

Cardiac phenotype and long-term prognosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia patients with late presentation



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BACKGROUND The clinical profile of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) patients with late presentation is unknown.

OBJECTIVE The purpose of this study was to characterize the genotype, cardiac phenotype, and long-term outcomes of ARVC/D patients with late presentation (age ≥ 50 years at diagnosis).

METHODS Five hundred two patients with an ARVC/D diagnosis from Johns Hopkins and Utrecht Registries were studied and long-term clinical outcomes ascertained.

RESULTS Late presentation was seen in 104 patients (21%; 38% PKP2 carriers); 3% were ≥ 65 years at diagnosis. Sustained ventricular tachycardia was the major (43%) mode of presentation in patients with late presentation, whereas cardiac syncope was infrequent ($P < .001$). Those with late presentation were significantly less likely to harbor a known pathogenic mutation (53%; $P = .005$), have less precordial T-wave repolarization changes ($P < .001$), and have lower ventricular ectopy burden ($P = .026$). Over median 6-year follow-up, 68 patients with late presentation (65%) experienced sustained

ventricular arrhythmias, with similar arrhythmia-free survival at 5-year follow up ($P = .48$). Left ventricular dysfunction and heart failure were seen in 24 (32%) and 15 patients (14%), respectively, without need for cardiac transplantation. In the late presentation cohort, male sex, pathogenic mutation, right ventricular structural disease, lack of family history, and electrophysiologic study inducibility were associated with increased arrhythmic risk.

CONCLUSION One-fifth of all ARVC/D patients present after age 50 years, often with sustained ventricular tachycardia, and are less likely to have prior syncope, ECG changes, ventricular ectopy, or identifiable pathogenic mutation. In ARVC/D, late presentation does not confer a benign prognosis and is associated with high arrhythmic risk.

KEYWORDS Cardiomyopathy; Arrhythmogenic right ventricular cardiomyopathy/dysplasia; Late onset; Outcome; Genotype

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Introduction

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is an inherited cardiomyopathy characterized by

right ventricular (RV) dysfunction, ventricular arrhythmias, and increased risk of sudden cardiac death (SCD).¹ This disease has age-dependent penetrance, and most patients present

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in the second to fourth decade of life; presentation in older patients is rare.^{2–4} As such, the current body of literature is limited to a handful of case reports.^{5–11} Consequently, the clinical characteristics, genotype, and long-term outcome of patients with an ARVC/D diagnosis established at a later age are largely unknown. Also unknown is whether they present differently, have a different spectrum of genetic defects, or are associated with a more benign prognosis compared to those who present earlier. The prognosis and arrhythmic risk factors in patients diagnosed as having ARVC/D at a later age have not been well defined, mainly because of the lack of large cohorts to allow systematic study of patients ≥ 50 years at ARVC/D diagnosis.

This study was designed to clarify and resolve the clinical profile of older patients with ARVC/D. The study has 3 main objectives: (1) to characterize the clinical presentation, genotype, cardiac phenotype, and long-term outcomes in ARVC/D patients diagnosed at a late age (≥ 50 years); (2) to ascertain clinical factors associated with delayed-onset ARVC/D and to identify predictors of arrhythmic risk in this unique ARVC/D population; and (3) to investigate the difference in cardiac phenotype in ARVC/D patients at various ages of diagnosis (i.e., from children to the elderly).

Methods

Study population

The study population was identified from the Johns Hopkins ARVC/D Registry (ARVD.com) and the University Medical Center Utrecht ARVC/D Registry. Both registries prospectively enroll ARVC/D patients and their family members with a possible history of the disease. For the purposes of this study, we included 502 individuals who were diagnosed with ARVC/D based on revised 2010 Task Force Criteria (TFC) at last follow-up.¹² All probands in this study underwent comprehensive mutation testing (see [Supplemental Table 1](#)) for an ARVC/D-associated pathogenic mutation. Family members were screened specifically for the mutation identified in the probands. For the purposes of this study, patients were grouped into those with late presentation (≥ 50 years at time of diagnosis) and a comparative group (ARVC/D diagnosis before 50 years of age). The only prior study that grouped ARVC/D patients into early and late presentation used a cutoff >50 years.¹³ Also, it has been noted that HCM patients >50 years of age had a significantly different course compared to younger ones.¹⁴ All registry participants provided informed consent, and the study protocol was approved by the respective institutional review boards.

Clinical characterization

Participants were evaluated as described previously.^{15,16} The medical history of each individual was obtained by review of medical records, clinical evaluation, and/or patient interview. Detailed clinical information regarding demographics, presentation, symptom onset, and noninvasive and invasive tests was obtained for every participant. Per diagnostic TFC, precordial T-wave inversions were not taken into

account for individuals ≤ 14 years of age.¹² Twenty-four-hour Holter monitoring was evaluated for premature ventricular complex (PVC) count, which according to the 2010 TFC was regarded as abnormal if >500 PVCs were recorded. In addition, echocardiography, cardiac magnetic resonance imaging, and RV angiography were reviewed to determine the severity and extent of structural abnormalities according to the TFC.¹²

Follow-up and outcome measures

The primary outcome of interest was a composite arrhythmic outcome comprising occurrence of either spontaneous sustained ventricular tachycardia (VT), ventricular fibrillation/resuscitated sudden cardiac arrest, SCD, or appropriate implantable cardioverter-defibrillator (ICD) intervention for a ventricular arrhythmia, as described previously (see [Supplemental Table 1](#) for definitions).¹⁵ The secondary outcome of interest was the occurrence of cardiac transplantation or death due to heart failure (HF).

Statistical analysis

All continuous data are presented as mean \pm SD and categorical variables as number (percentage). Continuous variables were compared using the independent Student *t* test or Mann–Whitney *U* test and categorical data using the χ^2 or Fisher exact test. Nonparametric trend test was used to evaluate the change in clinical phenotype with each decade (age at presentation: <20 years, 20–29 years, 30–39 years, 40–49 years, ≥ 50 years). The cumulative freedom from our outcome measures since presentation was determined by the Kaplan–Meier method for outcome measure. In patients with multiple endpoints, the first event was considered the outcome event. Differences in survival were evaluated with a log-rank or Wilcoxon test. Univariable and multivariable logistic regression was used to identify independent predictors of late-onset ARVC/D.

Within family dependency was evaluated using a robust variance estimator, clustered by family. $P < .05$ was considered significant. Statistical calculations were performed using STATA 13.1 (Stata Corp, College Station, TX).

Results

Study population

We included 502 definite ARVC/D patients enrolled in the Johns Hopkins ($n = 392$) or University Medical Center Utrecht ($n = 110$) ARVC/D Registry. Approximately half of study subjects were male ($n = 264$ [53%]), with a mean age of 35.1 ± 14.9 years at the time of presentation. The majority of study participants ($n = 346$ [69%]) were probands.

Presentation

As shown in [Table 1](#), 104 patients (21%) were diagnosed at >50 years of age. Sustained VT was the predominant mode of presentation in the late presentation cohort (43% vs 31% in the younger group), with significant age-associated trend in the nature of presentation ([Figure 1](#)). Proband status (64%

Table 1 Baseline characteristics and cardiac phenotype in patients diagnosed with ARVC/D at late age (≥ 50 years) compared to those diagnosed earlier (< 50 years)

Clinical variable	< 50 yrs (n = 398)	≥ 50 yrs (n = 104)	P value
Male sex	200 (50)	64 (61)	NS
Proband	279 (70)	67 (64)	NS
Mutation carrier	269 (67)	55 (53)	.005
ARVC/D in first degree relative (TFC)	114 (31)	30 (31)	NS
Premature SCD in first degree relative	31 (8)	7 (7)	NS
Presentation			
SCD	28 (7)	6 (6)	.039
Resuscitated SCA	22 (5)	2 (2)	
Sustained VT	122 (31)	45 (43)	
Symptomatic	145 (36)	26 (25)	
Asymptomatic	81 (20)	25 (24)	
Multiple VT morphology (n = 447)	133/351 (38)	36/96 (37)	NS
AA medications (n = 482)	178/384 (46)	54/98 (55)	NS
Cardiac syncope	141 (38)	22 (23)	.005
Holter PVC count (median [IQR])	2497 [5387]	1503 [4187]	.026
EPS inducibility (n = 323)	195/264 (74)	43/59 (73)	NS
TFC criteria (not autopsy) (median [IQR])	6 [3]	5 [2.5]	.004
Repolarization criteria			
No abnormality	30 (8)	20 (20)	.0013
Minor	47 (13)	18 (19)	
Negative T wave V_1 - V_2	26 (7)	10 (10)	NS
Negative T wave V_4 - V_6	14 (4)	5 (5)	NS
Negative T wave V_1 - V_4 with CRBBB	23 (6)	7 (7)	NS
Major			
Negative T wave V_1 - V_3	290 (79)	59 (61)	$< .001$
Depolarization criteria			
No abnormality	141 (38)	40 (41)	NS
\geq TAD	148 (40)	38 (39)	NS
Late potentials	136 (44)	35 (50)	NS
Epsilon wave	38 (10)	12 (12)	NS
Arrhythmia criteria			
LBBB superior-axis VT	142 (38)	41 (42)	NS
LBBB VT	217 (59)	47 (48)	.054
Holter monitor > 500 PVCs/24 hrs (n = 366)	226/296 (76)	46/70 (66)	.067
Imaging criteria			
Major structural abnormality	220 (60)	55 (57)	NS
Minor structural abnormality	51 (14)	14 (14)	NS
Left ventricular dysfunction (n = 312)	53/238 (22)	24/74 (32)	.077

Phenotypic (ECG, arrhythmia, echocardiography) characteristics are reported only from the patients who presented alive to the registry.

AA = antiarrhythmic; ARVC/D = arrhythmogenic right ventricular cardiomyopathy/dysplasia; CRBBB = complete right bundle branch block; EPS = electrophysiologic study; IQR = interquartile range; LBBB = left bundle branch block; PVC = premature ventricular complex; SCA = sudden cardiac arrest; SCD = sudden cardiac death; TFC = Task Force criteria; VT = ventricular tachycardia; \geq TAD = prolonged terminal activation delay.

vs 70%) and male sex (61% vs 50%) were similarly distributed among older and younger ARVC/D subjects, respectively. Use of antiarrhythmic medications (55%) and presence of multiple VT morphologies (37%) was not significantly different in the late presentation ARVC/D patients. The median number of TFC expressed by the study population progressively declined with increasing age at diagnosis, with the late presentation group having significantly lower score (P for trend $< .001$) (see [Supplemental Table 2](#)). However, syncope was significantly less common in late presentation compared to younger patients (23% vs 38%; $P = .005$) ([Table 1](#)), with significant age-related trend (see [Supplemental Table 2](#)).

Genotype and family history

Overall, pathogenic mutations were identified in 324 patients (64%) in the cohort. As shown in [Table 1](#), older patients were

less likely to harbor a mutation (53% vs 67%; $P = .005$). The genotypic characteristics of the population stratified by age are given in [Supplemental Table 3](#). Among patients with late presentation and presence of a pathogenic mutation, plakophilin-2 (*PKP2*) mutations were most common (73%), with phospholamban (*PLN*) mutations present in 10 patients (18%). One late presentation patient harbored more than 1 mutation (compound heterozygosity for *PKP2*; TFC = 8); none had desmoplakin (*DSP*) or desmoglein-2 (*DSG2*) mutations. No significant trend was seen in the nature of mutation (truncating vs splice site vs missense) with increasing age ($P = .329$) ([Figure 2A](#)). As shown in [Figure 2A](#) and [Supplemental Table 2](#), increasing age at diagnosis was associated with a significantly lower proportion of mutation carriers and a significant trend for nondesmosomal variants. More than one-third (38%) of late presentation

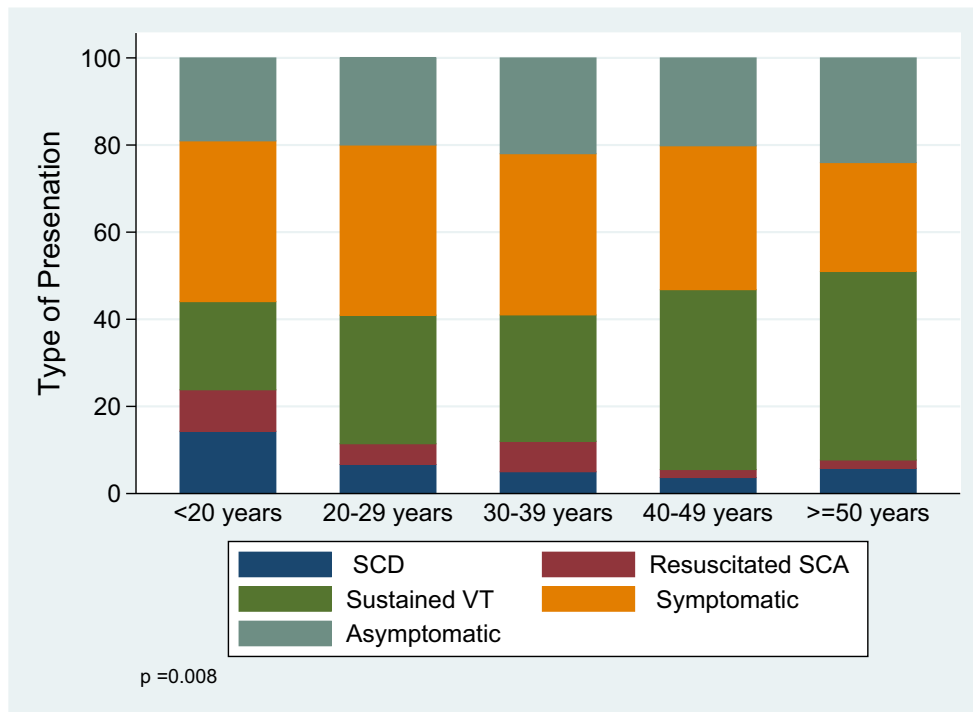


Figure 1 Nature of presentation with increasing decade of age in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. SCA = sudden cardiac arrest; SCD = sudden cardiac death; VT = ventricular tachycardia.

patients met 1 or more of the ARVC/D TFC family history criteria. No significant trend in the occurrence of any of the family history parameters (in isolation or together) was seen with age at diagnosis (see [Supplemental Table 2](#)).

Cardiac phenotype

ECG

Patients with ARVC/D diagnosis at >50 years were less likely to have precordial T-wave changes ($P < .001$) and less likely to meet major repolarization criteria (negative T wave V_1 – V_3 ; $P < .001$). Increasing age at diagnosis was also associated with a significant trend for less frequent major precordial repolarization changes ([Figure 2B](#)). No significant trend in depolarization characteristics was seen with increasing age at diagnosis (see [Supplemental Table 2](#)).

Arrhythmia

Electrophysiologic study (EPS) was performed in 59 patients >50 years of age. EPS inducibility was noted in 43 patients (79%), comparable to the 74% noted in those with earlier disease diagnosis. Median PVC count was significantly lower in late-onset patients (1503 PVCs per day) ([Table 1](#)), with a significant trend in declining PVC burden observed with increasing age at diagnosis ([Figure 2C](#) and [Supplemental Table 2](#)).

Structural abnormality

No significant difference in the pattern of structural abnormality was seen in the late presentation ARVC/D patient group, with comparable occurrence of minor (14% vs 14%)

and major RV structural abnormality (57% vs 60%) and a trend toward more left ventricular dysfunction (32% vs 22%; $P = .07$).

Outcome

The late presentation cohort was followed for a median follow-up period of 6 years [interquartile range 10 years], which was not different from the younger groups ([Table 2](#)). The composite arrhythmic outcome was seen in 68 patients (65%; $P = .500$) ([Table 2](#) and [Supplemental Table 4](#)). Arrhythmia-free survival in late presentation patients without sustained ventricular arrhythmia at presentation at 1 and 5 years of follow-up were similar to those who presented earlier (82% vs 80% and 60% vs 73% respectively; $P = .0757$) ([Figure 3A](#)). HF was seen in 15 patients (14%), with none requiring cardiac transplantation ([Figure 3B](#)), and no significant changes in the occurrence of HF with increasing age (see [Supplemental Table 4](#)). ICD insertion was performed in 69 patients (66%) with primary prevention of SCD as the indication in 17 (25%). The appropriate ICD therapy occurrence was significantly less frequent in the late presentation group compared to a younger population (43% vs 58%; $P = .027$), with significant change with increasing age ([Figure 4A](#)). The occurrence of VT storm (7% vs 19% in younger population) and atrial arrhythmias (30% vs 12%) showed a significant age trend, with VT storms being less common and atrial tachyarrhythmias being progressively more common ([Figure 4B](#) and [Supplemental Table 4](#)). Overall, 12 patients (11%) experienced cardiac death during follow-up, with SCD being the initial presentation for 6 late presentation patients (6%) (see [Supplemental Table 4](#)).

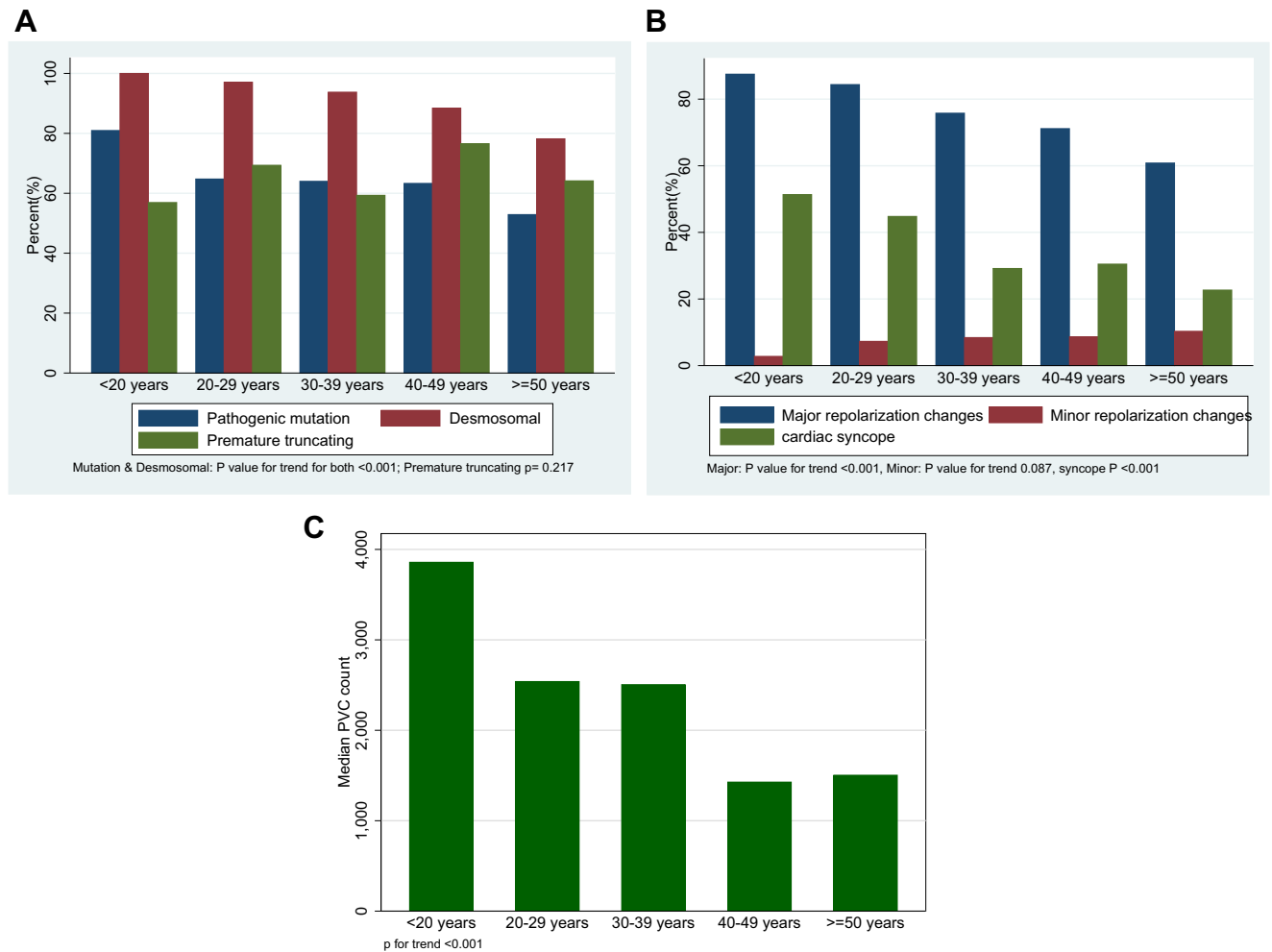


Figure 2 A: Trend in genotypic characteristics with increasing age at diagnosis in ARVC/D. B: Change in ECG repolarization abnormalities with increasing age at diagnosis in ARVC/D. C: Bar graph showing decline in Holter-recorded ventricular ectopy with increasing age at diagnosis in ARVC/D. ARVC/D = arrhythmogenic right ventricular cardiomyopathy/dysplasia; PVC = premature ventricular complex.

Patients >65 years at diagnosis

Sixteen ARVC/D patients (3%) were diagnosed at >65 years, with a age in this group of 71 years (minimum 65, maximum 76). Clinical and genetic characteristics of these 16 patients are detailed in [Supplemental Table 5](#). The average TFC score was 6; 12 of 16 were male. Two patients had a pathologic diagnosis after presenting with SCD, whereas 7 of 14 presented with sustained VT. Pathogenic mutations (all in *PKP2*) were identified in 7 of 16 patients. The clinical outcome in these patients is detailed in [Supplemental Table 6](#), with a mean follow-up duration of 6.6 years. Two patients experienced VT storm, and 10 of 16 underwent ICD insertion. Left ventricular dysfunction was seen in 2 patients, with 4 of 16 receiving HF diagnosis. The composite arrhythmic outcome was noted for 11 of 16 patients (69%). The individual TFC for these patients are detailed in [Supplemental Table 7](#).

Predictors of late presentation and arrhythmic risk

Multivariable logistic regression was performed to identify clinical factors associated with age ≥ 50 years among ARVC/D patients. Male sex (odds ratio [OR] 2.12, 95%

confidence interval [CI] 1.31–3.45; $P = .002$), absence of an identifiable pathogenic mutation (OR 1.89, 95% CI 1.18–3.02; $P = .008$), and family member status (OR 2.72, 95% CI 1.43–5.18; $P = .002$) were independently associated with age at diagnosis >50 years (see [Supplemental Table 8](#)). [Supplemental Figure 1](#) shows the distribution of these 3 risk factors in the younger and older populations (0 = no risk factor implies a female proband with pathogenic mutation, and 3 risk factors implies a male family member without an identifiable mutation). As shown in [Supplemental Table 9](#), on univariable analysis, male sex ($P = .002$), presence of an identifiable pathogenic mutation ($P = .001$), inducibility at EPS ($P < .001$), presence of major structural disease ($P = .022$), and absence of a family history ($P < .001$) were associated with increased risk of arrhythmic outcome. ECG changes and ventricular ectopy were not associated with the occurrence of an arrhythmic event.

Discussion

Inherited cardiomyopathies including ARVC/D are often characterized by incomplete penetrance and variable

Table 2 Long-term outcome in patients with ARVC/D diagnosed at a later age

Clinical outcome	Age <50 yrs (n = 398)	Age ≥50 yrs (n = 104)	P value
Duration of follow-up (yrs) (presenting alive) [median (IQR)]	7 (10)	5 (6)	.085
ICD insertion (n = 370)	301 (76)	69 (66)	.056
Primary prevention ICD	121 (40)	17 (25)	.016
Appropriate ICD therapy after ICD insertion	175/301 (58)	30/69 (43)	.027
VT ablation	127 (32)	30 (29)	NS
VT storm	68 (18)	7 (7)	.007
AF/AFL	45 (12)	27 (30)	<.001
Heart failure	52 (13)	15 (14)	NS
Cardiac transplantation	19 (5)	0	.023
Composite arrhythmic outcome (first occurrence)	274 (69)	68 (65)	NS
Sustained VT as first event	170 (43)	55 (53)	.018
SCA as first event	28 (7)	1 (1)	.018
ICD therapy as first event	44 (11)	4 (4)	.018
Cardiac death	41 (10)	12 (11)	NS

AF/AFL = atrial fibrillation/atrial flutter; ARVC/D = arrhythmogenic right ventricular cardiomyopathy/dysplasia; ICD = implantable cardioverter-defibrillator; IQR = interquartile range; SCA = sudden cardiac arrest; VT = ventricular tachycardia.

expression. In hypertrophic cardiomyopathy, studies point toward age-related differences in both clinical and morphologic expression.¹⁷ In these patients, the genetic profile underlying late presentation may be different^{18,19} and associated with better survival and benign prognosis.²⁰ Once regarded as a disease most relevant to the young, ARVC/D has been identified with increasing frequency in older patients, largely as a result of heightened physician awareness and careful assessment of phenotype after cascade genetic screening. Prior large cohorts have often focused on young patients to describe the clinical features.^{3,21} Late presentation patients clearly have the advantage of a disease-free life before the condition appears; however, this does not guarantee that all issues associated with ARVC/D will be less severe after diagnosis of the condition. Our current large transatlantic cohort is well suited to shed light on this unique group. The present data from >100 late presentation patients, selected by age ≥50 years at diagnosis, provide insight into the clinical course of ARVC/D. Our study has 3 important results. First, we clarify the presentation, cardiac phenotype, and long-term outcomes among this late presentation cohort. Second, we identify significant trends in the phenotype that occur with each decade of diagnosis. Third, we elucidate clinical risk factors associated with late presentation and the arrhythmic risk in this unique ARVC/D population.

Our study shows that nearly one-fifth of ARVC/D patients present at >50 years of age predominantly with sustained VT. Sudden death was most common in the young,³ although this risk remains throughout the entire adult life. This adds to previous observations that the mechanism of arrhythmia

might be different in the young compared to the very old.^{3,22} This suggests that ARVC/D should be considered as a possible cause of life-threatening ventricular arrhythmias in older patients as well and that clinical screening should be continued throughout adult life in people who are at risk for ARVC/D. Cardiac syncope occurs rarely in the elderly, but its occurrence suggests a higher risk of ventricular arrhythmias.

This study showed that late presentation patients were less likely to harbor a pathogenic mutation and that increasing age at diagnosis (by decade) was associated with a significantly lower proportion of mutation carriers. It is likely that yet unidentified genetic changes may underlie this subgroup of patients with late clinical expression. Genetic factors influencing low penetrance and later-onset disease are not well understood,¹³ and endurance exercise as an environmental trigger may lead to variable onset of ARVC/D phenotype in these gene elusive patients.²³ A significant age trend for nondesmosomal variants in this study complements the previous observation of later disease presentation in the *PLN* gene group.^{22,24} Our study suggests no significant trend in the occurrence of truncating or missense mutations with age in contrast to prior reports.²⁵ It is likely that the genotypic trends contribute at least in part to the phenotypic expression patterns. Patients with late presentation are less likely to have diagnostic precordial T-wave repolarization that could contribute to their late recognition. In addition, this cohort has less ventricular ectopy, which did not associate with occurrence of arrhythmic outcome despite prior reports suggesting this relationship in younger groups.²⁶ Given this finding, ARVC/D diagnosis should be entertained in older patients with less than typical ECG and ectopy characteristics.

The study of this late-onset group suggests that these patients are not at low risk for disease-related morbidity and mortality and have a similar arrhythmic course as those with earlier onset of the phenotype. However, despite this considerable arrhythmic risk, patients with late presentation have significantly fewer VT storms or appropriate ICD interventions, suggesting that their clinical trajectory is somewhat less severe than that in the young. Family members with ARVC/D diagnosis have been noted to have less arrhythmic risk than probands.²⁷ In our study, family members with ARVC/D diagnosis in both the younger and late presentation cohorts were noted to have similar (21% vs 33 %; $p = 0.197$) arrhythmic outcomes. The occurrence of significant RV dysfunction was similar, with similar incidence of HF indicating the need for careful follow-up in this cohort. Prior studies have identified multiple independent risk factors for SCD in ARVC/D patients.²⁸ Our study points toward male sex, presence of a pathogenic mutation, inducibility at EPS, major RV structural disease, and lack of family history of ARVC/D as being associated with increased risk of arrhythmic outcome in late presentation ARVC/D patients. On the other hand, ECG changes and ventricular ectopy that were associated with SCD in prior studies^{15,28} do not relate to arrhythmic events.

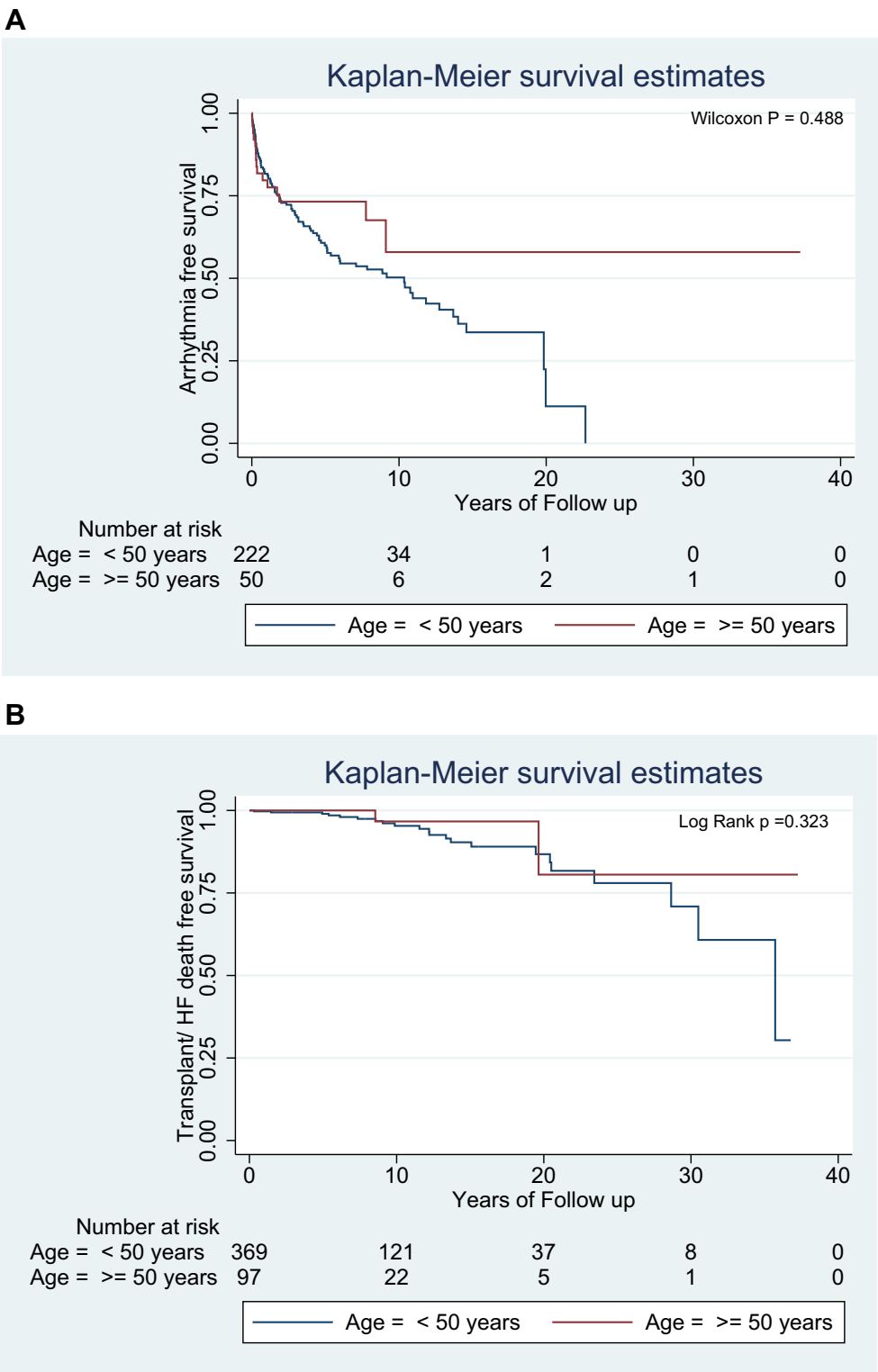


Figure 3 **A:** Arrhythmic-free survival in ARVC/D patients without sustained ventricular arrhythmia at presentation stratified according to age at diagnosis. **B:** Transplant/heart failure (HF) death-free survival in ARVC/D patients presenting at later age (≥ 50 years) compared to those presenting earlier (< 50 years). ARVC/D = arrhythmogenic right ventricular cardiomyopathy/dysplasia.

Study limitations

The patient cohort reported here constitutes the experience of 2 large ARVC/D centers for which some patient referral selection bias was unavoidable. The true incidence of

late-onset ARVC/D, however, may be underestimated because of the presence of other comorbidities such as coronary atherosclerosis and myocardial infarction. In addition, phenotypic testing for ARVC/D after age 50 years may be

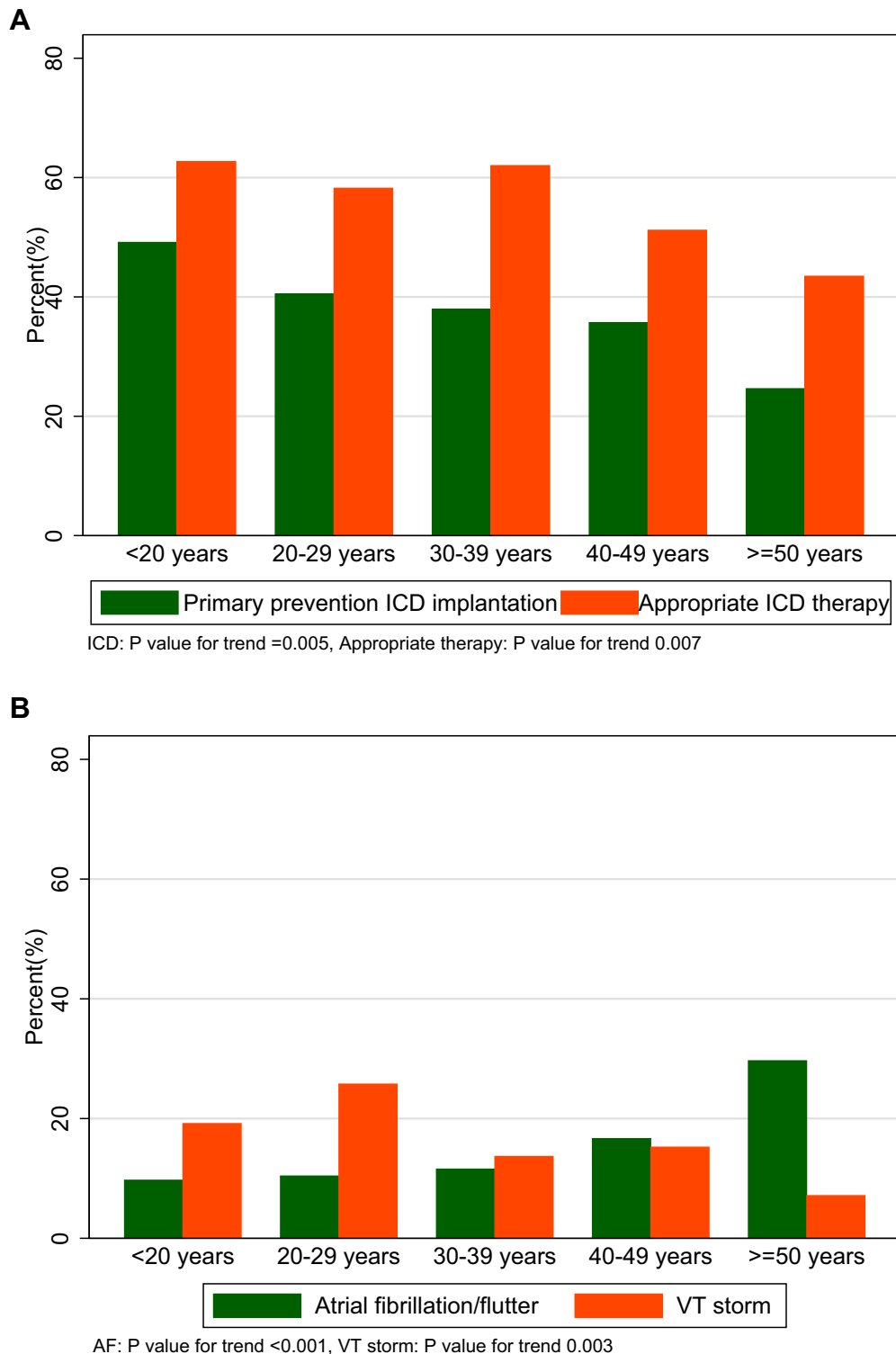


Figure 4 A: Trend in proportion of patients receiving primary prevention ICD and overall appropriate ICD intervention with increasing age of diagnosis in ARVC/D. B: Change in proportion of patients with atrial fibrillation and those experiencing VT storms with increasing age at diagnosis in ARVC/D. ARVC/D = arrhythmogenic right ventricular cardiomyopathy/dysplasia; ICD = implantable cardioverter–defibrillator; VT = ventricular tachycardia.

misleading. Finally, the age at diagnosis of ARVC/D occasionally is not easily defined and for a family member is dependent on the age at which a proband first sought evaluation for ARVC/D.

Conclusion

One-fifth of all ARVC/D patients present after age 50 years, often with sustained VT, and are less likely to have prior syncope, ECG changes, ventricular ectopy, or identifiable

pathogenic mutation. In ARVC/D, late presentation does not confer a benign prognosis and is associated with high arrhythmic risk. The influx of ARVC/D patients with late presentation, often recognized for the first time and frequently without conventional SCD risk factors, creates unique clinical decision-making and management uncertainties, particularly with respect to recommendations for ICD insertion. This diagnosis should be considered as a potential cause of sustained VT of RV origin among the elderly and should be treated per current consensus guidelines,²⁹ with careful assessment and follow-up as for every other patient who presents with this condition for the first time.

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Appendix Supplementary data

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.hrthm.2017.02.013>.

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