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CARDIOMIOPATIA ARITMOGENA: WHAT'S NEW?

DISPLASIA ARITMOGENA DEL VENTRICOLO DESTRO: LONG-TERM FOLLOW-UP

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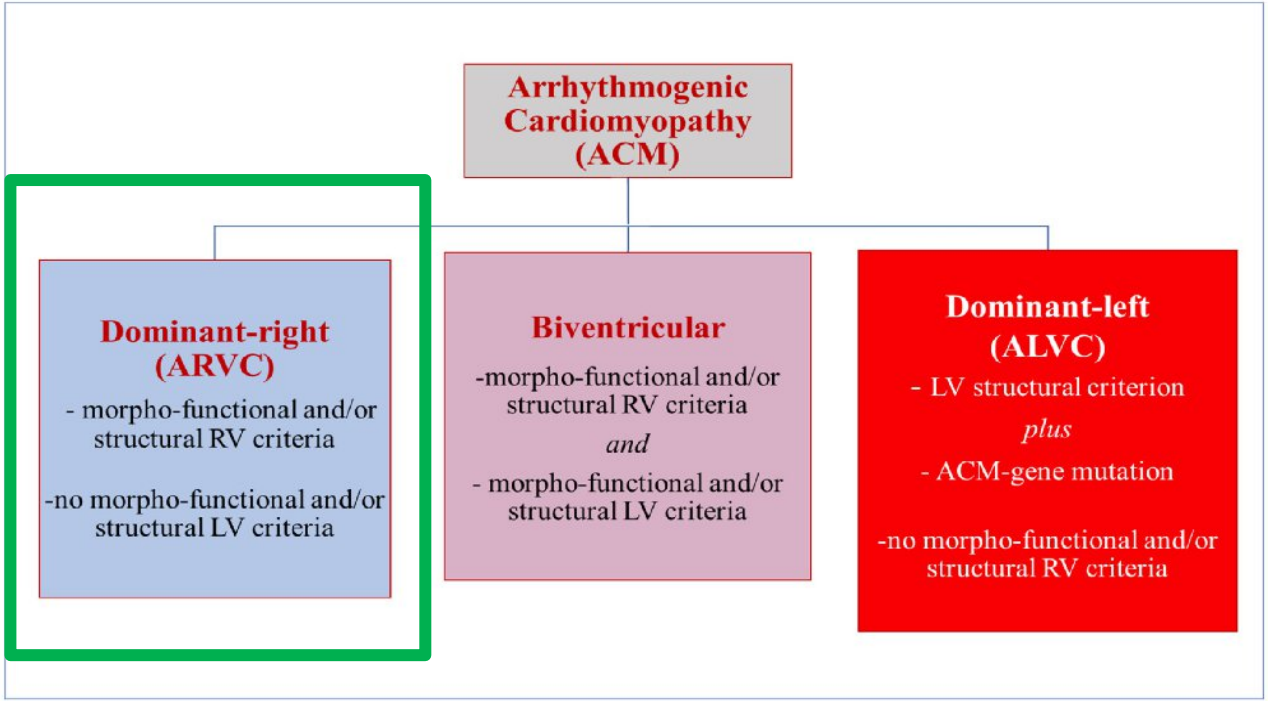
Diagnosis of arrhythmogenic cardiomyopathy: The Padua criteria

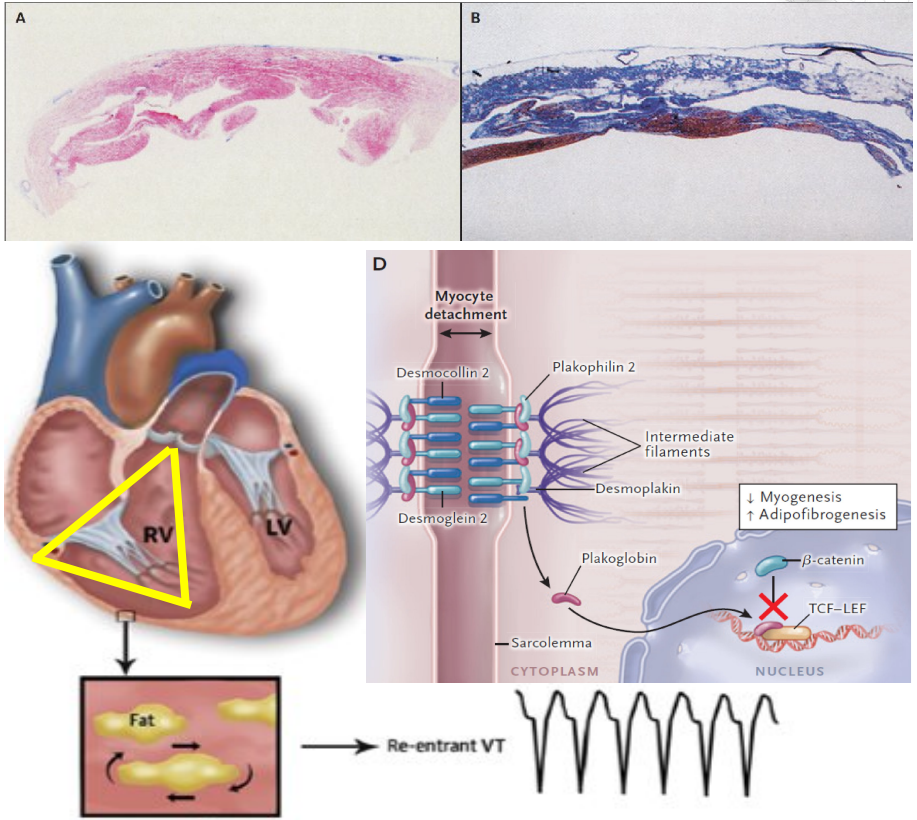


- **Genetic** heart muscle disease
- **RV, LV or both**
- Pathologic hallmark: **fibro-fatty myocardial replacement**
- Global and/or regional ventricular dysfunction
- Distinctive **propensity** of ACM to develop potentially lethal **scar-related ventricular arrhythmias** (regardless of the severity of the systolic ventricular dysfunction)

Corrado D, et al. Int J Cardiol. 2020;319:106–114

ARVC: main disease hallmarks

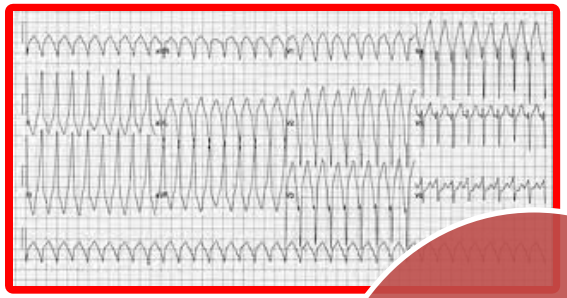
- Autosomal dominant pattern of inheritance.
- Mutations in genes encoding desmosomal proteins related to cellular connection (such as desmoplakin, plakoglobin, plakophilin 2, desmocollin 2, and desmoglein 2; genetically abnormal desmosomes lead to disruption of intercellular junctions, with myocytes detachment and cell death).
- The distinctive histopathological feature is the loss of RV myocardium, with the substitution of fibrous and fatty tissue (from epi to endo, predominantly in the RV free wall such as inflow tract, outflow tract and apex).
- The fibrofatty tissue replacement sustains ventricular arrhythmias (by slowing intraventricular conduction and through a scar-related macro-reentry mechanism).



Basso C et al. The Lancet. 2009;373:1289

Corrado D, et al. NEJM. 2017;376:61

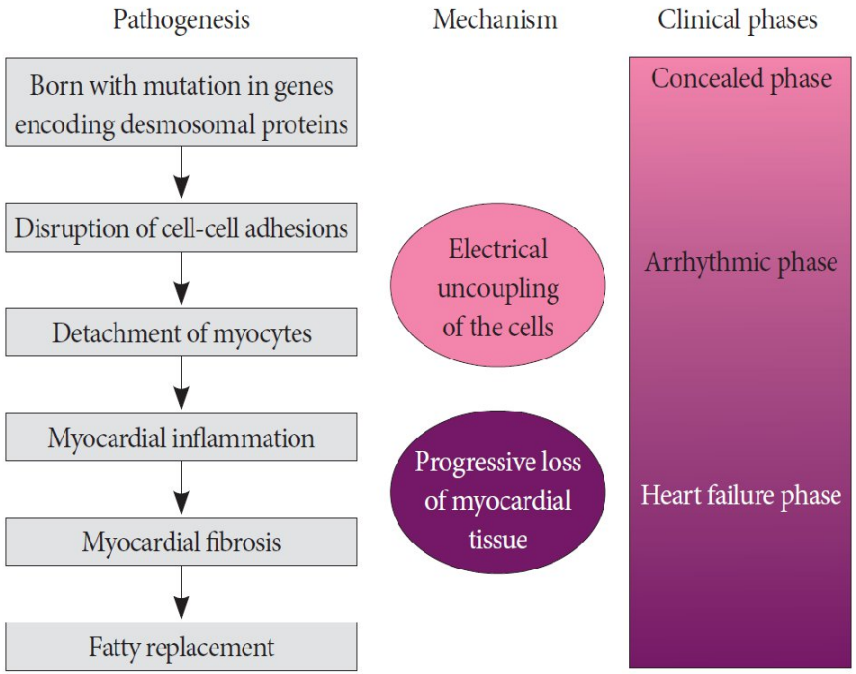
Clinical course of ARVC



Occurrence of arrhythmic events

Impairment of biventricular systolic function

Proposed pathogenesis and natural history of ARVC



1) Concealed phase. Minor structural RV changes without over ECG, CMR and histological findings. At this stage, SCD and life-threatening VAs can be the first manifestation in young patients, especially if engaged in competitive and endurance sports.

2) Arrhythmic phase. RV structural remodeling and dysfunction became overt. Recurrent VAs are frequent.

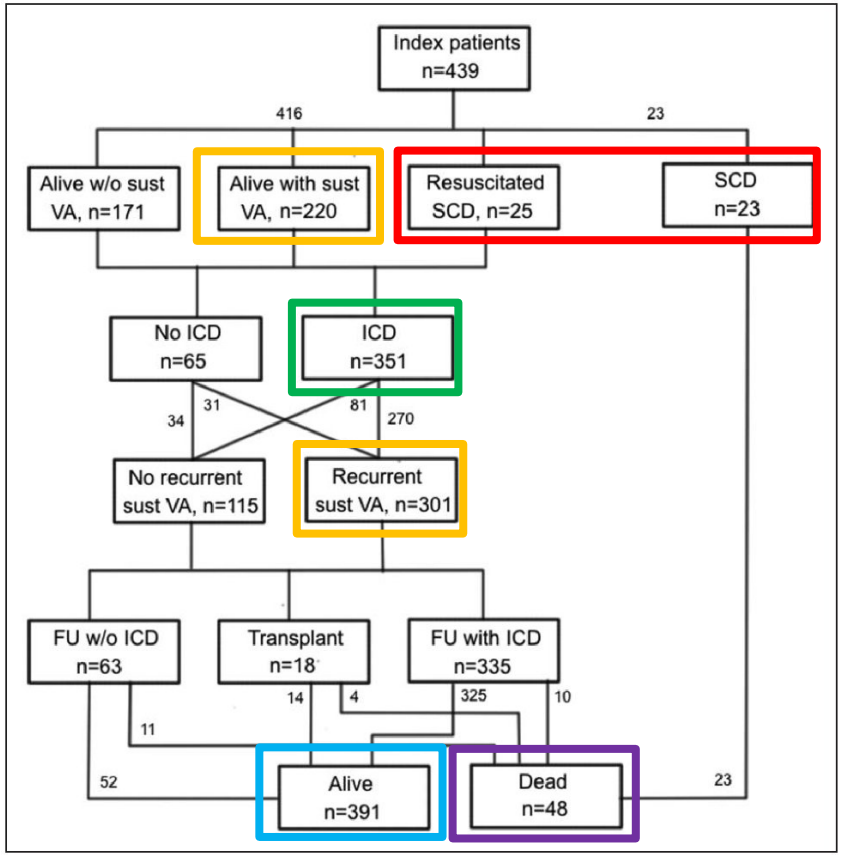
3) RV HF phase. Diffuse progressive fibrofatty replacement of RV myocardium. LV function is typically preserved. Symptoms of volume overload and congestive HF appear gradually.

4) Biventricular HF phase. Biventricular HF with global dilatation and LV involvement. A small proportion of ACM patients reaches this phase.

Yoo SJ, et al. Korean Circ J. 2010;40:357-67

Chen S, et al. J Clin. Med. 2021;10:4782

Clinical course of ARVC



- 439 index patients with ARVC
- Mean age at presentation 36±14 years (only
- 4 presented before the age of 13 years and none before the age of 10 years)
- Median follow-up of 5 years

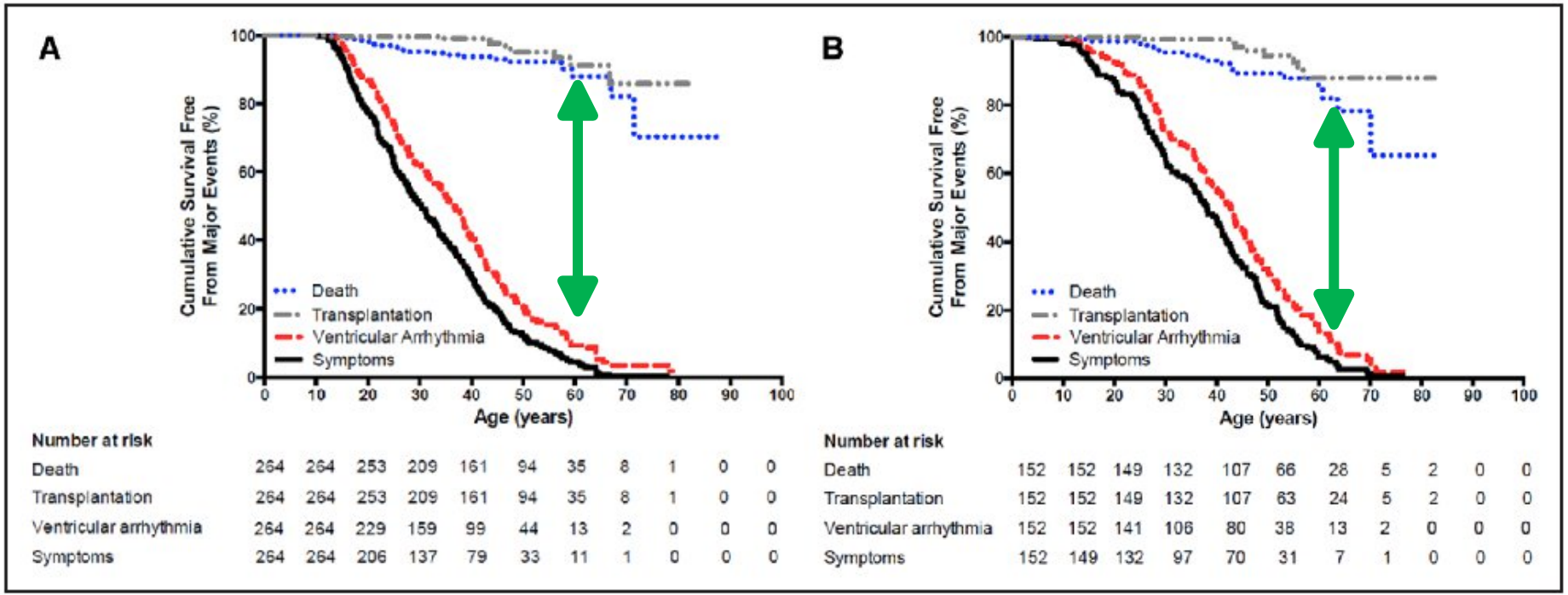
↓

- **11% presented with cardiac arrest** (5% SCD as first manifestation, median age 25)
- Other **50% presented with sustained VT**
- **80% ICD implanted**
- **72% recurrent VT**
- **6% died (3% SCD, 1% HF, 0.7% non cardiac)**
- **94% were living at the last follow-up.**

The incidence of SCD was 16% in index patients without an ICD compared with 0.6% among those with an ICD (P<0.001).

Calkins H, et al. Circulation. 2017;136:2068–2082

Index-patients presenting alive with and without identified mutations had similar proportions of symptoms (99% versus 97%; P=0.197) and sustained VA (83% versus 83%; P=0.934).



Number at risk											
Death	264	264	253	209	161	94	35	8	1	0	0
Transplantation	264	264	253	209	161	94	35	8	1	0	0
Ventricular arrhythmia	264	264	229	159	99	44	13	2	0	0	0
Symptoms	264	264	206	137	79	33	11	1	0	0	0

Number at risk											
Death	152	152	149	132	107	66	28	5	2	0	0
Transplantation	152	152	149	132	107	63	24	5	2	0	0
Ventricular arrhythmia	152	152	141	106	80	38	13	2	0	0	0
Symptoms	152	149	132	97	70	31	7	1	0	0	0

Groeneweg JA, et al. Circ Cardiovasc Genet. 2015;8:437–446

Pooled ARVC outcomes with/out ICD implanted

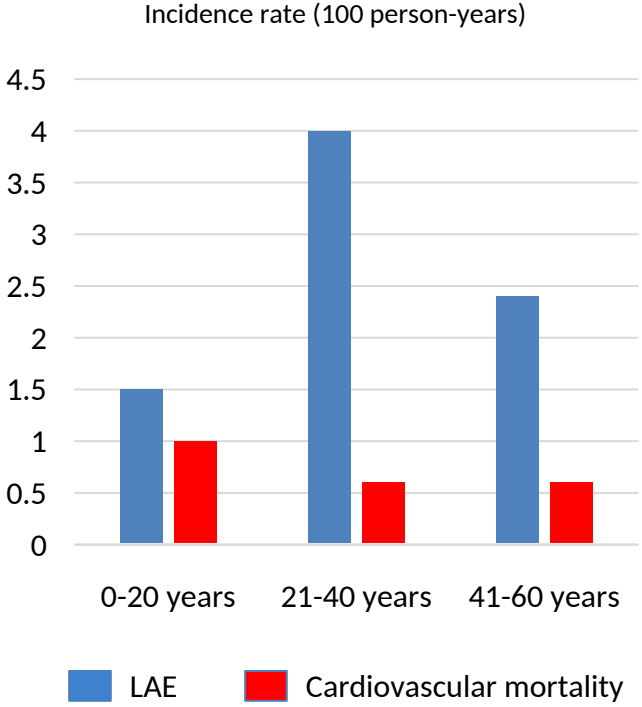
Study	Pts	F-up (y)	ICD (%)	All-cause mortality	SCD	HF-related death	Non-cardiac death	Sustained VT	HF	HTx
Median follow-up: 8 years			ICD (%)	All-cause mortality	SCD	HF-related death	Non-cardiac death	Sustained VT	HF	HTx
Overall results (100 person-years)			**30**	**1.5**	**0.8**	**0.5**	**0.2**	**8.1**	**1.5**	**0.5**
2016 Martin	30	7.4	87	0.9	0.45	0	0.45	6.81	-	-
2016 Kimura	110	10	35	1.45	0.64	0.82	-	5.8	2.6	0.18
2016 Brun	88	9.1	0	1.50	0.62	0.62	0.25	6.49	-	0.47
2016 Mazzanti	301	5.9	29	2.24	1.78	0.17	0.29	17	-	0

Pooled ARVC outcomes with ICD implanted

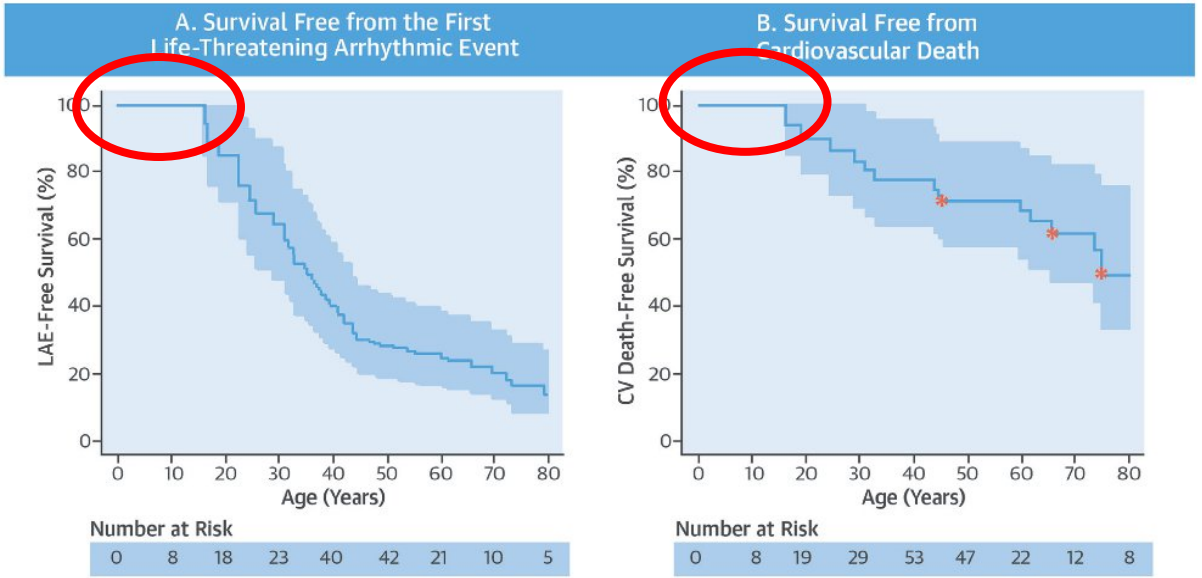
Study	Pts	F-up	Primary	All-cause	SCD	HF	Approp	ICD int	Inapprop	ICD complic	HTx
Median follow-up: 5 years				All-cause mortality	SCD	HF death	Approp ICD	ICD int VF/VFL	Inapprop ICD	ICD complications	HTx
Overall results (100 person-years)				**0.6**	**0.1**	**0.2**	**12.4**	**4.8**	**4.6**	**4.4**	**0.5**
2014 Link	108	3.3	52	0	0	0	13.46	6.17	4.76	0.56	0
2017 Orgeron	312	8.8	100	0.18	0	0.11	6.82	2.16	2.38	2.38	0.44

Young age and life-threatening VAs

Median follow-up: 5.8 years



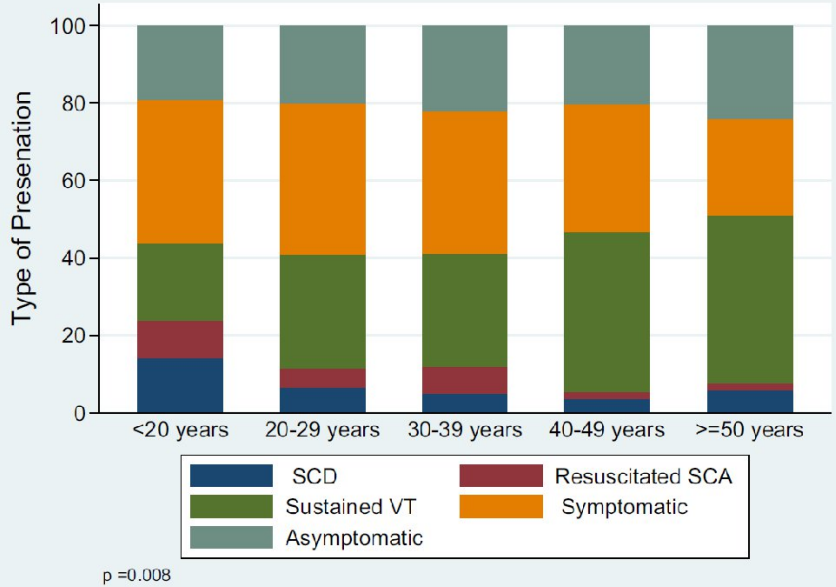
The high risk of LAE spans from adolescence to advanced age (no events before age 16), reaching its peak between the third and the fourth decade of life. The risk of CV death is constant in all age groups.



Mazzanti A, et al. JACC. 2016;68:2540–50

Long-term prognosis of ARVC in patients with late presentation

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)	23 (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
≥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

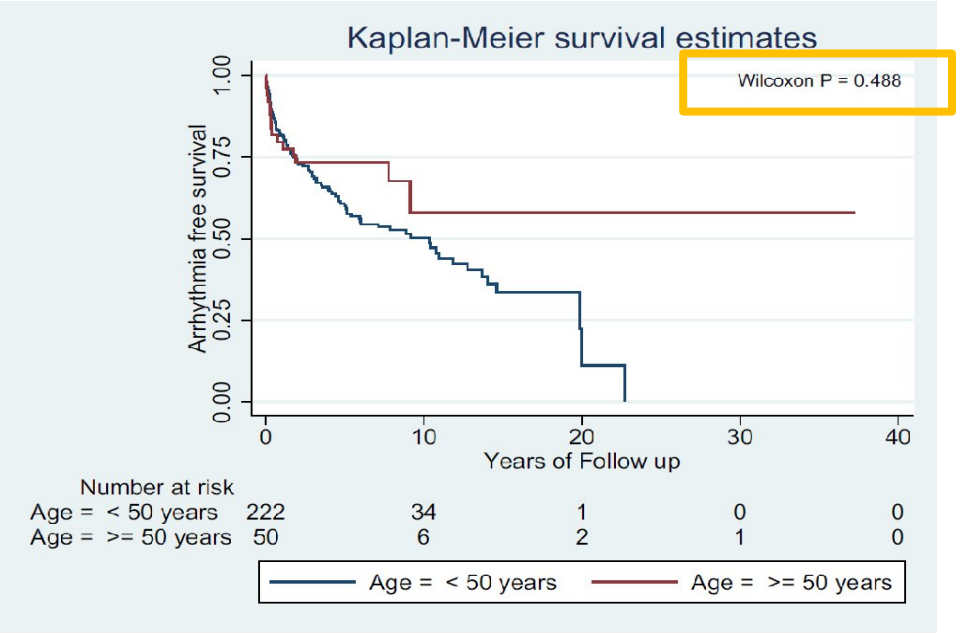


Bhonsale A, et al. Heart Rhythm 2017;14:883–891

Long-term prognosis of ARVC in patients with late presentation

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

Arrhythmic - free survival

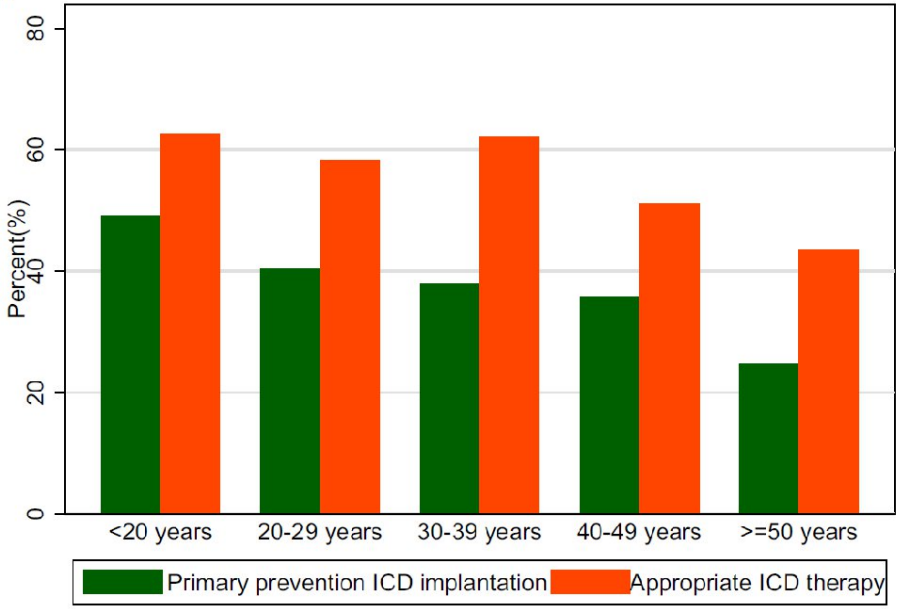


Bhonsale A, et al. Heart Rhythm 2017;14:883–891

Long-term prognosis of ARVC in patients with late presentation

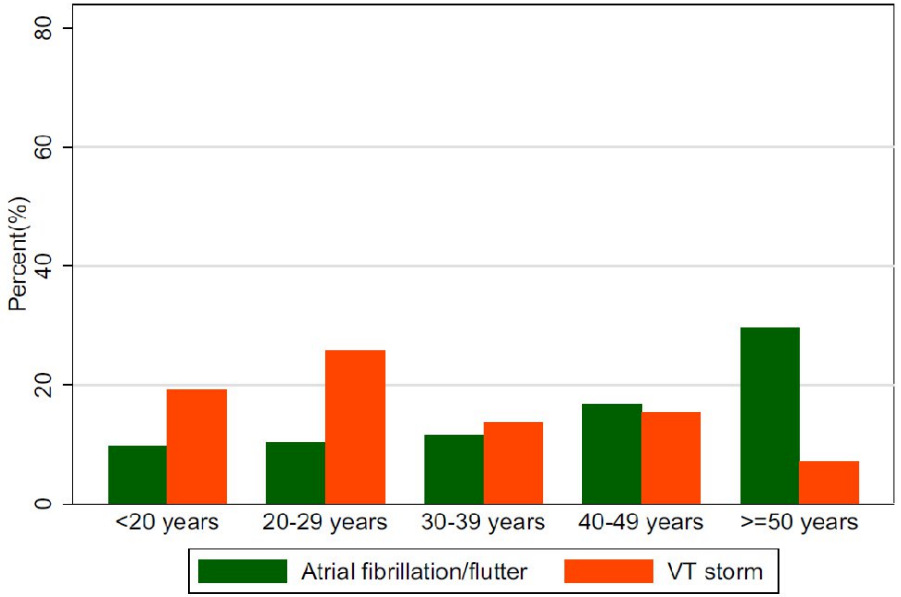
Despite the considerable arrhythmic risk, patients with late presentation have significantly fewer VT storms or appropriate ICD interventions, suggesting that their clinical trajectory is somewhat less severe than that in the young.

A



ICD: P value for trend =0.005, Appropriate therapy: P value for trend 0.007

B

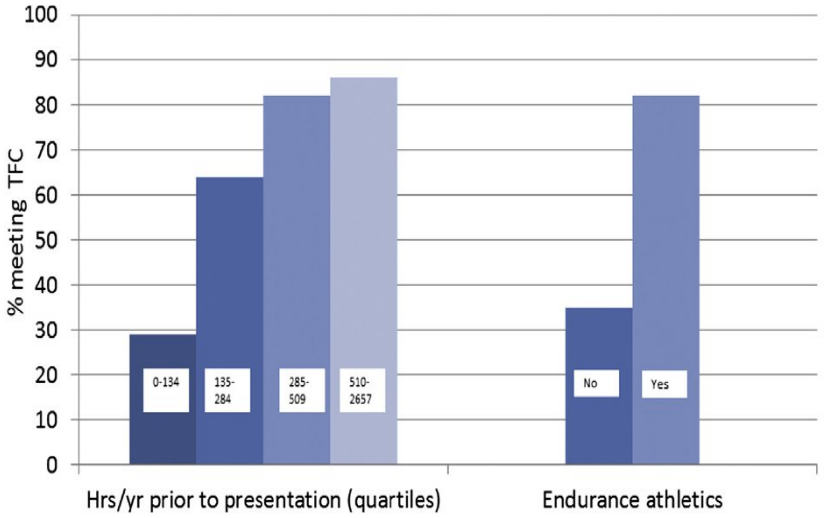


AF: P value for trend <0.001, VT storm: P value for trend 0.003

Bhonsale A, et al. Heart Rhythm 2017;14:883–891

Impact of exercise of ARVC clinical course

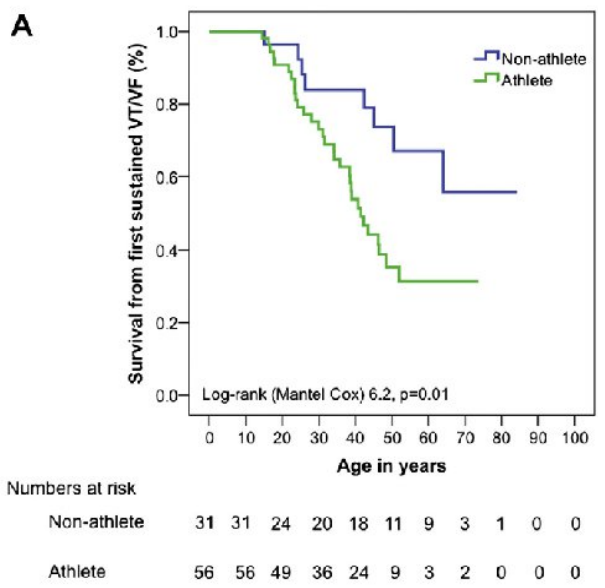
	Overall (N = 87)	Endurance Athlete (n = 56)	Not Endurance Athlete (n = 31)	p Value
Male	46 (53)	32 (57)	14 (45)	NS
Proband	36 (41)	28 (50)	8 (26)	0.028
Age at interview, yrs	44 ± 18	42 ± 15	45 ± 22	NS
Presentation				
Age at clinical presentation, yrs	35 ± 17	32 ± 14	38 ± 20	NS
Type of presentation				
Symptomatic presentation	44 (51)	36 (64)	8 (26)	0.002
Resuscitated SCD	3 (3)	2(4)	1 (3)	
Asymptomatic	40 (46)	18 (45)	22 (71)	
Sustained VT/VF at presentation	26 (30)	18 (32)	8 (26)	NS
Stage C HF at presentation	0 (0)	0(0)	0(0)	NS
Age at first symptom, yrs	32 ± 15	30 ± 13	41 ± 21	0.05
Task Force Criteria at LFU, yes	56 (64)	46 (82)	11 (35)	<0.001
Structural alterations	30 (35) major 10 (12) minor	24 (44) major 8 (15) minor	6 (20) major 2 (7) minor	0.021
Repolarization abnormalities*	43 (50) major 15 (17) minor	34 (62) major 12 (22) minor	9 (29) major 3 (10) minor	<0.001
Depolarization abnormalities*	5 (6) major 35 (41) minor	5 (9) major 28 (51) minor	0 (0) major 7 (23) minor	0.003
Arrhythmias†	17 (21) major 30 (36) minor	13 (24) major 24 (44) minor	4 (14) major 6 (21) minor	0.011
Family history/genetics	87 (100) major	56 (100) major	31 (100) major	1.000



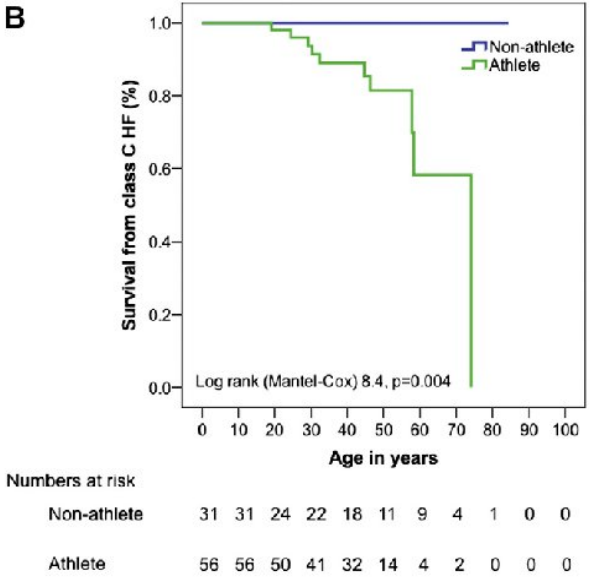
James CA, et al. J Am Coll Cardiol 2013;62:1290–7

Impact of exercise of ARVC clinical course

Sustained VT/VF



Class C HF

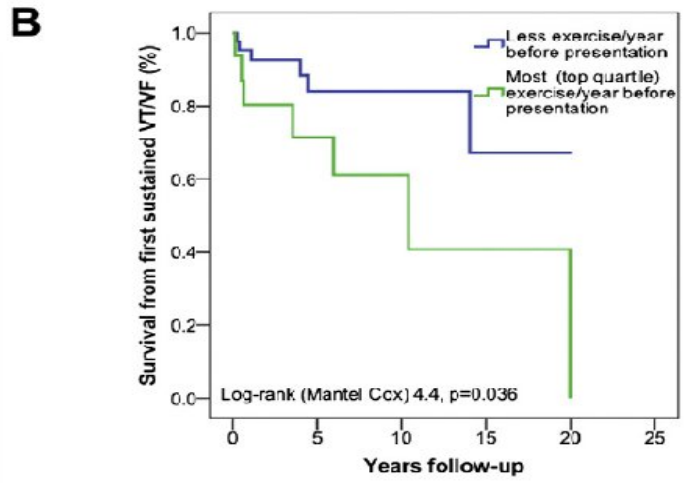


- Lifetime event-free survival from VT/VF and class C HF was significantly lower in endurance athletes (p=0.013 and p=0.004).
- No patients had HF at baseline. HF developed only in endurance athletes (18% vs. 0%, p=0.012).

James CA, et al. J Am Coll Cardiol 2013;62:1290–7

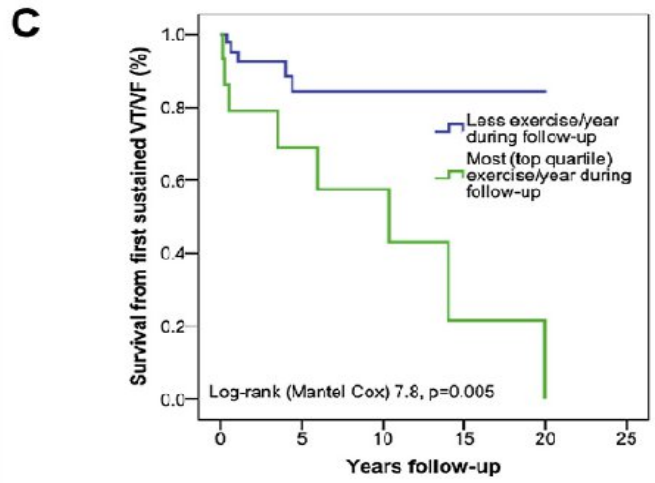
Impact of exercise of ARVC clinical course

In non-athlete patients, higher amount of exercise **before the diagnosis** increases the risk of VAs.



Numbers at risk						
Less exercise (0-515 hrs/yr)	45	18	8	2	1	0
Most exercise (>515 hrs/yr)	16	8	3	1	0	0

In non-athlete patients, low amount of exercise **during follow-up** reduces the risk of VAs.



Numbers at risk						
Less exercise (0-425 hrs/yr)	46	19	7	2	1	0
Most exercise (>425 hrs/yr)	15	7	4	1	0	0

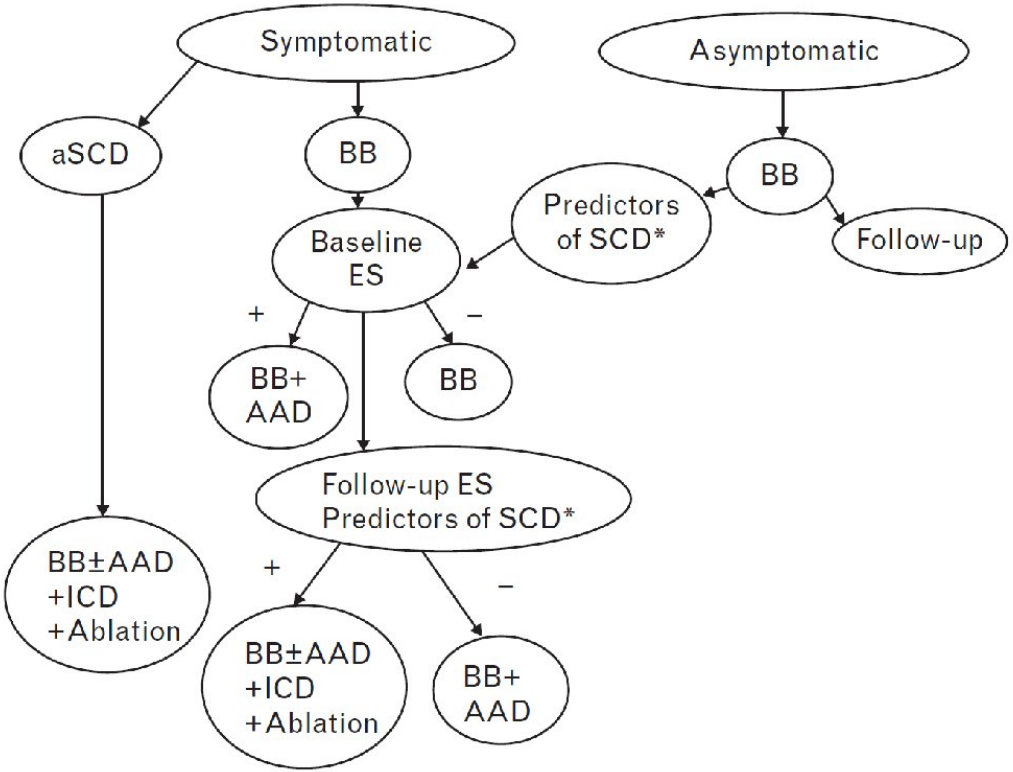
James CA, et al. J Am Coll Cardiol 2013;62:1290–7

Arrhythmogenic right ventricular cardiomyopathy: ECG progression over time and correlation with long-term follow-up

Cristina Gallo[a], Alessandro Blandino[b], Carla Giustetto[a], Matteo Anselmino[a], Davide Castagno[a], Elena Richiardi[c] and Fiorenzo Gaita[a]

Gallo C, Blandino A, et al. J Cardiovasc Med. 2016;17:418-424

Therapeutic flow-chart

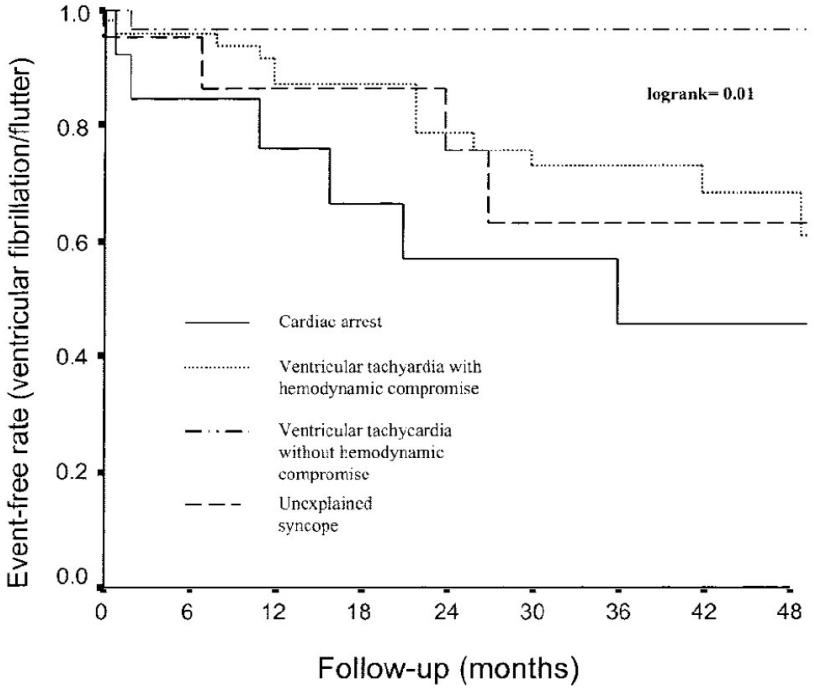


Major risk factor (for SCD)
Cardiac arrest due to VF
Hemodynamically unstable sustained VT
Unexplained syncope
Severe RV or LV dysfunction
Inducibility on EP study
Frequent nonsustained VT
Large amount of RV fibrofatty scarring (CMR/endocardial mapping)

Gallo C, Blandino A, et al. J Cardiovasc Med. 2016;17:418-424

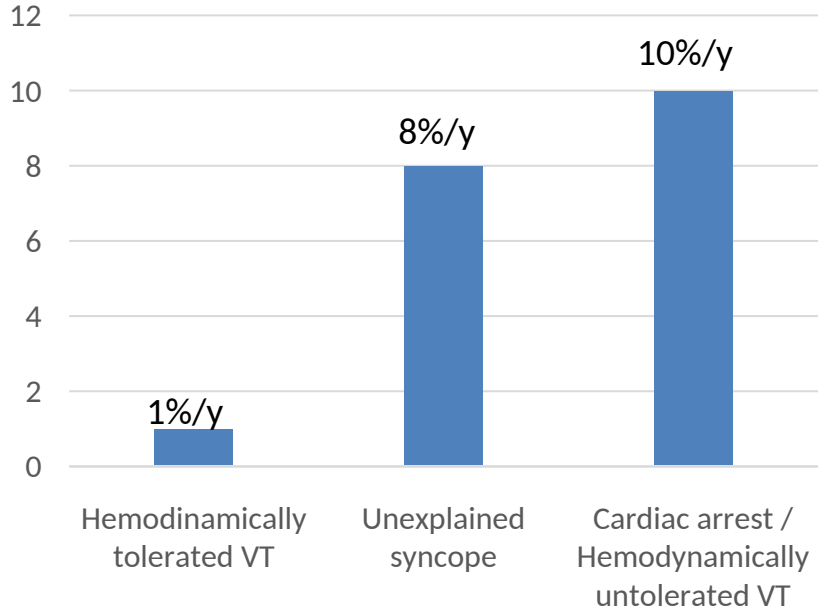
SCD risk in patients with hemodynamically stable VT

Mean follow-up: 3.3 years



ICD-detected incidence of VF

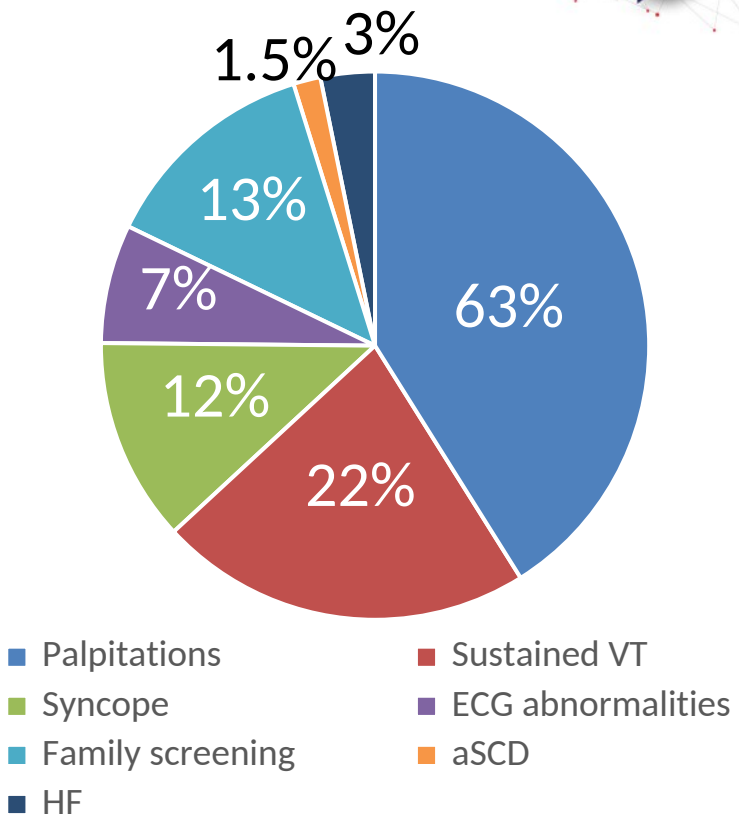
(100 person-years)



Corrado D, et al. Circulation. 2003;108:3084-3091

Patient population

- 68 patients
- 1970 - 2014
- 47 (69%) M
- Mean age of 31±19 years
- Family history of ARVC in 18 (26%) patients while 22 (32%) had family history of SCD.
- Mean LVEF: 58±8%
- 33 (57%) moderate-severe RV dilatation at CMR
- 16 (28%) CMR-detected RV dyskinesia
- 37 (64%) fibrofatty RV involvement



Gallo C, Blandino A, et al. J Cardiovasc Med. 2016;17:418-424

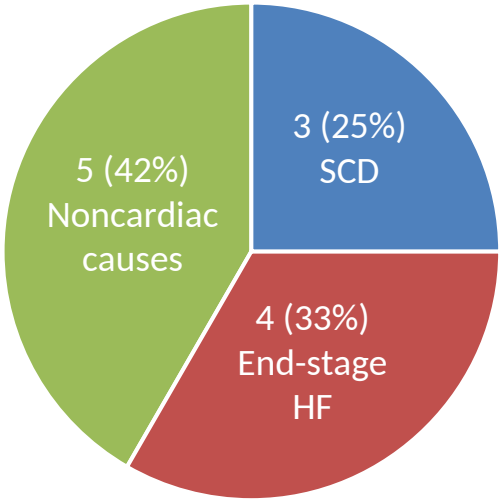
Adverse clinical outcomes

- **Medical therapy only: 24 (35%)**
- **ICD: 24 (35%)**
- **VT catheter ablation: 17 (25%)**
- **Heart transplant: 3 (5%)**

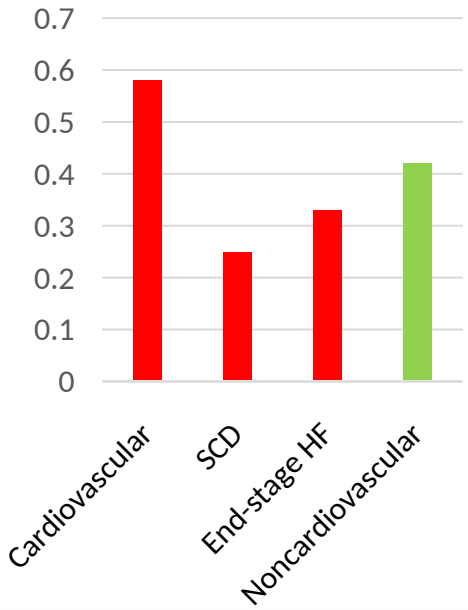
Mean follow-up: 17±8 years

SCD: drug therapy withdrawal, postponed ICD implantation, and ICD malfunctioning

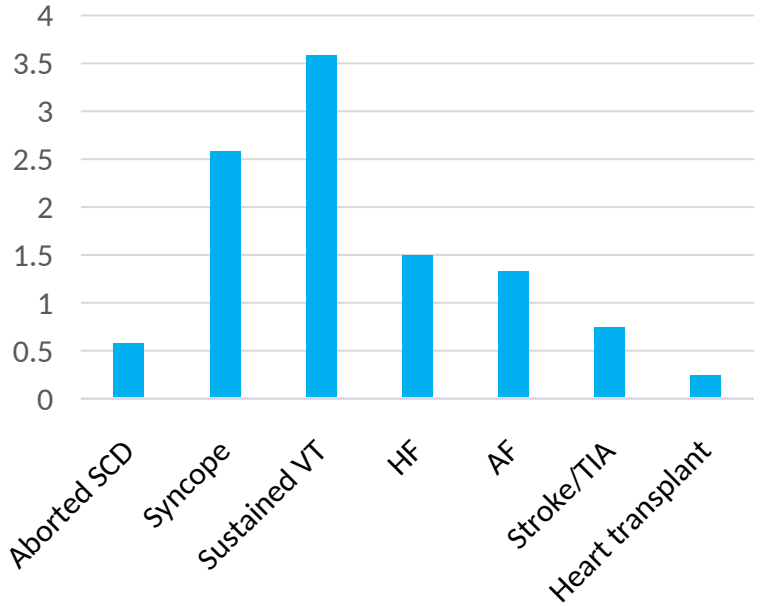
Death: 12 (18%) patients



Mortality rate
(100 person-years)



Other adverse events
(100 person-years)



Gallo C, Blandino A, et al. JCM. 2016;17:418-424

Conclusions:

- ARVC leads to a wide spectrum of clinical manifestations, ranging from ventricular life-threatening arrhythmias, potentially causing SCD in young adults, to atrial fibrillation, stroke, and progressive right or biventricular HF.

- The clinical onset is clearly postponed to adolescence and young adulthood (ARVC as “a disease of the young adult”) with the risk of VAs rapidly increasing in the teenage years. So, in families with ARVC children should be screened when they approach adolescence, hopefully at 2- to 3-year intervals.

- Despite the high arrhythmic burden, patients with late presentation have globally a less severe clinical course.

- Duration and intensity of exercise are clearly associated with increasing risk of VAs and progressive HF. Exercise restriction is very important in this regard.

- Long-term outcome of ARVC remains favorable in diagnosed and appropriately treated patients.