Primary Prevention of Sudden Cardiac Death With Implantable Cardioverter-Defibrillator Therapy in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy

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Implantable cardioverter-defibrillator (ICD) therapy remains a corner stone of sudden cardiac death (SCD) prevention in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC). We aimed to assess predictors of appropriate ICD therapies in the Scandinavian cohort of ARVC patients who received ICD for primary prevention of SCD. Study group comprised of 79 definite ARVC patients by 2010 Task Force criteria (60% male, age at ICD implant 39 ± 14 years) who were enrolled in the Nordic ARVC Registry and received an ICD for primary SCD prevention. The primary end point of appropriate ICD shock or death from any cause was assessed and compared with 137 definite ARVC patients who received ICD for secondary SCD prevention (74% male, age at ICD implant 42 ± 15 years). In the study group, 38% were ≤35 years of age at baseline, 25% had non-sustained ventricular tachycardia, and 29% had syncope at baseline. Major repolarization abnormality (hazard ratio = 4.00, 95% confidence interval 1.30 to 12.30, p = 0.015) and age ≤35 years (hazard ratio = 4.21, 95% confidence interval 1.49 to 11.85, p = 0.001) independently predicted the primary end point. The outcome did not differ between the primary prevention patients with either of these risk factors and the secondary prevention cohort (2% to 4% annual event rate) whereas patients without risk factors did not have any appropriate ICD shocks during follow-up. In conclusion, young age at ARVC diagnosis and major repolarization abnormality independently predict ICD shocks or death in the primary prevention ICD recipients and associated with the event rate similar to the one observed in the secondary prevention cohort. Our data indicate the benefit of ICD for primary prevention in patients with any of these risk factors. **(Am J Cardiol 2019;123:1156−1162)**

Increased awareness of arrhythmogenic right ventricular cardiomyopathy (ARVC) as a progressive inherited disease associated with the risk of sudden cardiac death (SCD) has lead to implementation of family screening strategies in clinical management guidelines[1] and revision of diagnostic criteria, which increased their sensitivity.[2] As a result, the number of ARVC patients requiring risk stratification regarding implantation of an implantable cardioverter-defibrillator (ICD) for primary prevention of SCD is growing. Although secondary prevention ICD implantation in ARVC is based on a well-documented increased risk of life-threatening ventricular arrhythmias,[3−5] the literature regarding the primary prevention ICD indications is limited.[6,7] We aimed to assess the predictors of ICD therapy in a large unselected cohort of patients with definite ARVC, who were diagnosed according to 2010 Task Force criteria (TFC2010) and received ICD implants for primary prevention of SCD, and compare the prognosis with secondary

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Dr Platonov was supported by The Swedish Heart-Lung Foundation (grant #20150574), governmental funding within the Swedish health care service and donation funds at Skåne university hospital. Dr Henrik K. Jensen is supported by the Novo Nordisk Foundation (NNF18OC0031258).

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https://doi.org/10.1016/j.amjcard.2018.12.049

prevention ICD recipients, who represent an a priori high-risk group in regard to ventricular arrhythmia recurrence. We also aimed to evaluate the risk factors associated with appropriate ICD therapies, identify patients at the highest risk of ventricular arrhythmias and describe subgroups of low-risk patients, in whom ICD implantation for primary prevention may not be needed.

Methods

The Nordic ARVC Registry (www.arvc.dk) was launched in June 2010 and includes patients diagnosed with definite ARVC by TFC2010 and followed through ICD outpatient clinics and dedicated cardio-genetics units affiliated with tertiary referral centers in Scandinavia.[8] We also prospectively recruit newly diagnosed patients. The register captured baseline clinical characteristics and the data specific for ARVC diagnostic criteria as proposed in the original Task Force recommendations from 1994[9] and the updated TFC2010.[2] Ventricular tachyarrhythmia data included in the registry are reported either as electrocardiographic (ECG)-verified ventricular tachycardia (VT) or as captured by ICD device diagnostics. Historical information regarding VT before ARVC diagnosis or ICD implantation was retrieved from patients' medical records as assessed by a cardiology specialist.

Decision to implant ICD for primary prevention of SCD was guided by guideline documents, which were in force at the time when patients underwent clinical evaluation[10,11] and local practice. Patients who received ICD after aborted cardiac arrest or documented sustained VT were considered secondary prevention ICD recipients whereas all other, including those with documented nonsustained VT, were considered as a primary prevention cohort. Secondary prevention ICD patients were used for comparison of clinical characteristics and clinical outcomes observed in the primary prevention group. Prospective follow-up information was available until November 2017. Regional ethics committees approved the study. In Denmark, the approval was obtained from the Danish Data Protection Agency. The study complies with the Declaration of Helsinki.

Continuous data are presented as mean ± standard deviation. Nominal data are presented as number (% of cases). Chi-squared or Fischer's exact test was used for comparison between categorical variables, and *t* test was used for the comparison of continuous variables.

The primary study end point was appropriate ICD shock or death from any cause. The secondary study end point was any appropriate ICD therapy defined as either antitachycardia pacing (ATP) or shock or death from any cause. Subjects who did not have any appropriate ICD therapy were censored at the end of follow-up or heart transplantation. Kaplan-Meier product-limit method was used to generate a survival curve indicating time to end point from the ICD implantation date. Cox proportional hazard regression models were used to estimate the adjusted hazard ratios and their 95% confidence intervals (CI). Cox regression analyses were performed on the primary prevention cohort whereas the Kaplan-Meier curves representing the outcome in the secondary prevention cohort were included for comparison of cumulative incidence of ICD therapies with the a priori high-risk ARVC patients.

Univariable Cox regression analyses were performed for each component of TFC2010, including imaging and ECG characteristics, gender, age, and history of syncope or VT before ICD implantation. The impact of age was assessed as a continuous variable and dichotomized using 35 years as a threshold as earlier proposed.[6] Since the proband status, which in previous studies was reported a predictor of arrhythmic events in ARVC,[7] indicates the first patient in a family from whom cascade screening is initiated, the proband status *per se* may not necessarily be related to the presence of phenotypical characteristics of the disease. Therefore it was substituted by the "Definite ARVC by phenotype" status defined as patients who fulfill TFC2010 for definite ARVC diagnosis without accounting for the family history or mutation carrying status. Multivariable analysis was performed only individual phenotypical characteristics of the disease, which demonstrated p value <0.15 in the univariable analysis thus excluding composite disease characteristics such as proband status and the Definite ARVC by phenotype status. Multivariable analysis included a stepwise backward elimination using logistic regression. A 2-sided p value of 0.05 was considered statistically significant.

Results

Of the total number of 296 patients with definite ARVC recruited by November 2017, 216 had an ICD implanted. ICD was implanted for secondary prevention of SCD in 137 patients whereas 79 patients constituted the primary prevention cohort (Table 1). One-third of the study population was recruited prospectively with newly diagnosed ARVC after June 2010: 45 (33%) in the secondary and 23 (29%) in the primary prevention group.

Left ventricular involvement defined as reduced left ventricular ejection fraction ≤40% was uncommon. A large proportion of patients underwent cardiac magnetic resonance imaging in addition to a conventional echocardiography, which was performed in all subjects. Few patients underwent myocardial biopsy, which was performed on the right ventricular (RV) free wall in only 9 subjects (4.2%) and on the RV septum in 59 (27%).

Genetic evaluation was performed in more than 80% of probands from both the secondary and primary prevention groups and in nearly half of the tested patients it yielded positive identification of a disease-causing genetic variant (n = 93, 52%). The vast majority of mutation-positive probands carried a mutation in the plakophillin-2 (PKP2) gene (63%), followed by desmoglein-2 (DSG2, 18%), desmoplakin (DSP, 14%), DSC-2 (5.3%), and TMEM43 (3.2%). Four patients had mutations identified in 2 desmosomal genes.

Primary asymptomatic patients, that is, those who were diagnosed through cascade family screening and did not have any symptoms or documented ventricular arrhythmias before diagnosis constituted one-third of the primary prevention cohort (n = 25, 30%).

During a median follow-up of 89 (interquartile range 58 to 146) months after ICD implantation, 22 patients

Table 1
Clinical characteristics of patients with definite ARVC (TF2010) who received ICD for primary and secondary prevention of SCD in the Nordic ARVC Registry

	Secondary prevention n = 137 1	Primary prevention n = 79 2	p Value
Men	**101(74%)**	**47 (60%)**	**0.022**
Probands	**128 (93)**	**51 (65)**	**<0.001**
Definite ARVC by TFC2010 criteria without Family history/Genetics	**122 (89)**	**53 (67)**	**<0.001**
Age at ICD implantation (years)	42 ± 15	39 ± 14	0.154
Age at diagnosis (years)	41 ± 16	38 ± 14	0.093
Age ≤35 years at ICD implantation, n (%)	47 (34)	30 (38)	0.345
SCD in a 1st degree relative <35 years	**8 (6)**	**11(15)**	**0.038**
Competitive athlete	**57 (42%)**	**15 (19%)**	**<0.001**
VT prior to ICD implantation*	**111 (81%)**	**20 (25%)**	**<0.001**
Syncope prior to ICD implantation	**25 (18%)**	**23 (29%)**	**0.048**
Imaging criterion, major	**108 (79%)**	**53 (67%)**	**0.041**
Imaging criterion, minor	113 (83%)	57 (72%)	0.054
LVEF (%)	56 ± 8	53 ± 12	0.308
LVEF ≤40%	9 (6.6%)	8 (10%)	0.248
Cardiac CMR performed	97 (71%)	40 (50%)	
RVEF by CMR (%)	39 ± 9	41 ± 14	0.367
RVEDV/BSA by CMR (ml/m^2)	**129 ± 32**	**118 ± 52**	**0.009**
LGE-positive	33 (44%)	10 (25%)	0.321
Tissue criterion major	5 (3.6%)	3 (4%)	0.612
Tissue criterion minor	0	0	N/A
Repolarization criterion major	73(53%)	39 (49%)	0.339
Repolarization criterion minor	87 (64%)	47 (61%)	0.398
Depolarization criterion major	13 (9.5%)	6 (7.6%)	0.419
Depolarization criterion minor	**92 (67%)**	**36 (46%)**	**0.002**
T-wave inversion inferior	41 (30%)	18 (23%)	0.165
Arrhythmia criterion major	61 (45%)	13 (17%)	<0.001
Arrhythmia criterion minor	123 (89%)	71 (90%)	0.590
Family history criterion major	**78 (57%)**	**58 (73%)**	**0.011**
Family history criterion minor	**1 (0.7%)**	**8 (10%)**	**0.002**
Genetic evaluation performed in probands	104 (81%)	42 (82%)	1.000
Desmosomal mutations in probands	**68 (53%)**	**25 (49%)**	**0.024**

Variables that demonstrated significant differences between the primary and secondary prevention groups are highlighted in bold font.

ARVC = arrhythmogenic right ventricular cardiomyopathy; BSA = body surface area; CMR = cardiac magnetic resonance imaging; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; SCD = sudden cardiac death; TFC = Task Force criteria; VT = ventricular tachycardia.

* For the primary prevention group, VT history concerns history of non-sustained VT.

underwent heart transplantation and 5 died. One death occurred in the primary prevention group (cause unknown) and 4 in the secondary prevention group (2 noncardiac, 1 within a month after heart transplantation, and 1 unknown).

By the end of follow-up, 81 patients had experienced appropriate shocks (18 [23%] in the primary prevention and 63 [46%] in the secondary prevention group, p = 0.002), whereas 147 experienced either appropriate shocks or ATP (46 [58%] in the primary prevention and 107 [78%] in the secondary prevention group, p = 0.004). Out of 24 primary asymptomatic patients, 13 had ATP during follow-up and none experienced ICD shock. Inappropriate ICD shocks were seen in 24 patients and occurred with similar 10-year cumulative incidence in patients from primary vs secondary prevention cohort (15% vs 11%, p = 0.839).

Results of univariable Cox regression analyses performed for the disease manifestations and diagnostic work up data are presented in Supplemental Table 1. The proband status, definite ARVC by phenotype status, young age (≤35 years), the major repolarization and the major depolarization criteria were significantly associated with primary end point in the univariable analysis. RV ejection fraction demonstrated a borderline significant inverse association with the primary outcome in the univariate analysis but was available only for the subset of patients who underwent cardiac magnetic resonance imaging and therefore not included in the multivariate analysis. Proband status and definite ARVC by phenotype status, being composite characteristics of the disease phenotype, were not included in the multivariable model together with individual phenotypical features of the disease.

Young age (≤35 years), major repolarization criterion, major depolarization criterion, and the history of syncope entered the multivariable model that was also adjusted for gender. After stepwise backward elimination process using logistic regression, the age ≤35 and the presence of major repolarization criterion were included in the final model and appeared to be independent predictors of appropriate ICD shocks. For the secondary end point, only the major repolarization criterion remained the independent predictor of the outcome in the multivariable analysis (Table 2).

Figure 1 presents the outcome in the primary prevention cohort grouped by the presence of the risk factors identified in the multivariate analysis (age ≤ 35 years, major repolarization criterion). The presence of 2 risk factors was associated with the cumulative risk of events similar to the one demonstrated by the secondary prevention cohort whereas primary prevention patients who did not have either of the risk factors did not experience any appropriate ICD shock. C-statistics for the risk factor model was 0.80 (95%CI 0.69 to 0.89) for the primary and 0.62 (95%CI 0.50 to 0.75) for the secondary end points.

Cumulative risk of the study end points in the primary prevention group categorized by the presence of distinct disease phenotype, that is, fulfillment of the definite ARVC diagnosis based on the phenotypical characteristics of the disease only and not requiring criteria from the family history or genetics, is presented in Figure 2. Primary prevention ICD carriers had cumulative incidence of appropriate ICD therapies in the same range as the secondary prevention cohort. In contrast, the incidence of appropriate ICD shocks in patients without either of the risk factors or not fulfilling definite ARVC diagnosis without family history/genetic information was low and corresponded to the annual rate of 0% to 0.7% (Supplemental Table 2).

Discussion

Our findings are based on the Scandinavian cohort of patients with definite ARVC who received ICD implants for primary or secondary prevention of SCD. Two risk factors, young age and major repolarization criterion by ECG, each independently predicted appropriate ICD shocks or death in patients who received ICD for primary prevention of SCD. The cumulative incidence of appropriate ICD therapies in the primary prevention patients who had either of these 2 risk factors was similar to the one observed in the secondary prevention cohort. Patients with ARVC phenotype becoming apparent after 35 years of age who do not manifest with major repolarization abnormality or require family history/genetic criterion in order to fulfill definite ARVC diagnosis constitute a low-risk group in regard to arrhythmic complications of the disease and may not require primary prevention ICD implantation.

Table 2
Results of the multivariable analysis of appropriate ICD therapy predictors in the primary prevention ARVC cohort. Age <35 years, major repolarization abnormality, major depolarization abnormality and the history of syncope were included in the multivariable model that was adjusted for gender

	Multivariable Cox regression			
	HR	95% Confidence interval		p Value
Any appropriate ICD shock or death from any cause				
Age < 35 years	4.21	1.49	11.85	0.006
Major repolarization abnormality	4.00	1.30	12.30	0.015
Any appropriate ICD shock or ATP or death from any cause				
Major repolarization abnormality	2.32	1.22	4.43	0.010

ARVC = arrhythmogenic right ventricular cardiomyopathy; ATP = antitachycardia pacing; HR = hazard ratio; ICD = implantable cardioverter-defibrillator.

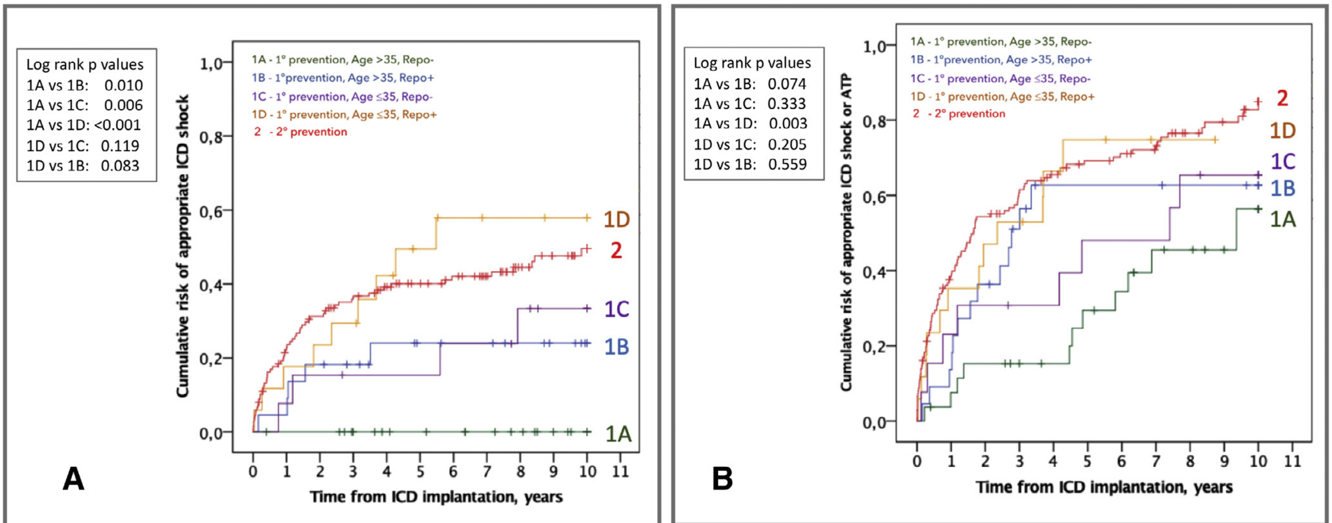
Clinical characteristics of primary prevention ICD recipients demonstrate significant variability in the literature, which may affect the results of analyses yielding different clinical characteristics as independent predictors of arrhythmic outcomes. Our patients can be compared with 2 earlier reported primary prevention cohorts[6,7] and the most recent report from the North American multidisciplinary study of ARVC, which included 56 patients who received ICD for primary prevention indication[12] (Table 3).

Similarly to the Johns Hopkins cohort,[7] our patients were diagnosed by TFC2010 and therefore also included patients with less severe disease manifestations. The prevalence of a history of syncope in our group was also remarkably similar to others.[7,12] Although being similar in regard to the ECG phenotype, our patients were older at ICD implantation, more often were men, and had less family members enrolled in the study than reported by Bhonsale et al.[7] The proportion of family members, who commonly demonstrate mild disease phenotype and low risk of arrhythmic complications of the disease, which may affect risk estimations, was strikingly similar in our and Johns Hopkins cohort.[7] The rate of ICD interventions, such as cumulative incidence of any appropriate ICD therapy by 10 years of follow-up is also similar to earlier reported being 63% in the Johns Hopkins cohort compared with 67% in ours.

Although syncope is a recognized risk factor in patients with ARVC and is listed as a class IIb indication[11] for ICD implantation, the data supporting this recommendation came mostly from the study on patients diagnosed by TFC1994[6] whereas contemporary primary prevention studies[7,12] did not support syncope as an independent predictor of appropriate ICD therapy. Our findings of the syncope lacking any predictive value for appropriate ICD therapies are therefore in accord with earlier findings in the primary prevention settings.

Previously published data in support of nonsustained ventricular tachycardia (NSVT) as a risk marker give a mixed picture. Although most of studies report NSVT as a predictor of appropriate ICD therapies un univariate analyses,[4,6,13] this was not supported by all[14] and only one earlier study devoted to the primary prevention found it to be an independent predictor of appropriate ICD therapies.[7] In our cohort, the prevalence of NSVT before ICD implantation is much lower than the one reported in the Johns Hopkins cohort.[7] Additional studies are therefore needed to resolve the uncertainty regarding predictive value of NSVT as a SCD risk indicator.

It has been observed that arrhythmic manifestations of ARVC are linked to other phenotypic characteristics of the disease[15] and its progression to the overt phenotype, which can be assessed as the age of ARVC diagnosis. Earlier data have consistently reported that younger age at diagnosis was associated with VT during follow-up.[6,7,12,13] Our findings are in line with these previous observations and support the use of age at disease presentation as a risk marker of arrhythmic events during follow-up. Although the age at



Numbers at risk (A)

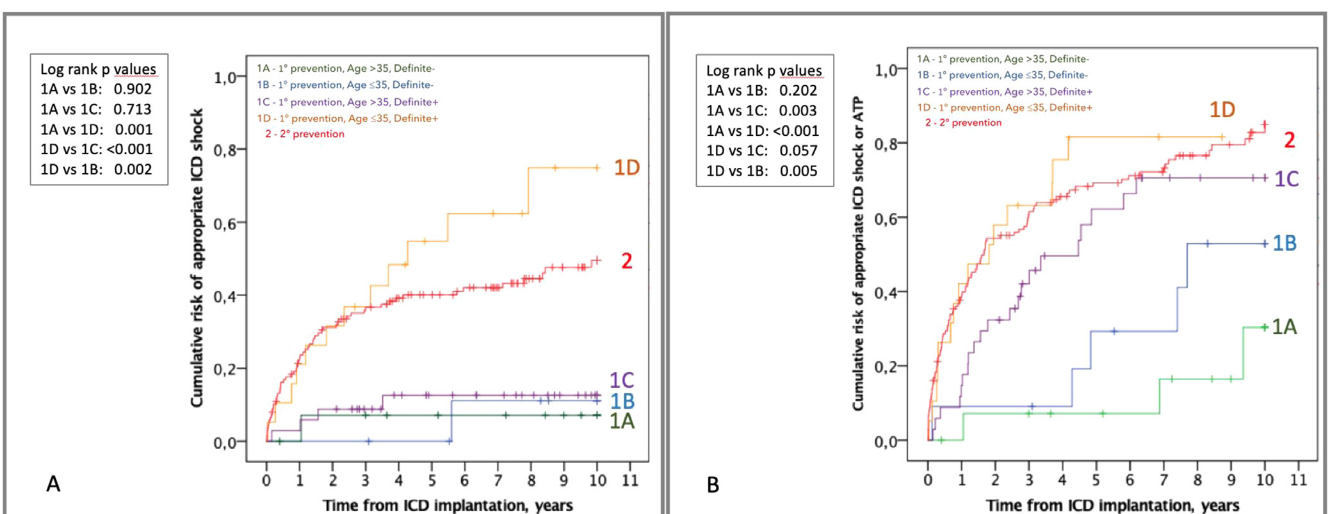
Year from ICD implant	0	2	4	6	8	10
2° prevention	137	90	70	58	39	25
1° prevention, Repo-, Age>35	27	26	20	18	14	8
1° prevention, Repo-, Age≤ 35	13	11	10	9	7	5
1° prevention, Repo+, Age>35	22	18	13	10	8	3
1° prevention, Repo+, Age≤35	17	13	9	4	3	2

Numbers at risk (B)

Year from ICD implant	0	2	4	6	8	10
2° prevention	137	60	40	30	17	8
1° prevention, Repo-, Age>35	27	22	18	13	8	4
1° prevention, Repo-, Age≤ 35	13	10	9	6	4	3
1° prevention, Repo+, Age>35	22	14	5	5	4	4
1° prevention, Repo+, Age≤35	17	9	5	2	1	0

Figure 1. Kaplan-Meier curve analysis of the risk of the primary (A) or secondary (B) end points in patients with ascertained ARVC diagnosis. Primary prevention cohort is presented as 4 groups (A−D) based on the presence of the disease characteristics identified in a multivariate analysis as independent predictors of appropriate ICD shocks or death from any cause: age at ARVC diagnosis ≤35 years and major repolarization criterion. Kaplan-Meier curves representing the risk of ICD therapies in the secondary prevention cohort is presented for comparison. ARVC = arrhythmogenic right ventricular cardiomyopathy; ICD = implantable cardioverter-defibrillator.

ICD implantation was included in the multivariable analysis as the time point for the start of follow-up in order to capture the study end points defined as appropriate ICD therapies or death, the mean difference between the age at diagnosis and the age at ICD implantation was less than 1 year and was not different between the groups.



Numbers at risk (A)

Year from ICD implant	0	2	4	6	8	10
2° prevention	137	90	70	58	39	25
1° prevention, Definite-, Age>35	15	13	11	10	9	6
1° prevention, Definite-, Age≤ 35	11	11	10	8	8	6
1° prevention, Definite+, Age>35	34	31	22	18	13	5
1° prevention, Definite+, Age≤35	19	13	9	5	2	1

Numbers at risk (B)

Year from ICD implant	0	2	4	6	8	10
2° prevention	137	60	40	30	17	8
1° prevention, Definite-, Age>35	15	13	11	10	8	5
1° prevention, Definite-, Age≤ 35	11	10	9	6	5	3
1° prevention, Definite+, Age>35	34	23	12	8	4	2
1° prevention, Definite+, Age≤35	19	8	4	2	1	0

Figure 2. Kaplan-Meier curve analyses of the risk of the primary (A) and secondary (B) end points in patients with ascertained ARVC diagnosis. Primary prevention cohort is presented as 4 groups (A−D) based on the age of diagnosis and the presence of definite ARVC diagnosis by TF2010, not requiring diagnostic criteria from the family history/genetic category. Kaplan-Meier curves representing the risk of ICD therapies in the secondary prevention cohort is presented for comparison. ARVC = arrhythmogenic right ventricular cardiomyopathy; ICD = implantable cardioverter-defibrillator.

Table 3
Clinical characteristics of ARVC patients with definite diagnostic category by TFC2010 from contemporary primary prevention cohorts

Variable	Bhonsale 2011[7] n = 84*	Link 2014[12] n = 56	Nordic ARVC registry n = 79
Age (years)	32 ± 12	40 ± 14	39 ± 14
Male gender	46%	60%	60%
Mean follow-up duration (months)	57	29	89
History of syncope	27%	25%	29%
History of NSVT	49%	16%	25%
Family History of SCD	17%	17%†	15%
Right precordial T-wave inversion (V_1-V_3)	68%	76%	49%
Major RV abnormality	29%	71%†	67%
LVEF <55%	25%	13%†	24%

* Only 70 of 84 patients fulfilled criteria for definite ARVC.
† data not published, provided by North American multidisciplinary ARVC study team. ARVC − arrhythmogenic right ventricular cardiomyopathy; LVEF − left ventricular ejection fraction; NSVT − non-sustained ventricular tachycardia; SCD − sudden cardiac death.

Our data suggest that early disease manifestation or T-wave inversion meeting criteria for major repolarization criteria are associated with 4-fold increased risk of appropriate ICD shocks or death. Cumulative incidence of ICD therapies in high-risk patients from the primary prevention cohort was also found to be very similar to the incidence observed in the secondary prevention cohort. This further illustrates the primary prevention risk stratification challenge as, based on our findings, patients with early disease manifestations may be expected to receive ICD therapies to the same extent as secondary prevention ARVC patients.

In the diagnostic criteria, which constitute the disease phenotype, ECG characteristics that reflect depolarization and repolarization abnormalities meeting definitions for major criteria appeared to be univariate predictors of the primary end point, of which abnormal ventricular repolarization consistent with the major diagnostic criterion appeared to be the strongest predictor whereas arrhythmic criteria were not significantly associated with the outcome.

Although the use of ICD therapies and inclusion of ATP in the secondary end point may overestimate the life-saving efficacy of ICD therapy, the lack of ICD therapies can be used for identification of patients who would not benefit from ICD implantation. Our data further support earlier observations that family members, and primary asymptomatic family members in particular, are at low risk of arrhythmic events.[7,16] In our study, primary asymptomatic patients did not have any appropriate ICD shocks during follow-up.

Our cohort consists of patients who were under clinical follow-up by the register launch in June 2010 and those who were prospectively enrolled with newly diagnosed ARVC since then, which is a limitation of the study. However, the main end point of the study, that is, delivery of ICD therapies, is governed by strict documentation requirements in the participating countries, which supports the validity of the study end point. We have not been able to distinguish delivery of ICD therapies dependent on the cycle length of VT/VF in our study and thus could not reliably distinguish whether ICD shocks were delivered for fast or slow VT. The rate of therapy delivery, however, appears to be in the same range as the one reported in an earlier contemporary long-term follow-up primary prevention ARVC population,[7] which supports clinical validity of our study findings. Finally, despite being a relatively large study in the context of ARVC, the size of our cohort is still not sufficient for definitive conclusions concerning other risk factors, which have not demonstrated predictive value in our study.

In conclusion, our data based on a contemporary cohort of patients with definite ARVC diagnosed using TFC2010 treated with ICD for primary prevention of SCD further supports the use of severe disease phenotype, young age at ARVC diagnosis, and electrocardiographic ventricular repolarization abnormalities in particular, as the major risk factors predicting appropriate ICD therapies. Family history of SCD at young age in a first degree relative was not associated with increased risk of ventricular arrhythmic events in primary prevention ICD recipients.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.12.049.

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