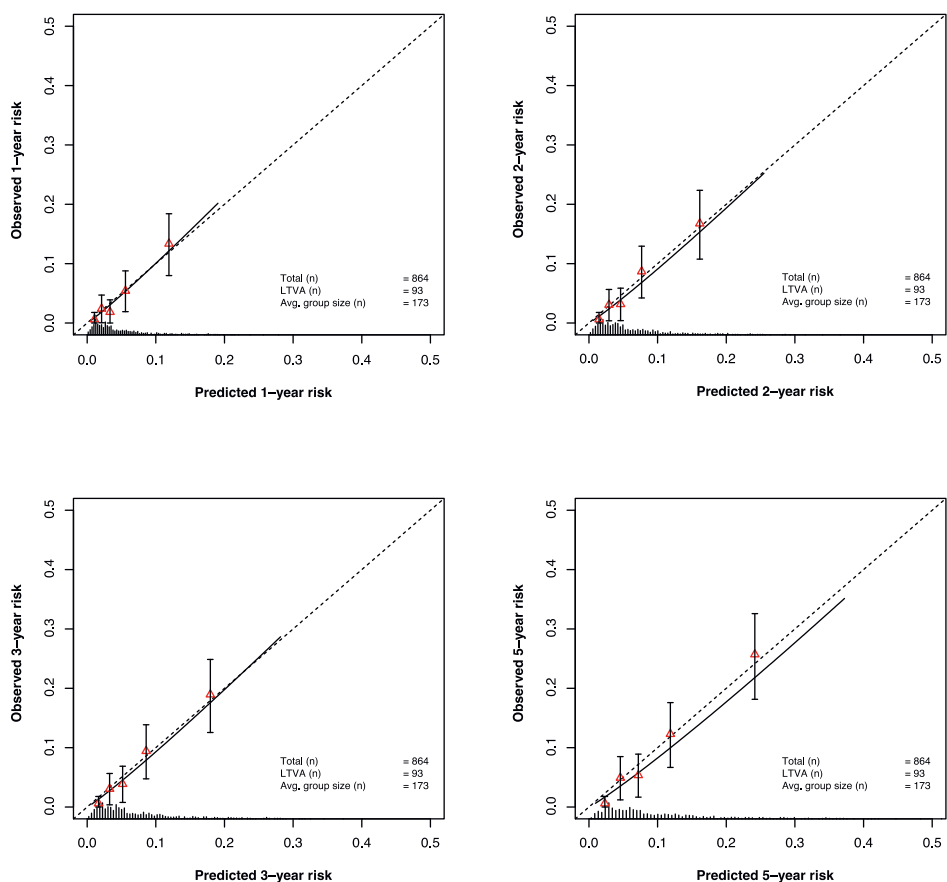
Abbreviations as per supplementary table 3.

Supplementary Table 7: LTVA risk prediction depending on Plakophilin 2 carrier status

	Current model		Effect of PKP2 carrier status	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Male sex	1.99 (1.28-3.10)	0.002	1.98 (1.27-3.08)	0.002
Age (per year increase)	0.96 (0.94-0.97)	<0.001	0.96 (0.94-0.97)	<0.001
24h. PVC count (ln)*	1.23 (1.04-1.38)	0.010	1.21 (1.04-1.39)	0.010
Leads with TWI ant.+inf.	1.12 (1.02-1.24)	0.024	1.12 (1.01-1.24)	0.029
PKP2 P/LP variant			1.21 (0.78-1.86)	0.397

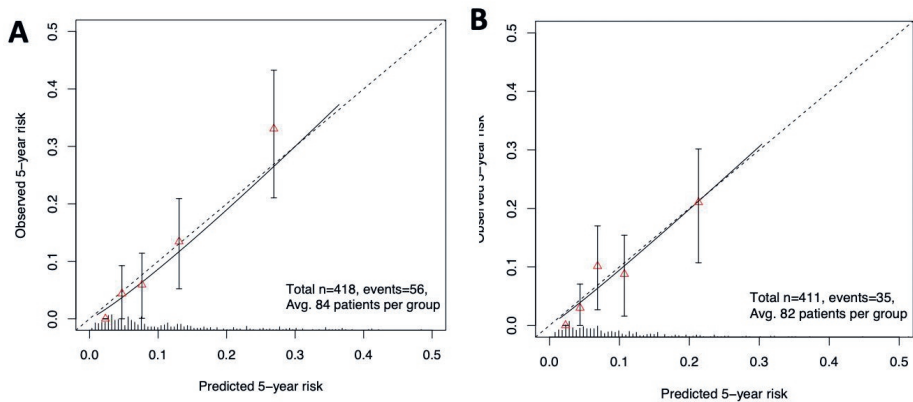
*PVC count had a log-linear relationship

PKP2; Plakophilin 2, P; pathogenic, LP; likely pathogenic. Abbreviations as per supplementary table 3.



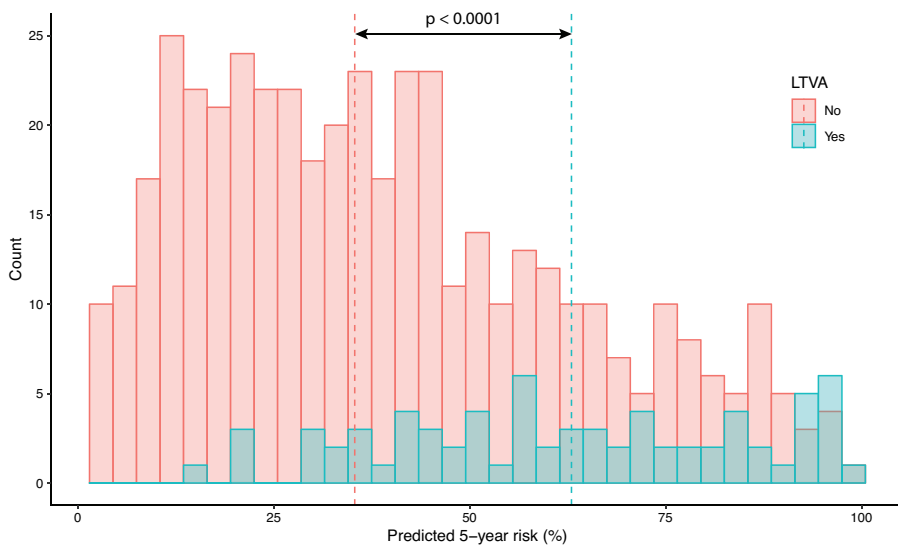
Supplementary Figure 1.

Calibration plot showing the agreement between predicted (X-axis) and observed (Y-axis) 1, 2 and 3 and 5 year risk of developing life-threatening ventricular arrhythmia. 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.



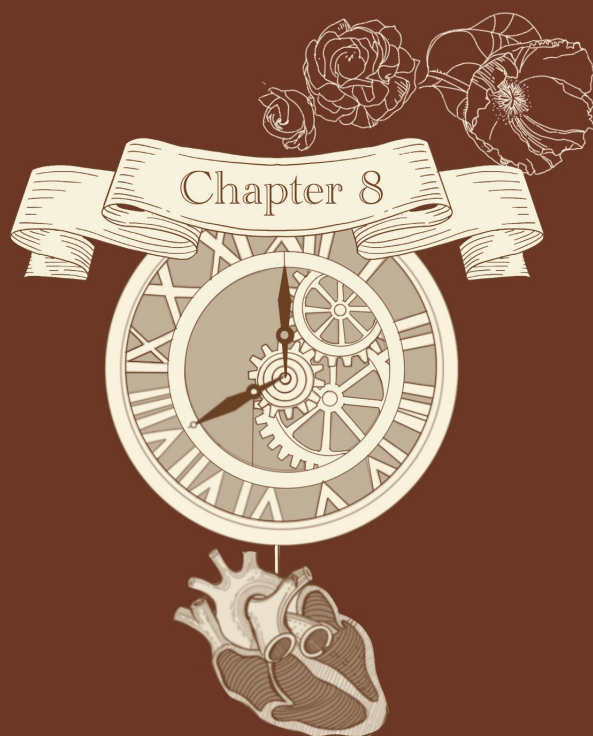
Supplementary Figure 2. Calibration according to Plakophilin 2 carrier status.

Calibration plot showing the agreement between predicted (X-axis) and observed (Y-axis) 5-year risk of developing life-threatening ventricular arrhythmia in patients with Plakophilin 2 (likely) pathogenic variants (panel A) and without Plakophilin 2 (likely) pathogenic variants. 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 3. Distribution of the calculated risk of any sustained VA within 5 years in patients with and without LTVA events at 5 years of follow-up.

Patients who experienced an LTVA event within 5 years are in blue (n=72) and those who did not (and had at least 5-year follow-up) are in red (n=442). The dotted lines represent the median of the calculated risk for patients with and without LTVA events. The lowest risk patient to experience a LTVA event at 5 years had a calculated risk of incident VA of 14.9%.



Chapter 8

Comparing clinical performance of current Implantable Cardioverter Defibrillator implantation recommendations in Arrhythmogenic Right Ventricular Cardiomyopathy

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Abstract

Aims: Arrhythmogenic right ventricular cardiomyopathy (ARVC) patients have increased risk of ventricular arrhythmias (VA). Four implantable cardioverter-defibrillator (ICD) recommendation algorithms are available: The International Task Force Consensus ("ITFC"), an ITFC modification by Orgeron et al ("mITFC"), the AHA/HRS/ACC guideline for VA management ("AHA"), and the HRS expert consensus statement ("HRS"). This study aims to validate and compare the performance of these algorithms in ARVC.

Methods: We classified 617 definite ARVC patients (38.5 ± 15.1 years, 52.4% male, 39.2% prior sustained VA) according to four algorithms. Clinical performance was evaluated by sensitivity, specificity, ROC-analysis and decision curve analysis for any sustained VA and for fast VA (>250bpm).

Results: During 6.4 [2.8-11.5] years follow-up, 282 (45.7%) patients experienced any sustained VA, and 63 (10.2%) fast VA. For any sustained VA, ITFC and mITFC provide higher sensitivity than AHA and HRS (94.0-97.8% vs. 76.7-83.5%), but lower specificity (15.9-32.0% vs. 42.7%-60.1%). Similarly for fast VA, ITFC and mITFC provide higher sensitivity than AHA and HRS (95.2-97.1% vs 76.7-78.4%) but lower specificity (42.7-43.1 vs. 76.7-78.4%). Decision curve analysis showed ITFC and mITFC to be superior for a 5-year sustained VA risk ICD indication threshold between 5-25%, or 2-9% for fast VA.

Conclusion: The ITFC and mITFC provide the highest protection rates, whereas AHA and HRS decrease unnecessary ICD placements. ITFC or mITFC should be used if we consider the 5-year threshold for ICD indication to lie within 5-25% for sustained VA or 2-9% for fast VA. These data will inform decision making for ICD placement in ARVC.

What's new?

1. There are currently four ICD recommendation algorithms for patients with ARVC available, but their relative clinical performance is unknown.
2. This study showed the performance of the ITFC and mITFC recommendations for ICD implantation to be nearly identical, as well as the performance of AHA and HRS.
3. Our results suggest that the AHA and HRS recommendations have higher overall accuracy, but ITFC and mITFC provide better protection rates.
4. If only fast VA (sustained VT>250bpm/VF/SCD) is considered a relevant outcome for ICD indication, all four ICD recommendation algorithms perform poorly.
5. At a $\geq 6\%$ 5-year fast VA risk threshold for ICD implantation (as currently applied to HCM patients), using ITFC results in the highest clinical benefit.

Introduction

Patients with arrhythmogenic right ventricular (RV) cardiomyopathy (ARVC) are at risk of sudden cardiac death (SCD), even at young age.¹ This inheritable cardiomyopathy is characterized by progressive fibrofatty replacement of myocardium and intercalated disk remodeling,^{2,3} leading to life-threatening ventricular arrhythmias (VA) and heart failure. A critical goal in clinical management is SCD prevention, for which implantable cardioverter-defibrillators (ICD) use is the only proven effective treatment. However, this invasive treatment inherently comes with risk of complications and inappropriate shocks.⁴ Especially in ARVC, in which young patients may live with an ICD for decades, the life-time risk of complications can accumulate significantly.⁵ Hence, this risk should be balanced against the risk of SCD, which varies widely amongst individuals.

Assessment of arrhythmic risk in ARVC has been an important research focus in the past decades, which resulted in the identification of a myriad of risk factors.⁶ However, the majority of studies presented relative risks of single predictors, with no direct clinical translation. Therefore, expert consensus and guideline documents have been published, proposing risk stratification algorithms for ICD implantation. Today, three major consensus-derived algorithms are available: the 2015 International Task Force Consensus (ITFC) statement⁷; 2017 AHA/ACC/HRS Guideline for management of patients with VA⁸; and 2019 HRS Expert Consensus Statement on Evaluation, Risk Stratification, and Management of Arrhythmogenic Cardiomyopathy.⁹ In addition, Orgeron et al.¹⁰ suggested a modification of the ITFC (mITFC) for improved performance, creating a fourth algorithm. In the absence of clinical validation studies comparing their performance, it remains uncertain which algorithm should be recommended. Therefore, we designed this study to provide a comprehensive comparison of the clinical performance of these four risk stratification algorithms in a large multicenter ARVC cohort.

Methods

Study design

This is a multicenter, observational, longitudinal cohort study, based on two established patient registries in which data is both retro- and prospectively collected. The study conforms to the Helsinki declaration and was approved by local ethics and/or institutional review boards.

Study population

The population was drawn from the Netherlands (acmregistry.nl)¹¹ and Johns Hopkins (arvd.com) ARVC Registries. Eligible for inclusion were all patients with definite ARVC diagnosis according to the 2010 Task Force Criteria (TFC),¹² with available follow-up data. Patients were excluded if missing data prohibited classification by at least one algorithm, with exception of missing electrophysiology study data as described below.

Of note, the patients in our cohort from Johns Hopkins were used to derive the mITFC algorithm. As such, a sensitivity analysis was performed to validate the mITFC algorithm using Dutch patients only.

Data collection

For each participant, we extracted data from the registries required for the four stratification algorithms. This included demographics, genetics, family history, history of cardiac syncope or VAs, and clinical test results at baseline. Baseline was defined as the date of diagnosis per 2010. Outcome data was collected from all available follow-up, as described below.

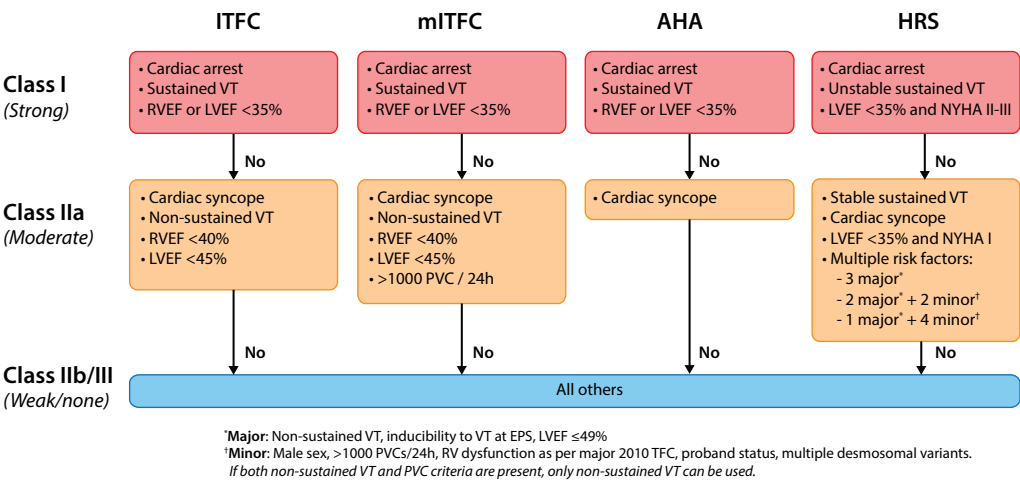


Figure 1. Schematic overview of the four ICD placement algorithms. Abbreviations as in Table 1.

Patient classification

All patients were retrospectively classified at baseline (i.e. time of diagnosis) as Class I (strong), Class IIa (moderate) or Class IIb/III (weak/no benefit) ICD indication, using the four stratification algorithms: 1) the 2015 International Task Force Consensus (onwards referred to as “ITFC”), 2) the modified ITFC as suggested by Orgeron et al. (onwards referred to as “mITFC”), 3) the 2017 AHA/ACC/HRS Guideline for management of patients with VA (onwards

referred to as “AHA”), and 4) the 2019 HRS Expert consensus statement (onwards referred to as “HRS”). A visual representation of these algorithms is provided in **Figure 1**. Of note, the Class I indication is nearly identical across the four algorithms - with exception of HRS not including RVEF \leq 40% and stable sustained VT - so differences observed will reflect primarily whether or not patients meet Class IIa criteria.

We assumed Class IIb indications to have limited value in prescribing ICD implantation. This reflects the fact that not all algorithms specify a Class IIb indication, and the strength of this indication is weak (“may be considered”). Furthermore, the risk factors that classify Class IIb indication in ITFC are not clearly defined. Since including a separate Class IIb group would introduce considerable subjective interpretation in the context of a weak ICD indication, we grouped these with Class III.

2015 International Task Force Consensus (“ITFC”)

In this algorithm, patients had a Class I indication if they had a history of cardiac arrest, sustained ventricular tachycardia (VT), and/or severe ventricular dysfunction (RV fractional area \leq 17%/ RVEF \leq 35% or LVEF \leq 35%). Class IIa includes patients who had cardiac syncope, non-sustained VT, and/or moderate ventricular dysfunction (RV fractional area \leq 24%/ RVEF \leq 40% or LVEF \leq 45%). All others were classified as Class IIb/III.

2018 Orgeron et al. modification of ITFC (“mITFC”)

In this algorithm, classification is as per ITFC, except for the addition of >1000 premature ventricular complexes (PVCs)/24 hours on Holter as a Class IIa criterion.

2017 AHA/ACC/HRS Guideline for management of patients with VA (“AHA”)

In this algorithm, criteria specified for Class I indication are identical to the ITFC. For Class IIa, only those with a history of cardiac syncope classified. All other patients were classified as IIb/III indication.

2019 HRS Expert Consensus statement (“HRS”)

Patients had a Class I indication if they had a history of cardiac arrest, unstable sustained VT and/or LVEF \leq 35% with NYHA class II/III. Class IIa indication was defined as those with a history of cardiac syncope, stable sustained VT, LVEF \leq 35% with NYHA I, and/or a combination of at least 3 major risk factors, 2 major and 2 minor, or 1 major and 4 minor risk factors. Major risk factors were defined as: non-sustained VT, inducible VT at electrophysiology study (EPS), and LVEF \leq 49%. Minor risk factors included: male sex, >1000 PVCs/24 hours, major 2010 TFC criterion for RV function, proband status, and two or more desmosomal (likely) pathogenic genetic variants.

Missing data

Of the 650 patients found eligible for inclusion, 33 (5.3%) were excluded due to missing data preventing classification in at least one algorithm. Of the remaining 617 patients, all data required for classification was complete except for EPS results on VT inducibility. Missing EPS results was relevant for HRS classification of 31 (5.0%) patients. As the reason for not performing EPS in these patients was a clinically assumed low pre-test probability (all classified as IIb/III in absence of risk factors), we followed clinical practice by assuming VT-inducibility to be negative. We repeated the analysis assuming a positive EPS result as sensitivity analysis.

Study outcomes

The outcome of interest in this study is the occurrence of potentially life-threatening ventricular arrhythmias during follow-up. We used two definitions: 1) any sustained VA, defined as VT>100bpm lasting >30s or with hemodynamic instability, ventricular fibrillation/flutter (VF), SCD or appropriate ICD therapy; and 2) fast VA, defined as sustained VT>250bpm lasting >30s or terminated by ICD, VF, or SCD.

Statistical analysis

Analyses were performed using Rstudio v1.1.414 (Boston, MA, USA). Variables were presented as frequencies (N,%), mean±standard deviation or median [interquartile range]. Incidence rates were calculated in person-years by Fishers mid-P Exact method. Event-free survival was determined by Kaplan-Meier analysis. Pair-wise comparisons were made using the log-rank test with Bonferroni correction. Baseline was defined as time of diagnosis (2010 TFC), and patients were censored at last clinical follow-up, death from any other cause, or heart-transplantation. Time-dependent sensitivity, specificity and ROC-analysis area under the curve (AUC) were based on presence/absence of ICD indication (present if Class I or IIa), and the presence/absence of the outcome during follow-up. Time-dependent clinical performance results are presented at a 5-year interval. Clinical benefit of the algorithms was compared by decision curve analysis based on the ‘net benefit’¹³; a weighted ratio between “true positive” and “false positive” ICD indications. Higher values indicate greater benefit, which are graphically presented for a range of risk thresholds that can be considered to indicate an ICD. A two-sided p-value <0.05 was considered significant.

Results

Study population

The baseline characteristics of the 617 patients are shown in **Table 1**. Half (52.4%) of the population was male, with an average age at diagnosis of 38.5 ± 15.1 years. Overall, 242 (39.2%) patients had a history of sustained VA (i.e. secondary prevention). Over the course of 6.4 [2.8, 11.5] years of follow up, 282 (45.7%) experienced any sustained VA (median cycle length 280ms [250, 320]), and 63 (10.2%) experienced fast VA (median cycle length 225ms [210, 230]). This corresponded to an incidence rate of 10.2% (9.1-11.5) and 1.4% (1.1-1.8) per person-year, respectively. The characteristics separated by country are provided in **Supplementary Table 1**.

Table 1. Baseline characteristics

	Overall	Sustained VA in follow-up		p	Fast VA in follow-up		p	
		No	Yes		No	Yes		
n	617*	335	282		554	63		
Age at diagnosis (years)	38.5±15.1	39.8±15.8	36.9±14.0	0.020	39.6±15.0	28.7±12.3	<0.001	
Male sex	323 (52.4)	142 (42.4)	181 (64.2)	<0.001	282 (50.9)	41 (65.1)	0.045	
Proband	339 (54.9)	125 (37.3)	214 (75.9)	<0.001	283 (51.1)	56 (88.9)	<0.001	
Pathogenic mutation	422 (68.4)	232 (69.3)	190 (67.4)	0.595	377 (68.1)	45 (71.4)	0.585	
Cardiac syncope	158 (25.6)	64 (19.1)	94 (33.3)	<0.001	133 (24.0)	25 (39.7)	0.011	
24h PVC count	1200 [354, 4181]	887 [175, 3014]	2363 [849, 5655]	<0.001	1076 [306, 3866]	3021 [982, 5882]	0.001	
History of non-sustained VA	277 (44.9)	141 (42.1)	136 (48.2)	<0.001	241 (43.5)	36 (57.1)	0.086	
History of sustained VA	242 (39.2)	73 (21.8)	169 (59.9)	<0.001	214 (38.6)	28 (44.4)	0.447	
VT inducible on EPS (n=311)	217 (35.2)	64 (19.1)	153 (54.3)	<0.001	185 (33.4)	32 (50.8)	0.022	
RVEF (%)	43±10	45± 9	41±10	<0.001	43±10	42±9	0.547	
LVEF (%)	58±8	58±8	58±7	0.961	58±8	57±8.24	0.664	
ICD	At baseline	314 (50.9)	144 (43.0)	170 (60.3)	<0.001	276 (49.8)	38 (60.3)	0.148
implanted	At follow-up	149 (24.1)	53 (15.8)	96 (34.0)	<0.001	129 (23.3)	20 (31.7)	0.183
Follow-up (years)	6.4 [2.8, 11.5]	4.2 [1.7, 8.8]	9.3 [4.6, 14.4]	<0.001	6.4 [2.7, 11.4]	6.5 [3.2, 11.9]	0.319	

*340 patients from Johns Hopkins ARVC Registry and 277 from the Netherlands ACM Registry.

Abbreviations: EPS = electrophysiologic study; ICD = implantable cardioverter-defibrillator; LVEF = left-ventricular ejection fraction; PVC premature ventricular complex; RVEF = right-ventricular ejection fraction; VA = ventricular arrhythmia; VT = ventricular tachycardia.

Outcome per classification

Any sustained VA

As demonstrated in **Figure 2**, all four algorithms showed a significant difference in arrhythmia-free survival between ICD indications overall ($p < 0.001$). For the survival difference between indication classes, only AHA showed no significant difference between Class I and IIa ($p = 0.190$). In the groups without ICD indication (i.e. class IIb/III), mITFC showed the lowest incidence rate of sustained VA with 1.7% (0.8-3.3) per person-year, followed by ITFC with 2.4% (1.4-3.9), and both AHA and HRS with 3.6% (2.7-4.8) per person-year (**Table 2**).

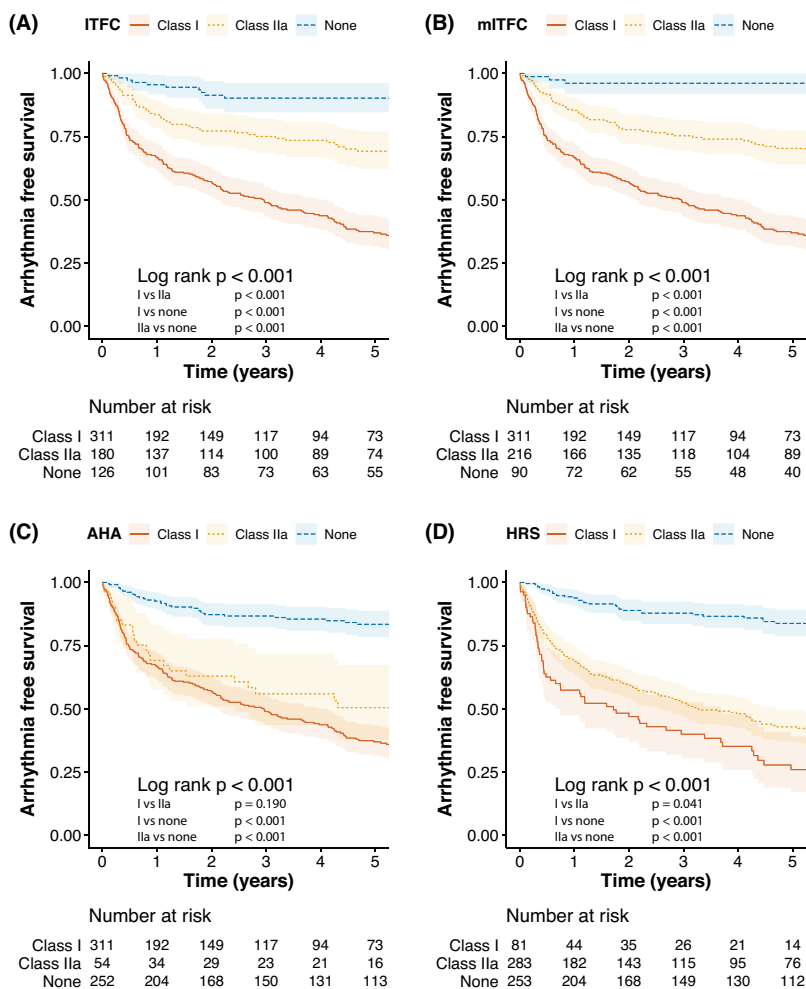


Figure 2.

Kaplan-Meier plots with 95%CI for survival free from any sustained VA for each of the four ICD placement algorithms; ITFC (A), mITFC (B), AHA (C), and HRS (D). Survival is significantly worse concordant with the class of ICD indication.

Fast VA

For fast VA (**Figure 3**), only AHA and HRS showed a significant difference in arrhythmia-free survival between ICD indications overall ($p=0.033$ and $p=0.016$ respectively). For the survival difference between indication classes, only AHA and HRS showed a significant difference, between class IIa and no indication ($p=0.041$ and $p=0.015$ respectively). Stratification by ITFC and mITFC resulted in the lowest incidence rate of fast VA with 0.6% (0.1-1.6) per person-year for patients without an ICD indication (i.e. class IIb/III), followed by HRS with 0.8% (0.4-1.4) and AHA with 0.9% (0.5-1.6) person-year (**Table 2**).

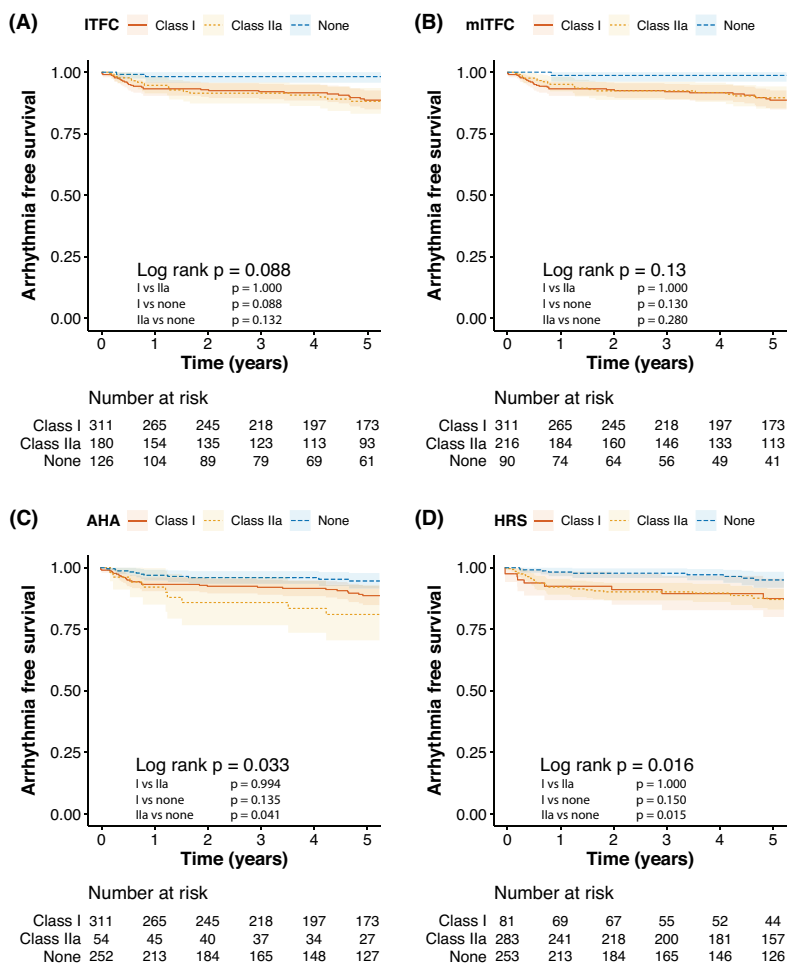


Figure 3.

Kaplan-Meier plots with 95%CI for survival free from fast VA for each of the four ICD placement algorithms; ITFC (A), mITFC (B), AHA (C), and HRS (D). Only HRS showed a significantly different survival between ICD indication classes, but only between class IIa and none (IIb/III).

Table 2. Incidence rates per ICD placement algorithm

	ITFC	mITFC	AHA	HRS
Incidence of any sustained VA (%/year)				
Class I	18.1 (15.7-20.7)	18.1 (15.7-20.7)	18.1 (15.7-20.7)	24.5 (18.7-31.5)
Class IIa	6.6 (5.0-8.5)	6.1 (4.7-7.7)	11.8 (7.7-17.2)	15.4 (13.2-17.9)
None	2.4 (1.4-3.9)	1.7 (0.8-3.3)	3.6 (2.7-4.8)	3.6 (2.7-4.8)
Incidence of fast VA (%/year)				
Class I	1.5 (1.1-2.1)	1.5 (1.1-2.1)	1.5 (1.1-2.1)	1.6 (0.8-2.9)
Class IIa	1.7 (1.0-2.6)	1.5 (0.9-2.3)	2.5 (1.1-4.8)	1.8 (1.2-2.4)
None	0.6 (0.1-1.6)	0.6 (0.1-1.6)	0.9 (0.5-1.6)	0.8 (0.4-1.4)

Abbreviations: VA=ventricular arrhythmia; algorithm names are abbreviated as in text.

Clinical performance

Any sustained VA

As can be observed in **Figure 4A**, ITFC and mITFC show high sensitivity (94.0% and 97.8% respectively) and consequently a low number of patients with sustained VA without ICD indication (i.e. “false negatives”, 2.6% and 1.0% respectively). Their specificities however were low (32.0% and 24.2%), resulting in an overall AUC of 0.63 and 0.61. This subtle difference in performance was not statistically significant ($p=0.229$).

Although AHA and HRS showed lower sensitivity (both 83.5%) resulting in more patients with sustained VA without ICD indication (both 7.2%), they showed superior specificity (59.9% and 60.1%, respectively). Their AUC of 0.72 (identical in both algorithms) was significantly higher than ITFC and mITFC ($p<0.001$). An overview of the time-dependent AUC plotted over time is provided in **Supplementary Figure 1**.

The decision curve analysis (**Figure 5A**) showed that the ITFC and mITFC algorithm result in the greatest net benefit for a sustained VA risk threshold for ICD placement ranging from 5-25% over 5-years, while AHA and HRS both had greater benefit for a risk threshold >25%.

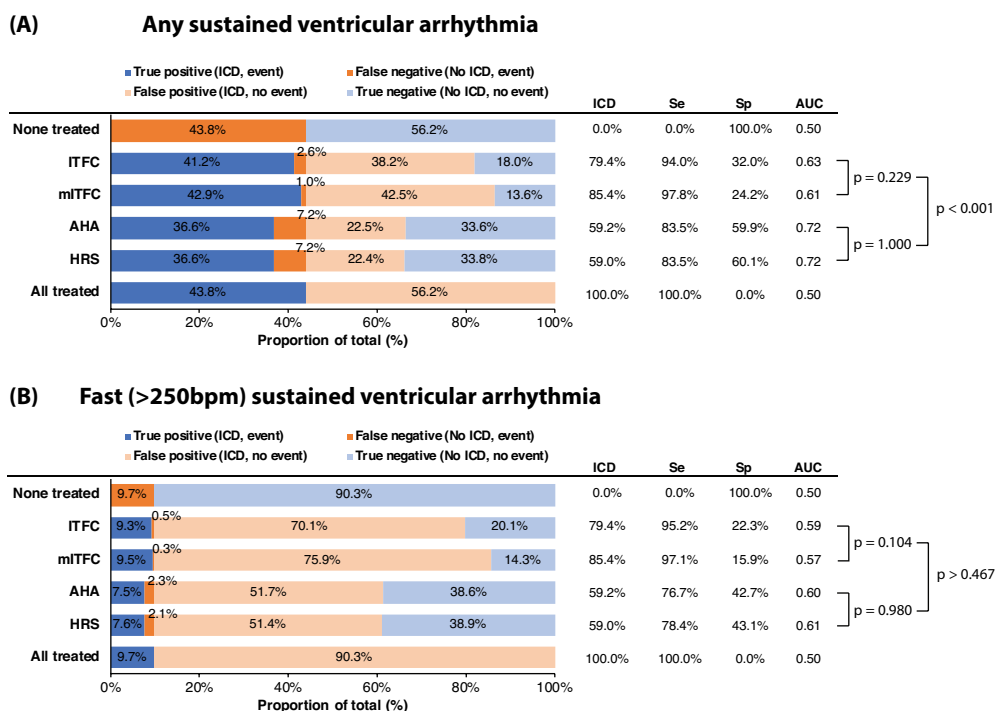


Figure 4.

Clinical performance measures of the four ICD placement recommendation algorithms at a 5-year time point for (A) any sustained VA, and (B) fast VA. Bar chart shows the proportion of patients correctly classified (blue) and incorrectly classified (orange), with dark coloring for those with events and light coloring for those without. Table on the right shows total proportion with ICD, sensitivity (Se), specificity (Sp) and time dependent area under the curve (AUC).

Fast VA

Similar as for the sustained VA outcome, ITFC and mITFC showed the highest sensitivity and therefore the lowest proportion of patients suffering from an event without ICD indication (“false negatives” 0.5% and 0.3%, respectively) (**Figure 4B**), but with low specificity (22.3% and 15.9%, respectively). Although AHA and HRS had superior specificity for predicting fast VA (42.7% and 43.1%), the overall AUC of all four algorithms was relatively low within a narrow range from 0.57 (mITFC) to 0.61 (HRS), showing no statistically significant difference in performance.

Based on the decision curve analysis (**Figure 5B**), using mITFC resulted in the highest net benefit for a fast VA risk threshold ranging from 2-4%, ITFC for 4-9%, and AHA and HRS both showed the highest benefit for a risk threshold >9%.

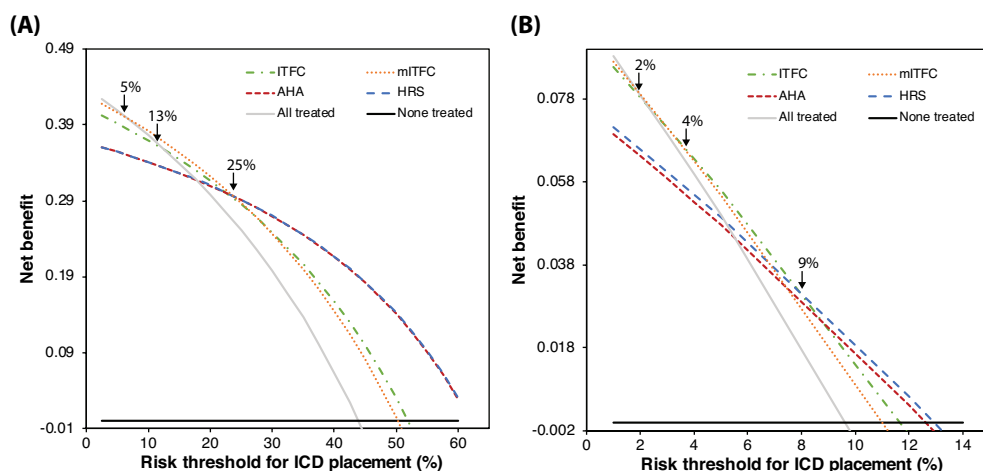


Figure 5.

Decision curve analysis with the 5-year risk threshold for ICD placement on the X-axis and net benefit on the Y-axis. (A) For any sustained VA, this graph demonstrates that when the risk threshold justifying ICD placement lies between 5-25%, ITFC and mITFC algorithms had the best performance, while AHA and HRS perform best if the risk threshold is >25%. (B) For fast VA, mITFC performs best when the threshold lies between 2-4%, ITFC when between 4-9%, and AHA/HRS when >9%.

Sensitivity and subgroup analyses

By study design, we assumed 31 cases with missing EPS data to have no VT inducibility. If VT inducibility would have been positive, the HRS classification of these patients would shift from class IIb/III to class IIa. This would result in a non-significant decrease in AUC for any sustained VA (0.72 to 0.70, $p=0.339$). The AUC for fast VA remained identical (0.61).

As shown in **Supplementary Figure 2**, we conducted three sensitivity analyses. First, using only the Dutch cohort (as the Johns Hopkins cohort was used to derive the mITFC algorithm) showed nearly identical results. Next, we stratified the cohort by history of sustained VA. For primary prevention patients ($n=375$), the AHA and HRS algorithms showed poor sensitivity, as low as 61.7%, meaning failure to protect 1 out of every 3 patients with incident sustained VA. Finally, we stratified the cohort into patients with ($n=374$) and without ($n=243$) pathogenic desmosomal variants. All four models performed somewhat better for patients with a desmosomal variant, with both a higher sensitivity and higher specificity.

Discussion

This study compares the clinical performance of all four available ICD placement recommendation algorithms in a large multicenter cohort of ARVC patients. In absence of a widely accepted ICD recommendation consensus, our study provides results highly relevant to clinical practice. First, we confirmed that all four algorithms are able to stratify the population in low-, intermediate- and high-risk, relative to the strength of ICD indication. Second, all four algorithms have limited accuracy, trading higher sensitivity for lower specificity (ITFC and mITFC) and vice versa (AHA and HRS). Lastly, we found that if we consider the 5-year risk threshold of $\geq 6\%$ currently used in hypertrophic cardiomyopathy (HCM) patients to be reasonable for ARVC patients too, it would be best to use ITFC.

ICD placement recommendations in ARVC: need for consensus

While multiple ICD placement recommendation algorithms have been proposed to guide clinical decision making for patients with ARVC, a widely accepted consensus on which algorithm to use is lacking. In the absence of sufficient validation data, an evidence-based consensus is unlikely to emerge. Prior to this study, the ITFC algorithm was validated by Orgeron et al¹⁰: using a cohort of 365 ARVC patients, the authors showed that the ITFC algorithm stratified the population with reasonable accuracy by comparing arrhythmia incidence rates to the strength of ICD indication, similar to our findings.

Of note, the four algorithms tested in this study are all flowchart based, depending on single risk factors sufficient to individually indicate an ICD, without considering the combined effect and interactions of other risk factors that may be present. Not only does this result in relatively crude stratifications, it may also fail to indicate an ICD in patients with high risk based on a combination of risk factors which individually would not justify an ICD. An example would be young athletic male patients, who we know can be at high risk of cardiac arrest even in absence of prior VA or ventricular dysfunction therefore having no ICD indication.¹⁴ Considering these limitations, a more elegant alternative may be multivariable prediction models, as previously established for HCM¹⁵. Two such models were recently developed for ARVC^{16,17}; one to predict a first sustained VA for primary prevention, and one to predict fast ($>250\text{bpm}$) VA. Risk estimations are based on effect combinations from sex, age, syncope, T-wave inversions on ECG, PVC count, (non-)sustained VT, and RVEF.

As the cohort in this study greatly overlaps with the cohort from which these ARVC risk score models were derived, we did not add the ARVC risk score models as a comparator in our main study results. For completeness, we do provide the results of this comparison in **Supplementary Figure 3**. Similar to the results of Aquaro et al.¹⁸, who compared the clinical

performance of the ITFC and HRS algorithms to the 5-year ARVC risk score in a cohort of 140 ARVC patients without prior VA, we observed that the risk score models have superior performance. However, prior to their widespread clinical application, external validation studies are required to confirm the performance of these models.

Comparison of clinical performance

As demonstrated in **Figure 4**, the accuracy of all four algorithms was low to moderate for any sustained VA (AUC 0.61-0.72), and low for fast VA (AUC 0.57-0.61). However, an interesting pattern can be observed: ITFC and mITFC have superior sensitivity (94.0-97.8%) at the expense of lower specificity (15.9-32.0%), while the lower sensitivity of AHA and HRS (76.7-83.5%) is compensated by superior specificity (42.7%-60.1%). Thus, as demonstrated in **Figure 4**, the ITFC and mITFC algorithms provide better protection rates, but result in a considerable number of ICD placements in patients not experiencing events. In contrast, the AHA or HRS algorithms provide lower protection rates, but result in a considerable reduction of patients treated with an ICD in whom outcomes do not occur.

The downside of the above-mentioned statistical measures is that patients developing the outcome while having no ICD indication (“false-negative”) weigh equal to patients not developing the outcome while having an ICD indication (“false-positives”), which is generally not true in real-life. A better measurement of clinical performance with a direct translation to clinical practice is the net-benefit¹³. The decision curve analysis (**Figure 5**) showed that ITFC and mITFC are the preferred algorithms to use when the desired sustained VA risk threshold for ICD implantation lies within 5-25%. For fast VA risk, mITFC is the preferred algorithm when the threshold lies within 2-4%, and ITFC for 4-9%. For both outcomes, AHA and HRS are superior when the risk threshold for ICD indication lies beyond those ranges (>25% sustained VA risk or >9% fast VA risk).

Any sustained VA vs. fast VA

Although SCD is the most clinically relevant outcome for ICD indication, studying this outcome would require a large prospective study in which patients do not receive an ICD, which cannot be justified ethically. Hence sustained VA and appropriate ICD therapies are generally used as surrogate. Prior literature predominantly uses an outcome similar to our “any sustained VA” outcome.⁶ However, as most sustained events likely do not lead to SCD (e.g. 39.2% of patients in this cohort survived a prior sustained VA), this outcome likely overestimates the risk of SCD. Some recent studies have shifted towards using the outcome of fast VA (sustained VT>250bpm/VF/SCD) to better approximate the risk of SCD.⁶ This aligns with the MADIT-RIT trial, which showed that more lenient ICD programming selectively targeting rapid and longer

events reduces mortality.¹⁹ In this study, results for both outcomes are presented, showing an alarming poor performance of the algorithms in predicting fast VA. While this is not surprising as the algorithms are based on literature that predominantly used the “any sustained VA” outcome, this is an important limitation of these algorithms.

Clinical recommendations

Ideally, ICDs are implanted only in those who will experience SCD, avoiding the physical and emotional burden of ICDs in those who do not need the device.²⁰ However, the protection rates of the four ICD recommendation algorithms reviewed in this study come at cost of unnecessary ICD placements. Which of the algorithms performs “best” depends on the preferred balance between protection rate and number of unnecessary ICD placements. Ultimately the final decision as to whether to implant an ICD is based on a shared decision-making process taking into consideration the preferences and values of the patient and judgement of the clinician. Some patients are very uncomfortable with the concept of ICD implantation and are willing to accept a higher risk of SCD, whereas others are unwilling to accept even the smallest risk. In our experience, most ARVC patients who face this decision are often young and otherwise healthy, have family responsibilities, and an otherwise promising future, and therefore unwilling to accept even a small risk of SCD and elect to undergo ICD implantation.

For HCM patients, another group of relatively young often otherwise healthy patients, ICD placement is recommended at a 5-year risk of SCD \geq 6%.²¹ This is a reasonable threshold for ARVC patients as well. Based on the decision curve analysis in **Figure 5B**, at an ICD indication threshold of 5-year risk of fast VA \geq 6% (closest approximation of SCD), the ITFC algorithm provides the best performance and should be the recommended algorithm to use. Nonetheless, both personal preference and healthcare system differences remain important considerations.

Limitations

Clinical testing was performed upon discretion of the clinician, and not all tests required by the prognostic algorithms were available. Patients with missing data preventing their classification were therefore excluded, potentially introducing bias. However, as only 33 (5.3%) patients were excluded, the effect is likely minimal. In 31 patients, missing EPS results may have influenced the reported results for the HRS algorithm, although our sensitivity analysis showed no significant shift of results. As described above, both any sustained VA and fast VA are imperfect surrogates of SCD, which may have been further impacted by non-uniform ICD-programming. Finally, this study assesses the performance of these risk stratification

algorithms for ICD placement at diagnosis over approximately the ICD life-time (i.e. 5-7 years). ARVC is a progressive disease with a long course and therefore arrhythmia risk needs to be periodically reassessed and ICD implantation decisions potentially revisited.

Conclusion

For sustained VA, ITFC and mITFC provide the highest ICD protection rates, whereas AHA and HRS have the highest overall accuracy (AUC 0.72) due to significantly less unnecessary ICD placements. However, for the arguable more clinically relevant fast VA outcome, all four algorithms performed poorly. If we consider a threshold of $\geq 6\%$ 5-year risk of fast VA (similar to the threshold for HCM patients) to indicate an ICD in ARVC, the ITFC is the best performing algorithm. These data may inform decision making for ICD placement in ARVC, but moreover indicate the need for better risk stratification methods to prevent SCD in this population.

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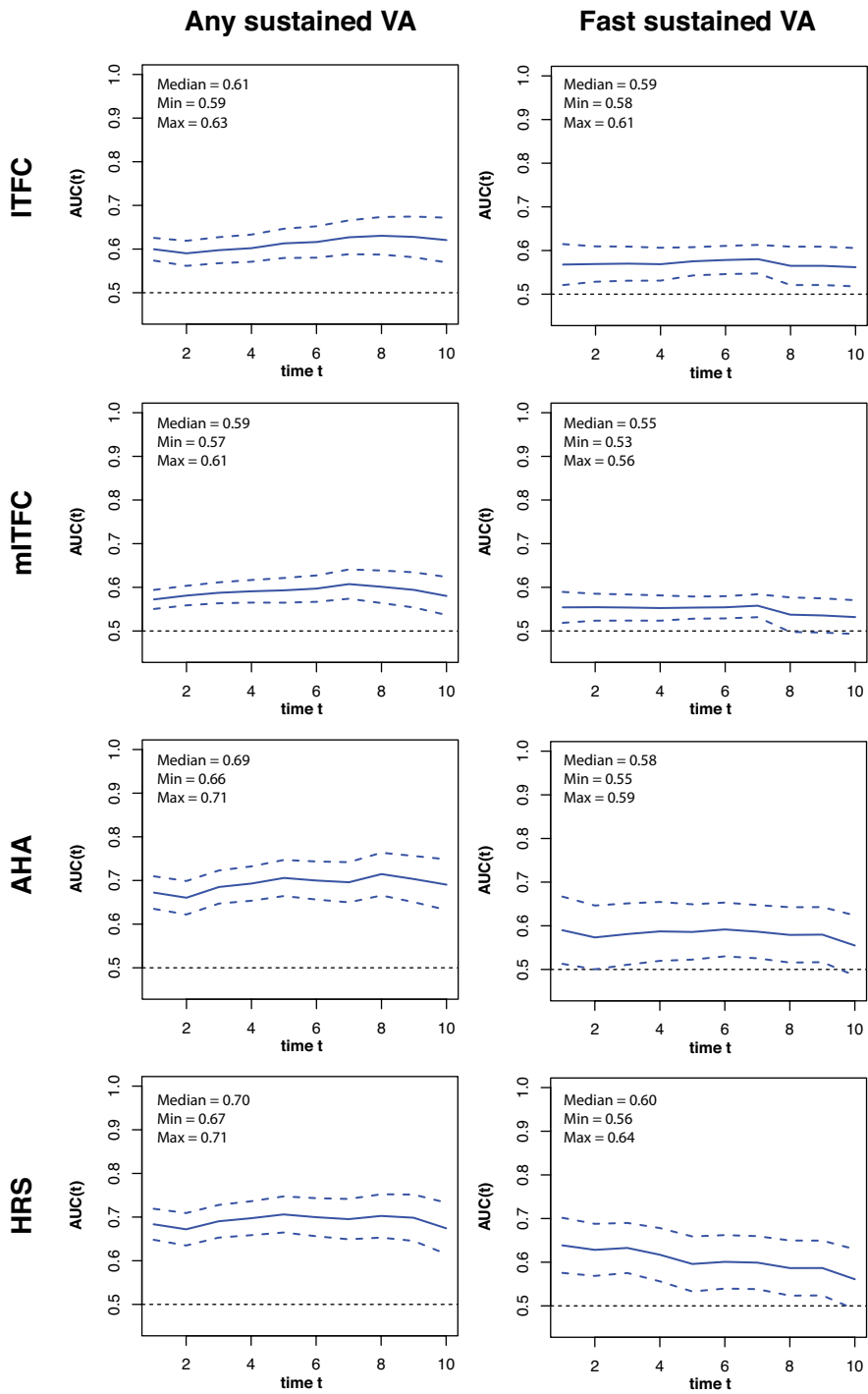
Supplementary Material

Supplementary Table 1. Baseline characteristics per country

	Overall	USA	NL	p
n	617	340	277	
Age at diagnosis (years)	38.5±15.1	35.8±14.2	41.8±15.4	<0.001
Male sex	323 (52.4)	166 (48.8)	157 (56.7)	0.063
Proband	339 (54.9)	204 (60.0)	135 (48.7)	0.007
Pathogenic variant	422 (68.4)	210 (61.8)	212 (76.5)	<0.001
Cardiac syncope	158 (25.6)	87 (25.6)	71 (25.6)	1.000
24h PVC count	1200 [354, 4181]	1366 [363, 4722]	1053 [345, 3196]	0.183
History of non-sustained VA	277 (44.9)	153 (45.0)	124 (44.8)	0.488
History of sustained VA	242 (39.2)	132 (38.8)	110 (39.7)	0.887
VT inducible on EPS (n=311)	217 (35.2)	146 (42.9)	71 (25.6)	<0.001
RVEF (%)	43±10	42±11	45±9	0.003
LVEF (%)	58±8	58±8	57±7	0.146
ICD implanted	463 (75.0)	281 (82.6)	182 (65.7)	<0.001
Follow-up (years)	6.4 [2.8, 11.5]	4.4 [1.8, 9.6]	8.5 [4.5, 13.2]	<0.001
Sustained VA	282 (45.7)	167 (49.1)	115 (41.5)	0.071
Fast VA	63 (10.2)	44 (12.9)	19 (6.9)	0.019

Abbreviations: EPS = electrophysiologic study; ICD = implantable cardioverter-defibrillator; LVEF = left-ventricular ejection fraction; PVC = premature ventricular complex; RVEF = right-ventricular ejection fraction; VA = ventricular arrhythmia; VT = ventricular tachycardia.

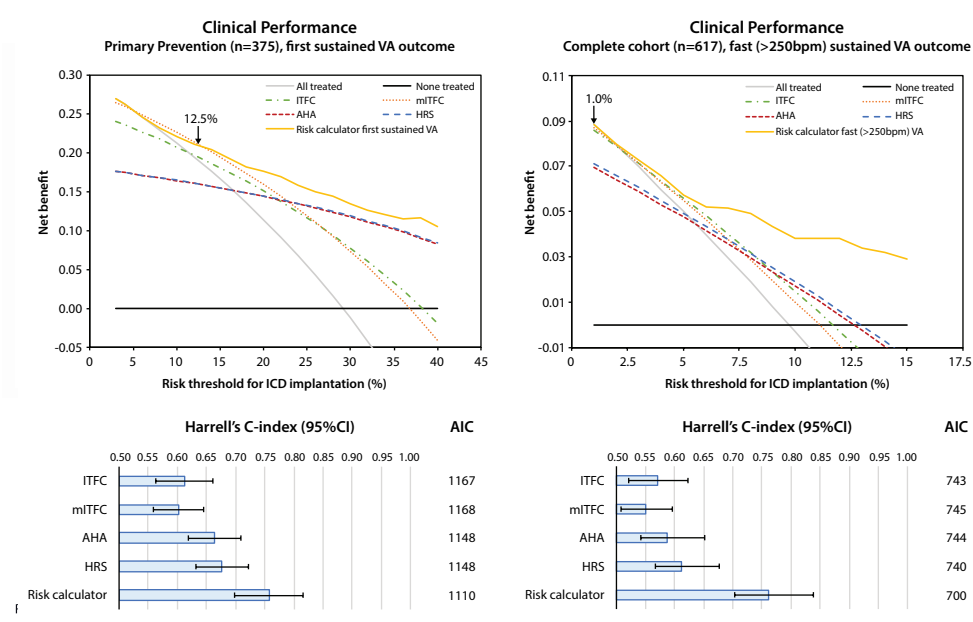
Supplementary Figure 1. Time-dependent AUC (95%CI) plotted over time.



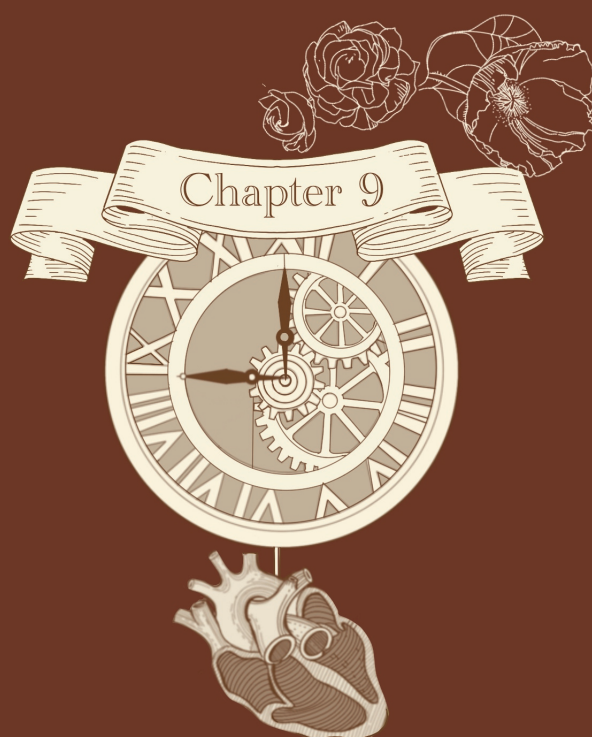
Supplementary Figure 2. Subgroup analyses of the clinical performance

		Any sustained VA			Fast sustained VA							
		Se	Sp	AUC			Se	Sp	AUC			
Complete cohort (n=617)	ITFC	94.0%	32.0%	0.63	$p = 0.229$	$p < 0.001$	ITFC	95.2%	22.3%	0.59	$p = 0.104$	$p > 0.467$
	mITFC	97.8%	24.2%	0.61			mITFC	97.1%	15.9%	0.57		
	AHA	83.5%	59.9%	0.72			AHA	76.7%	42.7%	0.60		
	HRS	83.5%	60.1%	0.72			HRS	78.4%	43.1%	0.61		
Dutch cohort (n=277)	ITFC	94.5%	23.8%	0.59	$p = 0.600$	$p < 0.001$	ITFC	100%	17.8%	0.59	$p = 0.866$	$p > 0.277$
	mITFC	98.7%	16.7%	0.58			mITFC	100%	11.5%	0.56		
	AHA	89.6%	54.8%	0.72			AHA	88.2%	39.8%	0.64		
	HRS	88.3%	52.4%	0.70			HRS	76.7%	38.2%	0.57		
Primary prevention (n=375)	ITFC	88.1%	38.7%	0.63	$p = 0.888$	$p < 0.041$	ITFC	94.1%	34.5%	0.64	$p = 0.055$	$p > 0.157$
	mITFC	97.0%	28.2%	0.63			mITFC	97.0%	23.2%	0.60		
	AHA	61.7%	79.6%	0.71			AHA	63.8%	71.8%	0.68		
	HRS	63.0%	78.9%	0.71			HRS	67.2%	71.2%	0.69		
Desmosomal mutation (n=374)	ITFC	97.2%	31.5%	0.64	$p = 0.031$	$p < 0.001$	ITFC	97.1%	20.0%	0.59	$p = 0.010$	$p > 0.059$
	mITFC	99.3%	22.6%	0.61			mITFC	97.1%	14.0%	0.56		
	AHA	88.3%	59.7%	0.74			AHA	81.1%	40.0%	0.61		
	HRS	88.7%	62.9%	0.76			HRS	85.7%	42.0%	0.64		
No desmosomal mutation (n=243)	ITFC	92.7%	20.5%	0.57	$p = 0.998$	$p < 0.019$	ITFC	95.2%	16.5%	0.56	$p = 0.969$	$p > 0.836$
	mITFC	98.1%	15.4%	0.57			mITFC	100%	10.2%	0.55		
	AHA	80.7%	50.0%	0.65			AHA	73.6%	37.0%	0.55		
	HRS	81.6%	43.6%	0.63			HRS	72.1%	33.1%	0.53		

Supplementary Figure 3. Comparing the four flow-chart algorithms to the two multivariable risk prediction models (arvc.com)



Comparing the clinical performance of the ITFC, mITFC, AHA and HRS ICD recommendation algorithms to the 5-year risk prediction model for first sustained VA in primary prevention patients (left side), and to the 5-year risk prediction model for fast (>250bpm) sustained VA (right side). Decision curve analyses (top graphs) show a superior performance of the first sustained VA prediction model when a 12.5% risk threshold for ICD implantation is applied, for the fast-sustained VA model the performance shows to be superior for any of the risk thresholds. Comparing Harrell's C-index (bottom graphs) similarly shows that the models have the highest C-index.



Chapter 9

Diagnosing Arrhythmogenic Right Ventricular Cardiomyopathy by 2010 Task Force Criteria: Clinical Performance and Simplified Practical Implementation

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Abstract

Aims: Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is diagnosed by a complex set of clinical tests as per 2010 Task Force Criteria (TFC). Avoiding misdiagnosis is crucial to prevent sudden cardiac death as well as unnecessary implantable cardioverter-defibrillator (ICD) implantations. This study aims to validate the overall performance of the TFC in a real-world cohort of patients referred for ARVC evaluation.

Methods: We included patients consecutively referred to our centers for ARVC evaluation. Patients were diagnosed by consensus of three independent clinical experts. Using this as a reference standard, diagnostic performance was measured for each individual criterion as well as the overall TFC classification.

Results: Of 407 evaluated patients (age 38 ± 17 yrs, 51% male), the expert panel diagnosed 66 (16%) with ARVC. The clinically observed TFC was false negative in 7/66 (11%) patients, and false positive in 10/69 (14%) patients. Idiopathic outflow tract VT was the most common alternative diagnosis. While the TFC performed well overall (sensitivity and specificity 92%), signal-averaged ECG (SAECG, $p=0.43$) and several family history criteria ($p \geq 0.17$) failed to discriminate. Eliminating these criteria reduced false positives without increasing false negatives (net-reclassification improvement 4.3%, $p=0.019$). Furthermore, all ARVC patients met at least one ECG or arrhythmia criterion (sensitivity 100%).

Conclusion: The TFC perform well, but are complex and can lead to misdiagnosis. Simplification by eliminating SAECG and several family history criteria improves diagnostic accuracy. ARVC can be ruled out using ECG and arrhythmia criteria alone, hence these tests may serve as a first-line screening strategy among at-risk individuals.

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by fibrofatty myocardial replacement, predisposing patients to life-threatening ventricular arrhythmias and progressive ventricular dysfunction¹. Diagnosis of ARVC has major implications for affected patients and their relatives, and may include lifestyle interventions, medication, and/or implantation of an implantable cardioverter-defibrillator². However, the clinical manifestation of ARVC is highly variable, and accurate diagnosis of ARVC can pose a challenge to the managing physician.

The pathologic gold standard for ARVC diagnosis is histological detection of fibrofatty replacement at autopsy or surgery³. However, due to the segmental nature of disease, histological evaluation has low sensitivity, while myocardial biopsy is an invasive procedure with inherent risks. In order to overcome these limitations, a composite reference standard was created in 1994 and modified in 2010 by an international task force^{3,4}. These “Task Force Criteria” (TFC) consist of consensus-based criteria in structural, histological, electrocardiographic, arrhythmic and familial features of the disease, and serve as the clinical standard for ARVC diagnosis.

While the TFC provide a uniform definition of ARVC that guides clinical practice and scientific research, a complete diagnostic work-up as per TFC is complex and time-consuming. Furthermore, the TFC is consensus-based and derived by comparison of severely affected ARVC patients to healthy controls⁴, thereby potentially overestimating its diagnostic value compared to the real-world clinical setting. Although prior studies have attempted to determine the diagnostic value of individual criteria for ARVC⁴⁻⁷, the TFC as a whole have never been validated in an independent patient cohort. Therefore, this study aims to validate the diagnostic performance of 1) individual; and 2) composite TFC in a large real-world cohort of patients referred for ARVC evaluation.

Methods

Study Population

We included consecutive patients referred to our hospitals (UMC Utrecht [UMCU], the Netherlands and Johns Hopkins Hospital [JHH], Baltimore, USA) for diagnostic ARVC evaluation between 2009-2011 including cardiovascular magnetic resonance (CMR) imaging. The study was approved by the local institutional ethics review boards.

Data Collection

All patients received clinical diagnostic evaluation upon discretion of the managing physician. Data were retrospectively collected from medical records and included clinical history and test results according to the standards and definitions of the TFC, including electrocardiograms (ECG), signal-averaged electrocardiograms (SAECG), Holter-recordings, CMR imaging, echocardiography, ventricular cine-angiography, genetic testing, three-generation pedigrees, and endomyocardial biopsies. In addition, results from other clinically relevant diagnostic tests (e.g., coronary angiograms, exercise stress tests and electrophysiology study) were collected when available.

Diagnostic Classification

Two diagnostic classifications of ARVC were used. First, patients were classified per TFC, which consist of major (2 points) and minor (1 point) criteria across six categories⁴. Within each category, a patient can fulfil a major, minor, or no criterion. Patients are classified as “definite ARVC” when the combined score over all categories is ≥ 4 points. Implicit to this classification score is the assumption that all minor and all major criteria within the same category are of equal diagnostic value; and that all six categories have equal diagnostic weight.

Second, in order to validate the diagnostic accuracy of the TFC, the consensus of a panel of ARVC-experts was used as a reference standard. This approach is consistent with international Task Force recommendations, which consider the proposed TFC to be a “working framework to improve the diagnosis and management of this condition”, while advocating for the totality of evidence to be considered on an individualized basis⁴. Prior studies have selected a reference population of ARVC patients that fulfilled diagnostic criteria independent of the criterion under investigation^{4,7}, however this method may potentially introduce bias⁸. Applying an expert panel is a recommended approach to test validity of diagnostic algorithms in the absence of a single diagnostic gold standard^{9,10}.

The expert panel protocol was designed in accordance with recommendations

(**Figure 1**)^{9,11}. The two panels, one in each hospital, consisted of three physicians specialized in ARVC (RNWH, JFVDH, ASJMTR [UMCU] and HC, JCT, ASJMTR [JHH]). First, each panel member evaluated the patients independently based on a standardized presentation of all available diagnostic information. To ensure the best possible diagnostic classification, experts were asked to re-evaluate all available information (with the possibility to overrule initial clinical assessments) including a re-review of CMR images by two expert

radiologists specialized in ARVC (IRK and SLZ). Using this information, the panel members scored the likelihood of ARVC diagnosis for each subject on a 5-step scale; 1) definitely not, 2) not likely, 3) possible, 4) likely, and 5) definitely ARVC. In case of disagreement (defined as >2 scale-step difference between two experts) or unclear diagnosis (defined as an overall average of 2.5-3.5), cases were discussed in a plenary session to reach consensus. After the initial classification by the expert panel, follow-up data (3.6 [0.3-6.3] years) was reviewed as an additional source of information to validate the initial diagnostic classification. The performance of the expert panel was evaluated by inter- and intra-observer agreement, calculated with Cohen's kappa statistic. To estimate intra-observer agreement, a stratified blinded random sample of 15 cases were re-evaluated 4-8 months after initial classification.

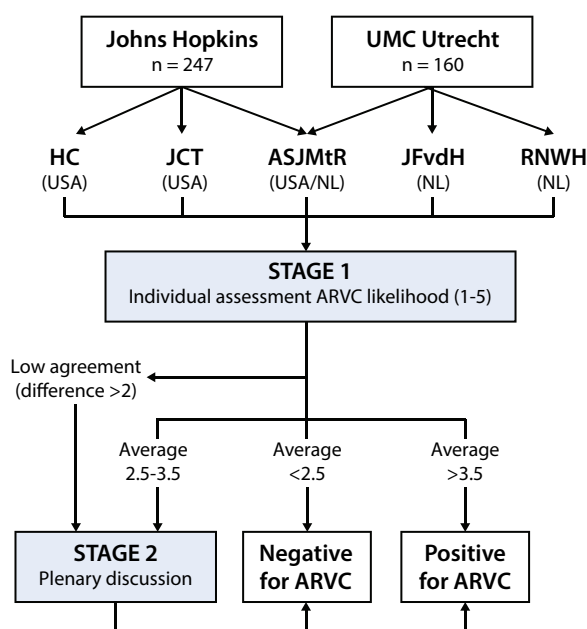


Figure 1: Flowchart of the expert panel protocol.

A staged decision-making process was utilized, in which every expert independently scored presence or absence of ARVC for every patient on a scale from 1 to 5. Patients with disagreement (>2 scale steps difference) or unclear diagnosis (average 2.5-3.5) were discussed in a plenary session to obtain final consensus classification. Abbreviations: ARVC=Arrhythmogenic Right Ventricular Cardiomyopathy; UMC=University Medical Centre.

Data Analysis

Data analysis was performed in RStudio version 1.1.414 (Boston, Massachusetts, USA). Continuous variables were compared using the t-test or Mann-Whitney-U test as appropriate,

and categorical variables using chi-squared or Fisher's exact tests. Patterns of missing data were evaluated and assumed to be missing at random. Missing values were replaced using multiple imputations by chained equations based on all collected variables and the expert panel diagnosis to create 100 imputed datasets¹². All analyses were repeated in every imputed dataset separately, and results were pooled using Rubin's rules¹³. To determine diagnostic values that reflect real-world clinical practice, data from original clinical test interpretations was analyzed as opposed to expert reviews, which were solely used to obtain the best possible diagnostic classification. Using the panel diagnosis as a reference, the diagnostic TFC performance was evaluated by analysis of test characteristics (i.e., sensitivity, specificity) and logistic regression with Firth bias correction to accommodate for the low numbers of events for certain predictors¹⁴. Additionally, the Youden's index ($[\text{false positive rate}] + [\text{false negative rate}] - 1$)¹⁵ was calculated to assess overall diagnostic value: Youden's index ranges from 0 to 1, with 1 indicating a test with 100% sensitivity and specificity. Overall classification performance was compared with the net-reclassification improvement. To estimate the relative weights of the diagnostic contribution of different categories of criteria, multivariable logistic regression was used and results were internally validated by bootstrapping. Two-tailed P-values <0.05 were considered statistically significant.

Results

Study Population

The study population included 407 patients who were evaluated for ARVC at UMCU or JHH. Baseline characteristics are presented in **Table 1**. Half (51%) of the population was male and mean age was 38 ± 17 years. Clinical evaluation was performed because of symptoms/abnormal test results in 261 (63%) patients and because of family history in the remaining 146 (37%) patients. Symptoms for which patients were referred included palpitations (n=88, 34%), symptomatic VT/VF/SCA (n=51, 20%), (pre-)syncope (n=49, 19%), dyspnea (n=18, 7%) and chest pain (n=17, 7%). Although all patients were referred for CMR evaluation of ARVC, CMR results of seven (2%) patients were excluded due to imaging artefacts. Extended and stratified versions of the baseline table is available in **Supplementary Table 1-3**, and a complete list of pathogenic mutations in **Supplementary Table 4**.

Table 1: Clinical characteristics.

			Overall (n=407)	Not ARVC (n=341)	ARVC (n=66)	p
Male sex			206 (51)	175 (51)	31 (47)	0.608
Age (yrs.)			38 ± 17	37 ± 17	40 ± 14	0.245
Indication	Symptomatic/abnormal test		261 (64)	219 (64)	42 (64)	1.000
	Family screening		146 (36)	122 (36)	24 (36)	
TFC score			2 [1-3]	1 [1-2]	5 [4-6]	<0.001
I. Structural	Echocardiography (n=315)	Major	12 (4)	2 (1)	10 (20)	<0.001
		Minor	8 (3)	5 (2)	3 (6)	
	CMR (n=400)	Major	53 (13)	25 (7)	28 (45)	<0.001
		Minor	30 (8)	15 (4)	15 (24)	
	RV cine-angiography (n=41)	Major	14 (34)	3 (13)	11 (61)	0.004
II. Tissue histology	Tissue histology (n=28)	Major	2 (7)	1 (8)	1 (6)	0.669
		Minor	1 (4)	-	1 (6)	
III. Repolarization	ECG (n=398)	Major	45 (11)	7 (2)	38 (58)	<0.001
		Minor	40 (10)	32 (9)	8 (12)	
IV. Depolarization	ECG (n=398)	Major	-	-	-	<0.001
		Minor	92 (24)	56 (17)	36 (58)	
	SAECG (n=119)	Minor	59 (50)	46 (50)	13 (50)	1.000
V. Arrhythmia	VT LBBB superior axis (n=407)	Major	19 (5)	8 (2)	11 (17)	<0.001
	VT LBBB other/unknown axis (n=407)	Minor	49 (12)	27 (8)	22 (33)	<0.001
	Holter monitor >500 PVC/24hrs (n=298)	Minor	127 (43)	78 (33)	49 (82)	<0.001
VI. Family history	Pathogenic mutation (n=190)	Major	67 (35)	31 (24)	36 (57)	<0.001
	First degree ARVC (n=407)	Major	70 (18)	50 (15)	20 (30)	0.005
	First degree ARVC autopsy (n=407)	Major	30 (8)	26 (8)	4 (6)	0.804
	First degree ARVC unconfirmed (n=407)	Minor	5 (1)	5 (2)	-	0.689
	First degree SCD <35 yrs (n=407)	Minor	29 (7)	24 (7)	5 (8)	1.000
	Second degree ARVC (n=407)	Minor	27 (7)	26 (8)	1 (2)	0.109

Abbreviations: ARVC=arrhythmogenic right ventricular cardiomyopathy; CMR=cardiac magnetic resonance imaging; ECG=electrocardiogram; LBBB=left bundle branch block; PVC=premature ventricular complex; RV=right ventricular; SAECG=signal-averaged ECG; SCD=sudden cardiac death; TFC=Task Force Criteria; VT=ventricular tachycardia.

Expert Panel Diagnosis and Clinical TFC Score

In total, 66 (16%) patients were diagnosed with ARVC by the expert panel, with an excellent level of agreement ($K \geq 0.81$) and intra-observer reproducibility ($K \geq 0.85$) (**Supplementary Table 5**). **Figure 2** shows the results of the expert panel evaluation versus the TFC score. Using the expert panel as a reference, 7/66 (11%) patients with ARVC were not detected by the TFC (i.e. false negatives), while 10/69 (14%) of patients fulfilling TFC did not have ARVC (i.e. false positives) (**Supplementary Table 6A/B**). The most common alternative diagnosis of patients meeting TFC was idiopathic right ventricular (RV) outflow tract ventricular tachycardia (VT) or premature ventricular complexes (PVCs) (**Supplementary Figure 1**). After reviewing the information from 3.6 [0.3-6.3] years of follow-up, 6 cases (1.5%) received a different classification at last follow-up: all were cases classified as at risk of ARVC who developed definite ARVC during follow-up, confirming their initial “at-risk” classification (**Supplementary Figure 2**).

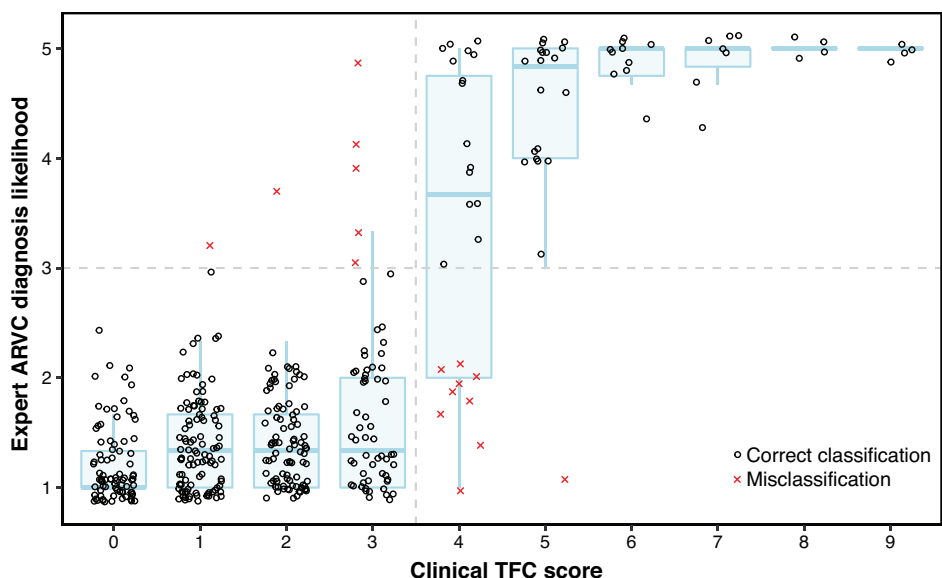


Figure 2: Expert panel score vs. clinically observed TFC score.

Box plot with jitter plot (using small random jitter) overlay. Observed clinical TFC score (X-axis) is plotted against the average expert panel diagnosis likelihood (Y-axis). Dotted horizontal and vertical lines represent classification cut-off values (TFC ≥ 4 ; expert diagnostic likelihood > 3). Patients in the left upper (false negative) and right lower (false positive) quadrants are misclassified (red crosses). Abbreviations as in Table 1.

Evaluation of the Individual TFC

Of all tests included in the TFC, RV cine-angiography (available in 10%) and tissue biopsy (available in 7%) were not routinely performed and therefore excluded from further analyses. In addition, epsilon waves (0%) and T-wave inversions (TWI) V1-4 in combination with complete right bundle branch block (cRBBB)(1%) were rarely observed, precluding further analysis. The diagnostic accuracy of the remaining individual TFC is summarized in **Figure 3**.

As can be appreciated from **Figure 3**, most individual TFC were significantly associated with ARVC diagnosis. Of note, the only criteria not significantly associated with ARVC diagnosis were late potentials on SAECG ($p=0.43$), autopsy diagnosis in a first-degree relative ($p=0.72$), and all minor family history criteria ($p \geq 0.17$).

As TFC in the category “global or regional dysfunction and structural alterations” can be measured by either echocardiography or CMR, we performed a head-to-head comparison of these modalities. Compared to CMR, echocardiographic criteria were less frequently fulfilled (8% echocardiography vs. 22% CMR) which lead to a highly specific, yet poorly sensitive diagnostic yield. As such, CMR had superior diagnostic accuracy compared to

echocardiography (Youden's index 0.57 and 0.25 respectively, net-reclassification improvement 32%, $p<0.001$).

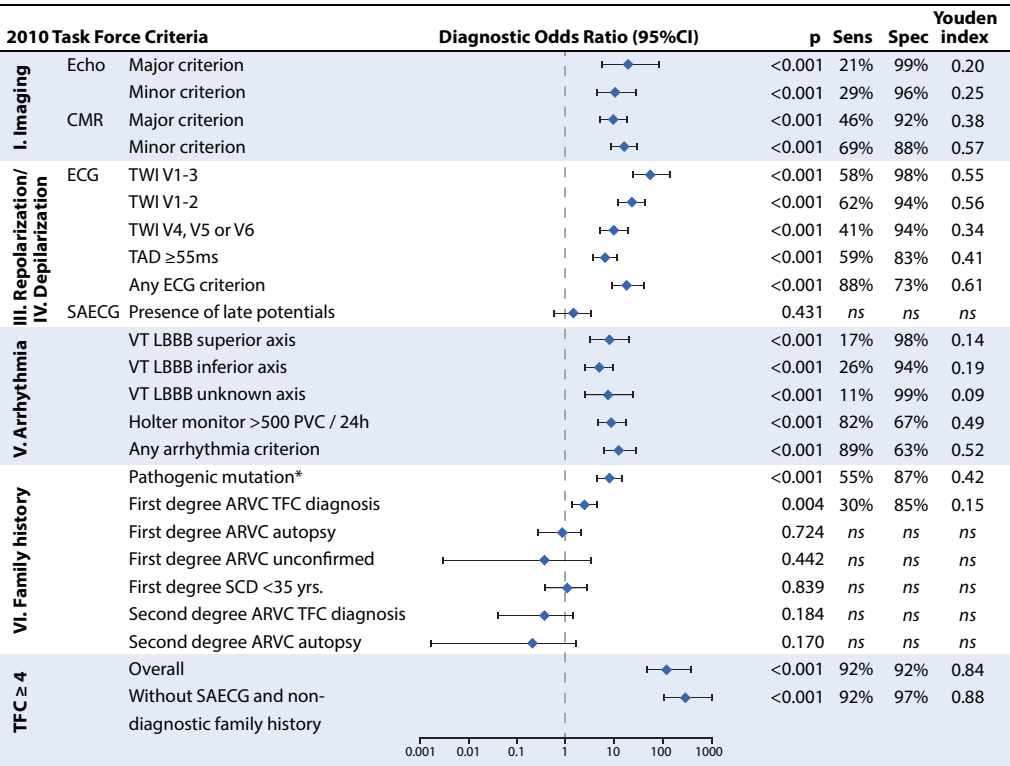


Figure 3: Diagnostic performance of individual and composite Task Force Criteria.

Forest plot of the diagnostic odds ratios and 95% confidence intervals. *Considered positive if a pathogenic or likely pathogenic variant²⁵ is found in ARVC-associated genes as defined by the TFC: Plakophilin-2, Desmocollin-2, Desmoglein-2, Desmoplakin, Plakoglobin, or Transmembrane protein-43. Abbreviations: Echo=echocardiography; Sens=sensitivity; Spec=sensitivity; TAD=terminal activation duration; TWI=T-wave inversion. Other abbreviations as in Table 1.

Evaluation of the Composite TFC

The overall sensitivity and specificity of the composite TFC score (which was defined as fulfilment of ≥4 points [i.e. “definite ARVC” as per TFC]) were both 92% (**Figure 3**). Elimination of SAECEG and family history criteria, which individually failed to discriminate, increased specificity to 97% while retaining 92% sensitivity. Comparing classification with and without these criteria showed a significant net-reclassification improvement of 4.3% ($p=0.019$), confirming an increase in diagnostic accuracy.

We subsequently set out to compare the performance of TFC categories using a multivariable logistic regression model. Results are shown in **Table 2**. As can be appreciated from the regression coefficients, diagnostic values of categories were not equal: the strongest association with ARVC diagnosis was observed for repolarization criteria and weakest association for depolarization criteria (β 2.67 and 1.23, respectively, indicating a two-fold difference of association with ARVC diagnosis). As a result, the likelihood of having ARVC varied between patients with the same overall TFC score, yet comprised of different categories (see **Supplementary Table 7**).

Table 2. The Task Force Criteria as a multivariable model predicting ARVC diagnosis.

TFC category	Criterion fulfilment	β	SE	p
I. Structural	None / Minor / Major	1.54	0.36	<0.001
II. Tissue histology	-	-	-	-
III. Repolarization	None / Minor / Major	2.67	0.47	<0.001
IV. Depolarization	None / Minor	1.23	0.72	0.088
V. Arrhythmia	None / Minor / Major	2.50	0.60	<0.001
VI. Family history	None / Minor / Major	1.73	0.41	<0.001

Abbreviations: β =regression coefficient, SE=standard error. Other abbreviations as Table 1.

Furthermore, as shown in **Figure 3**, the highest sensitivities of ARVC diagnosis were observed for having any ECG criterion (88%) or any arrhythmia criterion (89%). In combination, these criteria yielded a sensitivity of 100%, indicating a strong potential to rule out disease using these criteria alone.

Discussion

In absence of a single gold standard test, ARVC is diagnosed by the TFC: a composite set of major and minor criteria that were based upon comparison of ARVC patients with healthy subjects. As a result, the diagnostic performance of the TFC is likely substantially lower in a real-world clinical setting, in which patients suspected of ARVC may more closely resemble each other. In our study, we evaluated the diagnostic performance of the TFC in a consecutive cohort of patients referred for ARVC evaluation. This study has several interesting results. First, the TFC perform well but are not without risk of misdiagnosis. Second, the risk of misdiagnosis can be reduced by simplification of the TFC. Third, the relative weights of individual major and minor criteria as well as different categories are not equal. Last, ECG and arrhythmia criteria alone can rule out ARVC with remarkably high sensitivity. This information may help clinicians evaluating subjects for this potentially life-threatening, yet clinically challenging disease.

ARVC Misdiagnosis: An Important Clinical Problem

Although the TFC are a crucial tool for ARVC diagnosis, their complexity renders ARVC diagnosis prone to misinterpretation, hence leading to misdiagnosis. This was already shown by Bomma et al.¹⁶, demonstrating that 73% of presumed ARVC patients were misdiagnosed, most commonly based on CMR misinterpretation. In our study, in which CMRs were overread by two blinded radiologists and final diagnosis was determined by a robust expert panel, 11% false negatives and 14% false positives occurred. A false positive TFC classification occurred most commonly in idiopathic VT/PVC patients, which can be difficult to distinguish from ARVC¹⁷.

Performance of the Individual TFC

Our study reveals a significant difference in diagnostic performance of individual TFC. Results from RV cine-angiography and tissue biopsy were not included, as these tests were not routinely performed. However, with acceptable non-invasive alternatives for RV cine-angiography and questionable sensitivity of tissue biopsy¹⁸, the use of these invasive tests may no longer be justifiable in most situations. Also, we did not include epsilon waves and TWI V1-4 in the presence of cRBBB, as these were rarely observed. Nonetheless, the low prevalence of these criteria may itself be an indication that their contribution to ARVC diagnosis is limited. This may be explained by the fact that these signs are a late manifestation of disease^{6,19}. Furthermore, the diagnostic value of the epsilon wave was recently disputed by Platonov et al.⁶, showing that its reproducibility is unacceptably low.

Of note, almost all other individual TFC were significantly associated with ARVC diagnosis. The highest sensitivity was observed for ECG and Holter monitoring criteria, which are indeed thought to occur early in the disease process²⁰⁻²². Although both echocardiography and CMR criteria were significantly associated with ARVC, echocardiography had poor sensitivity and was outperformed by CMR in overall diagnostic accuracy. This is in line with the recent finding by Borgquist et al.⁵, showing that conventional echocardiography is unreliable to detect subtle structural changes in the RV. Of note, newer techniques such as strain echocardiography (i.e. deformation imaging) may have incremental value for ARVC diagnosis, but this is not yet part of the TFC and therefore not specifically investigated in this study.

In our cohort, late potentials on SAEKG were not significantly associated with ARVC diagnosis. Late potentials occurred in 50% of the ARVC cases as well as in 50% of non-ARVC cases (**Table 1**), therefore lacking both sensitivity and specificity. Other criteria not significantly associated with ARVC include autopsy diagnosis in a first-degree relative, and all minor family

history criteria. For autopsy diagnosis, this may be due to the uncertainty associated with a post-mortem ARVC diagnosis as well as limited pathologist' experience with ARVC, as previously suggested²³. Uncertainty also exists for a first-degree relative with SCD below the age of 35 years, which can be caused by many different entities. As for second-degree relatives, the chance of genetic predisposition is 25% (assuming the proband carries a pathogenic mutation). In combination with the incomplete penetrance of disease, the risk of ARVC may simply be too low to find a significant association in this cohort. Conversely, the presence of a pathogenic mutation confirmed by genetic analysis had the strongest diagnostic value of all family history criteria, especially high in specificity (87%), indicating its strong potential to confirm the diagnosis in patients receiving cardiologic evaluation for ARVC.

It is important to note that criteria not significantly associated with ARVC diagnosis in this study (e.g. family history and SAECG) may have better diagnostic value should they be better standardized or technologically improved. If not, they may still serve a relevant purpose such as indication for cardiologic screening or risk stratification. For example, the presence of any family history criteria provides a compelling indication for clinical evaluation, as the risk of ARVC in these relatives strongly exceeds that of the general population.

Performance of the Composite TFC

The current clinical rule for diagnosing ARVC by a TFC score of ≥ 4 shows overall good sensitivity and specificity of 92%. Nevertheless, the long list of criteria and modalities in the TFC make diagnosing ARVC complex and time-consuming. Our results indicate that not all criteria are required to diagnose ARVC, since they have low diagnostic accuracy and/or low prevalence. Not only does removing these criteria simplify the TFC, it may also lead to a significant improvement of its diagnostic accuracy.

Important implicative assumptions of the TFC are equality of diagnostic value of all six categories (i.e. 0-2 points per category); and equality of diagnostic value of minor (1 point) and major (2 points) criteria within the same category. If the former were true, the results from our multivariable model (**Table 2**) would have revealed similar regression coefficients, which was not the case: instead, our results indicated that some categories contribute stronger to the probability of ARVC diagnosis than others. Furthermore, as demonstrated by the analyses of the individual TFC (**Figure 3**), even the latter assumption is not justified. Overall, these results suggest an opportunity to improve TFC performance by redistribution of the relative weights ("points") attributed to each criterion.

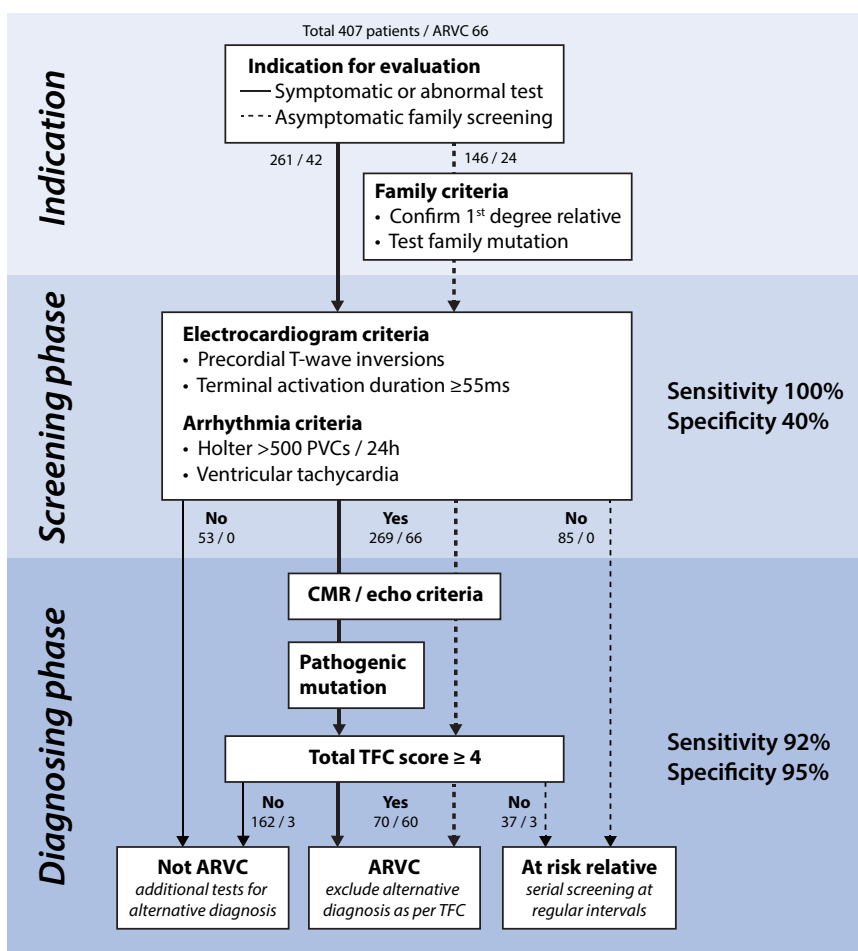


Figure 4: Simplified practical implementation of the TFC.

Diagram of simplified practical implementation of the TFC, using a stepwise approach of highly sensitive ECG and arrhythmia criteria in an initial 'screening phase' to rule out ARVC. Numbers denote overall number/those with ARVC. Abbreviations as in Table 1

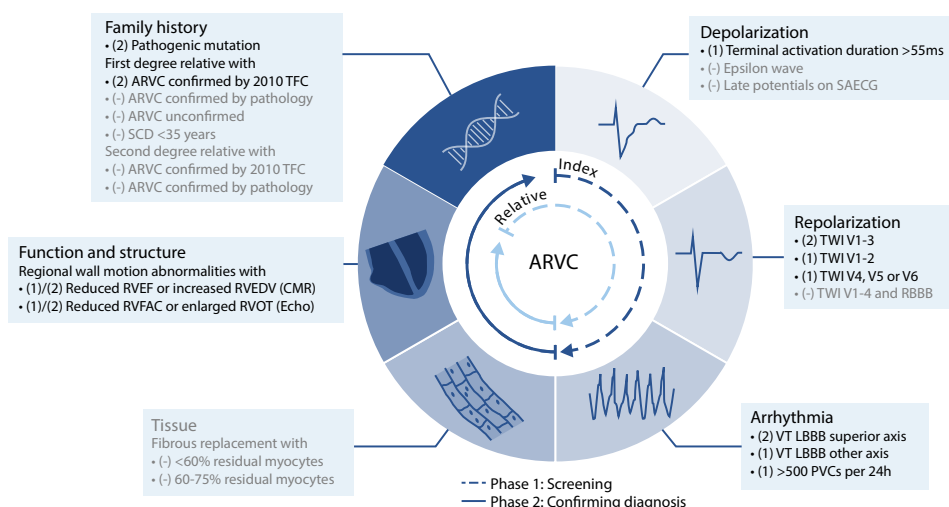
Clinical Implementation

Our study indicates that ECG and arrhythmia criteria have very high sensitivity for ARVC diagnosis, while echocardiography and CMR criteria have high specificity. This provides important information for ARVC screening and diagnosis, which need a fundamentally different, yet complimentary, approach. For screening purposes, high sensitivity is desired to not miss any affected patients. For diagnosis, high specificity is necessary to avoid a false positive diagnosis in essentially healthy individuals. Based on the results of our study, a stepwise evaluation approach may be justifiable, starting with a "screening phase" using ECG

and arrhythmia criteria to rule out ARVC, followed by a “diagnostic phase” using imaging criteria to rule in disease. Not only would this screening phase save time and resources, most notably in serial evaluation of relatives in whom cardiac imaging may not be required for a differential diagnosis, it could also prevent false positive diagnosis by misinterpretation of imaging criteria. This approach is in line with a recent publication from the European Association of Cardiovascular Imaging, stating that structural abnormalities in the absence of ECG changes should be interpreted with caution as this is unlikely to be caused by ARVC²⁴. An example of the practical implementation of our results is depicted in **Figure 4**: in our cohort, ARVC could be ruled out in 138 (34%) patients using ECG and arrhythmia criteria alone. An overview the simplification of the TFC is provided in the **Take Home Figure**.

Limitations

Our study population was drawn from two tertiary care centers, which may impact extrapolation to other settings. However, diagnosing ARVC is a complex process requiring a certain level of expertise which most often takes place in tertiary care centers (if not for initial diagnosis, then for second opinion). As this is an observational study, not all clinical tests were performed in all patients. For the analysis we used appropriate statistical measures to correct for this. However, we cannot rule out the possibility that missing test results caused misclassification by the expert panel in certain cases, such as genetic analysis in borderline probands. To check for potential misclassification, the experts examined all available follow-up information. However, this would preferably require life-time follow-up, which was not available at the time of this study. Only 6 patients classified as “at-risk for ARVC” developed ARVC during follow-up. Therefore, sub-analysis to evaluate the performance to identify early disease was not feasible. Since the expert review included all available test results, incorporation bias may have impacted our results. Nonetheless, as ARVC diagnosis is based on a large number of tests, and patients were scored by multiple experts independently, we expect this effect to be limited and equally distributed among tests. Finally, the results presented in this study depend on the assumption that the expert panel classification is the closest approximation of a gold standard, which is currently not available.



(2) = major criterion; (1) = minor criterion; (-) = consider to eliminate from standard diagnostic work-up for ARVC

Take Home Figure.

Overview of the TFC for diagnosing ARVC with potential simplification by eliminating several criteria (in grey). While these criteria are not required in standard diagnostic work-up for ARVC, they may still serve purpose in differential diagnosis, risk stratification, or indication for cardiologic evaluation. For relatives, the starting point should be to confirm the diagnosis of the index patient and/or genetic analysis, whereas for index patients this is the final step. Abbreviations: EF=ejection fraction; EDV=end-diastolic volume; FAC=fractional area change; OT=outflow tract. Other abbreviations as in Table 1.

Conclusion

Using the largest cohort to date of patients consecutively evaluated for ARVC, our study shows that most individual TFC perform well, with the exception of SAECCG and several family history criteria. Removing these criteria from the overall TFC score not only simplifies the TFC, but also improves diagnostic accuracy. Furthermore, the relative weights of individual major and minor criteria as well as different categories may not be as equal as is currently assumed, suggesting the potential for possible improvement in future TFC iterations. Last, ECG and arrhythmia criteria alone can rule out ARVC with high sensitivity. This indicates that these criteria can be used as a first-line screening test, while limiting the use of more expensive imaging tests (echocardiography and CMR) among those unlikely to derive benefits from its results. Finally, this study underlies the need for an individual evaluation beyond the current criteria and to identify additional diagnostic tools for ARVC diagnosis.

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Supplementary Material

Supplementary Table 1. Baseline characteristics

		ARVC (n=66)	At risk (n=83)	Idiopathic PVC/VT (n=94)	Sarcoid/Myocarditis (n=11)	Other (n=70)	Normal heart (n=83)
Male sex		31 (47)	44 (53)	39 (42)	8 (73)	44 (63)	40 (48)
Age (yrs.)		40 ± 14	30 ± 16	40 ± 18	48 ± 14	45 ± 18	33 ± 15
Center	UMCU	29 (44)	28 (34)	46 (49)	4 (36)	30 (43)	23 (28)
	JHU	37 (56)	55 (66)	48 (51)	7 (64)	40 (57)	60 (72)
Indication	Symptomatic / abnormal test	42 (64)	3 (4)	91 (97)	11 (100)	62 (88)	52 (63)
	Family screening	24 (36)	80 (96)	3 (3)	0 (0)	8 (11)	31 (37)
TFC score		5 [4-6]	2 [2-3]	1 [1-2]	1 [0-3]	1 [0-1]	1 [0-2]
I. Structural	Echocardiography (n=315)	10 (20)	0 (0)	1 (1)	0 (0)	1 (2)	0 (0)
	Major	3 (6)	2 (4)	3 (4)	0 (0)	2 (3)	0 (0)
	Minor	28 (45)	3 (4)	6 (6)	4 (40)	6 (9)	6 (7)
	CMR (n=400)	15 (24)	5 (6)	12 (13)	4 (40)	9 (13)	10 (12)
	Major	11 (61)	0 (0)	0 (0)	1 (100)	2 (22)	0 (0)
II. Tissue histology	RV angiography (n=41)	1 (6)	NA	1 (50)	0 (0)	0 (0)	NA
	Tissue histology (n=28)	1 (6)	NA	1 (50)	0 (0)	0 (0)	NA
	ECG (n=398)	38 (58)	0 (0)	2 (2)	0 (0)	0 (0)	5 (6)
III. Repolarization	ECG (n=398)	8 (12)	10 (12)	7 (7)	3 (27)	8 (12)	4 (5)
	Major	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
IV. Depolarization	ECG (n=398)	36 (58)	10 (12)	13 (14)	5 (46)	16 (24)	12 (15)
	Major	13 (50)	19 (43)	8 (62)	1 (100)	5 (50)	13 (52)
V. Arrhythmia	SAECG (n=119)	11 (17)	0 (0)	5 (5)	1 (9)	1 (1)	1 (1)
	VT LBBB superior axis	22 (33)	0 (0)	21 (22)	0 (0)	3 (4)	3 (4)
	VT LBBB other/unknown axis	49 (82)	5 (7)	56 (76)	1 (50)	13 (35)	3 (6)
	Holter (n=298)	36 (57)	31 (49)	0 (0)	0 (0)	0 (0)	0 (0)
VI. Family history	Pathogenic mutation (n=190)	20 (30)	41 (50)	2 (2)	0 (0)	0 (0)	7 (9)
	First degree ARVC	4 (6)	16 (20)	1 (1)	0 (0)	0 (0)	9 (11)
	First degree ARVC autopsy	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	4 (5)
	First degree ARVC unconfirmed	5 (8)	11 (13)	1 (1)	0 (0)	3 (5)	9 (11)
	First degree SCD <35 years	1 (2)	24 (29)	0 (0)	0 (0)	0 (0)	2 (2)

Abbreviations: ARVC = arrhythmogenic right ventricular cardiomyopathy; CMR = cardiac magnetic resonance imaging; ECG = electrocardiogram; LBBB = left bundle branch

block; PVC = premature ventricular complex; RV = right ventricular; SAECEG = signal-averaged ECG; SCD = sudden cardiac death; TFC = Task Force Criteria; VT = ventricular tachycardia.

Supplementary Table 2. Baseline characteristics stratified by referral reason

		Symptomatic / abnormal test		Family history		p	*vs.† p
		Not ARVC (n=219)	ARVC* (n=42)	Not ARVC (n=122)	ARVC† (n=24)		
Male sex		116 (53)	23 (55)	59 (48)	8 (33)	0.260	0.155
Age (yrs.)		41 ± 18	39 ± 16	31 ± 15	42 ± 12	0.002	0.446
Total TFC score		1 [0-2]	5 [4-6]	2 [2-3]	5 [4-5]	<0.001	0.317
I. Structural	<i>Echocardiography (n=315)</i>	Major	2 (1)	0 (0)	3 (17)	<0.001	0.054
		Minor	3 (2)	0 (0)	2 (3)	3 (17)	
	<i>CMR (n=400)</i>	Major	21 (10)	23 (61)	4 (3)	5 (21)	<0.001
		Minor	11 (5)	7 (18)	4 (3)	8 (33)	
II. Tissue histology	<i>RV cine-angiography (n=41)</i>	Major	3 (14)	7 (70)	0 (0)	4 (50)	0.628
	<i>Tissue histology (n=28)</i>	Major	1 (9)	1 (11)	0 (0)	0 (0)	0.705
III. Repolarization	<i>ECG (n=398)</i>	Major	0 (0)	0 (0)	0 (0)	1 (14)	0.356
IV. Depolarization	<i>ECG (n=398)</i>	Major	7 (3)	28 (67)	0 (0)	10 (42)	<0.001
		Minor	22 (10)	6 (14)	10 (8)	2 (8)	
V. Arrhythmia	<i>SAECG (n=119)</i>	Major	0 (0)	0 (0)	0 (0)	0 (0)	0.323
	<i>VT LBBB superior axis (n=407)</i>	Minor	41 (20)	25 (64)	15 (13)	11 (48)	
	<i>VT LBBB other/unknown axis (n=407)</i>	Major	17 (47)	9 (56)	29 (51)	4 (40)	0.771
	<i>Holter monitor >500 PVC/24hrs (n=298)</i>	Minor	8 (4)	7 (17)	0 (0)	4 (17)	<0.001
VI. Family history	<i>Pathogenic mutation (n=190)</i>	Major	27 (12)	19 (45)	0 (0)	3 (13)	0.002
	<i>First degree ARVC (n=407)</i>	Minor	70 (52)	34 (94)	8 (8)	15 (63)	<0.001
	<i>First degree ARVC autopsy (n=407)</i>	Major	0 (0)	20 (48)	31 (25)	16 (67)	<0.001
	<i>First degree ARVC unconfirmed (n=407)</i>	Major	0 (0)	0 (0)	50 (41)	20 (83)	<0.001
	<i>First degree SCD <35 yrs (n=407)</i>	Major	0 (0)	0 (0)	26 (22)	4 (17)	0.797
	<i>Second degree ARVC (n=407)</i>	Minor	1 (1)	0 (0)	4 (3)	0 (0)	0.825
		Minor	4 (2)	0 (0)	20 (17)	5 (21)	0.830
			2 (1)	0 (0)	24 (20)	1 (4)	0.119
							0.775

Abbreviations: as Table 1.

Supplementary Table 3. Baseline characteristics of the 66 ARVC patients stratified by referral reason and mutation status

		Symptomatic / abnormal test		p	Family history		p
		Mutation negative (n=22)	Mutation positive (n=20)		Mutation negative (n=8)	Mutation positive (n=16)	
I. Structural	Male sex	11 (50)	12 (60)	0.734	3 (38)	5 (31)	1.000
	Age (yrs.)	44 ± 15	33 ± 15	0.027	46 ± 9	40 ± 13	0.282
	TFC score	4 [4, 5]	7 [5, 8]	<0.001	5 [4, 5]	5 [4, 7]	0.081
	Total without mutation criterion	4 [4, 5]	5 [3, 6]	0.887	5 [4, 5]	5 [4, 7]	0.100
II. Tissue histology	Echocardiography (n=51)	3 (18)	4 (25)	0.928	1 (17)	2 (17)	0.392
	CMR (n=62)	0 (0)	0 (0)	0.060	0 (0)	3 (25)	0.170
	RV cine-angiography (n=14)	12 (63)	11 (58)	0.060	0 (0)	5 (31)	0.170
	Tissue histology (n=16)	1 (5)	6 (32)	1.000	4 (50)	4 (25)	0.414
III. Repolarization	Major	3 (60)	4 (80)	1.000	0 (0)	4 (67)	0.414
	Minor	1 (17)	0 (0)	1.000	0 (0)	0 (0)	1.000
	ECG (n=66)	0 (0)	0 (0)	0.215	0 (0)	1 (25)	0.490
	ECG (n=66)	14 (64)	14 (70)	0.215	3 (38)	7 (44)	0.490
IV. Depolarization	Minor	5 (23)	1 (5)	0.789	0 (0)	2 (13)	0.775
	Major	0 (0)	0 (0)	0.789	0 (0)	0 (0)	0.775
	SAECG (n=26)	15 (68)	10 (59)	0.657	3 (38)	8 (53)	0.519
	VT LBBB superior axis (n=66)	3 (43)	6 (67)	1.000	3 (60)	1 (20)	0.333
V. Arrhythmia	VT LBBB other/unknown axis (n=66)	4 (18)	3 (15)	0.779	0 (0)	4 (25)	0.333
	Holter monitor >500 PVC/24hrs (n=66)	9 (41)	10 (50)	1.000	1 (13)	2 (13)	1.000
	First degree ARVC (n=66)	19 (95)	15 (94)	NA	5 (63)	10 (63)	0.846
	First degree ARVC autopsy (n=66)	0 (0)	0 (0)	NA	6 (75)	14 (88)	0.846
VI. Family history	First degree ARVC unconfirmed (n=66)	0 (0)	0 (0)	NA	2 (25)	2 (13)	0.846
	First degree SCD <35 yrs (n=66)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
	Second degree ARVC (n=66)	0 (0)	0 (0)	NA	2 (25)	3 (19)	1.000
	Minor	0 (0)	0 (0)	NA	0 (0)	1 (6)	1.000

Abbreviations: as Table 1.

Supplementary Table 4. List of pathogenic variants

Gene	Nucleotide change	Amino acid change	Classes	Total (n)	Proband (n)	Relative (n)	ARVC (n)
DSC2	c.154+1G>A	p.?	4	1	1	0	1
DSG2	c.137G>A	p.Arg46Gln	5	2	0	2	1
	c.523+2T>C	p.?	4	1	1	0	1
DSP	c.478C>T	p.Arg160*	5	3	1	2	2
PKP2	c.1132C>T	p.Gln378*	5	1	1	0	1
	c.1170+4_1170+7delAGTG	p.?	4	1	1	0	1
	c.1211dup	p.Val406Serfs*4	5	3	1	2	2
	c.1237C>T	p.Arg413*	5	2	1	1	1
	c.1369_1372delCAAA	p.Gln457*	5	2	0	2	1
	c.1378+1G>C	p.?	5	2	0	2	0
	c.148_151delACAG	p.Thr50Serfs*61	5	3	1	2	1
	c.1613G>A	p.Trp538*	5	2	0	2	0
	c.1643delG	p.Gly548Valfs	5	1	0	1	0
	c.1760delT	p.Val587fs*69	5	1	0	1	1
	c.1803delC	p.Asp601fsGlufs*55	5	1	1	0	1
	c.1844C>T	p.Ser615Phe	4	1	0	1	1
	c.1849C>T	p.Gln617*	5	1	1	0	1
	c.2013delC	p.Lys672Argfs*12	5	2	1	1	1
	c.2146-1G>C	p.Met716fs	5	4	1	3	3
	c.218dup	p.Gln74fs*83	5	2	0	2	0
	c.2197_2202delCACACCinsG	p.His733Alafs*8	5	3	1	2	2
	c.235C>T	p.Arg79*	5	3	1	2	2
	c.2386T>C	p.Cys796Arg	5	2	0	2	1
	c.2489+1G>A	p.?	5	4	1	3	1
	c.2489+4A>C	p.?	5	3	1	2	3
	c.2509delA	p.Ser837Valfs*94	5	1	0	1	0
	c.2544G>A	Trp848*	5	2	0	2	0
	c.337-2A>T	p.?	5	1	1	0	1
	c.397C>T	p.Gln133*	5	3	1	2	1
	c.968_971delAGGC	p.Gln323fs	5	3	1	2	2
	deletion exon 1-14	p.?	5	1	0	1	0
	deletion exon 1-4	p.?	5	3	0	3	1
	deletion exon 10	p.?	4	1	0	1	1
	deletion exon 8-14	p.?	5	1	1	0	1
Total (n)				67	20	47	36

The adjudication of genetic variants was done by consensus of a team of specialists in cardiac genetics from both our institutions according to the American College of Medical Genetics and Genomics guidelines¹, as previously described.² Variants classified as pathogenic (class 5) or likely pathogenic (class 4) were considered as disease causing mutations in the clinical evaluation.

Abbreviations: *DSC2* = desmocollin-2, *DSG2* = desmoglein-2, *DSP* = desmoplakin, *PKP2* = plakophilin-2.

¹Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL and Committee ALQA. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in medicine: official journal of the American College of Medical Genetics. 2015;17:405-24.

²van Lint FHM, Murray B, Tichnell C, Zwart R, Amat N, Lekan Deprez RH, Dittmann S, Stallmeyer B, Calkins H, van der Smagt JJ, van den Wijngaard A, Dooijes D, van der Zwaag PA, Schulze-Bahr E, Judge DP, Jongbloed JDH, van Tintelen JP and James CA. Arrhythmogenic Right Ventricular Cardiomyopathy-Associated Desmosomal Variants Are Rarely De Novo. Circ Genom Precis Med. 2019;12:e002467.

Supplementary Table 5. Performance of the expert panel

UMC Utrecht	Expert 1	Expert 2	Expert 3	Johns Hopkins	Expert 1	Expert 2	Expert 3
Expert 1	0.89	0.81	0.83	Expert 1	0.90	0.87	0.89
Expert 2	0.81	0.94	0.83	Expert 2	0.87	0.91	0.92
Expert 3	0.83	0.83	0.85	Expert 3	0.89	0.92	0.94

Values are weighted Cohen's K

Supplementary table 6A – Overview of false positive cases

Patient	Clinical Task Force Criteria	Expert review
FP1 Female 55 yrs.	Total score = 5 <ul style="list-style-type: none">- TAD ≥55ms- CMR major criterion- RV angiography major criterion- Sustained VT LBBB sup. axis- Sustained VT RBBB	Panel diagnosis: myocarditis <i>Although CMR and RV angiography technically fulfill major TFC for ARVC, blinded expert review of the CMR images show a biventricular dilated cardiomyopathy caused by non-specific myocarditis. Biopsy was negative for ARVC or sarcoidosis. Patient died after 6.26 years of follow-up, autopsy showed non-specific inflammation and fibrosis.</i>
FP2 Male 57 yrs.	Total score = 4 <ul style="list-style-type: none">- TAD ≥55ms- SAECEG LP+- Holter >500 PVC- CMR major	Panel diagnosis: idiopathic PVCs <i>Asymptomatic, negative family history, PVCs seen during arthroscopy. PVCs originating from RV apex. Not inducible during EPS. Blinded expert review of the CMR showed that the RV dyskinesia was caused by tethering (normal variant). During limited follow-up (0.18 years) no additional signs of ARVC.</i>
FP3 Male 69 yrs.	Total score = 4 <ul style="list-style-type: none">- SAECEG LP+- Holter >500 PVCs- Echo minor- CMR major	Panel diagnosis: idiopathic PVCs <i>Idiopathic PVCs in combination with RV enlargement. Blinded expert review of CMR images showed no wall motion abnormalities therefore refuting ARVC. During 7.79 years of follow-up no additional signs of ARVC.</i>
FP4 Female 29 yrs.	Total score = 4 <ul style="list-style-type: none">- SAECEG LP+- Holter >500 PVCs- ARVC in first degree relative	Panel diagnosis: idiopathic PVCs <i>Idiopathic PVCs. Father diagnosed with ARVC, however, patient was proven negative for the family mutation. During 0.86 years of follow-up stable, no additional signs of ARVC.</i>
FP5 Female 50 yrs.	Total score = 4 <ul style="list-style-type: none">- SAECEG LP+- Holter >500 PVCs- CMR major criterion	Panel diagnosis: idiopathic PVCs <i>Second opinion for ARVC diagnosis. Frequent PVCs and CMR major criterion overruled by blinded expert review of the images as there were no regional wall motion abnormalities. No follow-up available.</i>
FP6 Female 45 yrs.	Total score = 4 <ul style="list-style-type: none">- TWI V3 and V4- Holter >500 PVC- PLN mutation (not in TFC)- ARVC in first degree relative	Panel diagnosis: at risk of ARVC <i>PLN mutation carrier with systemic scleroderma and pulmonary hypertension (PAP 27 mmHg). Mother was diagnosed with ARVC. At presentation besides PVC count and limited T wave inversion on ECG (V3 and V4) no signs of ARVC. During 6.52 years of follow-up no arrhythmias or structural disease, on sequential echocardiography studies no signs of pulmonary hypertension. As the extend of precordial T-wave inversions increased during follow-up the patient was treated as ARVC and received an ICD for primary prevention.</i>
FP7 Male 22 yrs.	Total score = 4 <ul style="list-style-type: none">- CMR major criterion- SCD in first degree relative age 19, ARVC on autopsy	Panel diagnosis: at risk of ARVC <i>Brother had SCD at age 19, ARVC diagnosis on autopsy. Patient is asymptomatic and mutation negative. No signs of ARVC on ECG, no PVC or arrhythmias. Blinded expert review of CMR was inconclusive due to artifacts. During 3.49 years of follow-up no signs of ARVC.</i>
FP8 Male 24 yrs.	Total score = 4 <ul style="list-style-type: none">- TWI V1-V2- SAECEG LP+- PKP2 mutation- ARVC in first degree relative	Panel diagnosis: at risk of ARVC <i>Family history of ARVC, PKP2 mutation carrier, asymptomatic. TWI V1-2. SAECEG LP + but no TAD on ECG and no sign of LP or scarring on EPS. No arrhythmias inducible. Holter and exercise test were unremarkable. During 5.53 years of follow-up patient remained asymptomatic and had no additional signs of ARVC.</i>

FP9 Female 46 yrs.	Total score = 4 <ul style="list-style-type: none">- SAEKG LP+- Holter >500 PVC- ARVC on autopsy in first degree relative	Panel diagnosis: at risk of ARVC <i>First degree relative with SCD at age 40, diagnosed as ARVC on autopsy. Patient showed >500 PVCs per 24h, SAEKG LP+ but ECG was unremarkable. No other ARVC features. Genetic testing not performed.</i> <i>During 8.03 years of follow-up no additional signs of ARVC.</i>
FP10 Male 35 yrs.	Total score = 4 <ul style="list-style-type: none">- TAD ≥55ms- Holter >500 PVCs- CMR major criterion	Panel diagnosis: other <i>Referred for evaluation because of symptomatic PVCs and family history of SCD. Although technically fulfilling TFC criteria, patient was known with dextrocardia, situs inversus and VSD repair at age 2. SCD at age 50 in father with known with 3-vessel disease was during exercise.</i>

Supplementary table 6B – Overview of false negative cases

Patient	Clinical Task Force Criteria	Expert review
FN1 Female 29 yrs.	Total score = 3 <ul style="list-style-type: none">- Holter >500 PVCs- PKP2 mutation- ARVC in first degree relative- SCD in Father and uncle	Panel diagnosis: ARVC <i>Expert review of CMR showed dilated RV, but no regional wall motion abnormalities therefore no major criterion. At time of evaluation T-wave inversion in V1, III and AVF, but one year later additionally in V2.</i> <i>During 9.25 years of follow-up there was progression of disease, 1.5 years after evaluation regional RV dyskinesia was seen on RV angiography and a tissue biopsy showed fibrofatty replacement consistent with ARVC. Primary prevention ICD was placed.</i>
FN2 Male 52 yrs.	Total score = 1 <ul style="list-style-type: none">- Holter >500 PVCs	Panel diagnosis: ARVC <i>Referred because of symptomatic PVCs from RV. No VT observed but cardiac syncope with loss of consciousness 6 months prior to evaluation. Although no criterion fulfilled on initial CMR report, blinded expert review of CMR fulfilled a major criterion with RV dilatation and regional dyskinesia.</i> <i>No follow-up available.</i>
FN3 Female 49 yrs.	Total score = 3 <ul style="list-style-type: none">- CMR minor criterion- ARVC in first degree relative- PLN mutation (not in TFC)	Panel diagnosis: ARVC <i>Non-sustained VT (182 bpm) on Holter, no criterion fulfilled as morphology could not be objectified. Small aneurysm in RV on echocardiography. Regional dyskinesia and fatty infiltration RV with reduced ejection fraction suggestive of ARVC on blinded expert review of CMR (minor criterion). Low-voltage areas RV basal to mid-anterior inferior on EPS. Tissue biopsy fatty infiltration but inconclusive.</i> <i>During 5.44 years of follow-up, no sustained VT. Primary prevention ICD was placed 1 year after evaluation.</i>
FN4 Female 27 yrs.	Total score = 3 <ul style="list-style-type: none">- TWI V1-3- TAD ≥55ms- SAEKG LP +	Panel diagnosis: ARVC <i>Patient experienced SCA during exercise and received an ICD. Blinded expert CMR review was inconclusive due to ICD artifacts, but on ECG TWI V1-3 and TAD. RV angiography showed mild regional hypokinesia in RV not fulfilling criterion. Coronary angiogram was unremarkable.</i> <i>Patient was lost to follow-up.</i>
FN5 Female 61 yrs.	Total score = 2 <ul style="list-style-type: none">- TAD ≥55ms- SAEKG LP+- Holter >500 PVCs- VT from RVOT	Panel diagnosis: ARVC <i>Patient experienced several syncopal episodes prior to evaluation and a remote family history of ARVC (eight cousins, 3rd degree relatives). Echocardiography showed dilated RV with mild global dysfunction. Blinded expert review of CMR showed microaneurysms and fat infiltration in RV wall suggestive of ARVC but not fulfilling criterion.</i> <i>Patient was lost to follow-up.</i>
FN6 Female 30 yrs.	Total score = 3 <ul style="list-style-type: none">- TWI V1-3- Holter >500 PVCs- VT LBBB inferior axis	Panel diagnosis: ARVC <i>Strictly fulfilling only a major ECG and minor arrhythmia criterion. No imaging criteria as blinded expert review of CMR was inconclusive due to artifacts. RV angiogram showed regional RV hypokinesia not fulfilling a criterion. During EPS sustained VT with LBBB inferior axis morphology was inducible, and showed evidence of LP and scarring in RV suggestive of</i>

		<p>ARVC. Tissue biopsy inconclusive and gene panel was negative.</p> <p>Patient received an ICD for secondary prevention, during 8.33 years of follow-up she had several recurrences of appropriately ICD treated VT justifying amiodarone and 4 VT ablations. She did not have any recurrences after epicardial ablation.</p>
FN7 Female 48 yrs.	Total score = 3 <ul style="list-style-type: none"> - TWI V4 and 5 - TAD ≥55ms - Holter >500 PVCs 	<p>Panel diagnosis: ARVC</p> <p>Echocardiography showed mild RV dilatation, severe RV dysfunction, but no regional WMA. Blinded expert review of CMR showed RVEF of 35%, no regional wall motion abnormalities but late gadolinium enhancement suggestive of ARVC. During EPS only VF was induced. Gene panel was negative.</p> <p>Patient received an ICD shortly after evaluation. During 1.0 year of follow-up two episodes of non-sustained VT on ICD monitoring.</p>

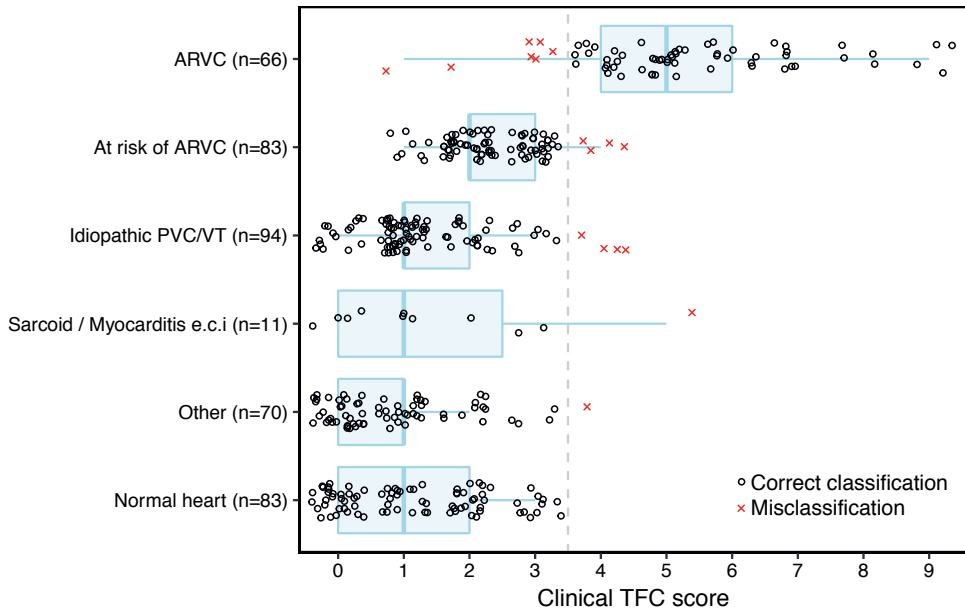
Supplementary Table 7 Probability of ARVC depending on the fulfilled criteria

Example patients, all with a TFC score of 4									
Patient 1 (TFC = 4)		Patient 2 (TFC = 4)				Patient 3 (TFC = 4)			
-	Major imaging criterion	-	-	-	TWI V1-2 (minor)	-	-	-	TWI V1-3 (major)
-	TAD≥55ms (minor)	-	-	-	>500 PVCs on 24h Holter (minor)	-	-	-	VT LBBB superior axis (major)
-	>500 PVCs on 24h Holter (minor)	-	-	-	Pathogenic PKP2 variant (major)	-	-	-	
Step 1: Calculate Ln(odds) for ARVC									
Patient:	Intercept	+	Structural x1.54	+	Repolarization x2.67	+	Depolarization x1.23	+	Arrhythmia x2.50 + Family history x1.73 = Ln(odds)
1:	-8.21	+	2 x1.54	+	0 x2.67	+	1 x1.23	+	1 x2.50 + 0 x1.73 = -1.40
2:	-8.21	+	0 x1.54	+	1 x2.67	+	0 x1.23	+	1 x2.50 + 2 x1.73 = 0.44
3:	-8.21	+	0 x1.54	+	2 x2.67	+	0 x1.23	+	2 x2.50 + 0 x1.73 = 2.14
Step 2: Transform Ln(odds) to predicted probability for ARVC									
Patient:	Exp(Ln(Odds)) / (1+Exp(Ln(Odds)))				=				Predicted probability
1:	Exp(-1.40) / (1+Exp(-1.40))				=				20%
2:	Exp(0.44) / (1+Exp(0.44))				=				61%
3:	Exp(2.14) / (1+Exp(2.14))				=				89%

Results from multivariable logistic regression model, with major criteria scored as 2 and minor as 1 point. Intercept -8.21 (S.E. 1.23), C-statistic 0.97, Brier 0.039, internal validation using 1000 bootstrap samples showed a calibration slope of 0.92. Abbreviations as per Table 2.

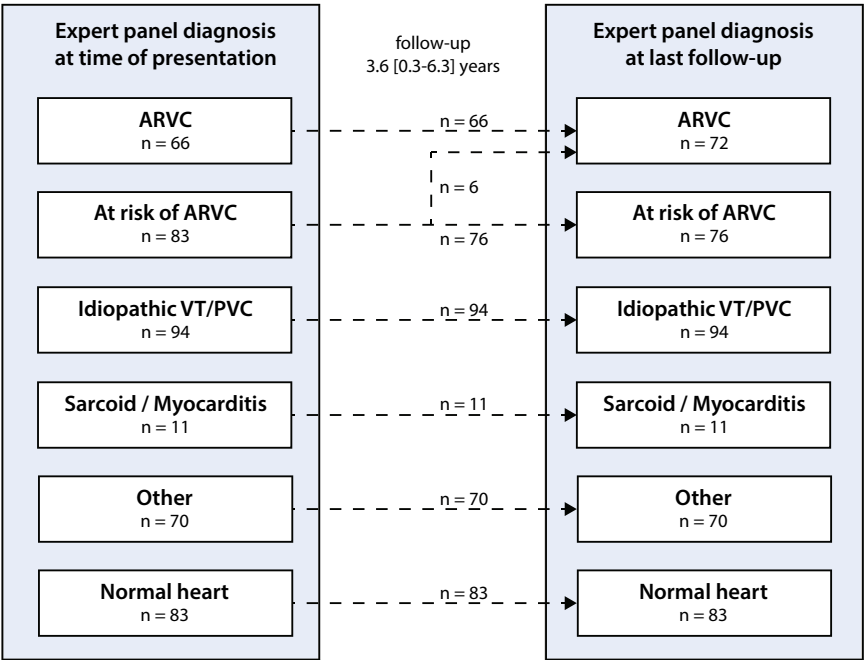
Supplementary Figure 1. Alternative diagnosis and misdiagnosis by 2010 TFC

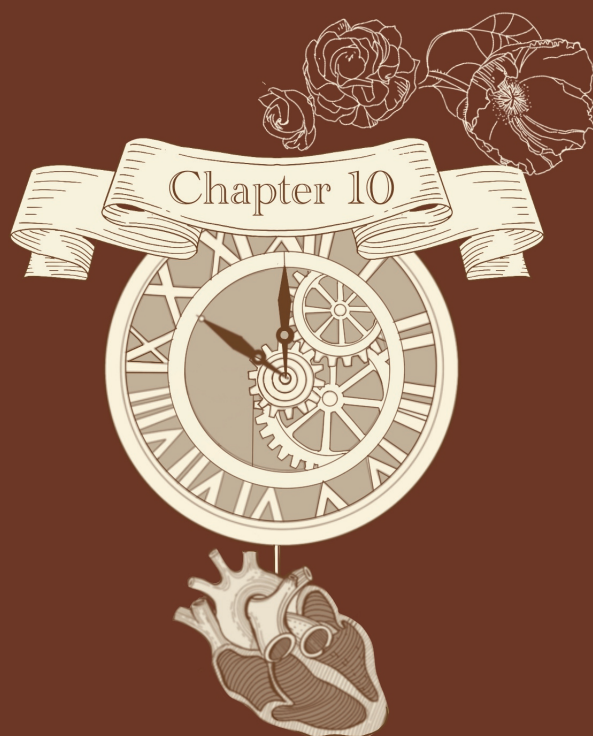
Box plot with jitter plot overlay. Subjects are grouped by their diagnosis. Observed clinical TFC scores are plotted on the X-axis. Dotted line represents cut-off value of the clinical TFC score for classification of ARVC. Subjects depicted by red crosses are misclassified by the TFC.



Supplementary Figure 2. Expert panel diagnosis after review follow-up information

After all cases were diagnosed by the expert panel (left box), all available follow-up information was reviewed for each case to determine the diagnosis at last follow-up to validate the initial diagnosis (right box).





Chapter 10

Summary and Future Perspectives

The aims of this thesis were to evaluate the current state-of-the-art diagnosing and prognosing methods for patients with Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), study evidence-based methods for improvement, and to design a sustainable hypothesis-free collaborative registry database to facilitate these and future studies. Here, I summarize and discuss the main findings reported in this thesis, and suggest potential new research directions.

Registry Based Research

The primary aim of this thesis was to improve ventricular arrhythmia risk prediction for patients with ARVC on a more individual level, to prevent sudden cardiac death (SCD) by accurate and timely implantable cardioverter-defibrillator (ICD) placement. To accomplish this, we needed to develop a large longitudinal dataset of ARVC patients, describing their disease course over time. Arguably the most optimal data would be obtained through a long-term prospective trial, in which treatments and interventions that may change the natural course of events are eliminated or randomized. However, this is not feasible for various reasons, primarily because it would be unethical to deprive patients from the option to receive an ICD when they may risk SCD. In addition, such a study would take decades to complete: not only is there often a long time-interval between first presentation and arrhythmic event, the inclusion rate would be relatively slow as well given the estimated prevalence of 1:2000-5000.¹ We therefore aimed to find answers from observational data, starting with a systematic evaluation of the literature, and a redesign of our national Arrhythmogenic Cardiomyopathy (ACM) Registry database to accommodate the longitudinal design of prognostic research.

Lessons from earlier studies

First, we conducted a systematic review and meta-analysis on ventricular arrhythmia risk prediction (**Chapter 3**). Our search yielded numerous data from 45 studies reporting on a myriad of risk factors predicting arrhythmic events. After systematic aggregation and meta-analysis, we selected risk factors with strong relevance for clinical practice. However, there were also significant limitations obstructing the path to clinical translation.

One common limitation was insufficient statistical power in studies with a small cohort size, increasing the likelihood of spurious findings.² In fact, the 45 studies included in the systematic review had a median cohort size of only 70 ARVC patients. This was to be expected, since ARVC is less common than for example ischemic heart disease. As a result, assembling a cohort with sufficient statistical power is a challenge. Despite this shortcoming, many results were published, possibly due to an urgent need to find answers of relevance for

patient care. To provide at least a partial solution for this limitation, we performed a random-effects meta-analysis, as to filter out potential false significant and false non-significant findings.

Our meta-analysis highlighted another important limitation, namely highly variable definitions of study populations, risk factors, and outcomes in these studies. In our view, these differences could have been prevented by more international collaborations among research groups. The more so, as even small differences in risk factor or outcome definitions can result in large changes in the effect estimate. This is not just a limitation for proper meta-analysis. It also hampers comparison of study results important for clinical translation.

Yet another limitation was a missing step in the analysis required for translation. Most studies only expressed effect estimates of risk factors as relative risks, predominantly odds ratios or hazard ratios. While hazard ratios are useful to study and compare different risk factors within a study, relative effect sizes provide little information for patients in clinical practice without knowing their absolute risk. In theory, even a high hazard ratio may not result in a clinically relevant risk increase if the baseline risk is low. Thus, these relative values first need to be converted into absolute risks to obtain a meaningful translation to clinical practice. Furthermore, effect estimates of single risk factors are likely not enough, as patients frequently present with a combination of risk factors. Certain risk factors may interact in combination with others, resulting in different effects on the arrhythmic event risk. Fortunately, there are established statistical methods to account for the effect of multiple risk factors and translating this into absolute risk estimates³, as discussed below.

Designing the New Netherlands ACM Registry

With the strengths and weaknesses of prior studies in mind, we decided to redesign the Netherlands ACM Registry into a modern state-of-the-art, high quality, longitudinal, hypothesis-free, and collaborative database (**Chapter 4**). The ACM registry, initiated by Dr. Hauer in 2000, already served as a valuable source of data to many research studies. Also, Dr. Hauer and colleagues realized the importance of international collaboration. They collaborated for years with the Johns Hopkins ARVD/C Registry team (Baltimore, Maryland, USA), led by Dr. Calkins and Dr. James. By synchronizing their protocols and definitions that enabled the merging these two cohorts, statistical power was greatly increased.⁴

At the start of this PhD research, however, the design of the registry's database had had become outdated. The data was limited to the first presentation and last clinical follow-up, thereby limiting the possibilities for study designs. Furthermore, data was stored offline at

a single secure location, complicating multicenter collaboration. Another key concern was that much of the collected data was dependent on prevailing definitions at the time. Consequently, changes in these definitions would require a tremendous amount of work to recollect outdated data, as evidenced by the many changes in the diagnostic criteria in 2010.⁵⁻⁸

Our new database designed with REDCap⁹ is now fully longitudinal, as it stores data from all follow-up time points. In addition, we avoided the need for manual data collection based on the complex ARVC definitions and criteria. To this end, we developed a large set of algorithms that automatically generated the TFC data real-time. Besides reducing workload, it reduces human errors, while future changes in definitions may be resolved by simply changing the algorithms. We also strengthened national collaborations by providing secure remote online access to all participating centers. To improve international collaborations, we freely share the template file of our database design and data definitions to colleagues who want to initiate or upgrade their own ARVC registry database. After years of synchronizing definitions and protocols with our colleagues at Johns Hopkins, the same REDCap database is now run at Johns Hopkins. For others, the benefits of using our template are not only the time saved for designing such a large database, but also the effortless merging of their cohort with two of the largest ARVC registries worldwide to increase statistical power.

The new longitudinal database of the redesigned ACM Registry (in which data is collected free from hypotheses), allows many types of longitudinal or cross-sectional study designs to answer many different research questions. As a source for future national and international studies, the impact of this work will hopefully extend well beyond this thesis. Nonetheless, we may keep running into design flaws and limitations, so we have to continue our efforts to improve the registry. Although algorithms replace much of the manual work, total amount of time to maintain the new database actually increased due to the extension of the collected variables and to the follow-up timepoints at which the variables are collected. We should continue to explore possibilities to replace manual labor with automated processes, such as automatic data extraction from and reconfiguration of electronic patient records systems in hospitals and linkage to external data sources such as GP records, national pharmacy records, and outcome data. Moreover, we envision in the near future an online platform that enables to link health record data with patient-centered data obtained through wearables and online questionnaires to provide deep phenotype data and non-medical outcomes.

Risk Prediction Modelling

As briefly introduced above, a first aim of this thesis was to improve personal ventricular arrhythmia risk prediction for patients with ARVC. The only proven life-saving treatment is the placement of an ICD, which is an invasive treatment with inherent risks of complications and may cause lifelong physical and psychological burden.¹⁰ Therefore, ICD placement should only be indicated when the risk of SCD outweighs the risk of ICD-related harm. Unfortunately, estimating the risk of SCD is challenging as this varies strongly between individuals. The average mortality reported in studies range from 0.1% to 3.6% per year.^{11,12} While previous studies have identified several risk factors associated with a significant relative increase risk, as described in **Chapter 3**, these results contribute little to the clinical problem. To aid clinicians with estimating the risk of SCD for individuals, these relative risk effect estimates require translation to absolute risks in patients. In addition, patients frequently express multiple risk factors. Therefore, one also needs to determine how combinations of risk factors affect absolute risk.

Multivariable time-to-event prediction models, such as the Cox Proportional Hazard model, can estimate the overall relative effect of multiple risk factors. These can then be translated into absolute risk estimates at different follow-up time points. The limitation is that easy utilization requires access to a computer or smart device in clinical practice, but this is nowadays rarely a problem (**Figure 1**). While this method is well established and accepted, no prior attempts were published, perhaps due to the relatively large cohort size required to fit such a model with sufficient statistical power. Thus, the studies in **Chapter 5** and **Chapter 7** describe the development of the first multivariable risk prediction models for ARVC patients. As the required cohort size is determined by the number of risk factor variables tested, we used the results from **Chapter 3** to preselect a maximum of eight risk factors. To ensure sufficient statistical power, we collaborated with 15 academic medical centers from six countries in North America and Europe to assemble the largest cohort of ARVC patients to date.

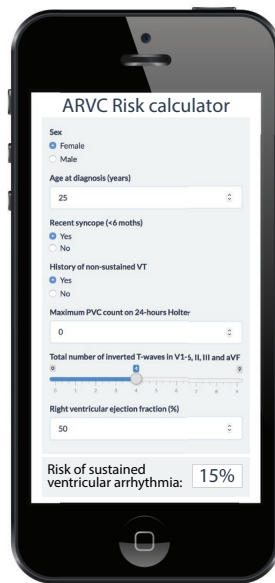


Figure 1.

Mock-up of an app for easy online or offline utilization of a multivariable risk prediction model. Compared to flow-chart diagrams or nomograms, multivariable prediction algorithms are more sophisticated but not as easy to visualize or memorize. However, this is a limitation of the past as in modern medicine most clinicians have access to computers, smart phones or tablets.

Predicting the First Sustained Ventricular Arrhythmia

In our first prediction model, described in **Chapter 5**, we focused on patients without a prior sustained ventricular arrhythmia, i.e. “primary prevention”. We considered a prediction model to be most urgent for the primary prevention population, as most patients generally already receive an ICD after experiencing a sustained ventricular arrhythmia. In a cohort of 528 primary prevention ARVC patients, we successfully fitted a model predicting the risk of a first sustained ventricular arrhythmia with a C-index of 0.77, based on seven risk factors (sex, age, syncope, non-sustained VT, 24h PVC count, number of ECG leads with T-wave inversion, and RVEF), as shown in the summarizing **Figure 2**.

Even though we had sufficient statistical power, our methods carefully followed the TRIPOD-guidelines^{3,13} and tested for potential overfitting, the performance of our model should be confirmed in external cohorts before its use in clinical practice can be recommended. As of today, five independent external validation studies have been published. One of these reported a reassuring C-index of 0.84 using the model in a European cohort of

128 ARVC patients.¹⁴ In another study the authors tested the model in 25 athletes with ARVC.¹⁵ As exercise is shown to increase arrhythmic risk it was hypothesized that the model would underestimate the risk in athletes. Surprisingly, the authors found predictions to correspond well with the observed risks, although the study size is too small to draw definite conclusions. In the remaining three studies, the authors tested the model in a mixed ARVC cohort including classical and non-classical phenotypes (i.e. left-ventricular or biventricular), as well as both patients with and without a prior sustained ventricular arrhythmia.^{16–18} While reporting favorable results that predictions are accurate in classical ARVC patients, and that the model outperforms the ICD placement guidelines, these results should be interpreted with great caution. Even the stratified analyses with only classic ARVC patients is at high risk of bias due to the inclusion of secondary prevention patients, without correcting for their known higher risk. Thus, despite these five studies, future external validation studies with sufficient statistical power are still required to confirm the performance of the prediction model.

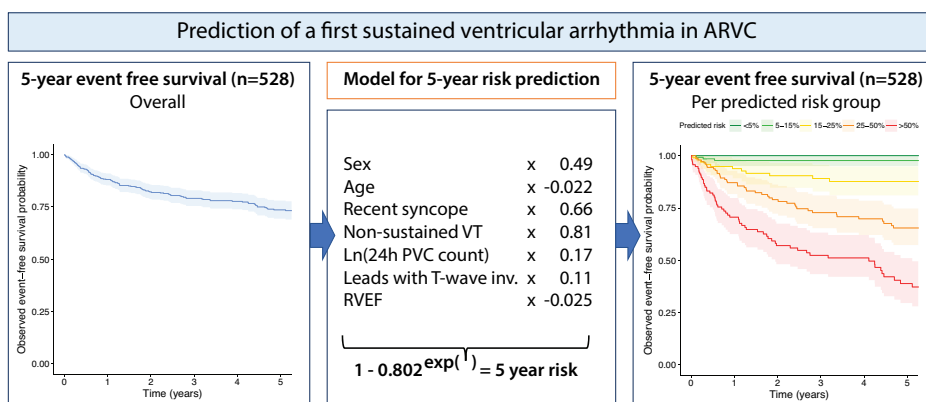


Figure 2.

First sustained VA risk prediction model performance visualized by Kaplan-Meier curves. The left panel shows the overall event free survival of the overall cohort, the right panel the survival stratified by five risk groups based on the individual risks predicted by the model (Dark green <5%, light green 5-15%, yellow 15-25%, orange 25-50%, and red >50%).

Can Exercise Throw a Spanner in the Works of the Prediction Model?

Accumulating evidence suggests that exercise, specifically rigorous and competitive, may increase the risk of ventricular arrhythmias in ARVC.^{19–27} Therefore, the absence of exercise in our prediction model raised valid concerns about the accuracy of predictions in athletic patients.²⁸ Although the above mentioned study in 25 athletes with ARVC found the predictions from the model to be accurate, more evidence was required to confirm the results.¹⁵ We

conducted a study to evaluate the influence of exercise by interviewing patients in our cohort on their exercise habits. As described in **Chapter 6**, the level at which patients participated at diagnosis was indeed positively correlated with their risk of ventricular arrhythmia during follow-up. However, similar correlations were found between exercise and the expression of risk factors in the current model. This resulted in higher risk predictions in patients that exercised more, which corresponded well with the higher observed risk in these patients. Concordantly, adding exercise to the model did not significantly improve its performance. Although reassuring, more research is required to further explore the mechanism of exercise on the risk of arrhythmia, and the potential risk modifying effects of exercise reduction after diagnosis.

The Issue with “Life-Threatening” Events as Surrogate for Death

Publication of the risk prediction model (**Chapter 5**) provoked a not unexpected discussion about the arrhythmic outcome used in this study. As ultimately the aim is to predict the risk of SCD to justify ICD placement, SCD should ideally be used as the outcome. However, reliable observation of SCD occurrence is only possible in a study which prohibits ICD placement in all patients for the entire follow-up duration, which is unethical. The most widely used surrogate outcome is a composite of any type of sustained ventricular arrhythmia, including ventricular arrhythmias terminated by ICD intervention. This same outcome was used for the prediction model to allow comparability with most prior studies. The downside of this outcome is the inevitable inclusion of non-lethal arrhythmias, resulting in an unknown amount of overestimation of the SCD-risk. This may in turn lead to ICD overtreatment and unnecessary risk of complications, inappropriate shocks and physical and emotional burden.

An alternative option, used in some prior ARVC studies, is to restrict the outcome to fast sustained VT >250bpm, VF, SCD, or ICD interventions terminating one of these fast arrhythmias. This outcome is more in line with the widespread programming of ICDs after the MADIT-RIT trial, showing that more lenient therapy programming not only resulted in less inappropriate shocks but a reduction in mortality as well.²⁹ Also, these fast events are considered to be more life-threatening, therefore a closer approximation of SCD occurrence. Another reason for the interest in studying this alternative outcome, is the hypothesis that these fast events in ARVC patients are caused by a different mechanism. One mechanism of arrhythmogenesis may be explained by scar-mediated re-entrance which results mostly likely in (stable) monomorphic VT. While fast and unstable VT are considered to be caused by a complex mechanism of abnormal impulse conduction caused by gap junction protein and ion-channel dysfunction following disruption of desmosome integrity.^{30,31} If so, risk factors for

these two types of arrhythmia are likely to differ as well. For these two reasons, we planned a follow-up prognostic modelling study using both arrhythmic outcomes (**Chapter 7**).

Predicting Fast Ventricular Arrhythmias

As the fast VA outcome occurs less frequently, the cohort of 528 primary prevention ARVC patients used in the first risk prediction model study needed to be extended to 864 patients to ensure sufficient statistical power (**Chapter 7**). Secondary prevention patients were included as well, to allow analysis of the relation between the different arrhythmia types. The first interesting finding in this study, was that the risk of fast VA was independent of prior sustained events. Fast VA revealed to occur equally in those without a prior event, those with a prior stable sustained VT, and those with a prior fast unstable VA. This is in contrast with the results for any sustained VA, frequently shown to be a strong predictor for recurring events and again confirmed in this study. While not to be considered as evidence, this observed more stochastic appearing nature of fast unstable VA does fit the popular hypothesis that these events are caused by a distinct arrhythmogenic mechanism as described above.

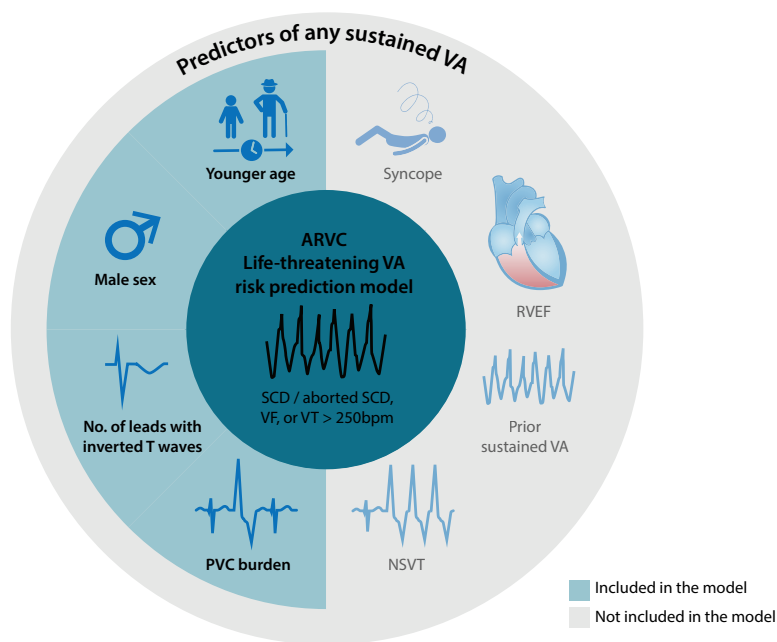


Figure 3.

Of the our selected eight well known predictors for sustained VA (grey circle), only younger age, male sex, T-wave inversions, and PVC burden were independent predictors for fast (>250bpm) VA (i.e. life-threatening VA). These four predictors were included in the fast VA prediction model.

Fitting the same eight risk predictors into a multivariable prediction model for fast VA, resulted in a model with only four variables: male sex, age at diagnosis, 24h PVC count, and number of leads with inverted T-waves (**Figure 3**). Simpler than the primary prevention model, yet showing similar performance (C-statistic 0.75). Prior events and ventricular dysfunction variables did not stay in the model, which is also in line with the different mechanism hypothesis for fast VA. However, confirming this theory requires additional evidence from future etiologic studies.

Alternative Solutions for Risk Stratification

While two models in **Chapter 5** and **Chapter 7** are the first published multivariable risk prediction models for ARVC patients, they are not the first solution for risk stratification. Other available options have been provided over the years by three guideline and expert consensus documents, discussed in **Chapter 8**.^{32–34} The authors combined the evidence of risk factors with expert opinion to determine which risk factors indicate an increased risk, divided into two to four risk categories. Their results are presented as easy-to-use flow-chart algorithms, starting with the risk factors that would classify a patient in the highest risk category, moving on a lower category if none of these risk factors are present.

Using expert opinion to design such rules, scores, or flow-chart algorithms can result in useful tools for clinical practice, of which the most famous example is arguably the Apgar-score designed by Dr. Virginia Apgar in 1952. The Apgar-score proved to be an accurate rapid method to assess the clinical status of newborn infants and is still in use.^{35,36} However, unlike Dr. Apgar who tested her score in a clinical population prior to publication, the authors of these flow-chart algorithms unfortunately did not test their designs in an ARVC population. By ignoring this important step, they failed to provide the clinical performance estimations that are crucial to confirm their safety for clinical use, but they also did not state which of these options should be recommended to use. Therefore, the aim of the study in **Chapter 8** was to evaluate and compare the clinical performance of these flow-chart algorithms.

The same two arrhythmia outcome definitions were used as in **Chapter 7**, to allow evaluation and comparison of the performance for both any sustained VA as well as fast VA. The overall performance found by measured by ROC-AUC for both any sustained VA (0.61-0.72) and fast VA (0.57-0.61) may seem disappointing. However, in all algorithms the misclassifications responsible for lowering the AUC were predominantly “false positives” (i.e. those with an ICD indication but experiencing no event). This is a rather positive finding, as avoiding “false negatives” (i.e. failing to indicate an ICD in those experiencing an event) is generally considered much more important than false positives. Therefore, a decision curve

analysis was performed based on the net benefit, a clinical performance measure that adjusts for the different values of these classifications. With this adjustment, the decision curve analysis more closely reflects how these flow-chart algorithms perform relative to each other in real-life clinical practice.

This study provided much needed insight into the clinical performance of these algorithms, which is essential for informed ICD decision making. However, the results also showed that the accuracy of these algorithms is limited due to the many false positives. This indicates the need for improvements, which are potentially already available: the two multivariable risk prediction models. Although according to our own study these models have superior performance (see supplementary analysis in **Chapter 8**), the cohort of this study greatly overlaps with the cohort for which these models were developed. If they indeed are superior to the flow-chart algorithms, this needs to be confirmed by external validation studies.

On the Road to Improve ARVC Diagnosis

Due to the incomplete genetic penetrance and variable disease expression, ARVC can be complex to diagnose. No single clinical test or characteristic provides sufficient sensitivity and specificity to confirm diagnosis. Therefore, the diagnosis of ARVC is determined by a combination of tests and characteristics, as defined by the Task Force Criteria (TFC) first published in 1994, later modified in 2010. As SCD can occur at a young age at an early disease stage, early and accurate diagnosis is an essential part of SCD prevention. Research continuous to focus on finding new tools and criteria that may improve early detection of disease. However, in order to improve the 2010 TFC, we need diagnostic performance data of all the individual tests and criteria, the incremental value of combinations, and the performance of the TFC as a whole to evaluate its strengths and weaknesses. Yet, at the start of this thesis work, the available evidence was limited to studies estimating the diagnostic performance of individual tests and criteria only. Moreover, most of these studies used “cherry-picked” cases and control subjects instead of a consecutive diagnostic cohort, which may lead to overestimation of the real-life performance. The overall performance of the TFC framework as a whole remained unknown, as this framework was assembled by expert opinion.

Validation of the clinical performance of the 2010 TFC

In **Chapter 9** we validate the diagnostic performance of 2010 TFC, the individual criteria as well as the framework as a whole, in a real-world consecutive diagnostic cohort. As there is no golden-standard test for ARVC, we used an expert panel consensus diagnosis as a reference. The 2010 diagnostic framework as a whole showed to be highly sensitive (92%) as

well as specific (92%). As the first ever estimation of the performance of the 2010 TFC as a whole, this is a reassuring finding.

Our results of the performance of the individual criteria reveal that several criteria fail to detect ARVC. We show that removing these criteria would not affect the overall sensitivity of the TFC (92%), while increasing the sensitivity to 97%. This indicates an interesting opportunity to reduce the complexity of the TFC without reducing its diagnostic performance. Another interesting finding is that the ECG and arrhythmia criteria combined had a sensitivity of 100%, this indicates that the ECG and arrhythmia criteria alone may serve as a screening tool for ARVC at the regular clinical evaluations of non-affected at-risk relatives.

Our results provide many opportunities for improvement as they suggest relatively small and easy adjustments. The greatest improvement in performance may result from new or altered criteria. While we did not add or alter criteria, future studies may profit by doing so. For example, one weakness of our study concerns the low sensitivity of echocardiography criteria (21-29%). This be caused by the fact that echocardiography criteria depend on subjective visual assessment of wall motion abnormalities. Earlier studies indicate that objective quantitative measurement of wall motion using tissue deformation imaging (i.e. “strain”) show superior sensitivity.^{37–39} Hence, validating the effect of replacing visual assessment by strain on the sensitivity in a consecutive diagnostic cohort could be a promising subject of research.

Concluding Remarks and Future Perspectives

In the past decade, research brought major advancements in diagnosis and prognosis. Yet, researchers continue their quest to find further improvements as timely diagnosis and accurate risk assessment are crucial for SCD prevention and clinical management of ARVC. At the beginning of this decade new diagnostic TFC were published to improve sensitivity for the now growing population of at-risk relatives found through genetic cascade family screening. Over the following years, several risk stratification guidelines for ICD implantation were published, that were previously lacking. While major steps forward, they were based on evidence from studies that were frequently underpowered, using expert opinion for clinical translation, and lacked clinical validation data to estimate their real-world performance. The studies described in this thesis aimed to advance the field of diagnosis and prognosis by: 1) providing the first real-world performance evidence of the 2010 TFC and all the expert-opinion risk stratification methods; 2) supplanting expert opinion by two evidence-based personalized arrhythmia risk prediction models; and 3) facilitate these and future larger cohort studies with

more statistical power by designing a sustainable collaborative state-of-the-art registry database.

Even though these advancements are evidence-based, they should only be recognized as advancements after confirmation by future validation studies. Furthermore, these studies were designed as a first-step forward to more objective evidence-based methods, applied conservatively to conventional clinical variables and definitions from prior studies. Thus, future studies should focus on other known or unknown variables that may detect disease at earlier stages and/or increase the precision of personalized risk prediction. There are promising new methods available that may lead to the discovery of new important variables, for example by applying machine learning on ECGs and cardiac imaging files. Wearables such as Fitbits and Apple Watches are becoming increasingly accurate with the potential to provide reliable continuous monitoring data for future studies. Furthermore, large genome-wide association studies (GWAS) might provide answers to the mostly still unexplainable variation in penetrance and phenotype among patients.

Another important focus for future studies is to study disease progression and outcomes in pathogenic mutation carriers, to optimize screening protocols and prevent SCD. However, this is a relatively young and seemingly healthy population in which outcomes are less common than in patients with ARVC, hence requiring large cohorts to provide sufficient statistical power. Of note, the fast VA prediction model study in this thesis assembled the largest cohort of ARVC patients to date (n=864) collaborating with only 15 medical centers from 6 countries in North-America and Europe. Therefore, it is plausible that even larger cohorts can be assembled if we focus on further increasing international collaborations.

Now that we introduced the first multivariable prediction models in the field of ARVC, we will likely see rapid developments improving personalized risk prediction, family screening, and diagnosis by adjusted or new prediction models in the next decade. Furthermore, new and improved diagnostic criteria are expected soon, including diagnostic definitions that differentiate between phenotype variations such as left ventricular dominant disease. An important benefit of these new diagnostic categories is that this will reduce the variation between patients within the same category, and less variation will likely result in higher accuracy in future prediction models.

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Appendix

NEDERLANDSE SAMENVATTING

Aritmogene Rechter Ventrikel Cardiomyopathie (ARVC) is een erfelijke hartspierziekte die voornamelijk in het rechter ventrikel (RV) tot uiting komt, door de pathologische progressieve vervanging van spierweefsel door vette fibrose. ARVC gaat gepaard met een hoog risico op ventriculaire hartritmestoornissen of plotse hartdood. Vroeg detectie en risicopredictie zijn twee methodes waarmee plotse hartdood voorkomen kan worden, echter blijkt dit een uitdaging in de praktijk.

De diagnose ARVC is gebaseerd op de 2010 Task Force Criteria (TFC), die momenteel ter discussie staan gezien deze niet gevoelig genoeg zijn voor vroeg detectie. Uit recente studies zijn reeds enkele suggesties naar voren gekomen, zoals het toevoegen van objectieve wandbeweging analyse middels echocardiografie ("strain"), en/of vette fibrose weefsel analyse door gebruik te maken van MRI met gadolinium contrast. Helaas is er nog onvoldoende bewijs dat deze technieken daadwerkelijk zullen leiden tot verbetering. Een ander punt van discussie is dat de 2010 TFC zich teveel beperkt tot het rechter ventrikel, wat voortkomt uit de klassieke beschrijving van ARVC waar met name het rechter ventrikel wordt aangedaan. Door verbeterde beeldvorming technieken werd over de jaren herhaaldelijk aangetoond dat vaker dan gedacht dezelfde vette fibrose ook aanwezig is in het linker ventrikel. In toenemende mate worden nu atypische uitingen beschreven van patiënten waarbij het linker ventrikel zelfs meer is aangedaan dan het rechter ventrikel, of een combinatie beeld, die daardoor niet voldoen aan diagnose volgens de 2010 TFC. Als antwoord op dit probleem gebruiken veel onderzoekers tegenwoordig termen als aritmogene cardiomyopathie (ACM) of zelfs aritmogene linker ventrikel cardiomyopathie (ALVC). Dit schept helaas verwarring, omdat er nog geen consistente definitie is vastgelegd.

Na het vaststellen van de diagnose, het liefst in een zo vroeg mogelijk stadium, is het primaire behandeldoel het voorkomen van plotse hartdood. Op dit moment is de enige bewezen methode een implanteerbare cardioverter-defibrillator (ICD). Echter, het plaatsen en ook het dragen van een ICD gaat gepaard met risico's op complicaties en kan een fysieke en psychische belasting met zich meebrengen. Het is daarom in het belang van de patiënt om een zorgvuldige afweging te maken of het risico op plotse hartdood groot genoeg is om een ICD te verantwoorden. Hoewel voor patiënten met ARVC het risico op plotse hartdood relatief hoog is op populatieniveau, blijkt dit risico sterk te variëren op individueel niveau. Het zo nauwkeurig mogelijk inschatten van het risico van individuele patiënten is derhalve cruciaal om zoveel mogelijk plotse hartdood te voorkomen met tijdige ICD-plaatsing in patiënten die dit nodig hebben, en om tegelijkertijd zoveel mogelijk onnodige ICD-plaatsingen te

voorkomen. Om artsen te helpen met deze belangrijke klinische uitdaging, hebben onderzoekers en experts over de afgelopen jaren verschillende methoden en richtlijnen voorgesteld. De beschikbare opties op dit moment zijn in totaal vier verschillende op “expert-opinie” gebaseerde stratificatie schema’s, met daarnaast recentelijk ook twee op data-gebaseerde multivariabele risico predictie modellen. In afwachting van solide bewijs uit klinische validatie studies, ontbreekt het momenteel aan een consensus welk van deze methodes het beste is om toe te passen in de dagelijkse praktijk.

De hoofddoelen van het onderzoek in deze thesis zijn: (1) verbeteren van diagnostiek; (2) verbeteren van risicostratificatie; en (3) het ontwikkelen van een duurzaam patiënten register en database gebruik makende van de nieuwste technieken waarmee onderzoek sneller, efficiënter en veiliger kan worden uitgevoerd, en internationale samenwerking makkelijker maakt. Hieronder worden de hoofdstukken met de studies gebundeld in deze thesis kort samengevat.

Het vooronderzoek en database ontwerp

Het onderzoek in dit proefschrift start met het verzamelen, analyseren en samenvatten van de afgelopen decennia aan onderzoek. In **hoofdstuk 3** verrichtten we een systematische beoordeling en meta-analyse van al het beschikbare bewijs uit eerdere studies naar kenmerken die in ARVC-patiënten geassocieerd zijn met een verhoogd risico op levensbedreigende ritmestoornissen (i.e. “risicofactoren”). De elektronische zoekmethode verricht in MEDLINE en Embase leverde in totaal 45 studies op, met een mediaan cohort grootte van 70 patiënten en 5 jaar follow-up. De gemiddelde incidentie van levensbedreigende ritmestoornissen gerapporteerd in deze studies varieerde tussen 3.7-10.6% per jaar. Hoewel de ruw gebundelde resultaten van alle studies een groot aantal verschillende potentiële risicofactoren beschrijft, is het bewijs voor veel risicofactoren beperkt tot een enkele studie. Daarnaast valt op dat de onderzoekers tussen studies veel verschillende definities en methodes gebruiken, wat de mogelijkheid om resultaten te vergelijken tussen studies ernstig limiteert. Systematische analyse laat zien dat er overtuigend consistent bewijs is dat mannelijk geslacht, syncope, T-golf inversies op ECG, RV dysfunctie en eerdere ventriculair ritmestoornissen geassocieerd is met een hoger risico op levensbedreigende ritmestoornissen in ARVC.

Om verder onderzoek te verrichten naar de diagnose en prognose van ARVC-patiënten, is het cruciaal om een grote hoeveelheid data te verzamelen van een zo groot mogelijk cohort, over een zo lang mogelijke follow-up duur. Dit is vaak een uitdaging, omdat

ARVC een relatief zeldzaam ziektebeeld is, en tussen de eerste presentatie tot het ontstaan van levensbedreigende ritmestoornissen veel tijd zit kan zitten. Dat verklaart ook de opvallend kleine mediaan cohort grootte van de studies in hoofdstuk 30, wat vaak resulteert in onvoldoende statistische power voor robuuste analyse. De oplossing hiervoor is om een duurzame longitudinale database op te bouwen in samenwerking met meerdere centra. In **hoofdstuk 4** wordt de ontwikkeling, het ontwerp, de functionaliteit en de praktische implementatie van het nieuwe ACM Register en online database beschreven (www.acmregistry.nl). Dit register maakt gebruik van de nieuwste technieken gebaseerd op het REDCap (research electronic data capture) platform, conform de huidige richtlijnen van veilige data invoer en opslag. Daarnaast zijn verschillende algoritmes ontwikkeld en toegepast die real-time analyses uitvoeren op de ingevoerde data voor o.a. validatie en automatische bepalingen van alle 2010 TFC voor diagnose. Met de invoer van dit nieuwe register krijgen alle deelnemende onderzoekers een beveiligde directe onlineverbinding tot al hun data. Dit is niet alleen essentieel voor het bevorderen van de nationale samenwerking, maar het vergroot ook de mogelijkheden voor samenwerking op internationaal niveau.

Verbeteren van risicostratificatie

Hoofdstuk 5 beschrijft de eerste studie van het onderzoek naar het verbeteren van de risicostratificatie in ARVC-patiënten. Het doel in deze studie was om een predictiemodel te ontwikkelen voor het risico op levensbedreigende hartritmestoornissen van individuele patiënten met ARVC. In samenwerking met 5 patiënten registers uit Europa en Noord-Amerika werd een cohort opgesteld van 528 patiënten met definitieve ARVC-diagnose die niet eerder een aanhoudende ventriculaire ritmestooris hebben doorgemaakt. Voor het ontwikkelen van het model werd een multivariabel COX-PH-model gebruikt, waarin de lijst van potentiële risicofactoren uit hoofdstuk 3 wordt getest, voor het voorspellen van alle vormen van aanhoudende ventriculaire ritmestoornissen over een periode van maximaal 5 jaar. Het resultaat is een model gebaseerd op 7 risicofactoren: leeftijd, geslacht, syncope, niet-aanhoudende ventriculaire ritmestoornissen, aantal premature ventriculaire complexen per 24 uur, aantal T-golf inversies, en RV-ejectie fractie. Interne validatie analyse liet zien dat het model het risico van patiënten redelijk goed kan discrimineren met een C-statistiek van 0.77. Hoewel veelbelovend, kan het werkelijke functioneren van dit model pas vastgesteld worden na toetsing in externe populaties.

Na de succesvolle ontwikkeling van een predictiemodel, volgt in **hoofdstuk 6** een studie waarin de invloed van sport op het risico op ventriculaire ritmestoornissen in ARVC-patiënten wordt onderzocht, en of dit kan leiden tot onbetrouwbare voorspellingen door het

predictiemodel in hoofdstuk 5. Het predictiemodel beperkt zich tot 7 risicofactoren, een bewuste beperking omdat meer risicofactoren een groter patiënten cohort zou vereisen. Het toevoegen van meer risicofactoren kan potentieel tot betere voorspellingen leiden, maar vereist een groter cohort of het conservatief testen van een enkele risicofactor met sterk bewijs uit voorgaande studies. Op dit moment is sport een veelbesproken onderwerp, en inmiddels herhaaldelijk aangetoond dat het een risicofactor is, wat de noodzaak voor deze studie indiceert. In totaal werden 176 ARVC-patiënten uit drie verschillende centra in detail geïnterviewd over hun sportgedrag. De totale hoeveelheid sport werd berekend als gemiddelde over elk jaar, geconverteerd naar een standaard eenheid van MET-uur per week. Sport liet een significante dosis-afhankelijke maar niet lineaire associatie zien met het risico op ritmestoornissen. Opgedeeld in oplopende dosis categorieën valt op dat tot <15-30 MET uur/week geen verhoogd risico gaf, wat impliceert dat er mogelijk een veilige grens is. Het significant verhoogde risico dat voorafgaande studies rapporteerden in atleten werd in deze studie bevestigd, voor de drie verschillende definities (>18, >24 of >36 MET uur/week) uit voorgaande literatuur, met een HR van 2.53 tot 2.91. Maar als additionele risicofactor in het predictiemodel gaf geen van deze definities een significante verbetering van predicties, door de sterke associatie van atleten status met de risicofactoren reeds aanwezig in het model. Grafische analyse bevestigde eveneens dat het model zonder toevoeging van atleten status reeds accuraat het verhoogde risico voorspelde in atleten.

In **hoofdstuk 7** wordt het onderzoek vervolgd met de ontwikkeling van een tweede predictiemodel, bedoeld als aanvulling op het model uit hoofdstuk 5. In dit tweede model wordt gekeken naar het risico op enkel de snelle (>250/min) aanhoudende ventriculaire hartritmestoornissen, met als doel een meer reële inschatting te geven van daadwerkelijke risico op plotse hartdood. Daarnaast wordt gekeken naar een breder cohort dat naast de primaire preventie patiënten nu ook patiënten includeert die eerder een aanhoudende ventriculaire hartritmestoonis hebben doorgemaakt (i.e. secundaire preventie), resulterend in een totaal van 864 ARVC-patiënten. Herhalen van dezelfde methode zoals in hoofdstuk 5 leverde een predictiemodel op gebaseerd op vier risicofactoren: leeftijd, geslacht, aantal premature ventriculaire complexen per 24 uur en aantal T-golf inversies. Een eerder doorgemaakte aanhoudende ventriculaire hartritmestoonis bleek geen invloed te hebben op het risico van een snelle hartritmestoonis. Interne validatie analyse van het model liet een goede prestatie zien met een C-statistiek van 0.74, vergelijkbaar met het eerste model.

Voor dat beoordeeld kan worden dat deze nieuwe predictiemodellen in de praktijk gebruikt kunnen worden, zijn er momenteel vier risicostratificatie methodes beschikbaar uit eerdere richtlijnen en publicaties: de International Task Force Consensus ("ITFC"), de

modified ITFC van Orgeron et al ("mITFC"), de AHA/HRS/ACC guideline for VA management ("AHA"), en de HRS expert consensus statement ("HRS"). Welke van deze vier het beste is om te gebruiken is onduidelijk, en het is ook niet bekend hoe deze functioneren in de praktijk. In **hoofdstuk 8** wordt in een cohort van 617 ARVC-patiënten gekeken naar hoe deze vier schema's presteren in het correct stratificeren van patiënten die wel of geen aanhoudende ventriculaire hartritmestoonis kregen. Uit de resultaten komt naar voren dat de ITFC en mITFC vrijwel hetzelfde presteren, evenals de AHA en HRS. De ITFC en mITFC presteerde het beste op het gebied van bescherming, door een ICD-indicatie te stellen bij >95% van de patiënten die een hartritmestoonis kregen. Echter gaat dit ten koste van de specificiteit, en kregen meer dan de helft van de patiënten zonder hartritmestoonis onterecht ook een ICD-indicatie.

Verbeteren van diagnostiek

In **hoofdstuk 9** wordt onderzocht hoe de 2010 TFC presteren in het juist stellen van de diagnose ARVC in een cohort van 407 patiënten die verwezen werden voor diagnostiek. Als referentie methode werd gebruik gemaakt van een expert panel, welke de diagnose ARVC vaststelden bij 66 (16%) van de patiënten. Globaal scoorde de 2010 TFC goed met een sensitiviteit en specificiteit van 92%. Maar in detail gekeken naar alle individuele criteria, werd aangetoond dat de signal-averaged ECG criteria en een groot deel van de familie geschiedenis criteria geen toegevoegde waarde lieten zien, en het verwijderen van deze criteria gaf een kleine maar statistisch significante verbetering door afname van vals-positieve diagnoses. Daarnaast werd gevonden dat de "elektrische" criteria betreffende kenmerken op het ECG of het zien van ritmestoornissen hoog scoren in specificiteit, gecombineerd zelfs tot 100%. Dit suggereert de potentie voor eventuele toepassingen van deze criteria als een eenvoudige vorm van herhaaldelijke screening van bijvoorbeeld familieleden.

CURRICULUM VITEA

Laurens Pieter Bosman was born on the 11th of March 1990 in Lelystad, the Netherlands. After graduating from the Grotius College in Delft in 2008, he moved to Amsterdam to study Biomedical Sciences at the Vrije Universiteit. He obtained his Bachelor degree in 2011, and subsequently started a Master program in Oncology. In 2012 he was selected for the Selective Medical Master Utrecht (SUMMA) at the University Medical Center Utrecht (UMCU). Because of his interest in the combination of physiology with physics and technology, he did a research internship at the medical technology department, testing the application of a new non-invasive technique to obtain cardiac volume-time functions. During this internship, he discovered his passion for cardiology, and went on to do his senior clinical internship in cardiology at the UMCU. He received his Medical Degree in 2016.

He started working as a Ph.D. student in 2016 under supervision of Dr. te Riele, Dr. James, Prof. Dr. van Tintelen and Prof. Dr. Asselbergs at the UMCU, studying the diagnosis and prognosis of Arrhythmogenic Right Ventricular Cardiomyopathy. During his time as a Ph.D. student, he obtained a Master degree in Biostatistics and Epidemiology at the Julius Center Utrecht, and attended a research fellowship at the Johns Hopkins University supervised by Dr. James and Dr. Calkins. In 2019 he worked for one year as a cardiology resident (ANIOS) at the Meander Medical Center in Amersfoort, after which he returned to the UMCU to continue his research.

He finished writing his PhD thesis in 2021, after which he was admitted in a six-year residency program training to become a Cardiologist under supervision of Dr. Sieswerda and Dr. Clappers at the UMCU.

LIST OF PUBLICATIONS

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Lieve **Ella**

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