

GENETICA CARDIOVASCOLARE 3.0

**Test genetico nella Cardiomiopatia Aritmogena:
strumento di ricerca o necessità clinica?**

Barbara Bauce, Università degli Studi di Padova



Cardiomiopatia aritmogena

necrosi miocitaria

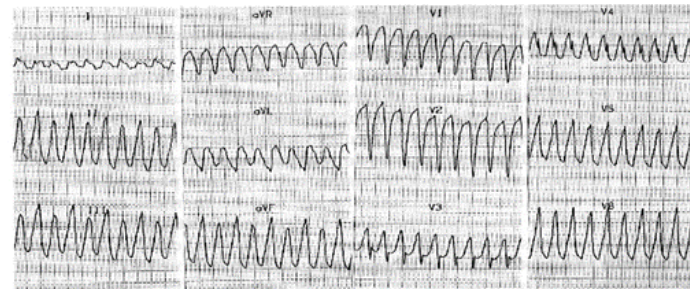
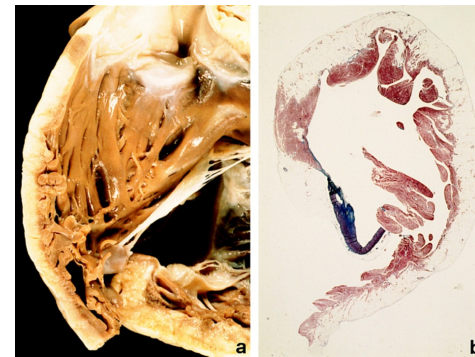
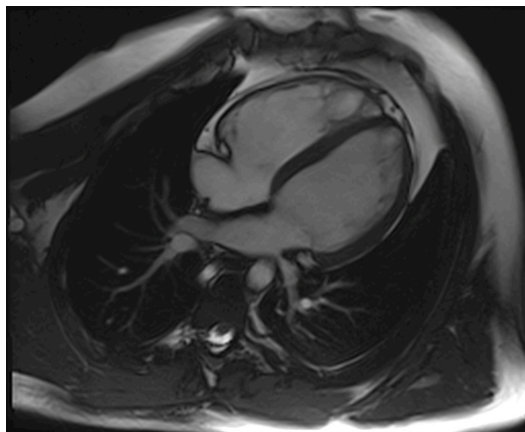


sostituzione fibro-adiposa

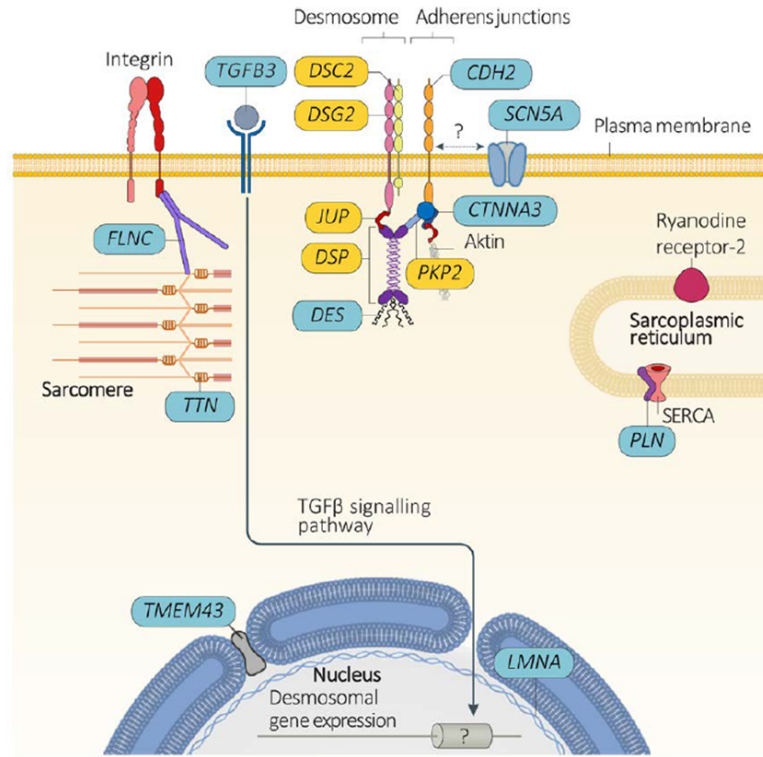


alterazioni morfologiche
ventricolari

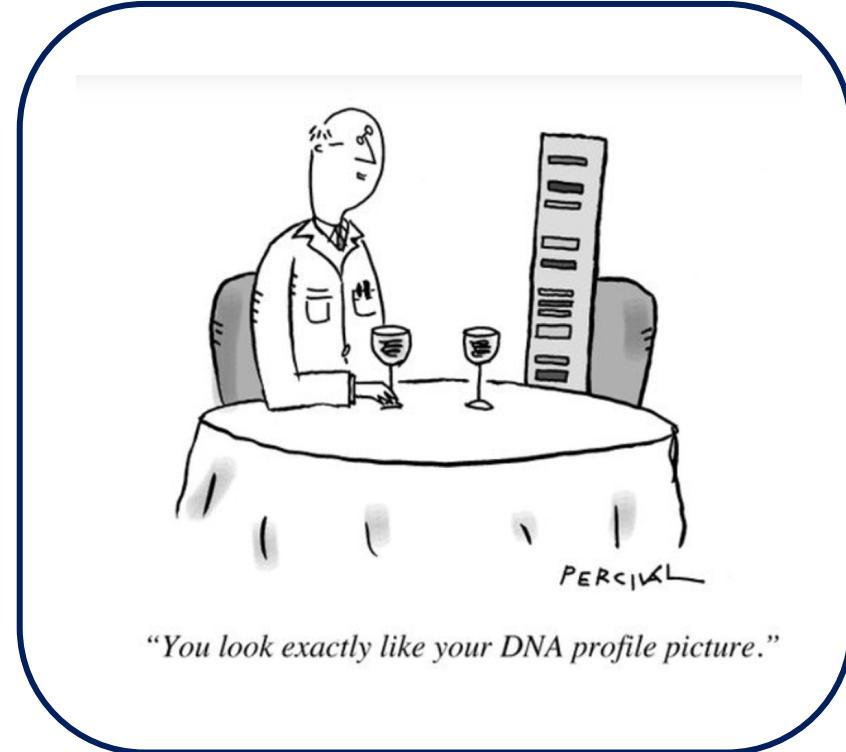
instabilità elettrica



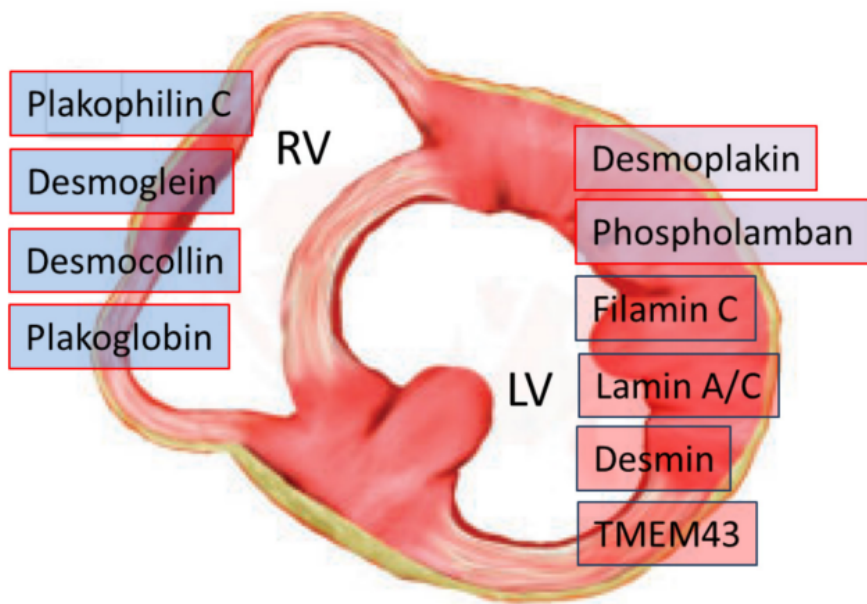
Ruolo della genetica nella ACM



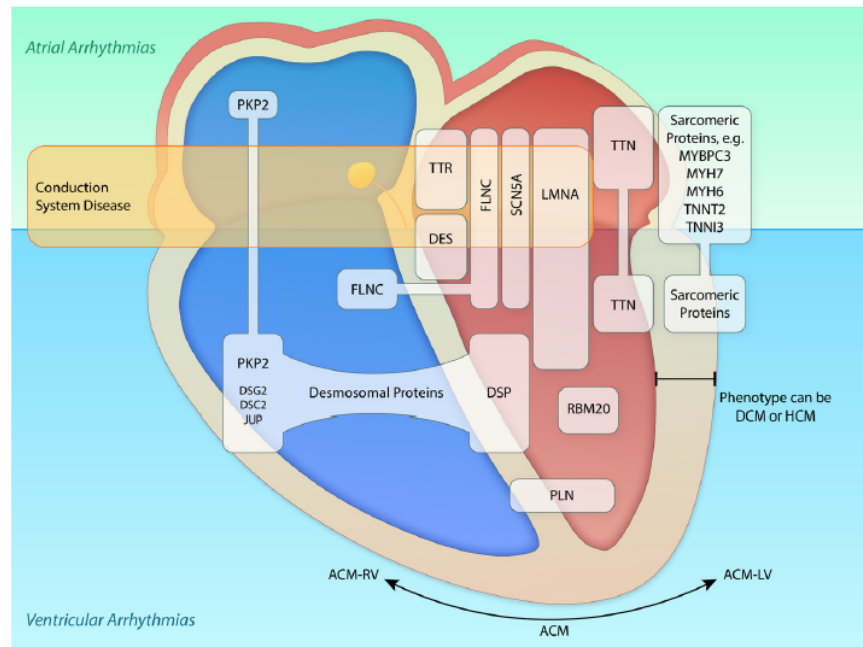
Asatryan et al, 2021



Correlazione genotipo-fenotipo

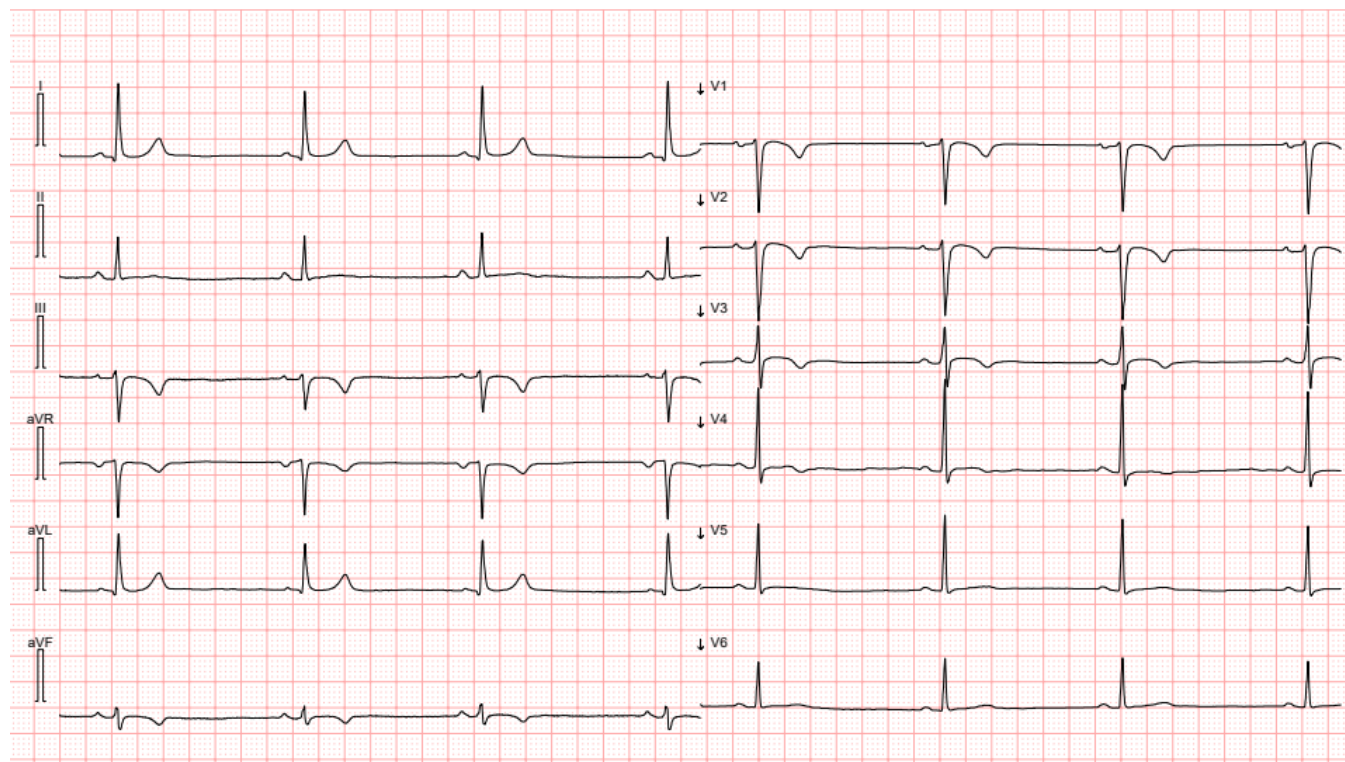


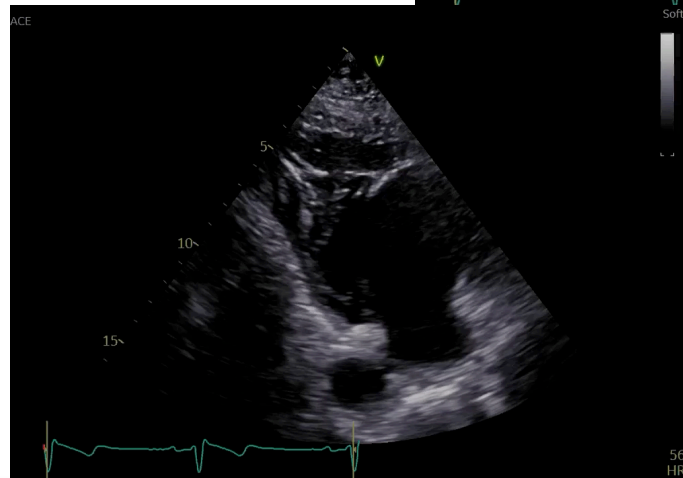
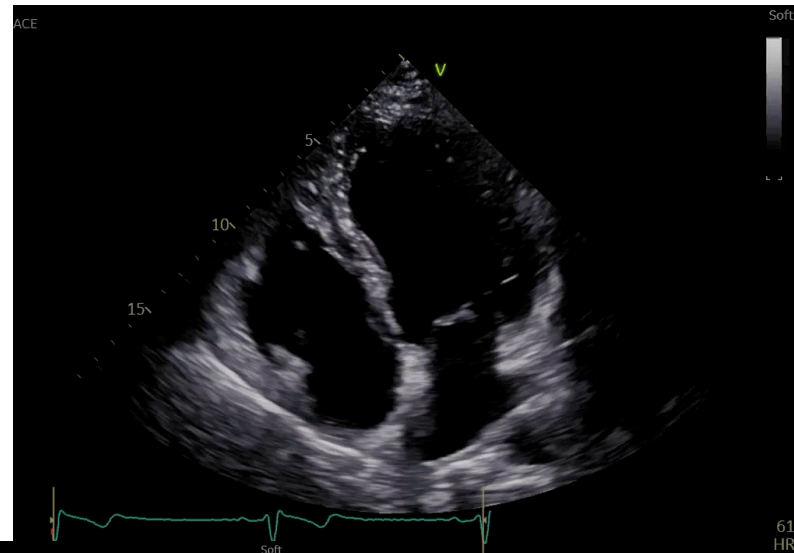
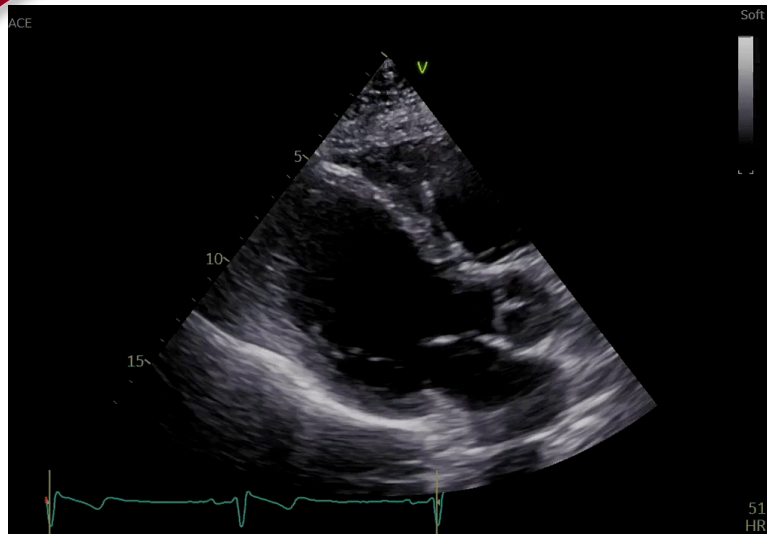
Corrado et al, Heart 2021

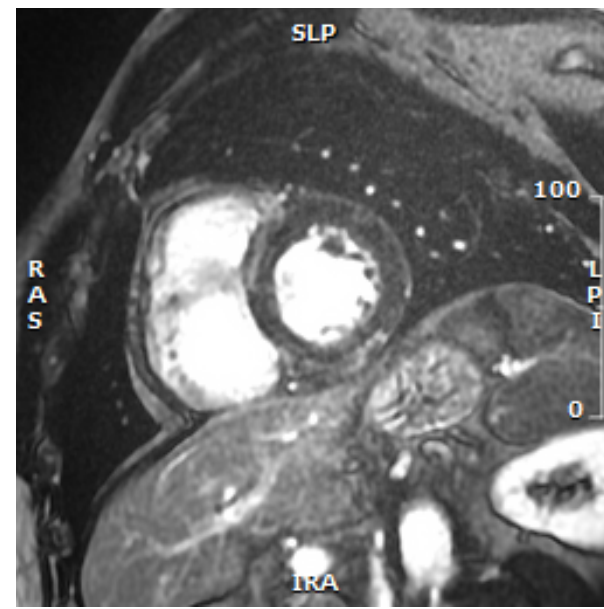
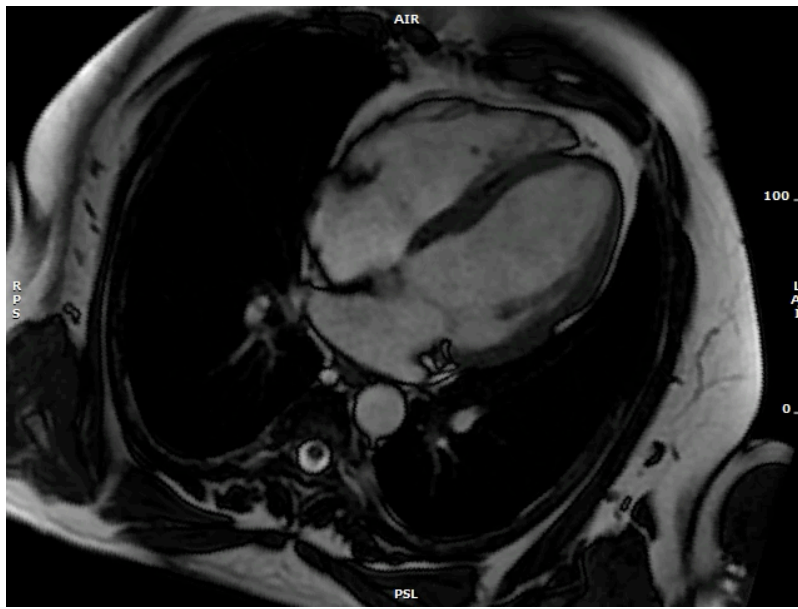


Laws et al, Circulation 2022

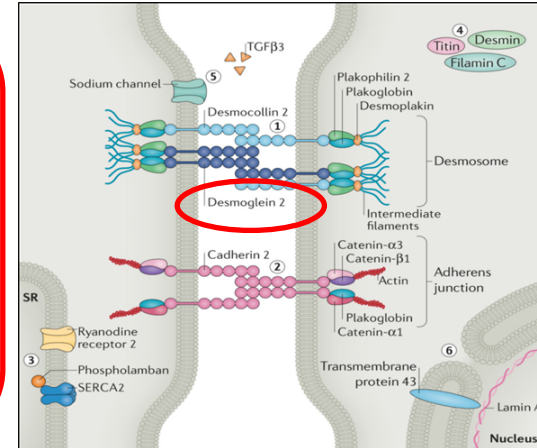
- Maschio, 34 anni
- Anamnesi familiare negativa
- Cardiopalmo, frequenti BEV politopiche (TVNS di 3 battiti)





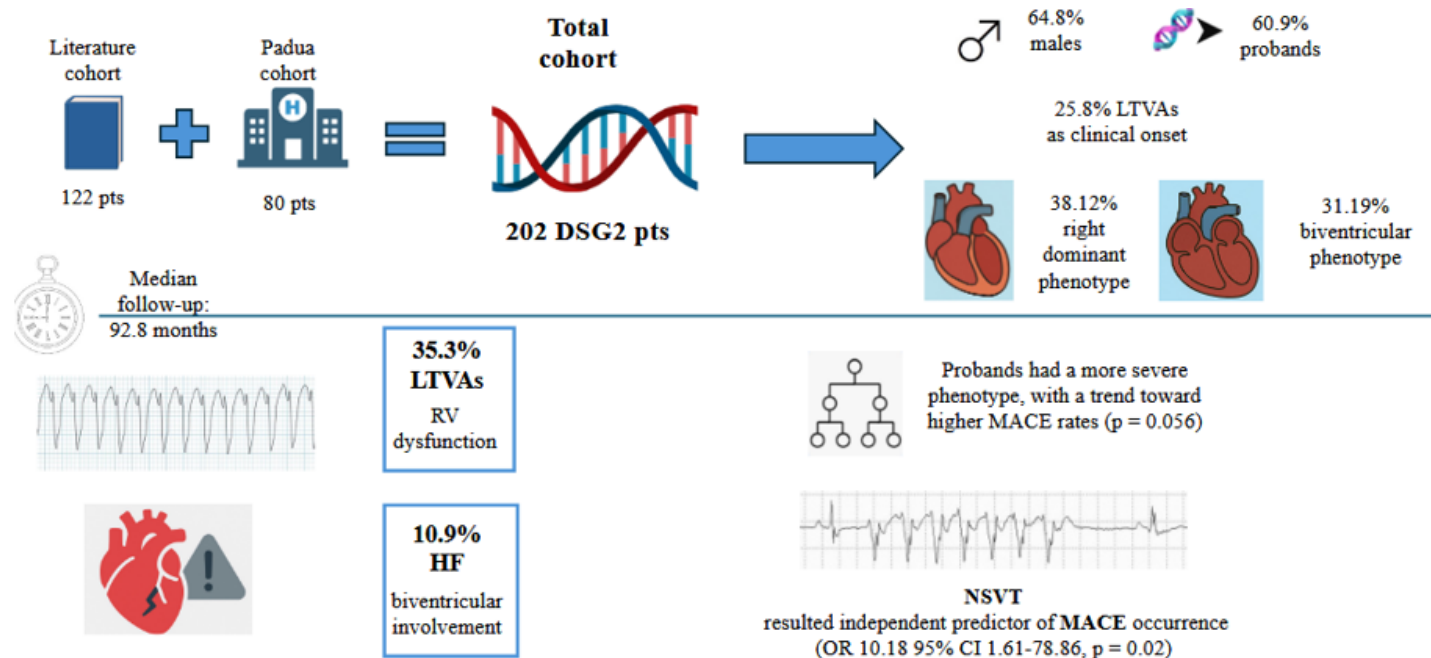


- 34 anni
- maschio
- non storia familiare ARVC o morte improvvisa
- Vdx moderatamente dilatato con moderata riduzione della funzione sistolica
- TVNS all'ECG Holter
- Scarsa tolleranza beta bloccanti e sotalolo per ipotensione ed astenia
- Presenza di mutazione patogena DSG2



Phenotypic spectrum and prognostic stratification in desmoglein-2-associated arrhythmogenic cardiomyopathy: Results from a pooled analysis ^e

Marika Martini, MD,¹ Luigi Filippo Brizzi, MD,¹ Serena Pinci, BSc,¹ Ilaria Rigato, MD, PhD,² Domenico Corrado,¹ Kalliopi Pilichou, BSc, PhD,¹ Barbara Bauce, MD, PhD¹



Ruolo del test genetico nella stratificazione del rischio aritmico

European Heart Rhythm Association (EHRA)/ Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases

Arthur A. M. Wilde (EHRA Chair)^{1,*†,‡,¶}, Christopher Semsarian (APHRS Co-Chair)^{2,*†}, Manlio F. Márquez (LAHRS Co-Chair)^{3,*†}, Alireza Sepehri Shamloo⁴, Michael J. Ackerman⁵, Euan A. Ashley⁶, Eduardo Back Sternick⁷, Héctor Barajas-Martinez⁸, Elijah R. Behr^{9,¶}, Connie R. Bezzina^{11,‡}, Jeroen Breckpot^{12,‡}, Philippe Charron^{13,‡}, Priya Chockalingam¹⁴, Lia Crotti^{15,16,17,‡,¶}, Michael H. Gollob¹⁸, Steven Lubitz¹⁹, Naomasa Makita²⁰, Seiko Ohno²¹, Martín Ortiz-Genga²², Luciana Sacilotto²³, Eric Schulze-Bahr^{24,‡,¶}, Wataru Shimizu²⁵, Nona Sotoodehnia²⁶, Rafik Tadros²⁷, James S. Ware^{28,29}, David S. Winlaw³⁰, and Elizabeth S. Kaufman (HRS Co-Chair)^{31,*†}

Europe, 2022

Disease	Diagnostic	Prognostic	Therapeutic
Arrhythmia syndromes			
Long QT syndrome	+++	+++	+++
CPVT	+++	+	+
Brugada syndrome	+	+	+
Progressive cardiac conduction disease	+	+	+
Short QT syndrome	+	+	+
Sinus node disease	–	+	–
Atrial fibrillation	–	+	–
Early repolarization syndrome	–	–	–
Cardiomyopathies			
Hypertrophic cardiomyopathy	+++	++	++
Dilated cardiomyopathy	++	+++	++
Arrhythmogenic cardiomyopathy	+++	++	++
Left ventricular non-compaction	+	+	–
Restrictive cardiomyopathy	+	+	+



ESC

European Society
of Cardiology

European Heart Journal (2023) 44, 3503–3626
<https://doi.org/10.1093/eurheartj/ehad194>

ESC GUIDELINES

2023 ESC Guidelines for the management of cardiomyopathies

Developed by the task force on the management of cardiomyopathies of the European Society of Cardiology (ESC)

Table 21 High-risk genotypes and associated predictors of sudden cardiac death

Gene	Annual SCD rate	Predictors of SCD
<i>LMNA</i> ^{185,186,438,541,865,878,879}	5–10%	Estimated 5-year risk of life-threatening arrhythmia using <i>LMNA</i> risk score (https://lmna-risk-vta.fr)
<i>FLNC</i> -truncating variants ^{866,867,880}	5–10%	LGE on CMR LVEF < 45%
<i>TMEM43</i> ^{868,881}	5–10%	Male Female and any of the following: LVEF < 45%, NSVT, LGE on CMR, >200 VE on 24h Holter ECG
<i>PLN</i> ^{542,882,883}	3–5%	Estimated 5-year risk of life-threatening arrhythmia using <i>PLN</i> risk score (https://plnriskcalculator.shinyapps.io/final_shiny) LVEF < 45% LGE on CMR NSVT
<i>DSP</i> ^{185,186}	3–5%	LGE on CMR LVEF < 45%
<i>RBM20</i> ⁸⁶⁹	3–5%	LGE on CMR LVEF < 45%

Phenotypic Expression and Clinical Outcomes in Patients With Arrhythmogenic Cardiomyopathy



TABLE 2 Genetic Findings

Riccardo Bariani
Alberto Cipriani
Martina Perini
Barbara Bauce

CENTRAL
Cardiomyopathy

1990



M

Patients were divided into 3 groups based on their phenotypic expression of arrhythmogenic cardiomyopathy: ALVC (arrhythmogenic left ventricular cardiomyopathy), ARVC (arrhythmogenic right ventricular cardiomyopathy), and BIV (biventricular arrhythmogenic cardiomyopathy). We compared the clinical and instrumental findings among these groups as well as evaluated their outcomes.

	Total (N = 446; 100%)	ARVC (n = 196; 44%)	ALVC (n = 104; 23%)	BIV (n = 146; 33%)	q Value
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Proband	307 (69)	135 (69)	57 (55)	115 (79)	0.002
Positive genetic test	217 (49)	84 (43)	69 (66)	64 (44)	0.001
DSP	82 (18)	12 (6)	44 (42)	26 (18)	<0.001
PKP2	82 (18)	58 (30)	6 (6)	18 (12)	<0.001
DSG2	24 (5)	11 (6)	3 (3)	10 (7)	1.000
FLNC	17 (4)	2 (1)	11 (11)	4 (3)	0.001
DSC2	2 (0)	1 (1)	0 (0)	1 (1)	1.000
LMNA	2 (0)	0 (0)	0 (0)	2 (1)	0.460
DES	5 (1)	0 (0)	4 (4)	1 (1)	0.038

The comparison of ACM phenotypes demonstrated that patients with right ventricular involvement, namely ARVC and BIV forms, exhibited a higher arrhythmic burden. Conversely, ACM forms characterized by left ventricular involvement, such as ALVC and BIV, showed a higher incidence of HF, heart transplantation, and HP.

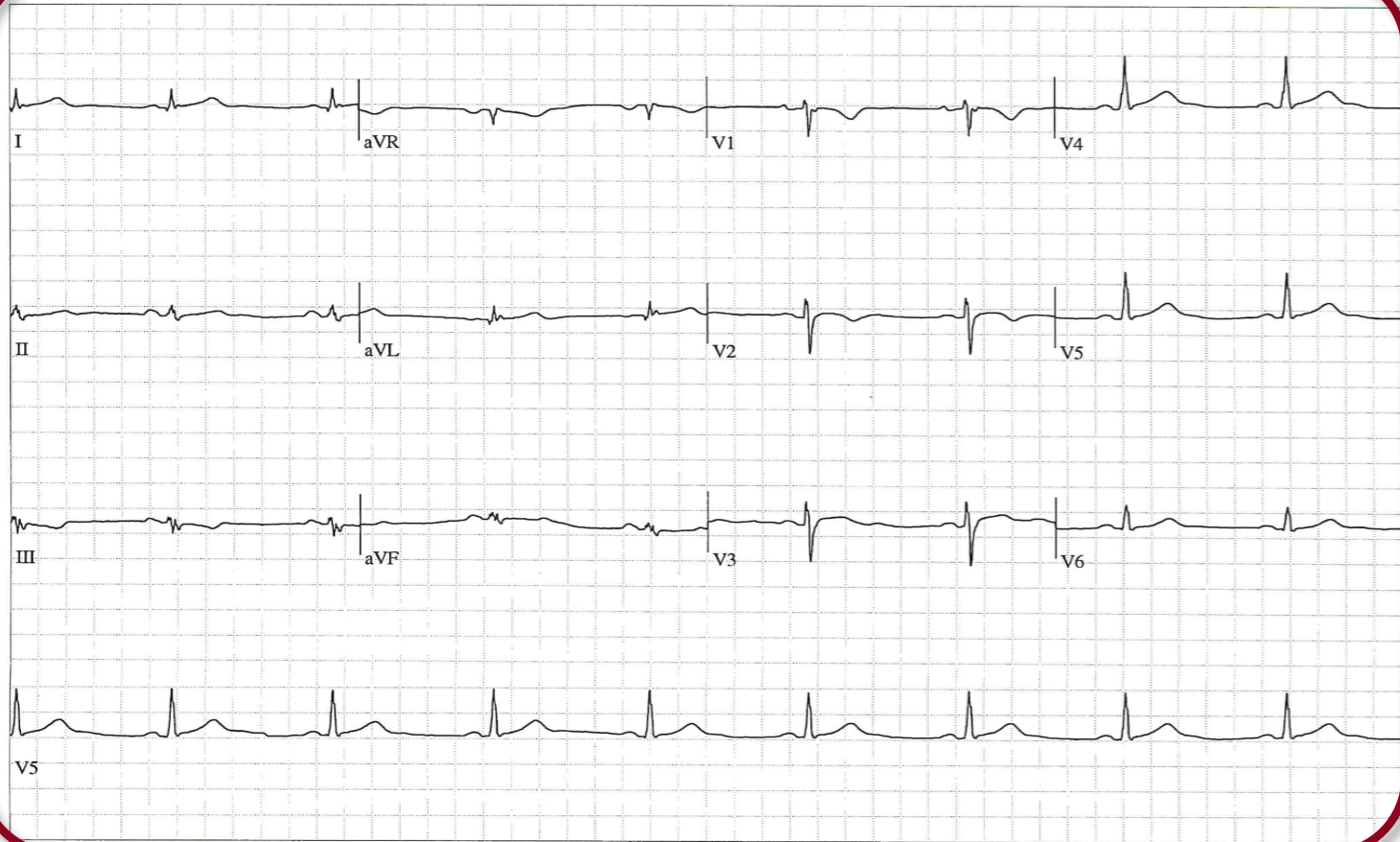
TABLE 2 Genetic Findings

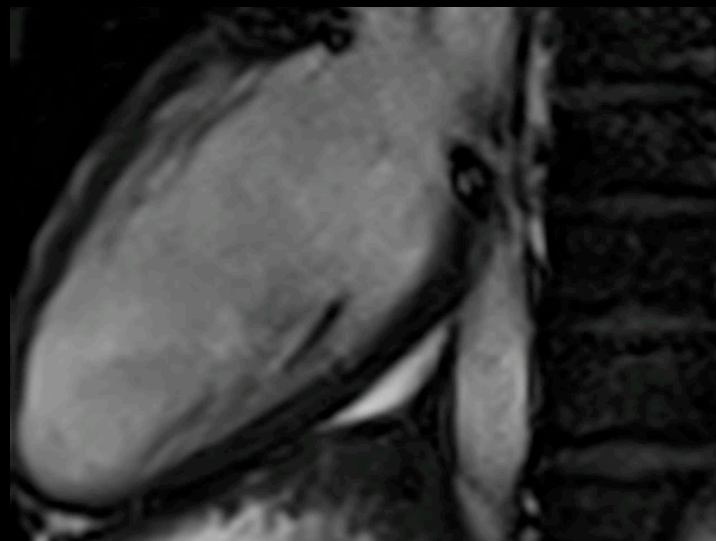
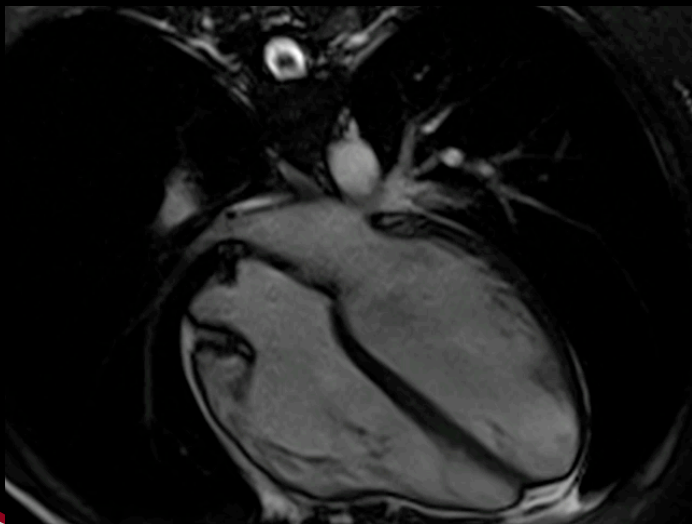
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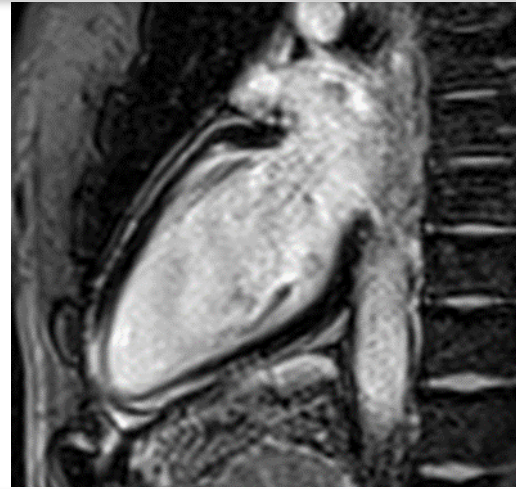
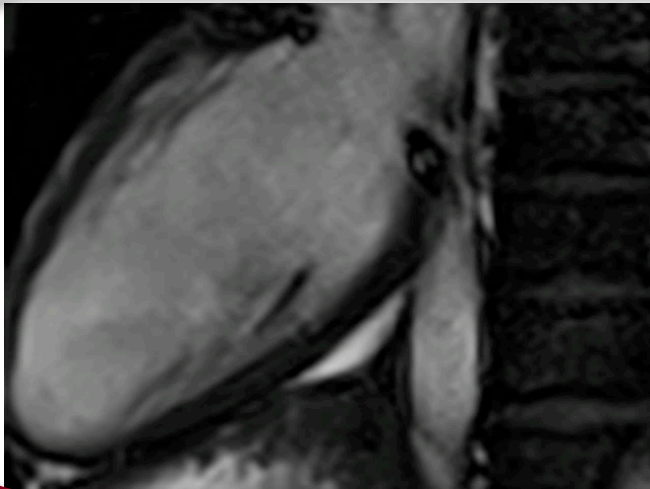
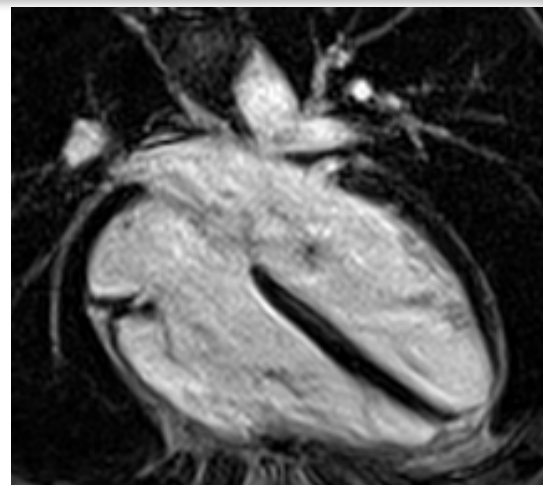
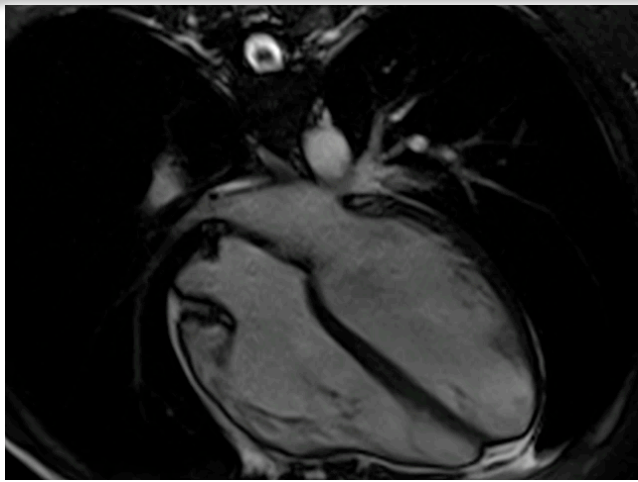
Caso clinico



- Maschio, non familiarità per cardiopatia aritmica
- Nel 2013 all'età di 27 anni ACC, FV con DC shock efficace
- Successiva diagnosi di Cardiomiopatia Aritmogena
- Test genetico: variante genetica PKP2 (ACMG:classe 4, LP)
- Terapia:
 - impianto ICD in prevenzione secondaria
 - sotalolo 80 mgX3







- Dal 2013 al 2016 buon controllo delle aritmie con la terapia
- Nel novembre 2016 prima recidiva aritmica con TV monomorfa sincopale, trattata con ATP (inefficace) e shock efficace.

Terapia: sotalolo 80 mg X3
mexiletina 200 mgX3

- Agosto 2017: intervento ICD su TV monomorfa
- Nel novembre 2017: ablazione con approccio endo ed epicardico
- Da allora non ulteriori interventi del device

A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy

Table 2 Ventricular arrhythmia risk prediction model

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

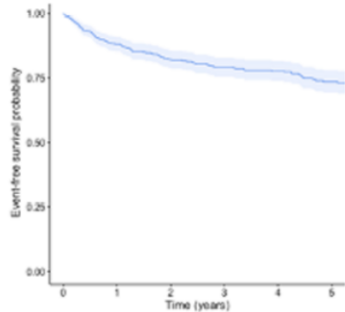
LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular complex; RVEF, right ventricular ejection fraction; TWI, T-wave inversion.

^aPVC count had a log-linear relationship.

A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy

Prediction of sustained ventricular arrhythmia in ARVC

5-year event-free survival (n = 528)
Overall

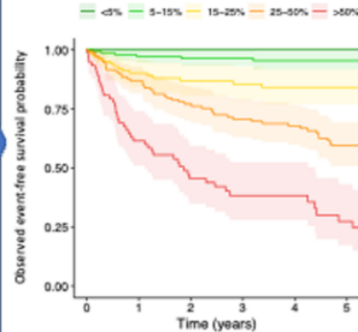


Model for 5-year risk prediction

Sex	x	0.49
Age	x	-0.022
Recent syncope	x	0.66
Non-sustained VT	x	0.81
Ln(24h PVC count)	x	0.17
Leads with T-wave inv.	x	0.11
RVEF	x	-0.025

$$1 - 0.8396^{\text{exp}(x)} = 5 \text{ year risk}$$

5-year event-free survival
Per predicted risk group



Legend: ARVC = arrhythmogenic right ventricular cardiomyopathy; VT = ventricular tachycardia; PVC = Premature ventricular complex; Inv, inversion; RVEF = right ventricular ejection fraction.

ARVC Risk Calculator v3.0

Age at diagnosis

Age at which the patient fulfilled ARVC diagnosis as per 2010 Task Force Criteria (Marcus et al. 2010)

Sex

☐ Male

☐ Female

Cardiac syncope (<6 months)

☐ Yes

☐ No

Syncope suspected to be caused by cardiac arrhythmia within 6 months prior to diagnosis.

Number of inverted T-waves

Total number of precordial and inferior leads with inverted T-waves on standard 12-lead ECG.

Maximum 24 hours PVC count

Maximum number of PVCs in 24 hours registered by continuous ECG monitoring (e.g. Holter)

History of non-sustained VT

☐ Yes

☐ No

Specified as a recorded ventricular tachycardia (>100bpm) ending spontaneously within 30 seconds.

Right ventricular ejection fraction (%)

As measured by cardiac MRI.

OPTIONAL: programmed ventricular stimulation (PVS)

☒ N/A ☐ Positive ☐ Negative

Positive if induction of sustained monomorphic VT lasting >30s or with hemodynamic compromise

Importance of genotype for risk stratification in arrhythmogenic right ventricular cardiomyopathy using the 2019 ARVC risk calculator

European Heart Journal (2022) 43, 3053–3067

Abstract

Aims To study the impact of genotype on the performance of the 2019 risk model for arrhythmogenic right ventricular cardiomyopathy (ARVC).

Methods and results The study cohort comprised 554 patients with a definite diagnosis of ARVC and no history of sustained ventricular arrhythmia (VA). During a median follow-up of 6.0 (3.1,12.5) years, 100 patients (18%) experienced the primary VA outcome (sustained ventricular tachycardia, appropriate implantable cardioverter defibrillator intervention, aborted sudden cardiac arrest, or sudden cardiac death) corresponding to an annual event rate of 2.6% [95% confidence interval (CI) 1.9–3.3]. Risk estimates for VA using the 2019 ARVC risk model showed reasonable discriminative ability but with overestimation of risk. The ARVC risk model was compared in four gene groups: *PKP2* ($n = 118$, 21%); desmoplakin (*DSP*) ($n = 79$, 14%); other desmosomal ($n = 59$, 11%); and gene elusive ($n = 160$, 29%). Discrimination and calibration were highest for *PKP2* and lowest for the gene-elusive group. Univariable analyses revealed the variable performance of individual clinical risk markers in the different gene groups, e.g. right ventricular dimensions and systolic function are significant risk markers in *PKP2* but not in *DSP* patients and the opposite is true for left ventricular systolic function.

Conclusion The 2019 ARVC risk model performs reasonably well in gene-positive ARVC (particularly for *PKP2*) but is more limited in gene-elusive patients. Genotype should be included in future risk models for ARVC.

Clinical features and outcomes in carriers of pathogenic desmoplakin variants

Alessio Gasperetti ^{1,2,3,*†}, Richard T. Carrick ^{1†}, Alexandros Protonotarios ⁴,

n = 800 patients with P/LP DSP variants

Clinical features of VA/HF risk on multivariable analysis



500+ PVC/24h

TWI in 3+ leads

Previous (N)SVT

LVEF ≤ 50%

High burden of adverse events



High VA and HF hospitalization rates (3.9%/yr and 1.8%/yr)

Almost 1/2 VA episodes are > 250 bpm

Unique characteristics of disease



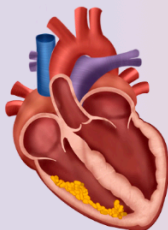
Myocardial injury episodes are common (8.7%) and associated with subsequent increases in VA (HR: 2.39) and HF (HR: 5.06)



Female patients experience higher rates of VA (HR: 1.55)

Multiple possible phenotypes

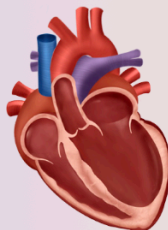
ARVC/TFC+ (36.8%)



VA:
6.5%/yr

HF:
2.1%/yr

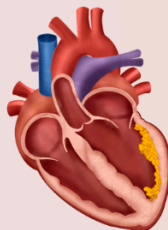
DCM (7.4%)



VA:
4.5%/yr

HF:
2.4%/yr

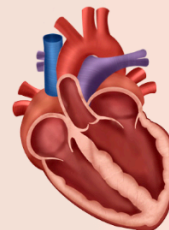
NDLVC (23.4%)



VA:
2.9%/yr

HF:
2.7%/yr

None (32.5%)



VA:
0.5%/yr

HF:
0.3%/yr

FENOTIPO
ETEROGENEO

Table 3 Follow-up data

Follow-up (years), median [IQR]	3.7 [1.4–7.1]
Patient with sustained VA, <i>n</i> (%)	139 (17.4)
Fast VA, <i>n</i> (%)	69 (8.6)
HF hospitalizations, <i>n</i> (%)	72 (9.0)
LVAD placement, <i>n</i> (%)	4 (0.5)
Transplant, <i>n</i> (%)	38 (4.8)
Death, <i>n</i> (%)	30 (3.8)

HF, heart failure; IQR, interquartile range; LVAD, left ventricular assist device; VA, ventricular arrhythmia.

PAZIENTI PORTATORI DI VARIANTE P/PL di DSP

RISCHIO MAGGIORE DI

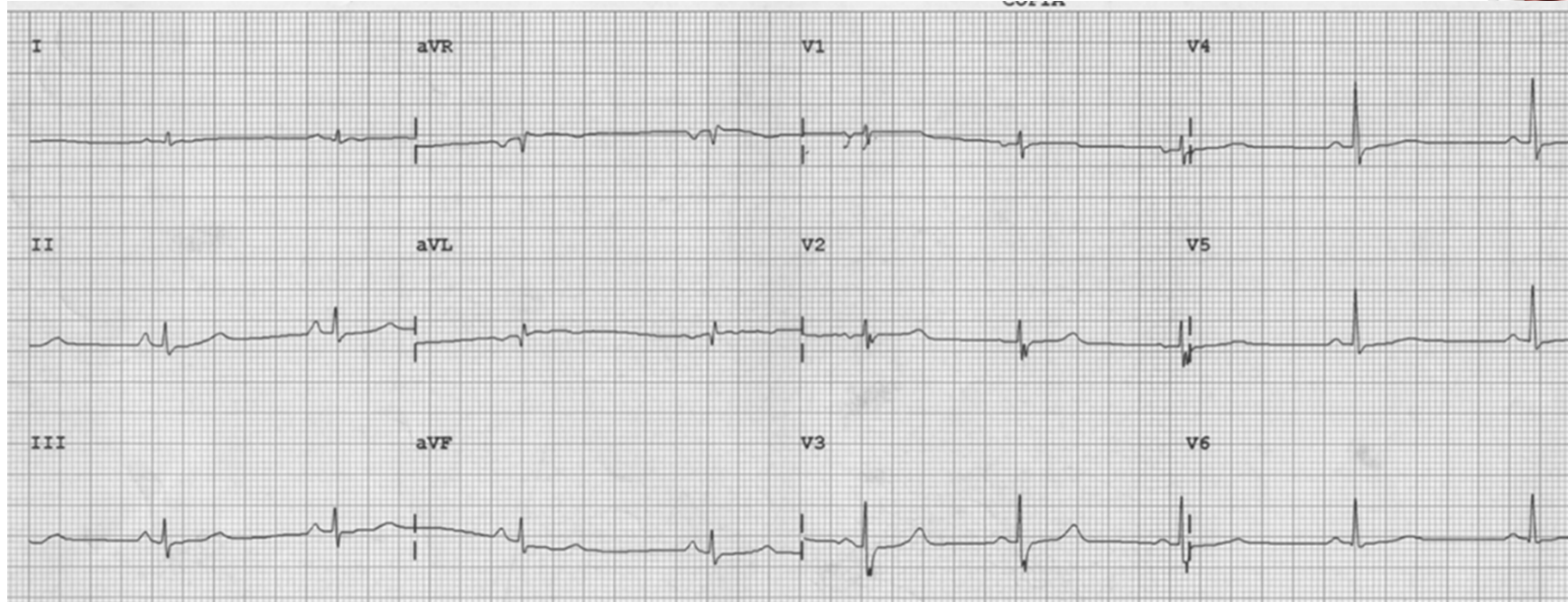
- **Aritmie ventricolari sostenute**
- **Ospedalizzazioni per HF**
- **Assistenza ventricolare/Trapianto/Decesso**

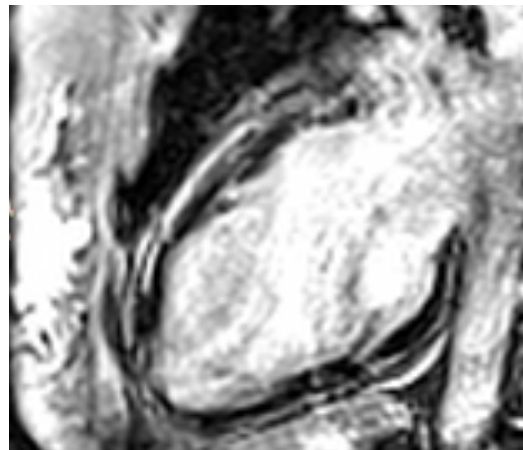
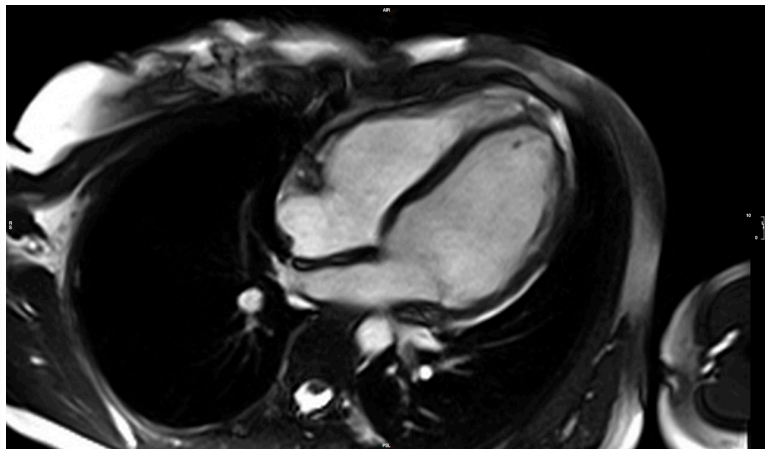
European Heart Journal (2025) 46, 362–376

***DONNE RISCHIO MAGGIORE DI
ARITMIE VENTRICOLARI (HR:
1.55)***



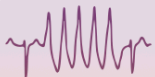
Femmina, 34 anni. Cardiopalmo. Storia familiare di CMD e ARVC. Numerosi BEV isolati politopici





Presenza di variante patogena gene DSP

A novel tool for arrhythmic risk stratification in desmoplakin gene variant carriers

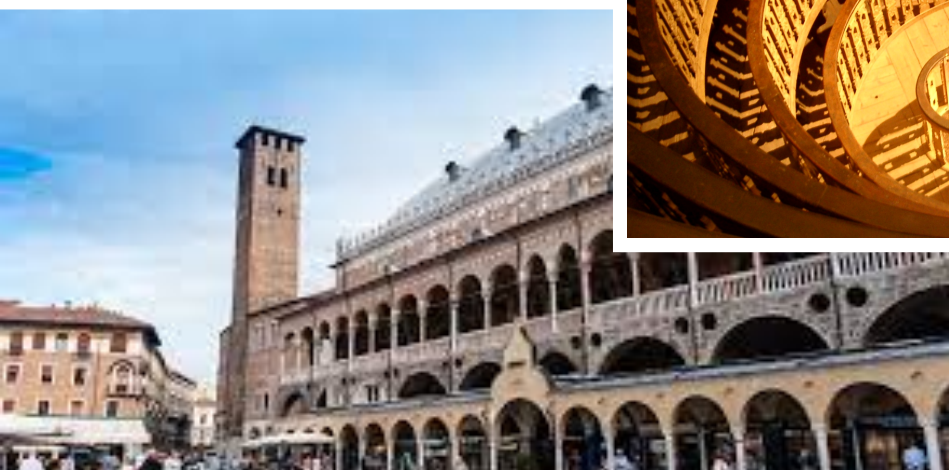
	Female sex	x (0.735)
		+
	NSVT	x (0.592)
		+
	ln (24-h PVC burden)	x (0.199)
		+
	LVEF < 50%	x (0.581)
		+
	Moderate to severe RV dysfunction	x (1.71) -1.787

DSP risk score for prediction of 5-year VA risk

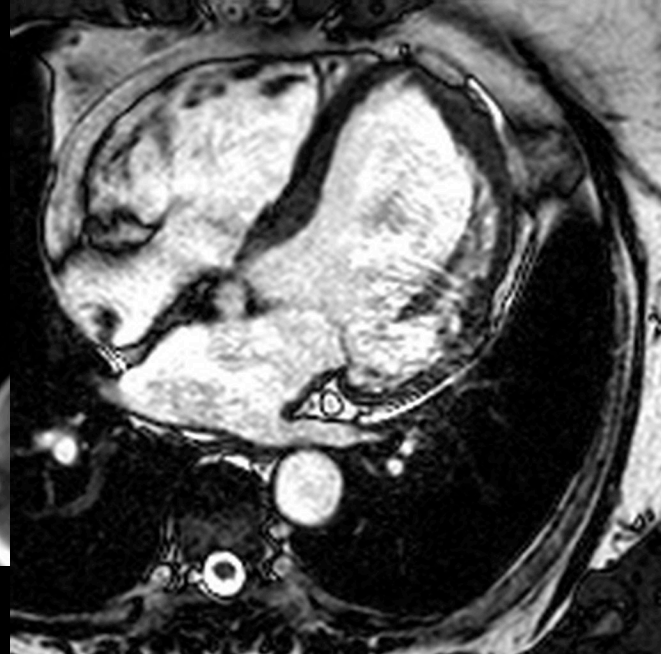
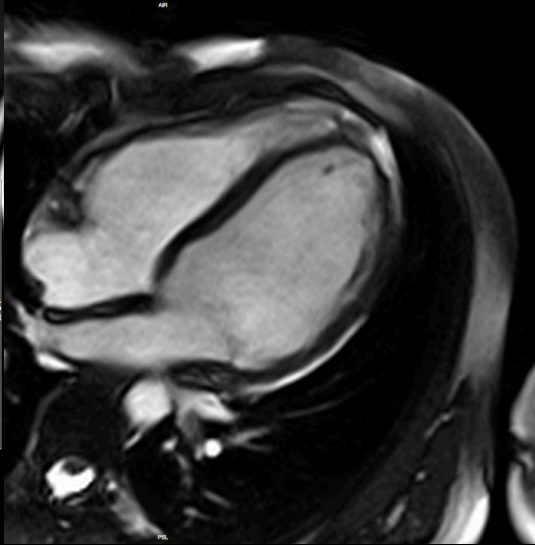
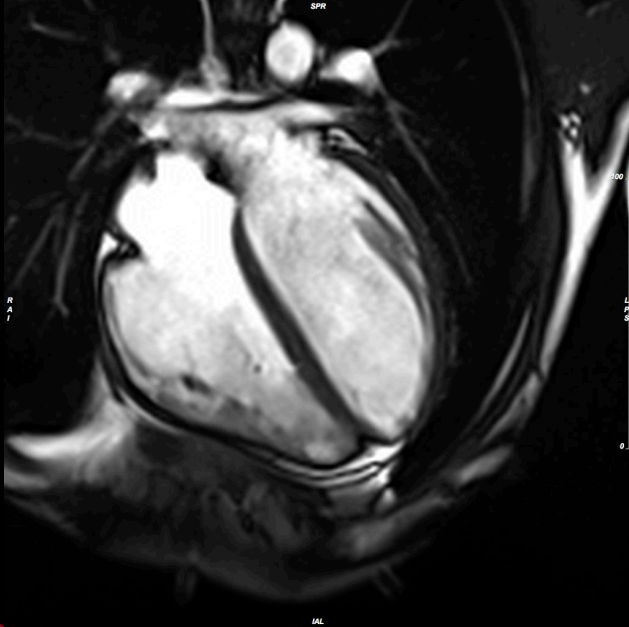
Genetica nella ACM

- Nella Cardiomiopatia Aritmogena la presenza di una variante genetica è rilevata nel 50-60% dei casi
- Vi sono elementi per una correlazione genotipo-fenotipo, sia diagnostica che prognostica
 - Pazienti portatori di mutazioni PKP2, DSG2, TMEM 43 presentano forme più aritmogene
 - Pazienti con varianti DSP hanno coinvolgimento importante del Vsin con tendenza a scompenso cardiaco ed episodi di HP





FENOTIPI DELLA CARDIOMIOPATIA ARITMOGENA



RIGHT-DOMINANT FORM

LEFT-DOMINANT FORM

BIVENTRICULAR FORM

