

Value of genetic testing in the diagnosis and risk stratification of arrhythmogenic right ventricular cardiomyopathy



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BACKGROUND Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by risk of malignant ventricular arrhythmia (VA). ARVC is diagnosed using an array of clinical tests in the consensus-based Task Force Criteria (TFC), one of which is genetic testing.

OBJECTIVE The purpose of this study was to investigate the value of genetic testing in diagnosing ARVC and its relation to the occurrence of first malignant VA.

METHODS A multicenter cohort of patients with ARVC was scored using the revised 2010 TFC with and without genetic criterion, analyzing any resulting loss or delay of diagnosis. *Malignant VA* was defined as sustained VA (≥ 30 -second duration at ≥ 100 beats/min or requiring intervention).

RESULTS We included 402 subjects (221 [55%] male; 216 [54%] proband; 40 [27–51] years old at presentation) who were diagnosed with definite ARVC. A total of 232 subjects (58%) fulfilled genetic testing criteria. Removing the genetic criterion caused loss of diagnosis in 18 patients (4%) (11 of 216 probands [5%] and 7 of 186

relatives [4%]) and delay of diagnosis by ≥ 30 days in 22 patients (5%) (21 of 216 probands [10%] and 1 of 186 relative [0.5%]). A first malignant VA occurred in no patients who lost diagnosis and in 3 patients (3 of 216 probands [1%] and no relatives) during their diagnosis delay, none fatal. Time-to-event analysis showed no significant difference in time from diagnosis to malignant VA between pathogenic variant carriers and noncarriers.

CONCLUSION Disregarding the genetic criterion of the TFC caused loss or delay of diagnosis in 10% of patients with ARVC (40 of 402). Malignant VA occurred in 1% of cases with lost or delayed diagnosis (3 of 402), none fatal.

KEYWORDS ARVC; ACM; Arrhythmogenic right ventricular dysplasia/cardiomyopathy; Screening; Diagnosis; Task Force Criteria; Malignant ventricular arrhythmia; Genetic screening

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Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC), the right dominant subform of arrhythmogenic cardiomyopathy (ACM), is characterized by fibrofatty replacement of cardiomyocytes leading to ventricular dysfunction and an increased risk of malignant ventricular arrhythmia (MVA).^{1,2} The

clinical criterion standard for ARVC diagnosis is the revised 2010 Task Force Criteria (TFC).¹ These TFC consist of electrocardiographic characteristics (depolarization and repolarization abnormalities), tissue characterization, imaging (echocardiographic and cardiac magnetic resonance imaging) abnormalities, as well as arrhythmic features and family history.

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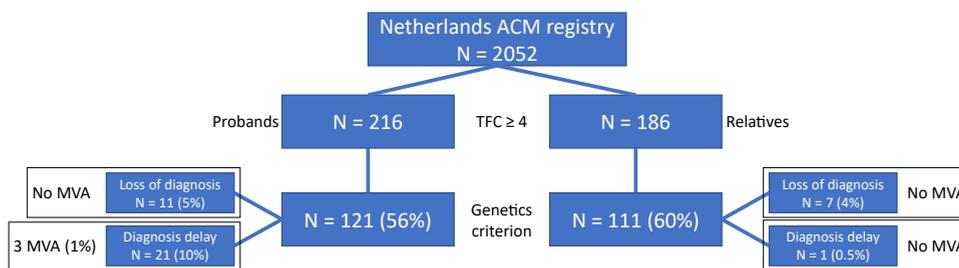


Figure 1 Flowchart of the study population. ACM = arrhythmogenic cardiomyopathy; MVA = malignant ventricular arrhythmia; TFC = Task Force Criteria.

ARVC is often familial with incomplete penetrance and variable expressivity. Genetic causes underlying the disease have mainly been identified in genes encoding proteins of the cardiac desmosome. As a result, genetic testing for pathogenic desmosomal variants is regularly performed. In contrast to other diseases, these genetic testing results are part of the diagnostic criteria; that is, the presence of a (likely) pathogenic variant in an ARVC-related gene is considered a major criterion for ARVC diagnosis. Of note, the presence of either 2 major or 1 major and 2 of 4 minor criteria is sufficient for a definite ARVC diagnosis, underscoring the importance of genetics in clinical diagnosis in the 2010 TFC framework. To complicate matters even further, determining pathogenicity of a genetic variant is challenging and is based on criteria proposed by the American College of Medical Genetics and Genomics/Association for Molecular Pathology. Indeed, a recent study showed that ~40% of variants believed to underlie ARVC were misclassified.³ This misclassification may easily lead to a misdiagnosis of ARVC by lowering the scoring threshold to reach a diagnosis. As such, previous studies^{4–6} have suggested that assigning the genetic criterion as a major criterion could result in overdiagnosis and its relative weight in the TFC may have to be reconsidered.^{7,8} However, objective studies that evaluate the diagnostic value of the genetic testing criterion in the 2010 TFC are lacking. Leveraging a large multicenter cohort containing relatives of proband patients with ARVC, the aim of this study was to determine the incremental value of the genetic TFC criterion for ARVC diagnosis and risk assessment.

Methods

Study population

The study population was recruited from the Netherlands Arrhythmogenic Cardiomyopathy Registry (www.acmregistry.nl) (Figure 1).⁹ This registry contains records from all 7 university medical centers in the Netherlands, minimizing center-based bias. All participants provided informed consent for research at the time of genetic testing. The institutional review board approved the protocol, and the registry is recorded in the Netherlands Trial Registry, project 7097 (www.trialregister.nl; <https://trialsearch.who.int/>, study ID NTR7097). The study was performed in line with the principles of the Helsinki Declaration as revised in 2013.

Clinical evaluation

Patients were evaluated as described previously.⁹ We used clinical data derived from anonymized medical records. Demographic characteristics, medical and family history, electrocardiograms, exercise stress tests, Holter registrations, signal-averaged electrocardiograms, echocardiograms, cardiac magnetic resonance imaging scans, electrophysiology studies, biopsies, genetic tests, and pathology reports were collected.

ARVC diagnosis

A definite ARVC diagnosis was ascertained using the aforementioned 2010 TFC,^{1,10} which evaluates 6 categories, each containing major (2 points) and minor (1 point) criteria. A total of at least 4 points from different categories is required for a definite diagnosis of ARVC. Notably, apart from a positive genetic testing result, a patient may score points for family history, for example, if they have a relative with ARVC in the absence of a currently known (likely) pathogenic variant, as specified below.

Genetic testing and family history evaluation

As per current guidelines, all probands with ARVC were offered genetic testing for ARVC-related genes while relatives were solely tested for the variant identified in the proband. Genetic testing results were acquired from the years 2002–2021 and consisted of next generation sequencing panels, Sanger sequencing, and multiplex ligation-dependent probe amplification; a list of tested genes included in these next generation sequencing panels can be found in [Supplementary Table 1](#). Genetic testing results were adjudicated as per American College of Medical Genetics and Genomics/Association for Molecular Pathology guidelines where class 4 (likely pathogenic) and class 5 (pathogenic) variants were classified as likely causative for disease. Of note, genetic testing was considered positive (ie, only major TFC were fulfilled) only if a (likely) pathogenic variant was found in a gene with definite evidence for ARVC causation (ie, *PKP2*, *DSP*, *DSG*, *DSC2*, *JUP*, and *TMEM43*), as specified by the Clinical Genome Resource.¹¹ Consequently, the Dutch founder variant in the *PLN* gene (p.Arg14del) was not considered as an ARVC-related gene for the purpose of the present analysis.

Family history was evaluated by cardiogenetic counselors with particular interest in ARVC. As in previous ARVC

Table 1 Characteristics of the total cohort

Characteristic	Overall (N = 402)	Proband (n = 216)	Relative (n = 186)	P
Age at presentation (y)	40 (27–51)	40 (29–49)	40 (24–51)	.487
Male sex	221 (55)	145 (67)	76 (41)	<.001
Pathogenic variant*	232 (58)	121 (56)	111 (60)	.523
<i>PKP2</i>	211 (52)	105 (49)	106 (57)	1.000
<i>DSP</i>	15 (4)	11 (5)	4 (2)	NA [†]
<i>DSG2</i>	6 (2)	4 (2)	2 (1)	NA [†]
<i>DSC2</i>	6 (2)	3 (2)	3 (2)	NA [†]
TFC points	6 (4–7)	6 (5–8)	5 (4–6)	<.001
Repolarization criteria [‡]	2 (1–2)	2 (1–2)	1 (0–2)	<.001
Depolarization criteria [‡]	1 (0–1)	1 (0–1)	1 (0–1)	.307
Arrhythmia criteria [‡]	1 (1–2)	1 (1–2)	1 (0–1)	<.001
Tissue criteria [‡]	0 (0–0)	0 (0–0)	0 (0–0)	.001
Imaging criteria [‡]	2 (0–2)	2 (0–2)	1 (0–2)	<.001
Follow-up duration (y)	11 (6–17)	13 (7–20)	10 (6–15)	<.001
Malignant ventricular arrhythmia	202 (50)	158 (73)	44 (24)	<.001

Values are presented as median (interquartile range) or n (%).

ARVC = arrhythmogenic right ventricular cardiomyopathy; NA = not available; TFC = Task Force Criteria.

*Only genetic variants related to ARVC determined as pathogenic/likely pathogenic in the following genes: *PKP2*, *DSP*, *JUP*, *DSG2*, *DSC2*, and *TMEM43*. Of note, a total of 90 patients (42 probands and 48 relatives) harbored the *PLN* p.Arg14del founder variant, which was not counted as an ARVC-related gene for the purpose of the present analysis.

[†]Insufficient group size for meaningful statistical comparison.

[‡]Major criteria = 2 points; minor criteria = 1 points.

studies,^{4,12–14} proband was defined as the first member of a family to be diagnosed with ARVC and in whom genetic testing began. The current TFC lists the following family history criteria: confirmed ARVC in a first-degree relative according to the TFC, pathologically confirmed ARVC in a first-degree relative, and identification of a (likely) pathogenic mutation in the subject themselves as major criteria, as well as unconfirmed ARVC in a first-degree relative, premature sudden death (<35 years old) due to suspected ARVC in a first-degree relative, and confirmed ARVC in a second-degree relative as minor criteria.

Outcomes

We collected data on the occurrence of MVA, which was defined as sudden cardiac death, resuscitated sudden cardiac arrest, spontaneous sustained ventricular tachycardia, or appropriate implantable cardioverter-defibrillator intervention. Definitions were used as described previously.¹⁵

Statistical analyses

Continuous data were presented as mean \pm SD or as median with interquartile range, as appropriate. Categorical variables were presented as absolute value followed by percentage. Variables were compared using the χ^2 test for categorical variables, the Student *t* test for normally distributed continuous variables, and the Mann-Whitney *U* test for

nonnormally distributed continuous variables. Univariable and multivariable analysis was performed to investigate potential risk factors for MVA occurrence. We plotted survival curves stratified by genetic testing results in order to analyze the occurrence of MVA over time. The start time was set at the date of ARVC diagnosis and the end time at the date of last follow-up or first MVA. Nonparametric survival analysis was performed using the Kaplan-Meier estimation. The resulting survival functions were tested for significance by using the log-rank test.¹⁶ Analyses were performed using RStudio version 1.3.1073 (<https://www.rstudio.com/>), a graphical interface for the R statistical package, version 4.0.2. *P* values <.05 were considered statistically significant.

Results

Study population

As of February 2022, the Netherlands Arrhythmogenic Cardiomyopathy Registry contained data from 2052 patients with ARVC (516 probands and 1536 relatives). From this initial cohort, 402 subjects (216 probands and 186 relatives) fulfilled definite ARVC criteria. Patient characteristics are summarized in Table 1. Overall, 55% of these patients (n = 221) were male, with a median age of 40 (27–51) years at presentation. Compared with relatives, probands were significantly more often male (*P* < .001). There was no significant difference in age at first clinical presentation. Not surprisingly, probands had more TFC points than did relatives, with a median of 6 (5–8) points vs 5 (4–6) points (*P* < .001). Genetic testing results revealed a (likely) pathogenic ARVC-associated variant in 232 subjects (58%), most commonly in the plakophilin-2 gene (n = 211 [52%]), followed by desmoplakin (n = 15 [4%]), desmoglein (n = 6 [2%]), and desmocollin (n = 6 [2%]) (see Table 1).

Family history evaluation

Table 2 presents the distribution of family history criteria in the study population. Overall, 290 subjects (72%) (124 probands [57%] and 166 relatives [89%]) fulfilled major family history criteria while 86 subjects (21%) (18 probands [8%] and 68 relatives [27%]) fulfilled minor family history criteria. Nongenetic family history criteria were fulfilled in 29 probands (13%) and 169 relatives (91%); the remaining 17 relatives without nongenetic family history criteria (9%) were distant family members of patients with ARVC and hence did not fulfill nongenetic TFC in the family history category.

Role of genetic testing in the clinical diagnosis of probands

Of the 216 included probands, 121 (56%) harbored a (likely) pathogenic ARVC-related variant. Removing genetic testing from the TFC led to a total of 11 probands who lost their diagnosis (5%) and 21 probands who had their diagnosis delayed by ≥ 30 days (range 38 days to 35 years) (10%). More information on the presentation and clinical course of these subjects can be found in Supplementary Tables 2 and 3. None

Table 2 Distribution of family history criteria

Variable	Overall (N = 402)	Proband (n = 216)	Relative (n = 186)
Any major family history criterion	290 (72)	124 (57)	166 (89)
Genetic testing positive	232 (58)	121 (56)	111 (60)
First-degree relative with ARVC	151 (38)	11 (5)	140 (75)
First-degree relative with ARVC (autopsy)	26 (6)	4 (2)	22 (12)
Any minor family history criterion	86 (21)	18 (8)	68 (37)
First-degree relative with uncertain ARVC diagnosis	8 (2)	2 (<1)	6 (3)
SCD (<35 y) due to suspected ARVC	33 (8)	14 (6)	19 (10)
Second-degree relative with ARVC	50 (12)	2 (<1)	48 (26)
Any nongenetic family history criterion	198 (49)	29 (13)	169 (78)
Loss of diagnosis with genetic criterion removed	18 (4)	11 (5)	7 (4)
Delay of diagnosis with genetic criterion removed	22 (5)	21 (10)	1 (<1)
Combined loss and delay with genetic criterion removed	40 (10)	32 (15)	8 (4)

Values are presented as n (%).

ARVC = arrhythmogenic right ventricular cardiomyopathy; SCD = sudden cardiac death.

of the probands lost their diagnosis upon removing the nongenetic family history criterion group.

Probands were followed over 13 (7–20) years. Of the 11 probands who would have been missed if genetic testing was disregarded (5%), none experienced MVA and all were still alive at last follow-up. Of the 21 probands with a diagnosis delay should genetic testing be disregarded (10%), 3 (1%) experienced MVA during that delay, all of whom were alive at the last date of follow-up.

Role of genetic testing in the clinical diagnosis of relatives

Of the 186 included relatives, 111 (60%) harbored a (likely) pathogenic ARVC-related variant. Removing genetic testing from the TFC led to a total of 7 relatives who lost their diagnosis (4%) and 1 relative who had their diagnosis delayed by ≥ 30 days (72 days) (0.5%). More information on the presentation and clinical course of these subjects can be found in [Supplementary Tables 2 and 3](#). In addition, 38 relatives (20%) lost their diagnosis upon removing the nongenetic family history criterion group.

Relatives were followed over 10 (6–15) years. Of the 7 relatives who would have been missed if genetic testing was disregarded (4%), none experienced MVA and all were alive at the time of last follow-up. The 1 relative with a diagnosis delay should genetic testing be disregarded (0.5%) did not

Table 3 Univariable and multivariable analysis of potential factors influencing the risk of malignant ventricular arrhythmia

Variable	Univariable		Multivariable	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age at presentation	0.99 (0.98–1.01)	.508	0.99 (0.97–1.01)	.329
Male sex	3.35 (1.85–6.23)	<.001	3.03 (1.64–5.19)	<.001
Relative status	0.30 (0.17–0.55)	<.001	0.31 (0.17–0.58)	<.001
Pathogenic variant	1.38 (0.77–2.51)	.284	1.50 (0.80–2.88)	.212

CI = confidence interval.

experience MVA during or after that delay and was still alive at last follow-up.

Association of genetic testing with outcome

A definite disease diagnosis is typically regarded as a prerequisite for subsequent arrhythmic events in patients with ARVC.^{4,17} As such, risk stratification efforts typically starts with a definite ARVC diagnosis.¹⁵ However, our data demonstrate that date of diagnosis may be delayed if genetic testing is disregarded as a diagnostic criterion. We therefore believe that it is important to evaluate how date of diagnosis relates to the development of subsequent MVA in these patients.

Since ARVC diagnosis cannot be ascertained if an individual has not yet come to medical attention, further analyses were restricted to those who did not present with sustained ventricular arrhythmia or equivalent event and in whom outcomes could be ascertained. We will refer to this group as the primary prevention cohort.

Of the 238 primary prevention ARVC patients in our cohort, 61 (26%) experienced first MVA during 11 (7–16) years of follow-up. Those who experienced MVA were 41 male (67%) with an age at first presentation of 36 (29–45) years. The mean time between diagnosis and MVA was 3 (1–8) years.

[Table 3](#) and [Figure 2](#) present predictors of the occurrence of first MVA in primary prevention ARVC patients. As can be observed in [Figure 2](#), there was no significant difference in time from confirmed ARVC diagnosis to first MVA between carriers of a pathogenic variant and noncarriers. [Table 3](#) depicts that male sex and proband status were significant risk factors for the occurrence of MVA while carrying a pathological genetic variant was not.

Discussion

The last decade has witnessed the identification of pathogenic variants associated with ARVC, and genetic testing for ARVC-related variants is now routinely performed. Different from all other forms of cardiomyopathy, these genetic testing results are an integral part of the diagnostic criteria for ARVC, counting as a major criterion toward ARVC diagnosis. Despite the relative importance of genetic testing in diagnosing ARVC, the TFC framework does not specify

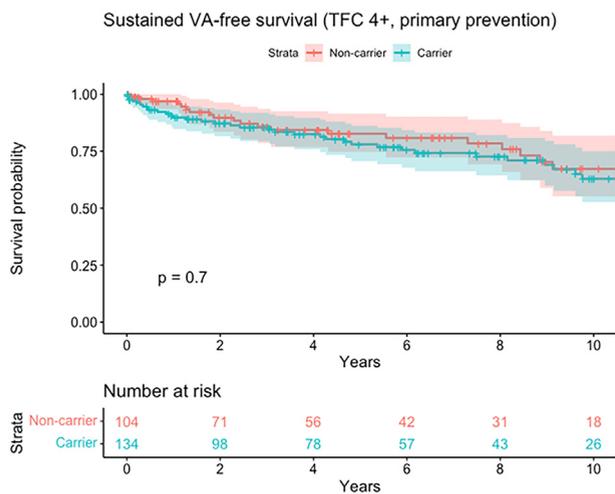


Figure 2 Survival curve of patients with arrhythmogenic right ventricular cardiomyopathy: pathogenic variant carriers vs noncarriers, showing no significant difference in time from the initial diagnosis to the first malignant ventricular arrhythmia. TFC = Task Force Criteria; VA = ventricular arrhythmia.

which genes should be considered disease causing, and determining pathogenicity of variants is challenging in the context of the background “genetic noise” (ie, presence of pathogenic variants in the healthy population).^{7,18} Our results show that removal of genetic testing from the 2010 TFC scoring system causes a loss or delay of diagnosis in 10% of patients with ARVC (40 of 402). While this is a sizable number, the number of subjects who experience a potential fatal outcome (MVA) during that delay is small (<1% [3 of 402]). Likewise, the presence of a pathogenic variant was not significantly associated with MVA during follow-up.

History of the TFC

Since there is no single criterion standard for ARVC diagnosis, a multitude of clinical tests is required to determine a definite ARVC diagnosis. The resulting “TFC” were first described in 1994 and revised in 2010 to increase the sensitivity for early disease. Of note, the revised TFC included genetic testing as a major diagnostic criterion together with other new diagnostic criteria (eg, the presence of prolonged terminal activation duration and quantitative cutoffs for imaging tests). The combined additional value of these revised criteria was tested through post hoc analysis in a cohort of 108 probands, but a focused analysis of the performance of the genetic criterion within this framework is lacking. Recently, Bosman et al⁶ showed a limited value of genetic and family history criteria within the TFC framework, while arrhythmic and electrocardiographic criteria provided 100% sensitivity in their cohort. This suggests that not all TFC can be considered equal and that a critical appraisal of the true diagnostic value of these criteria is warranted.

Value of genetic testing for diagnosis

Our study shows that 10% of patients with definite ARVC have a loss or >30-day delay of diagnosis upon removal of

genetic testing from the TFC framework. Of note, probands had greater reliance on genetic criteria than did relatives, which is understandable as relatives (by definition) fulfill other nongenetic family history criteria for ARVC.

The disappointing diagnostic value of genetic testing criteria can be explained by the incomplete penetrance of ARVC: simply carrying a pathogenic variant that can cause ARVC does not equal developing the cardiomyopathy itself. In addition, penetrance in relatives is known to be age dependent and only a third of relatives will develop ARVC.¹⁹ This is in sharp contrast to population-based cohorts, where penetrance of ARVC-related variants is estimated to be well under 10%.^{13,20} As such, one may conclude that a positive genetic testing result may contribute to overdiagnosis of ARVC by lowering the scoring threshold to reach a diagnosis by half. While this lower threshold may be helpful in the early detection of disease in at-risk family members, these early diagnoses should be balanced against the risk of misdiagnosis should pathogenicity of the variants be incorrectly classified and against the psychosocial impact of reaching a definite diagnosis in those who may never experience any adverse clinical events. This study was not designed to evaluate either one of these outcomes. However, a focused analysis on the relationship between genetic testing results and MVA may shed light on the clinical value of genetic testing results in the management of patients with ARVC.

Value of genetic testing for risk stratification

The results of our study show that MVA does not occur in any of the patients who rely on genetic testing for ARVC diagnosis and in only a minority of probands during their diagnosis delay should genetic testing be disregarded. Of note, none of these MVAs were lethal. Likewise, the presence of a pathogenic variant was not significantly associated with MVA in primary prevention ARVC patients in our cohort.

Our results are in line with previous studies that evaluated the value of genetic testing for ARVC risk stratification. In a cohort of 274 first-degree relatives of probands with ARVC,⁴ all subjects who experienced ventricular arrhythmias had phenotypic expression of disease and hence fulfilled TFC independent of family history. Similarly, Zorzi et al¹⁷ showed that an overt disease phenotype was a prerequisite for ventricular arrhythmias in patients with ARVC.¹⁷ Genetic testing was also evaluated as a prognostic marker in a multicenter “risk calculator” for ventricular arrhythmias,^{15,21} where genetic testing was not significantly associated with arrhythmic events and fell out of the model. While this finding was replicated in other cohorts, the presence of multiple genetic variants was significantly associated with worse outcome in patients with ARVC.²² In addition, a genotype-specific risk model was previously published for phospholamban cardiomyopathy,²³ a disease that associates with both an arrhythmogenic and a dilated cardiomyopathy phenotype. It would be interesting to compare the available risk models to provide further guidance on the optimal approach to personalized (and perhaps genotype-specific) risk stratification.

Clinical implications

According to general recommendations for genetic testing in inherited cardiomyopathies,²⁴ genotyping is indicated in a proband who already fulfills diagnostic criteria for ARVC and may be considered in those with borderline phenotypic manifestations, provided that the results are interpreted by experts in the field of molecular genetics who have experience with ARVC. In line with these recommendations, we believe that the identification of a likely pathogenic or pathogenic variant is of great importance for cascade genetic screening in relatives, family planning, and genotype-phenotype associations (eg, the finding that multiple pathogenic variants are associated with malignant outcomes) for the treating cardiologist.

The role of genetic testing in ARVC diagnosis may be less clear. In this context, one should take the incomplete penetrance and variable expressivity of this disease into account: the presence of a pathogenic variant will already lead an individual halfway toward the diagnosis, while only 1 in 3 variant carriers will actually develop disease and 1 in 10 relatives develop arrhythmias.⁴ Hence, while inclusion of genetic testing in the TFC leads to greater sensitivity for early disease, this may come at the expense of (psychosocial and/or therapeutic) consequences to subjects who will never develop adverse outcome in (1) those who have mild phenotypic ARVC expression and (2) those in whom genetic testing results are misinterpreted and a different disease is at play. We therefore believe that the presence of a pathogenic ARVC-related variant may be more strongly related to the a priori risk of developing ARVC rather than actually being diagnostic for the disease. The median time from ARVC diagnosis (by conventional TFC, ie, with genetic testing included) to ventricular arrhythmia in our cohort was 3 (1–8) years. This is important, as this is the time during which clinicians are able to intervene in order to prevent arrhythmias or manage disease progression, for example, by implementing preventive measures such as exercise restriction. Since disregarding genetic testing results only slightly delayed this interval and no lethal events occurred in missed or delayed diagnoses, removal of genotyping from the TFC does not seem to significantly affect the clinical outcome. Of note, the impact of loss of diagnosis in probands on their respective at-risk families remains uncertain. Future studies should confirm these findings and further evaluate the pros (ie, yield of early diagnosis and the ability to implement preventive measures such as exercise restriction) and cons (ie, repercussions in overdiagnosed and misdiagnosed patients) of genetic testing within the TFC framework.

Limitations

While the multicenter origin of our data helps mitigate center-based bias, data are typically collected retrospectively, which may have led to selection bias. Additionally, our registry mainly contains Western European ethnicities and thus results may not be directly extrapolated to other ethnicities. The delay in reaching a definite diagnosis by excluding

genetic testing has a wide span ranging from 38 days to 35 years. This may reflect the wide degree of disease progression, a detailed evaluation of which remains beyond the scope of the present study. It should be stressed that the potential loss of diagnosis in a proband may have potentially detrimental consequences in their respective relatives, who may not be evaluated and whose disease may go unnoticed.

Conclusion

Removing genetic testing from the 2010 TFC leads to lost or delayed ARVC diagnosis in 10% of patients with definite ARVC. A minority (1%) of these patients experienced potentially life-threatening ventricular arrhythmia during this delay. Moreover, genetic testing results were not associated with ventricular arrhythmias in primary prevention ARVC patients. These results will be of value for clinicians caring for these patients and their family members.

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Appendix Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrthm.2022.05.038>.

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