Prediction and Prevention of Sudden Cardiac Death: What's New?

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY-ARVC




Torino october 23, 2014



Cortile Antico

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Universitas Artistarum

Teatro Anatomico

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«The history and culture of Sudden Cardiac Death»

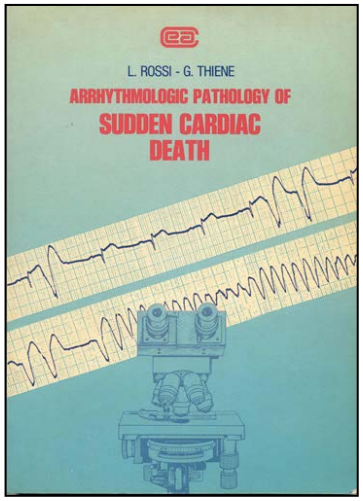
-490 b.c. Filippide-Marathon

-1970: *«The best, painless way to die…SCD: fate or fact ?»*

E Braunwald. Lecture, San Diego California USA

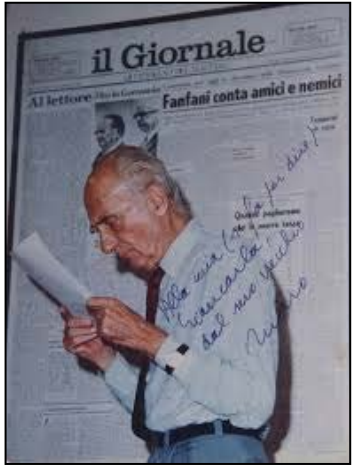
-*1977*: *«…the main challenge for cardiologists in the future…»* *B Lown. Am.J.Cardiol.*

-*1983*: *«…to overcome such a human tragedy, social plague and medical debacle of our age…»*



L.Rossi, G.Thiene-Padova 1983

Media and Sudden Cardiac Death



22 luglio 1988

29 settembre 1989

19 gennaio 1990

Anche l'aritmia è un killer

La morte improvvisa ed inaspettata di un soggetto in età giovanile e apparentemente in buona salute oltre ad essere un evento drammatico con un forte impatto emotivo rappresenta un problema con molti altri risvolti. Al medico viene richiesta una precisa diagnosi, che coinvolge anche responsabilità medico-legali, e la conoscenza dell'incidenza del fenomeno e delle cause più frequenti che ne stanno alla base; questi ultimi aspetti rivestono una grande importanza per una adeguata e tanto auspicata prevenzione. Studi epidemiologici, clinici e anatomopatologici hanno chiarito solo in parte alcuni aspetti di questa problematica. Nel nostro Paese mancano dei dati certi su questo tragico evento per cui i punti di riferimento debbono essere ricercati soprattutto negli studi condotti negli Stati Uniti che, per tipo di popolazione e per abitudini di vita possono rappresentare una realtà completamente diversa dal nostro Paese.

Per questo motivo l'Università di Padova, in collaborazione con centri universitari e ospedalieri regionali, ha promosso una ricerca sulla morte improvvisa giovanile nella regione Veneto che potesse dare qualche risposta ai numerosi interrogativi che tale problematica suscita. La regione Veneto ha aderito a questo progetto ed ha finanziato uno studio che ha portato, nel giro di qualche anno, a risultati interessanti, e per qualche aspetto sorprendenti, che sono stati oggetto di alcune pubblicazioni sulle più autorevoli riviste specializzate del mondo.

La ricerca è stata coordinata dal professor Gaetano Thiene dell'Istituto di anatomia patologica che ha curato l'aspetto organizzativo e lo studio istopatologico, e dal professor Andrea Nava della Cattedra di cardiologia che, assieme ad una équipe di cardiologi, si è occupato della parte clinica. Dal 1979 al 1986 le morti improvvise al di sotto di 35 anni di età sono state 60 con una media di 8,5 per anno e, tenendo conto che nel territorio il numero di abitanti è pari a circa 4.370.533, ne risulta un rapporto di uno ogni 73.000 abitanti; 56 decessi erano imputabili ad una malattia cardiaca.

Una causa medica (rottura aortica o tromboembolia polmonare) è stata evidenziata in 7 casi mentre i rimanenti 49 sono probabilmente deceduti per un evento aritmico improvviso. Tra questi 49 pazienti alterazioni congenite o acquisite delle coronarie erano presenti in 19 mentre la cardiomiopatia ipertrofica (3 casi), il prolasso mitralico (3 casi) ed altre anomalie soprattutto a carico del tessuto di conduzione (12 casi) erano ritenute responsabili dell'aritmia fatale nei rimanenti.

Il dato più sorprendente è venuto dal riscontro di ben 12 casi di cardiomiopatia del ventricolo destro. Questo tipo di patologia, descritta in precedenza da autori francesi e denominata «displasia aritmogena del ventricolo destro» o «malattia aritmogena del ventricolo destro», era stata in passato ritenuta un reperto raro ed era stata coinvolta nella morte improvvisa giovanile solo come possibilità teorica senza prove dirette.

Molte ragioni possono essere alla base di questo risultato: la selezione dei parenti esaminati con l'autopsia, una più attenta valutazione del ventricolo destro ritenuto in passato di scarsa importanza emodinamica e clinica ed un fattore genetico proprio della regione veneta.

A tal proposito sono stati individuati dei nuclei familiari nei quali l'incidenza della malattia era particolarmente elevata. Da questo studio è inoltre emerso che se è vero che questa malattia può portare alla morte improvvisa è altrettanto vero che una volta riconosciuta ed adeguatamente trattata è responsabile solo eccezionalmente di questo evento fatale.

Questi risultati, come è comprensibile, non debbono rappresentare un punto di arrivo ma implicano ulteriori approfondimenti indirizzati verso una diagnostica precoce di tutte le malattie a rischio.

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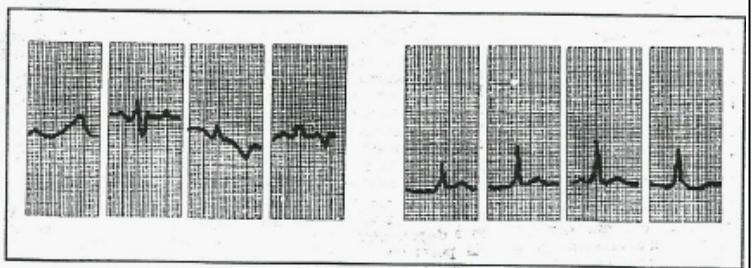
Sforzo fisico e fibrillazione

Se il racconto della mortale corsa da Maratona ad Atene del leggendario Filippide rappresenta la prima documentazione di una morte improvvisa legata allo sforzo, il caso Manfredonia ha riportato drammaticamente in tutte le case tale problematica creando discussioni, dubbi, allarmismi e reazioni emotive comprensibili ma che non aiutano a capire le luci e le ombre che stanno dietro a tale fenomeno.

Al di là quindi del caso specifico credo sia utile ricorda-



Il primo elettrocardiogramma (a sinistra) rivela la grave crisi cardiaca di un calciatore appena dopo il malore. Il secondo invece (eseguito quarantotto ore dopo) segna un ritorno a condizioni quasi normali e comunque non preoccupanti. Lo «sforzo» provoca spesso una perdita d'ossigeno

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«Sudden cardiac death during a football match»… Manfredonia suddenly collapsed…he was successfully resuscitated…»

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Università di Padova

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Lo sport agonistico dilata il volume del cuore

L'attività sportiva a diversi livelli, professionistico, dilettantistico o amatoriale, attira un numero sempre più elevato di proseliti spinti sia da istintivi meccanismi di difesa contro le conseguenze della vita sedentaria, dallo stress e del deterioramento dell'ambiente naturale, sia da motivazioni sociali, economiche e di immagine.

Ma qual è l'impegno cardiovascolare di un soggetto che pratica sport? Lo sport a qualsiasi livello può di per sé comportare effetti dannosi sul cuore? Queste ed altre problematiche sono state affrontate recentemente in un congresso organizzato dalla Società Italiana di cardiologia dello sport, che ha visto la partecipazione di numerose e qualificate scuole cardiologiche.

Innanzitutto esiste una sostanziale differenza tra i vari tipi di sport. Gli sport dinamici, siano essi aerobici (corse di fondo, sci da fondo, ciclismo su strada) od anaerobici (100 e 200 metri piani) o aerobico-anaerobico alternati (calcio, tennis) comportano il ripetersi continuo e regolare di esercizi che provocano da una parte un aumento significativo della frequenza cardiaca e della quantità di sangue che il cuore riesce a trasferire nell'unità di tempo (portata cardiaca), dall'altra uno scarso o nullo aumento della pressione arteriosa media. Infatti tali sport sono accompagnati da una vasodilatazione periferica per cui il cuore lavora al massimo delle sue possibilità ma in un sistema a bassa resistenza.

Negli sport statici, (sollevamento pesi, lotta) si nota un aumento notevole della pressione media, superiore a quello della frequenza cardiaca, a causa di una precoce e pronunciata vasocostrizione periferica. Inoltre il sangue che ritorna al cuore è diminuito con un inadeguato aumento della portata cardiaca. In questi sport quindi il cuore lavora in un sistema ad alta resistenza. Queste differenti situazioni provocano, con l'allenamento, diversi adattamenti cardiocircolatori.

Gli sport dinamici riducono il tono simpatico e aumentano il tono vagale, con conseguente riduzione della frequenza cardiaca e della pressione arteriosa, inoltre provocano la comparsa di una dilatazione delle cavità cardiache con aumento dello spessore delle pareti muscolari. Gli sport statici viceversa provocano un aumento dello spessore delle pareti (ipertrofia) senza aumento del diametro delle cavità; peraltro il sistema nervoso autonomo viene scarsamente influenzato.

Indipendentemente dal tipo di sport praticato, tali modificazioni regrediscono progressivamente ed entro 6-8 mesi di completo disallenamento si registra un ritorno alla situazione basale. Questi dati confermano che in un individuo sano lo sport provoca modificazioni parafisiologiche differenti e comunque reversibili.

Sul totale delle morti improvvise il 12-13 per cento circa avviene in relazione a sforzo. In uno studio su praticanti jogging vi sono state 13 morti ogni centomila praticanti per anno. Molti dei soggetti deceduti o rianimati (soprattutto oltre i 35 anni) mostravano segni di malattia coronarica che non aveva dato in precedenza manifestazioni cliniche evidenti; le morti cosiddette bianche (senza segni di cardiopatia o malattia) rappresentavano una percentuale esigua.

D'altra parte, nell'ormai classico studio di Framingham l'incidenza di morte improvvisa era inversamente proporzionale alla quantità di esercizio fisico giornaliero e al grado di allenamento, in una popolazione seguita per venti anni.

In definitiva lo sport o l'attività fisica non sono di per sé un fattore di rischio cardiovascolare ma anzi hanno un effetto benefico sia psicologico che fisiologico. Un controllo cardiologico accurato, un'adeguata preparazione e un prudente autocontrollo sono misure preventive necessarie soprattutto negli atleti amatoriali. Patologie latenti possono comunque emergere durante le attività sportive con possibile, anche se raro, rischio di morte improvvisa che nonostante accurati screening non può essere, allo stato attuale, completamente prevenuto.

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Date of birth ?

ARVC-history

Milestone paper

«Auricularization» of
right ventricular pressure curve
Dalla Volta S et al. 1961;61:25

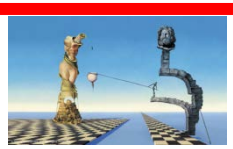
Right Ventricular Dysplasia:
A Report of 24 Adult Cases

FRANK I. MARCUS, M.D., GUY H. FONTAINE, M.D., GERARD GUIRAUDON, M.D., ROBERT FRANK, M.D., JEAN L. LAURENCEAU, M.D., CHRISTINE MALERGUE, M.D., AND YVES GROSGOGEAT, M.D.

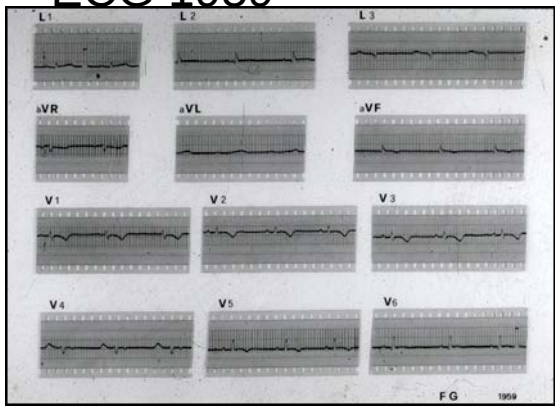
Circulation. 1982;65:384-398

ARVC-History-Padova (*FATE* ?)

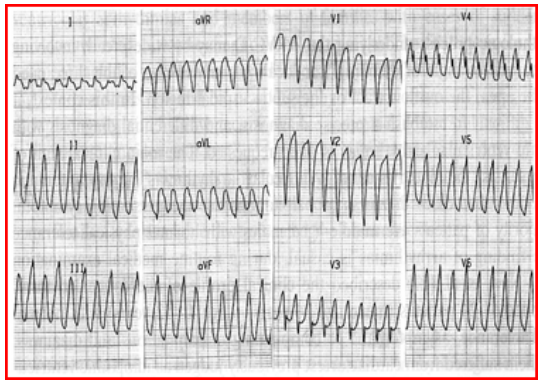
Nava A, Buja G.



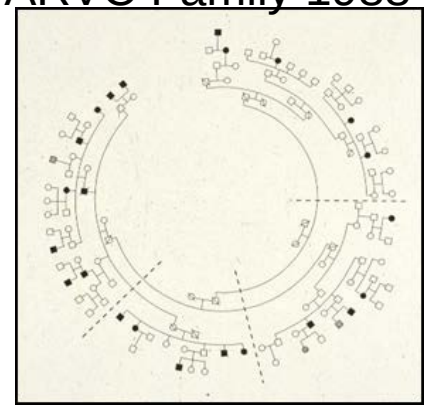
ECG 1959



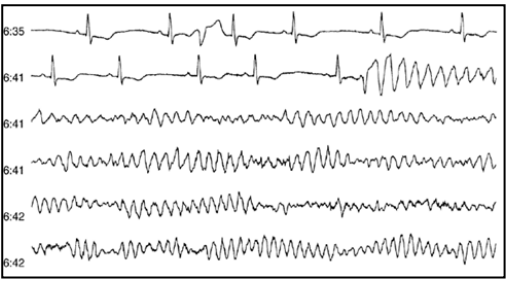
Sustained VT 1961

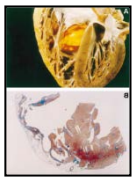


ARVC Family 1988



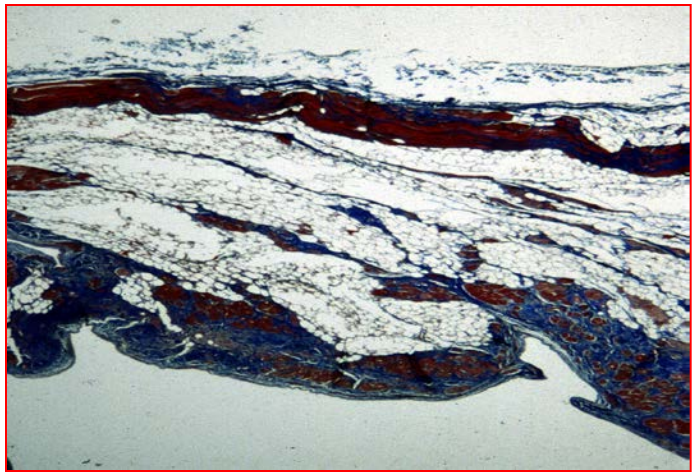
Right Ventricular Cardiomyopathy and sudden death in young people Thiene G, et al. New Engl J Med 1988;318:129





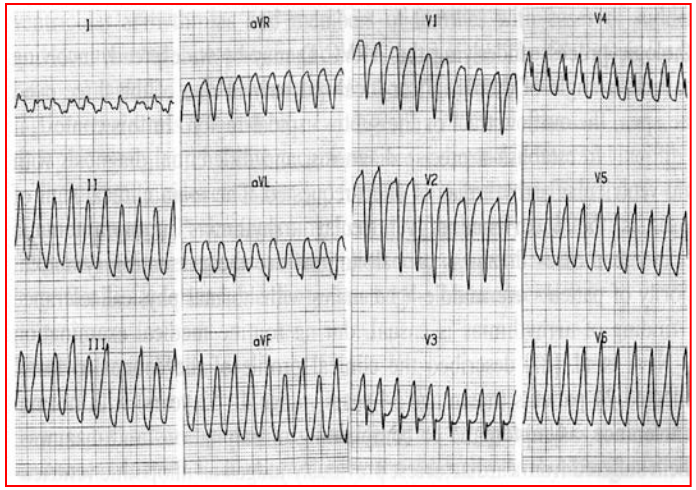
ARVC/D: Anatomo-Clinical Definition

Heart muscle disease, genetically-determined
("cardiomyopathy")



Pathology: Fibrofatty replacement of the "right ventricular" myocardium

Clinical presentation: ventricular tachycardia and arrhythmic sudden death ("arrhythmogenic")



ARVC/D : Clinical Outcome

- Ventricular electrical instability ⇒ sudden arrhythmic death (any time due the disease course)
- Progressive loss of RV myocardium and LV involvement ⇒ heart failure (late in life)

Buja G et al Progr Cardiovasc Dis 2008;50:282

Table 1. Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia—Mortality

	No. of Patients	Mean FU (y)	Death, n (Rate Per 100 Person-Years)
Blomstrom-Lunqvist et al[7]	15	8.8	2 (1.5)
Marcus et al[8]	12	5	2 (3.0)
Leclercq and Coumel[28]	39	8.8	1 (0.3)
Canu et al[29]	22	10.7	3 (1.2)
Nava et al[33]	151	8.5	1 (0.07)
Hulot et al[31]	130	8.1	21 (2.0)
Lemola et al[32]	61	4.5	10 (3.6)

Mortality
0.3-3.6
Rate per 100 person-Year

Nava A, ..Buja G et al. JACC 2000;36:2226

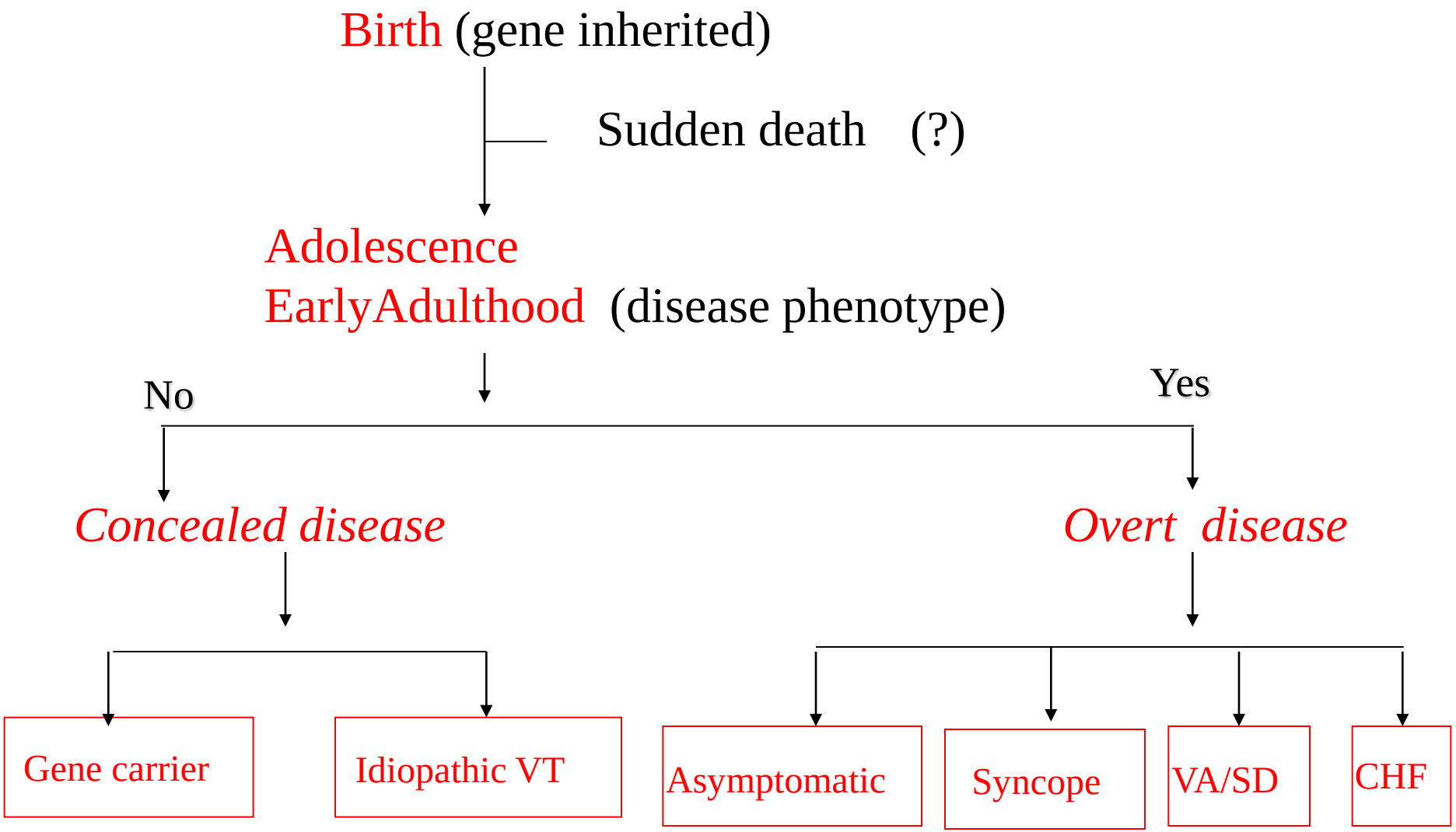
Clinical Profile and Long-term Follow-up of 37 Families With Arrhythmogenic Right Ventricular Cardiomyopathy

-Probands affected from 37 families

-365 subjects: 151 affected, 17 health carrier, 197 N-aff. or uncertain

1 SCD FU 8.5±4.6 years
0.08 pt/year mortality

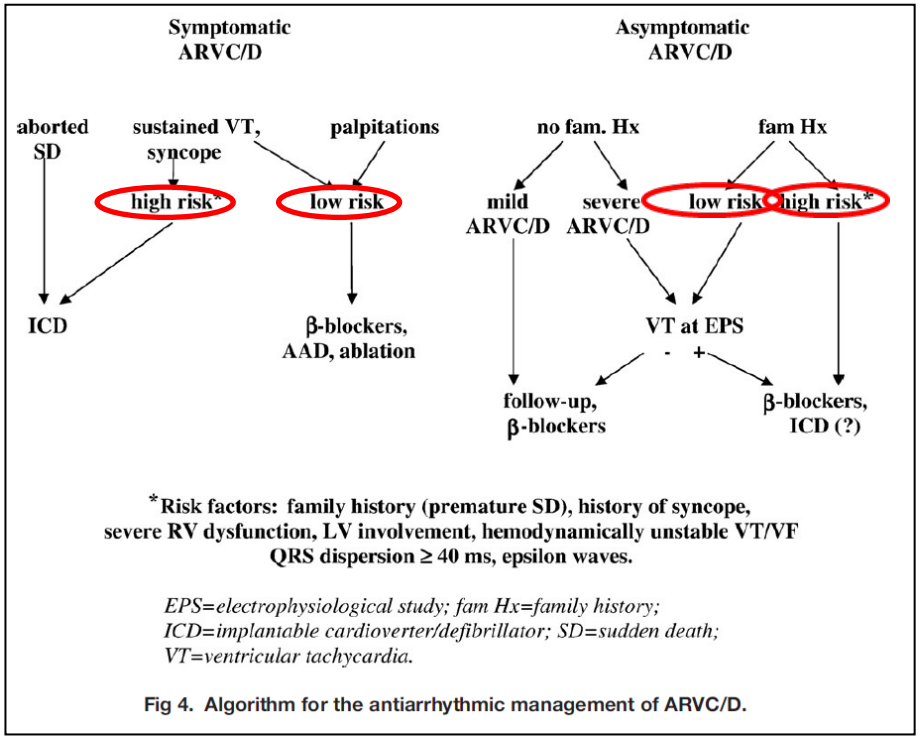
Natural history of ARVC/D



Corrado & Thiene, Circulation 2006;113:1634-7

Therapeutic strategies in ARVC

Buja G et al. Progr Cardiovasc Dis 2008;50:282

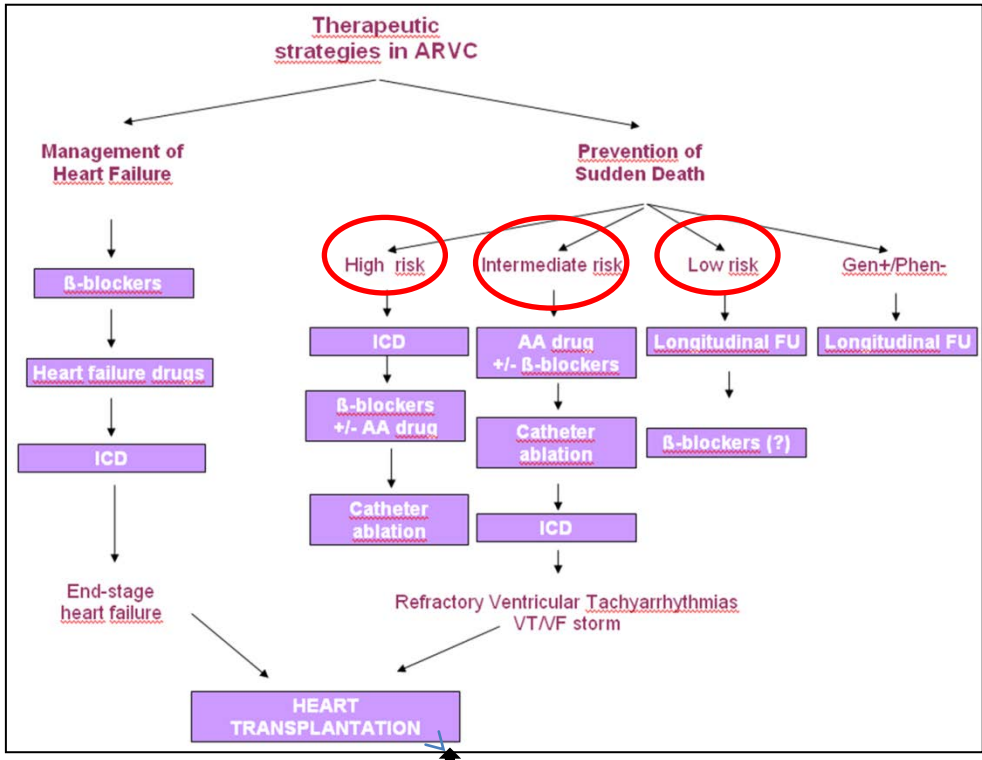


*Risk factors: family history (premature SD), history of syncope, severe RV dysfunction, LV involvement, hemodynamically unstable VT/VF QRS dispersion ≥ 40 ms, epsilon waves.

EPS=electrophysiological study; fam Hx=family history; ICD=implantable cardioverter/defibrillator; SD=sudden death; VT=ventricular tachycardia.

Fig 4. Algorithm for the antiarrhythmic management of ARVC/D.

2014-Padova strategies

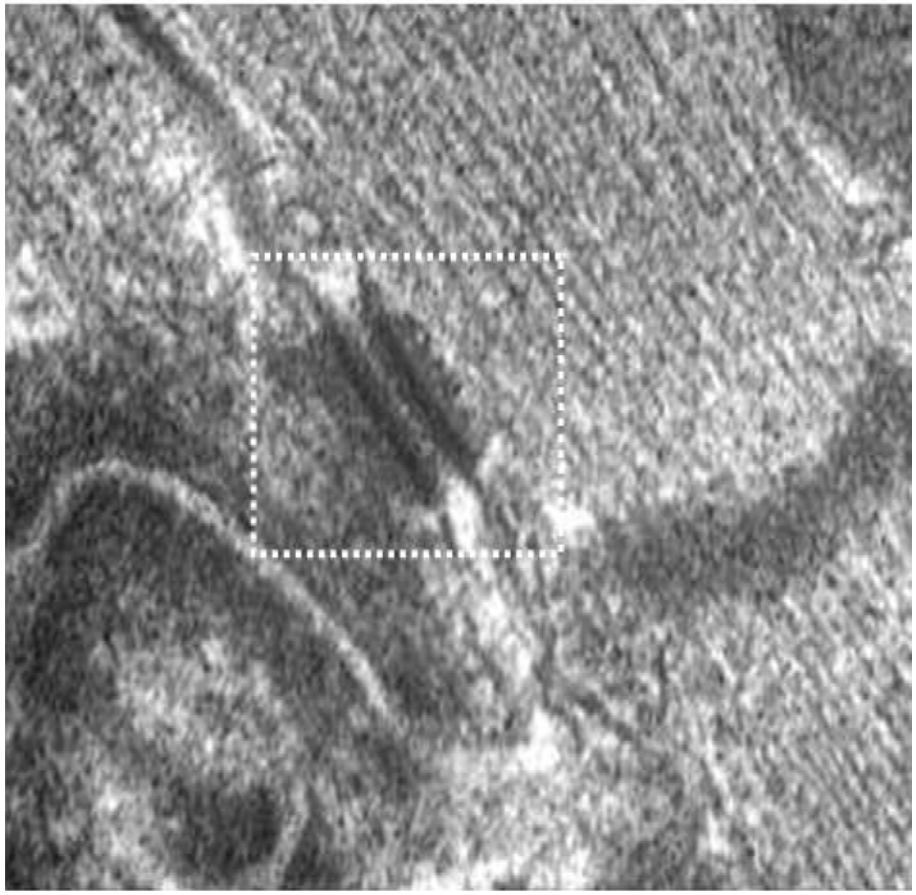


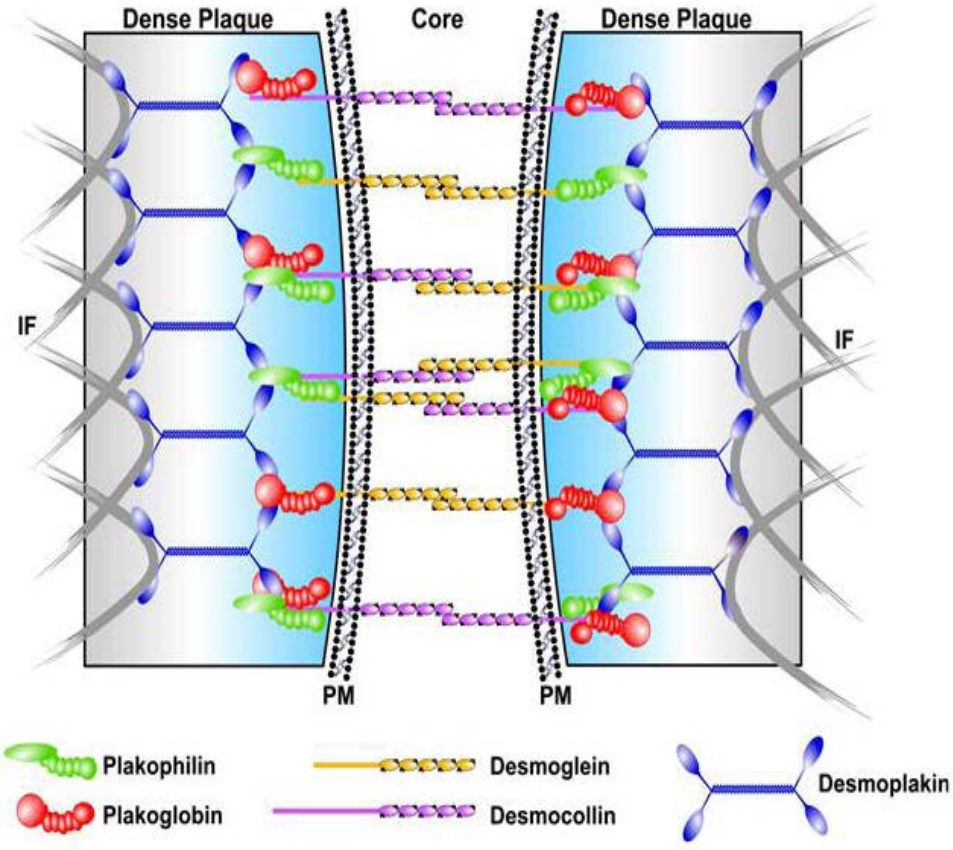
6 years

ARVC/D: Risk stratification

- Pre-clinical
  - Genetic screening
- Pre-symptomatic
  - Family history/ECG screening
- Clinical
  - Clinical symptoms and signs

ARVC/D: Pathogenesis





Basso C et al. Lancet 2009; 373: 1289–1300

Table 1 Chromosomal loci and disease-causing genes in arrhythmogenic right ventricular cardiomyopathy

Designation (pattern of inheritance)	Chromosomal locus	Gene mutations
ARVD1 (AD)	14q23-q24	Transforming growth factor-β3 (TGFβ3)
ARVD2 (AD)	1q42-q43	Cardiac ryanodine receptor (RyR2)
ARVD3 (AD)	14q12-q22	?
ARVD4 (AD)	2q32.1-q32.3	?
ARVD5 (AD)	3p23	Transmembrane 43 (TMEM43)
ARVD6 (AD)	10p12-p14	?
ARVD7 (AD)	10q22	?
Naxos disease (AR)	17q21	Plakoglobin (JUP)
ARVD8 (AD)	6p24	Desmoplakin (DSP)
ARVD 9 (AD)	12p11	Plakophilin-2 (PKP2)
ARVD 10 (AD)	18q12.1	Desmoglein-2 (DSG2)
ARVD 11 (AD)	18q12.1	Desmocollin-2 (DSC2)
ARVD 12 (AD)	17q21	Plakoglobin (JUP)

AD, autosomal dominant; AR, autosomal recessive.

Corrado D, Basso C, Thiene G ***Heart*** *2009*

Prognostic impact of genetic testing

Section # – Disease	Diagnostic	Prognostic	Therapeutic
Section I – LQTS	+++	+++	++
Section II – CPVT	+++	+	-
Section III – BrS	+	+	-
Section IV – CCD	+	+	+
Section V – SQTS	+/-	-	-
Section VI – AF	-	-	-
Section VII – HCM	+++	++	+
Section VIII – ACM/ARVC	+	+/-	-
Section IX – DCM	+/-	-	-
Section IX – DCM + CCD	++	++	+
Section X – LVNC	+	-	-
Section XI – RCM	+	+	+

Ackerman MJ et al. Heart Rhythm 2011;8:1308 –1339

Original Article

Compound and Digenic Heterozygosity Predicts Lifetime Arrhythmic Outcome and Sudden Cardiac Death in Desmosomal Gene–Related Arrhythmogenic Right Ventricular Cardiomyopathy

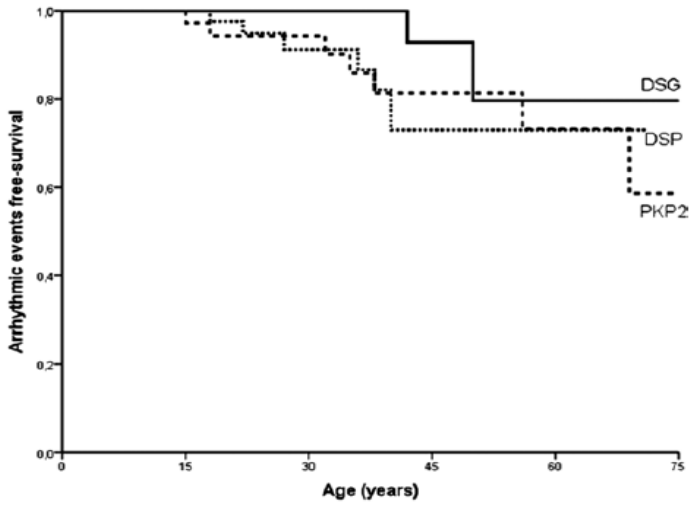
Ilaria Rigato, MD, PhD; Barbara Bauce, MD, PhD; Alessandra Rampazzo, BSc, PhD; Alessandro Zorzi, MD; Kalliopi Pilichou, BSc, PhD; Elisa Mazzotti, MD, PhD; Federico Migliore, MD, PhD; Martina Perazzolo Marra, MD, PhD; Alessandra Lorenzon, BSc, PhD; Marzia De Bortoli, BSc, PhD; Martina Calore, BSc, PhD; Andrea Nava, MD; Luciano Daliento, MD; Dario Gregori, MA, PhD; Sabino Iliceto, MD; Gaetano Thiene, MD; Cristina Basso, MD, PhD; Domenico Corrado, MD, PhD

Background—Mutations in genes encoding for desmosomal proteins are the most common cause of arrhythmogenic right ventricular cardiomyopathy (ARVC). We assessed the value of genotype for prediction of lifetime major arrhythmic events and sudden cardiac death (SCD) in desmosomal gene–related ARVC.

Methods and Results—The overall study population included 134 desmosomal gene mutation carriers (68 men; median age 36 years [22–52]) from 44 consecutive ARVC families undergoing comprehensive genetic screening. The probability of experiencing a first major arrhythmic event or SCD during a lifetime was determined by using date of birth as start point for the time-to-event analysis, and was stratified by sex, desmosomal genes, mutation types, and genotype complexity (single versus multiple mutations). One hundred thirteen patients (84%) carried a single desmosomal gene mutation in desmoplakin (n=44; 39%), plakophilin-2 (n=38; 34%), desmoglein-2 (n=30; 26%), and desmocollin-2 (n=1; 1%), whereas 21 patients (16%) had a complex genotype with compound heterozygosity in 7 and digenic heterozygosity in 14. Over a median observation period of 39 (22–52) years, 22 patients (16%) from 20 different families had arrhythmic events, such as SCD (n=1), aborted SCD because of ventricular fibrillation (n=6), sustained ventricular tachycardia (n=14), and appropriate defibrillator intervention (n=1). Multiple desmosomal gene mutations and male sex were independent predictors of lifetime arrhythmic events with a hazard ratio of 3.71 (95% confidence interval, 1.54–8.92; P=0.003) and 2.76 (95% confidence interval, 1.19–6.41; P=0.02), respectively.

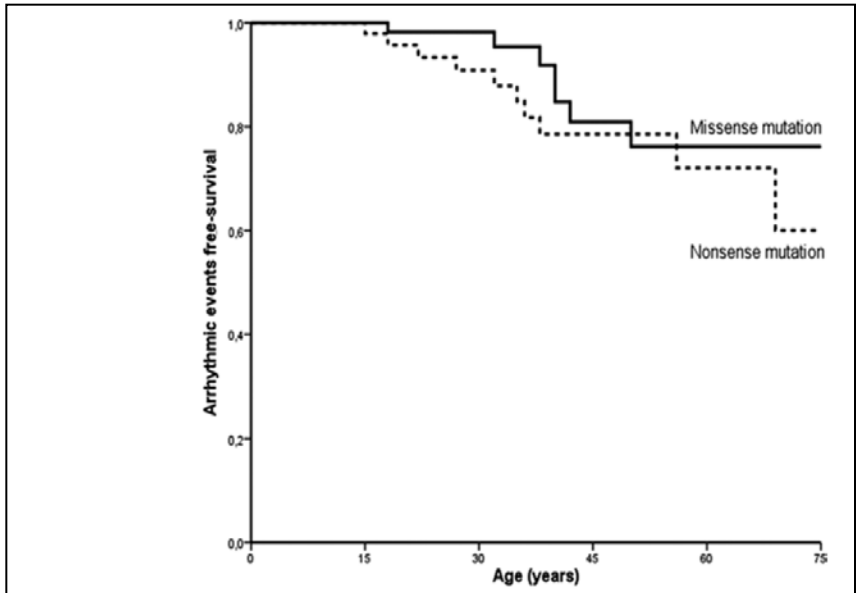
Conclusions—Compound/digenic heterozygosity was identified in 16% of ARVC-causing desmosomal gene mutation carriers and was a powerful risk factor for lifetime major arrhythmic events and SCD. These results support the use of comprehensive genetic screening of desmosomal genes for arrhythmic risk stratification in ARVC. (***Circ Cardiovasc Genet*. 2013;6:533-542.**)

Life-time arrhythmic outcome by DS-genes and mutations



DSG	30	29	25	18	11	1
DSP	44	44	21	13	7	0
PKP2	38	38	28	22	15	3

Figure 3. Kaplan–Meier analysis of survival from the composite arrhythmic end point in the subgroup with single mutation according to the defective desmosomal gene. The single carrier of *DSC-2* gene mutation was excluded from the analysis.

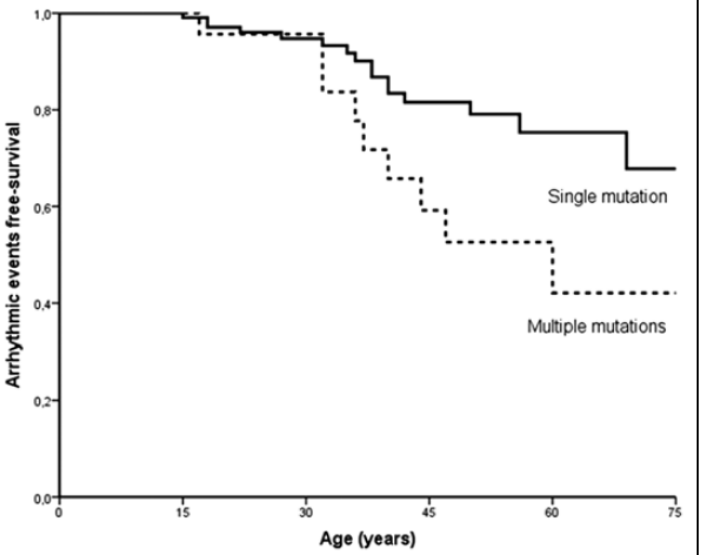


Missense mutation	62	61	40	26	15	1
Nonsense mutation	51	51	34	27	18	3

Figure 4. Kaplan–Meier analysis of survival from the composite arrhythmic end point in the subgroup with single mutation according to the functional meaning of the mutation.

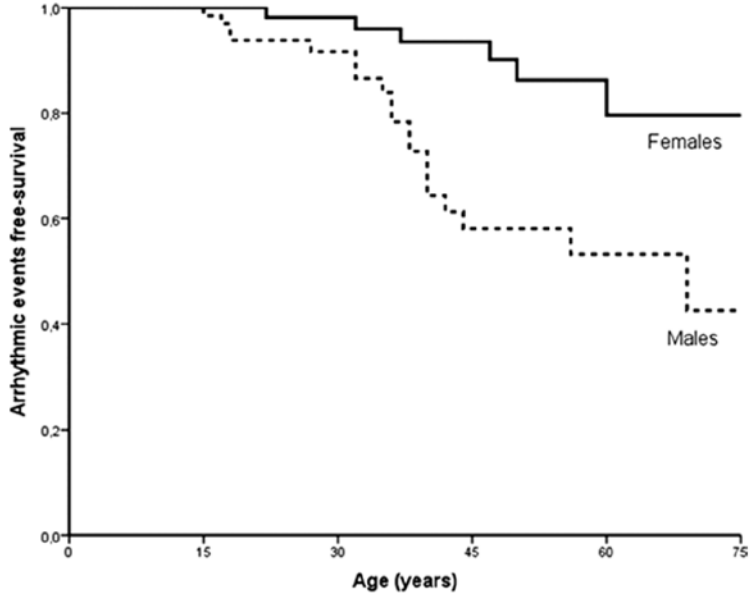
Rigato I et al, Circ Cardiovasc Genet. 2013;6:533-542

Life-time arrhythmic outcome by compound genotype and gender



Single mutation	113	112	74	53	33	4
Multiple mutations	21	21	16	10	3	1

Figure 2. Kaplan–Meier analysis of survival from the composite arrhythmic end point in the study population according to the presence of multiple mutations.



Females	66	66	59	41	23	2
Males	68	67	41	22	13	3

Figure 1. Kaplan–Meier analysis of survival from the composite arrhythmic end point in the study population according to sex.

Rigato I, Circ Cardiovasc Genet. 2013;6:533-542

Table 5. Genetic Determinants of Arrhythmic Events Since Birth

	Univariate Analysis			Multivariable Analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Sex (men)	2.24	0.92–5.46	0.07	2.76	1.19–6.41	0.02
Multiple mutations	3.01	1.42–6.37	0.004	3.71	1.54–8.92	0.003
Nonmissense mutations*	1.53	0.53–4.42	0.4321			
Desmosomal genes*,#						
PKP2	1					
DSP	1.41	0.28–3.05	0.89			
DSG2	1.53	0.38–6.15	0.38			

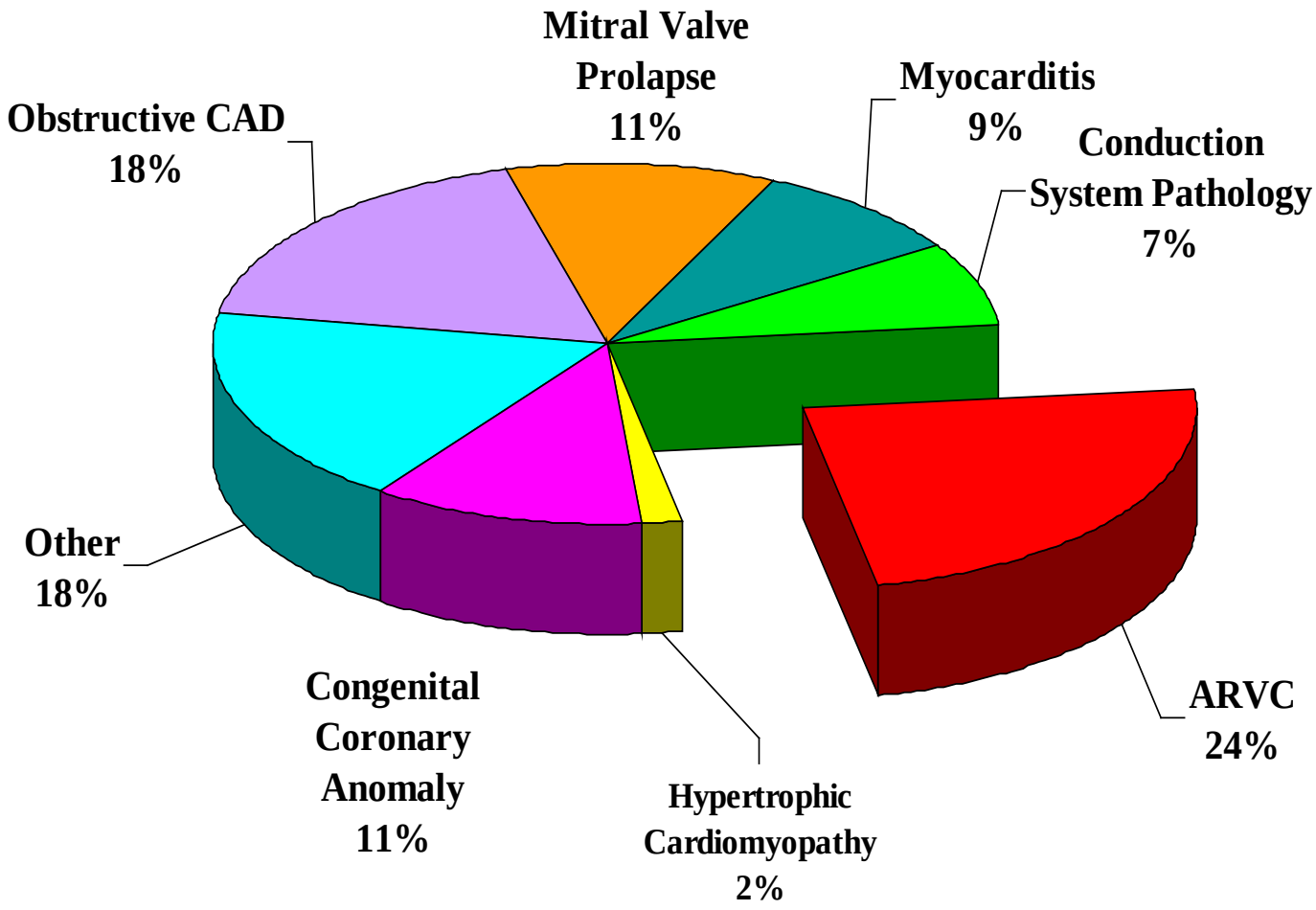
*Among patients with single mutation.
#Single carrier of *DSC-2* gene mutation was excluded from analysis.

Rigato I et al, Circ Cardiovasc Genet. 2013;6:533-542

ARVC/D: Risk Stratification

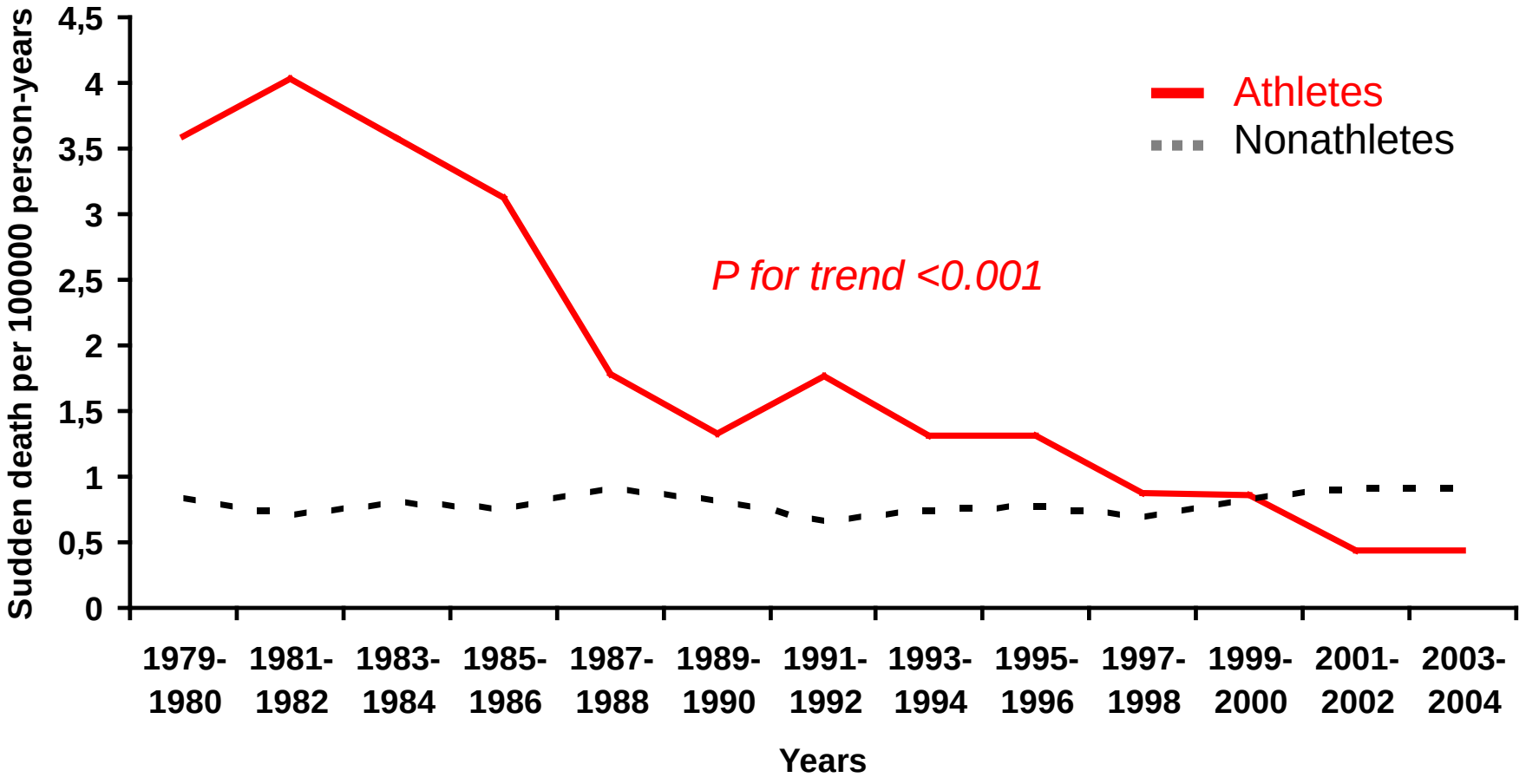
- Pre-clinical
  - Genetic screening
- Pre-symptomatic
  - Family history/ECG screening
- Clinical
  - Clinical symptoms and signs

ARVC/D is a leading cause of SD in young competitive athletes



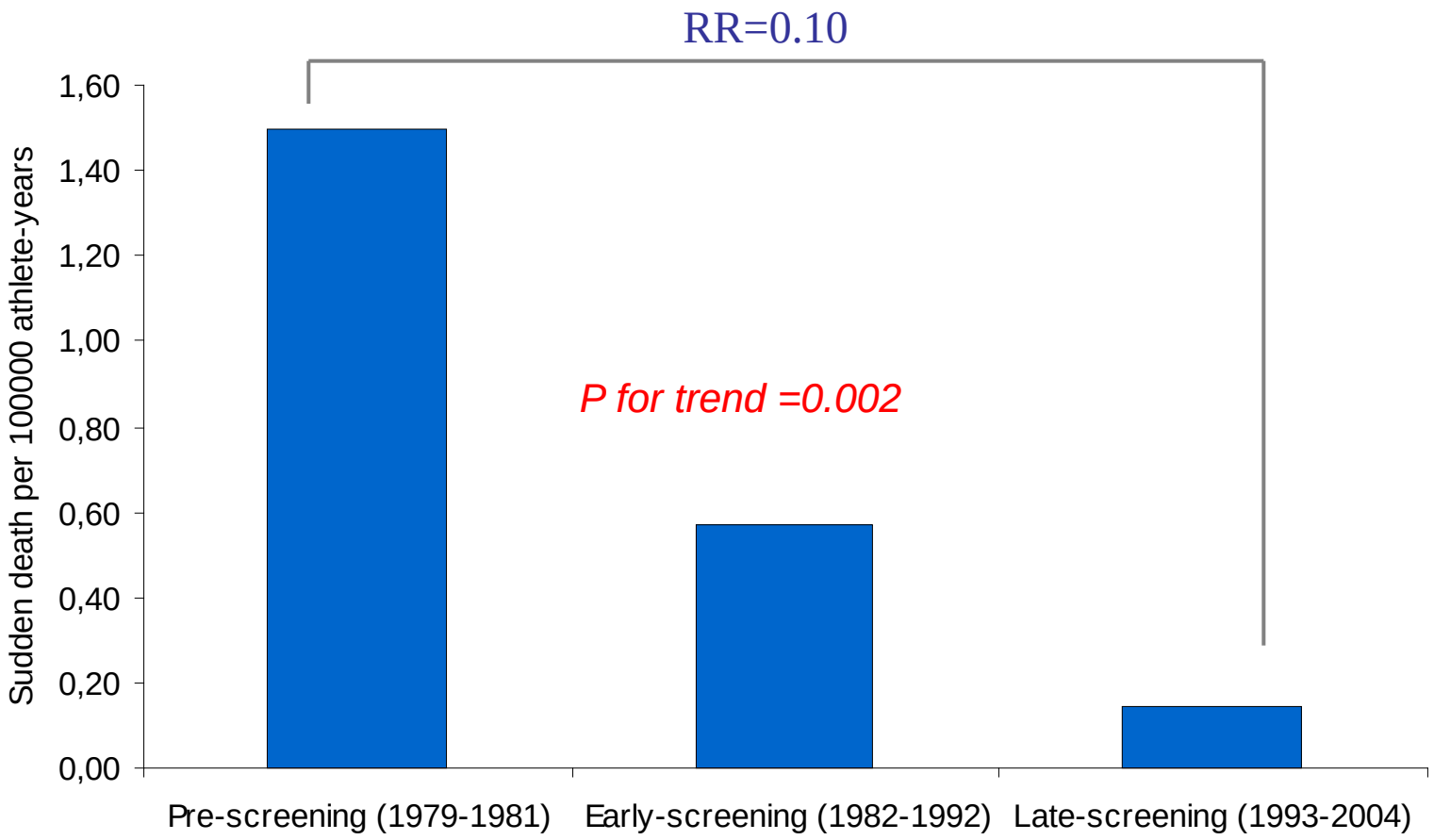
Corrado et al N Engl J Med 1998; 339: 364-369

Annual Incidence Rates of Sudden Cardiovascular Death in Screened Competitive Athletes and Unscreened Nonathletes Aged 12 to 35 Years in the Veneto Region of Italy (1979-2004)



Corrado et al. JAMA 2006;296:1593-1601

Mortality trend for sudden death from Cardiomyopathies



Corrado et al. JAMA 2006;296:1593-1601

Cardiovascular conditions causing disqualification from competitive sports in 879 athletes over 2 consecutive screening periods (1982-1992 and 1993-2004) at the Center for Sports Medicine in Padua, Italy

		NUMBER OF DISQUALIFIED ATHETES*		
CARDIOVASCULAR CAUSES OF DISQUALIFICATION	*Total Study Period (1982-2004) N=879 (%)*	*Early screening Period (1982-1992) N=455 (%)*	*Late screening Period (1993-2004) N=424 (%)*	**P-value**
Rhythm and conduction abnormalities	345 (39)	166 (36)	179 (42.2)	0.13
- ventricular arrhythmias	173 (19.6)	81 (18)	92 (21.6)	0.20
- supraventricular arrhythmias	73 (8.3)	39 (8.6)	34 (8.0)	0.56
- WPW Syndrome	55 (6.3)	29 (6.3)	26 (6.1)	0.88
- LBBB or RBBB & LAD	26 (3.0)	8 (1.7)	18 (4.2)	0.10
- second Degree AV Block	13 (1.5)	7 (1.5)	6 (1.4)	0.89
- long QT Syndrome	5 (0.6)	2 (0.4)	3 (0.7)	0.93
Systemic hypertension:	205 (23)	118 (25.9)	87 (20.5)	0.96
Valvular disease (including MVP):	184 (21)	106 (23.3)	78 (18.4)	0.09
Cardiomyopathies	**60 (6.8)**	**20 (4.4)**	**40 (9.4)**	**0.005**
- hypertrophic	**30 (3.4)**	**14 (3.0)**	**16 (3.8)**	**0.50**
- arrhythmogenic right ventricular	**16 (1.8)**	**2 (0.4)**	**14 (3.3)**	**0.004**
- dilated	**14 (1.6)**	**4 (0.9)**	**10 (2.4)**	**0.21**
Coronary artery disease	11 (1.3)	2 (0.4)	9 (2.1)	0.05
Other	74 (8.4)			

Corrado et al. JAMA 2006;296:1593-1601

ARVC-»Is ECG always accurate for prognostic purpose ?»

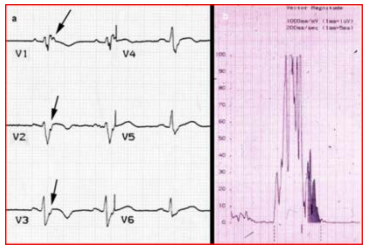
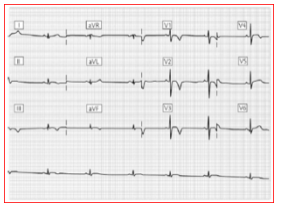


Table 1 Revised Task Force Criteria for Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy on 12-lead electrocardiogram

	Major criteria	Minor criteria
Depolarization criteria	Epsilon wave (reproducible low-amplitude signals between the end of QRS complex to the onset of T wave) in the right precordial leads (leads V_1–V_3)	Terminal activation duration ≥ 55 ms measured from the nadir of S wave to the end of QRS complex in leads V_1, V_2, or V_3 in the absence of CRBBB
Repolarization criteria	Inverted T waves in right precordial leads (leads V_1–V_3) or beyond in individuals >14 years of age (in the absence of CRBBB)	Inverted T waves in leads V_1 and V_2 in individuals >14 years of age (in the absence of CRBBB) or in leads V_4, V_5, or V_6 Inverted T waves in leads V_1–V_4 in individuals >14 years of age in the presence of CRBBB



Malignant Arrhythmogenic Right Ventricular Dysplasia/ Cardiomyopathy with a normal 12-lead electrocardiogram: A rare but underrecognized clinical entity

Anneline S.J.M. te Riele, MD,[*†] Cynthia A. James, PhD,[†] Aditya Bhonsale, MD,[†] Judith A. Groeneweg, MD,[*‡] Christian F. Camm, BA,[§] Brittney Murray, MS,[†] Crystal Tichnell, MGC,[†] Jeroen F. van der Heijden, MD, PhD,[*] Dennis Dooijes, MGC, PhD,[‖] Daniel P. Judge, MD,[†] Richard N.W. Hauer, MD, PhD,[‡] Harikrishna Tandri, MD,[†] Hugh Calkins, MD, FHRS[†]

(Heart Rhythm 2013;10:1484–1491)

Usefulness of electrocardiographic parameters for risk prediction in ARVC.
Saguner A et al. Am J Cardiol 2014;113:1728

Cox regression analysis:
-inferior leads TWI HR 2.44
-QRS fragmentation HR 2.65
-Precordial QRS amplitude ratio ≤0.48mV HR 2.92

Am J Cardiol 2014;113:1728

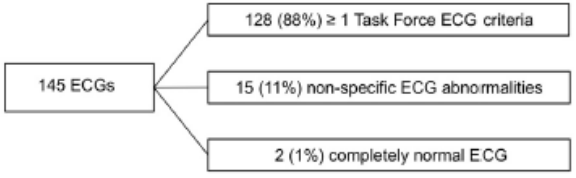


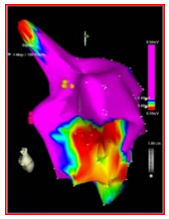
Figure 1 Twelve-lead ECG classification among 145 patients with ARVD/C experiencing an arrhythmic event. ARVD/C = Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy; ECG = electrocardiogram.

ECG RARELY FAILS !

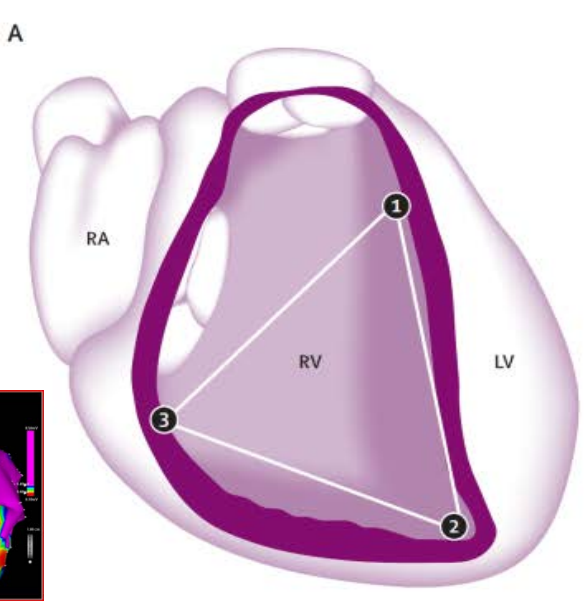
ARVC/D: Risk Stratification

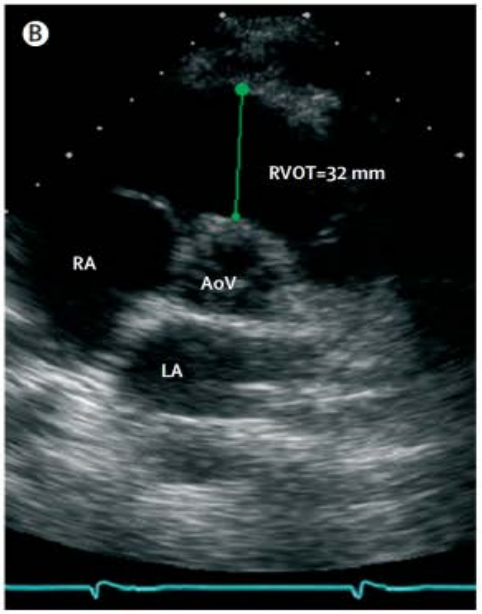
- Pre-clinical
  - Genetic screening
- Pre-symptomatic
  - Family history/ECG screening
- Clinical
  - Clinical symptoms and signs

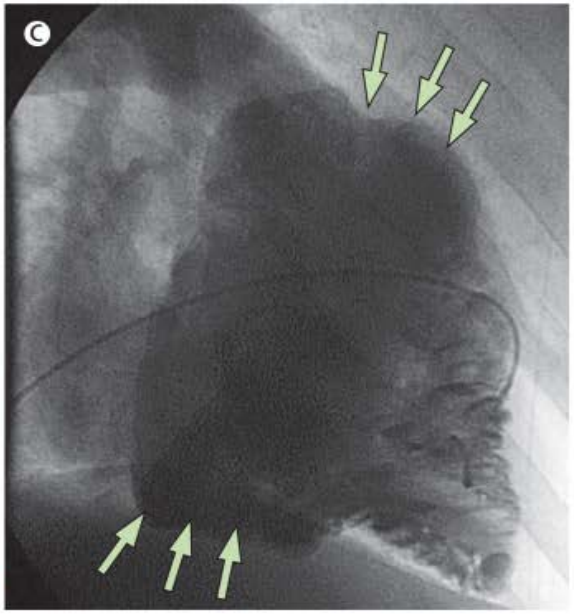
Clinical features and diagnosis

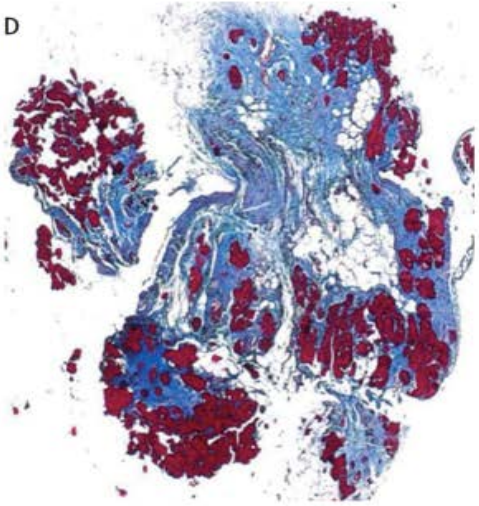


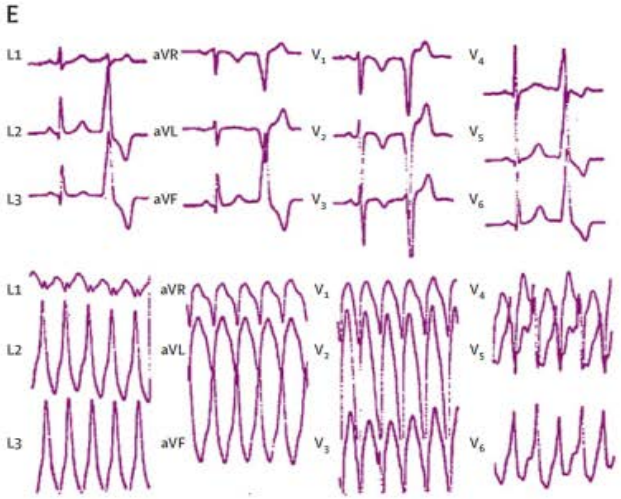
EAM

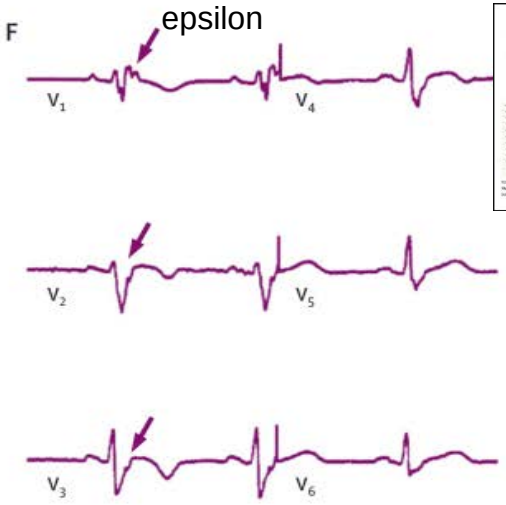


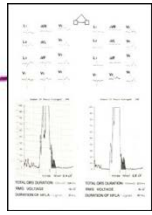












LP

Clinical Markers of Arrhythmic Risk in ARVC/D

Recognized risk factors

- Aborted SCD, sustained VT
- Syncope
- Non-sustained VT
- Moderate to severe RV dysfunction
- LV involvement with reduced ejection fraction
- Proband status
- Frequent PVC (≥1000/24 hours)
- Inducibility at PVS
- Physical exercise and sport activity
- Extent of negative T-waves in precordial leads
- Compound and digenic heterozygosity for desmosomal-gene mutations

Less well established risk factors

- Family history of premature SCD (≤35 years)
- Male gender
- Young age at the time of diagnosis
- QRS dispersion/delayed S wave upstoke/prolonged terminal activation duration in right precordial leads
- Extent of electroanatomic scar on electroanatomic voltage mapping
- Fractionated signals/delayed potentials on electroanatomic voltage mapping
- Extent of ventricular late-gadolinium enhancement

Exercise Increases Age-Related Penetrance and Arrhythmic Risk in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy–Associated Desmosomal Mutation Carriers

Cynthia A. James, ScM, PhD, Aditya Bhonsale, MD, Crystal Tichnell, MGC, Brittney Murray, MS, Stuart D. Russell, MD, Harikrishna Tandri, MD, Ryan J. Tedford, MD, Daniel P. Judge, MD, Hugh Calkins, MD
Baltimore, Maryland

(J Am Coll Cardiol 2013;62:1290–7)

From first sustained VT/VF

From class C CHF

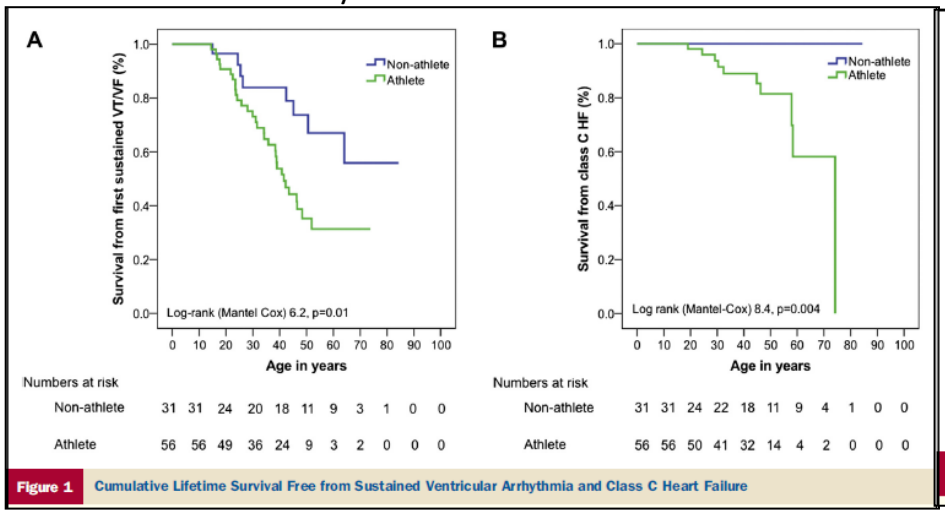


Figure 1 Cumulative Lifetime Survival Free from Sustained Ventricular Arrhythmia and Class C Heart Failure

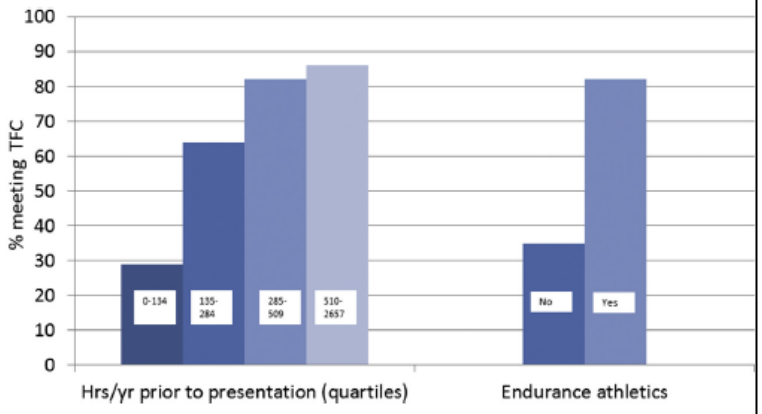


Figure 2 Likelihood of ARVD/C Diagnosis Is Associated With Exercise History

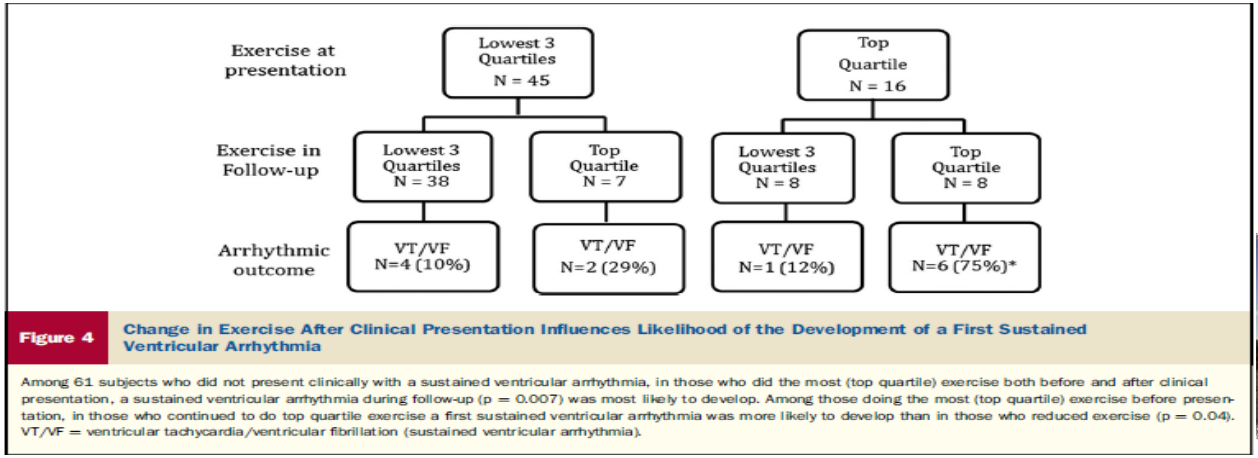


Figure 4 Change in Exercise After Clinical Presentation Influences Likelihood of the Development of a First Sustained Ventricular Arrhythmia

Among 61 subjects who did not present clinically with a sustained ventricular arrhythmia, in those who did the most (top quartile) exercise both before and after clinical presentation, a sustained ventricular arrhythmia during follow-up ($p = 0.007$) was most likely to develop. Among those doing the most (top quartile) exercise before presentation, in those who continued to do top quartile exercise a first sustained ventricular arrhythmia was more likely to develop than in those who reduced exercise ($p = 0.04$). VT/VF = ventricular tachycardia/ventricular fibrillation (sustained ventricular arrhythmia).

Implantable Cardioverter-Defibrillator Therapy for Prevention of Sudden Death in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

Domenico Corrado, MD, PhD; Loira Leoni, MD; Mark S. Link, MD; Paolo Della Bella, MD; Fiorenzo Gaita, MD; Antonio Curnis, MD; Jorge Uriarte Salerno, MD; Diran Igidbashian, MD; Antonio Raviele, MD; Marcello Disertori, MD; Gabriele Zanotto, MD; Roberto Verlato, MD; Giuseppe Vergara, MD; Pietro Delise, MD; Pietro Turrini, MD, PhD; Cristina Basso, MD, PhD; Franco Naccarella, MD; Francesco Maddalena, MD; N.A. Mark Estes III, MD; Gianfranco Buja, MD; Gaetano Thiene, MD

Background—Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a condition associated with the risk of sudden death (SD).

Methods and Results—We conducted a multicenter study of the impact of the implantable cardioverter-defibrillator (ICD) for prevention of SD in 132 patients (93 males and 39 females, age 40±15 years) with ARVC/D. Implant indications were a history of cardiac arrest in 13 patients (10%), sustained ventricular tachycardia in 82 (62%), syncope in 21 (16%), and other in 16 (12%). During a mean follow-up of 39±25 months, 64 patients (48%) had appropriate ICD interventions, 21 (16%) had inappropriate interventions, and 19 (14%) had ICD-related complications. Fifty-three (83%) of the 64 patients with appropriate interventions received antiarrhythmic drug therapy at the time of first ICD discharge. Programmed ventricular stimulation was of limited value in identifying patients at risk of tachyarrhythmias during the follow-up (positive predictive value 49%, negative predictive value 54%). Four patients (3%) died, and 32 (24%) experienced ventricular fibrillation/flutter that in all likelihood would have been fatal in the absence of the device. At 36 months, the actual patient survival rate was 96% compared with the ventricular fibrillation/flutter-free survival rate of 72% ($P<0.001$). Patients who received implants because of ventricular tachycardia without hemodynamic compromise had a significantly lower incidence of ventricular fibrillation/flutter (log rank=0.01). History of cardiac arrest or ventricular tachycardia with hemodynamic compromise, younger age, and left ventricular involvement were independent predictors of ventricular fibrillation/flutter.

Conclusions—In patients with ARVC/D, ICD therapy provided life-saving protection by effectively terminating life-threatening ventricular arrhythmias. Patients who were prone to ventricular fibrillation/flutter could be identified on the basis of clinical presentation, irrespective of programmed ventricular stimulation outcome. **(*Circulation*. 2003;108: 3084-3091.)**

Key Words: cardiomyopathy ■ death, sudden ■ defibrillation ■ prevention ■ tachyarrhythmias

DARVIN I (secondary prevention): ICD implant indications in 132 pts

- Cardiac arrest: 13
- Ventricular tachycardia (poorly tolerated): 52
- Ventricular tachycardia (well tolerated): 30
- Unexplained Syncope : 21
- Non-sustained ventricular tachycardia: 12
- Family history of sudden death: 4

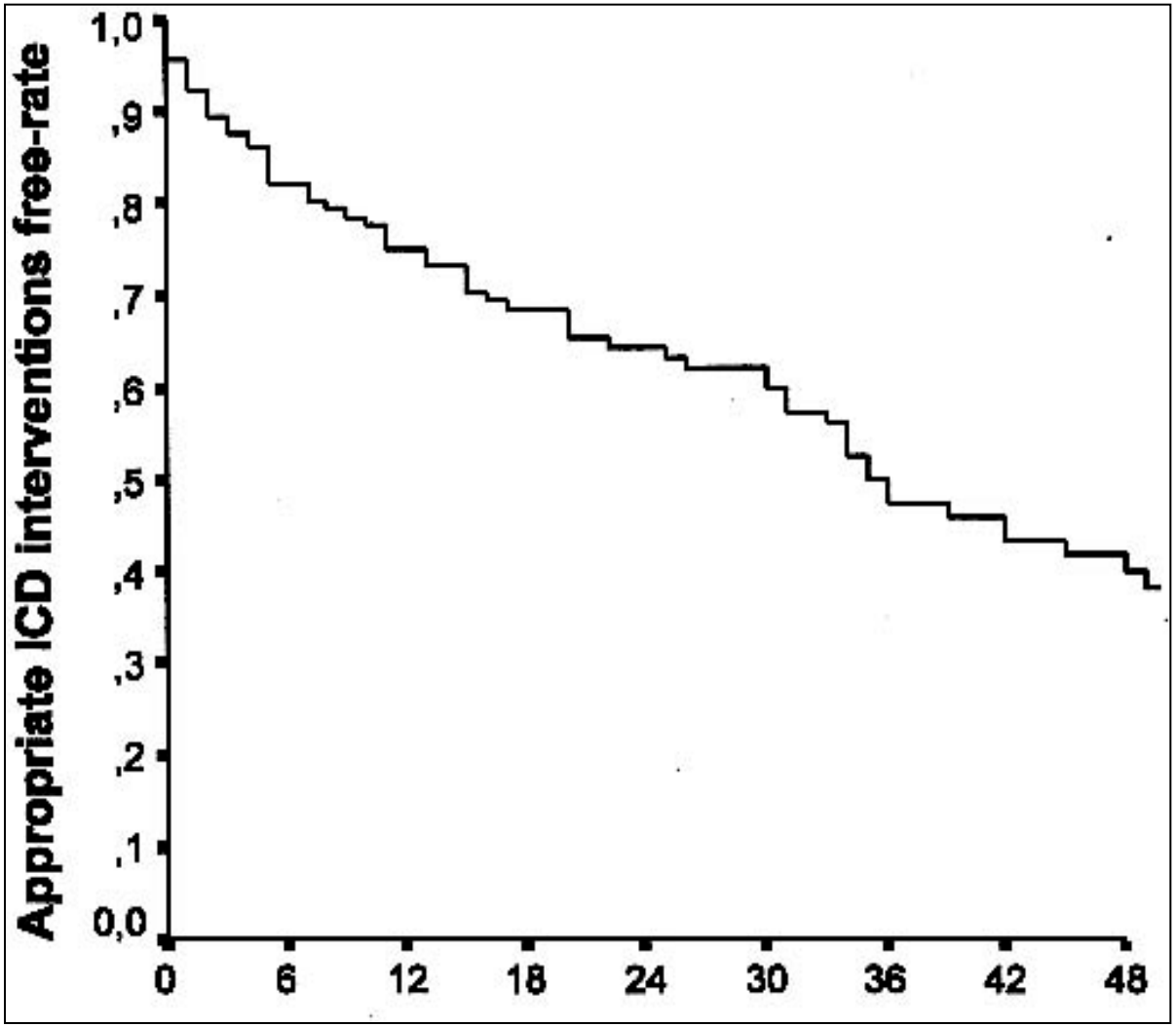
Corrado,..Buja et al. Circulation 2003 108: 3084 - 3091

Follow-up and ICD interventions in 132 ARVC/D pts

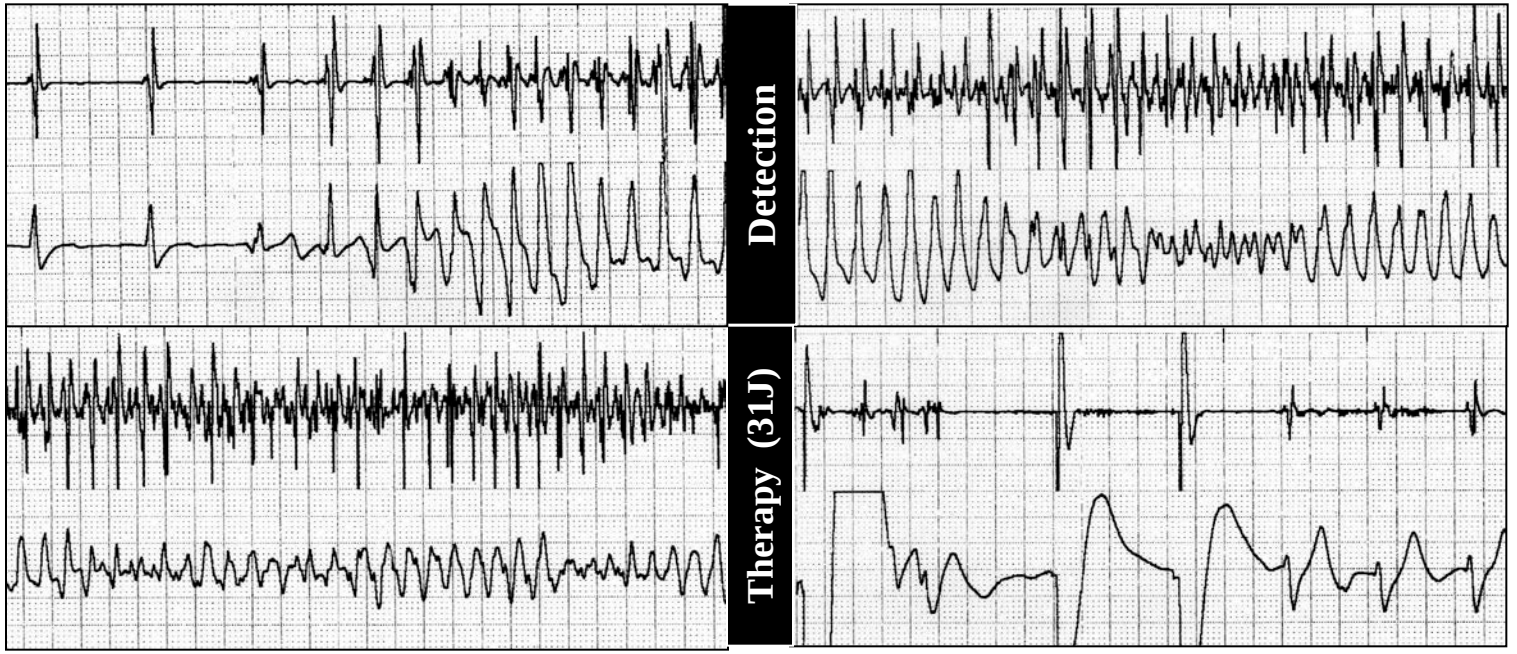
Mean follow-up:
39±27 months
(3.3 years)

Appropriate ICD interventions:
64/132 patients (48%)

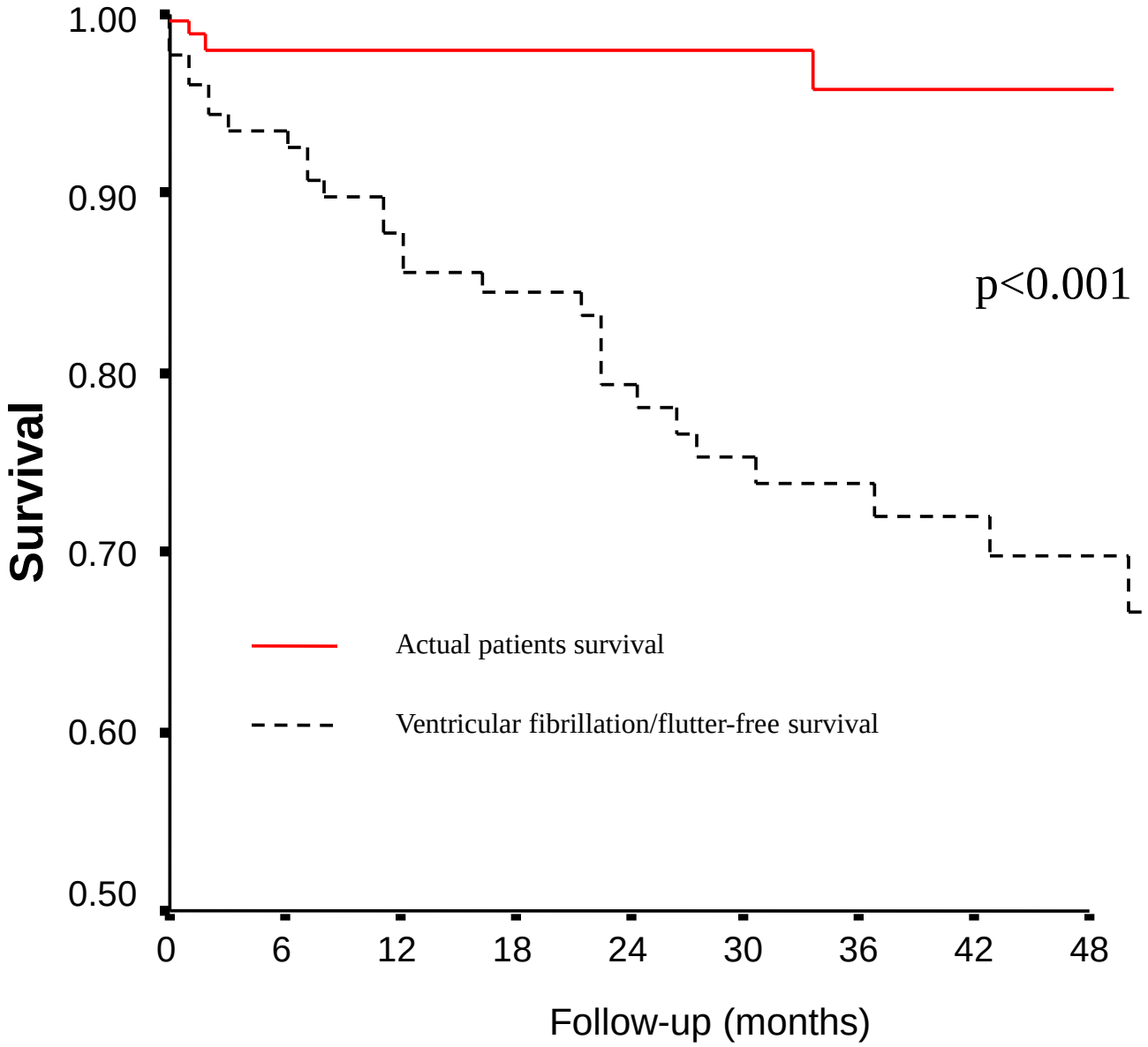
*Shocks (31)
*ATP (13)
*both (20)
(a total of 1271 disharges)



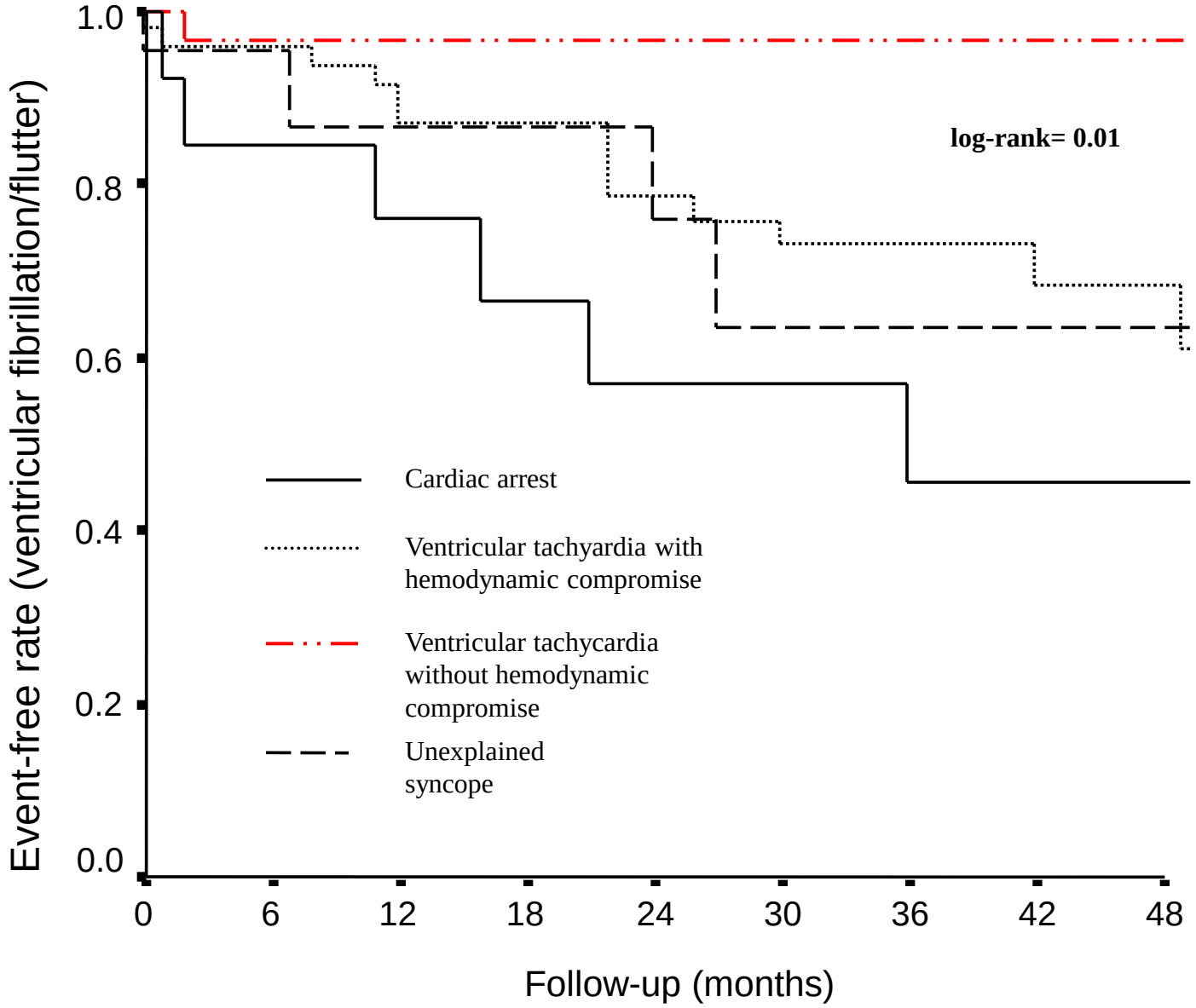
Classification of the ventricular arrhythmia according to the stored intracardiac electrograms



Ventricular fibrillation/flutter show no tendency to be self-terminating and result in sudden death unless corrective measures are undertaken promptly



Kaplan-Mayer analysis of actual patient survival compared with survival free of ventricular fibrillation/flutter that in all likelihood would have been fatal in the absence of the ICD.The divergence between the lines reflects the estimated survival benefit of ICD therapy



Kaplan-Mayer curves of freedom from ICD interventions on ventricular fibrillation/flutter for different patient subgroups stratified for clinical presentation. Patients presenting with ventricular achycardia without hemodynamiccompromise had a significantly lower incidence of ventricular fibrillation/flutte during the follow-up.

Prophylactic Implantable Defibrillator in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/ Dysplasia and No Prior Ventricular Fibrillation or Sustained Ventricular Tachycardia

Domenico Corrado, MD, PhD; Hugh Calkins, MD; Mark S. Link, MD; Loira Leoni, MD, PhD; Stefano Favale, MD; Michela Bevilacqua, MD; Cristina Basso, MD, PhD; Deirdre Ward, MD; Giuseppe Boriani, MD; Renato Ricci, MD; Jonathan P. Piccini, MD; Darshan Dalal, MD, MPH; Massimo Santini, MD; Gianfranco Buja, MD; Sabino Iliceto, MD; N.A. Mark Estes III, MD; Thomas Wichter, MD; William J. McKenna, MD; Gaetano Thiene, MD; Frank I. Marcus, MD

Background—The role of implantable cardioverter-defibrillator (ICD) in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and no prior ventricular fibrillation (VF) or sustained ventricular tachycardia is an unsolved issue.

Methods and Results—We studied 106 consecutive patients (62 men and 44 women; age, 35.6±18 years) with arrhythmogenic right ventricular cardiomyopathy/dysplasia who received an ICD based on 1 or more arrhythmic risk factors such as syncope, nonsustained ventricular tachycardia, familial sudden death, and inducibility at programmed ventricular stimulation. During follow-up of 58±35 months, 25 patients (24%) had appropriate ICD interventions and 17 (16%) had shocks for life-threatening VF or ventricular flutter. At 48 months, the actual survival rate was 100% compared with the VF/ventricular flutter–free survival rate of 77% (log-rank $P=0.01$). Syncope significantly predicted any appropriate ICD interventions (hazard ratio, 2.94; 95% confidence interval, 1.83 to 4.67; $P=0.013$) and shocks for VF/ventricular flutter (hazard ratio, 3.16; 95% confidence interval, 1.39 to 5.63; $P=0.005$). The positive predictive value of programmed ventricular stimulation was 35% for any appropriate ICD intervention and 20% for shocks for VF/ventricular flutter, with a negative predictive value of 70% and 74%. None of the 27 asymptomatic patients with isolated familial sudden death had appropriate ICD therapy. Twenty patients (19%) had inappropriate ICD interventions, and 18 (17%) had device-related complications.

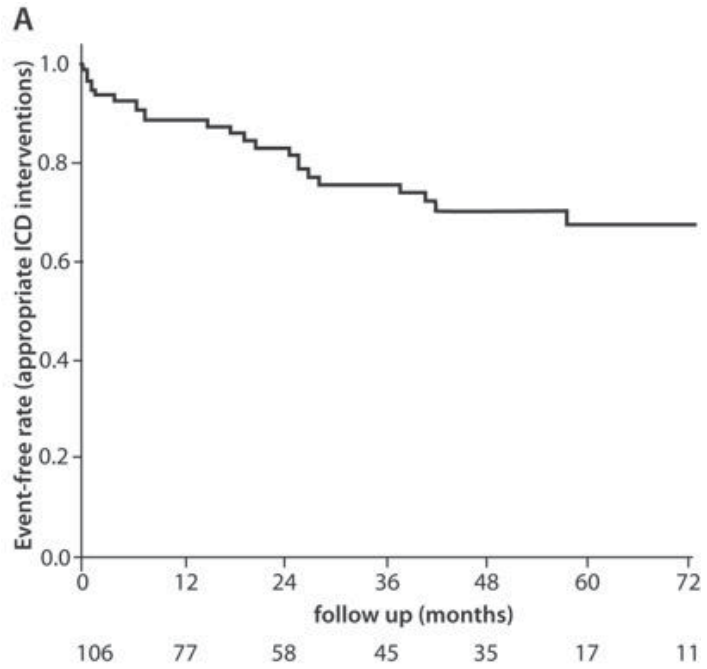
Conclusions—One fourth of patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and no prior sustained ventricular tachycardia or VF had appropriate ICD interventions. Syncope was an important predictor of life-saving ICD intervention and is an indication for ICD. Prophylactic ICD may not be indicated in asymptomatic patients because of their low arrhythmic risk regardless of familial sudden death and programmed ventricular stimulation findings. Programmed ventricular stimulation had a low predictive accuracy for ICD therapy. **(*Circulation*. 2010;122:1144-1152.)**

DARVIN II (primary prevention): ICD implant indication in 106 pts

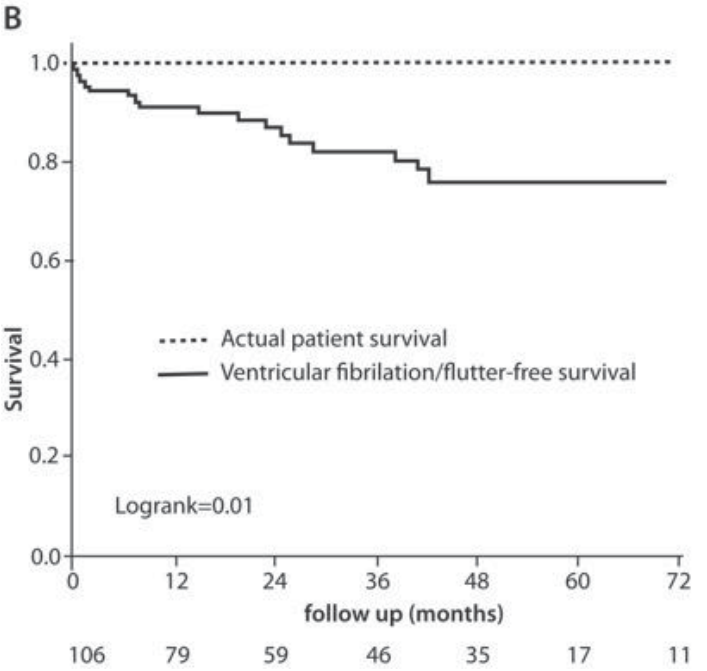
- Unexplained syncope : 42 (40%)
- Asymptomatic non-sustained VT (Holter and/or exercise testing): 56 (53%)
- Family history of sudden death: 49 (46%)
- Inducibility at PVS: 40/67 (60%)

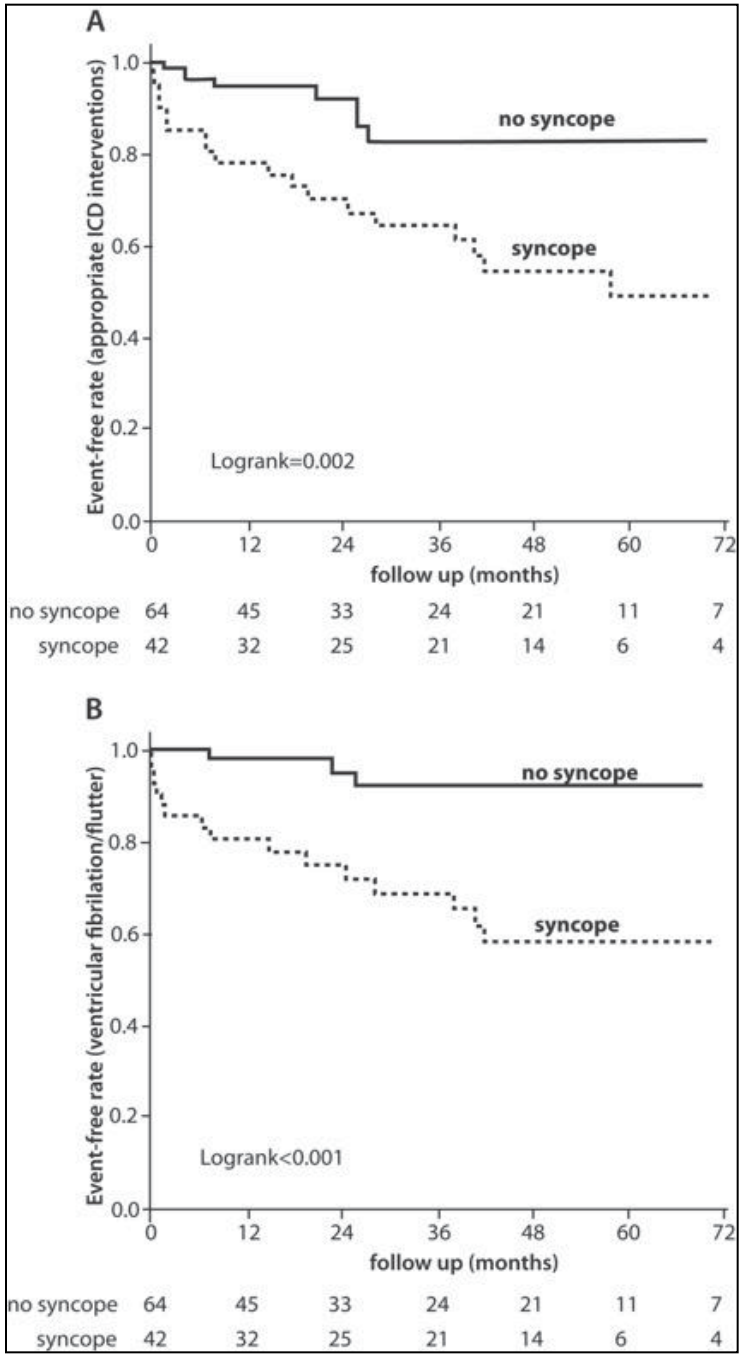
Corrado,..Buja et al. Circulation 2010;122:1144-1152

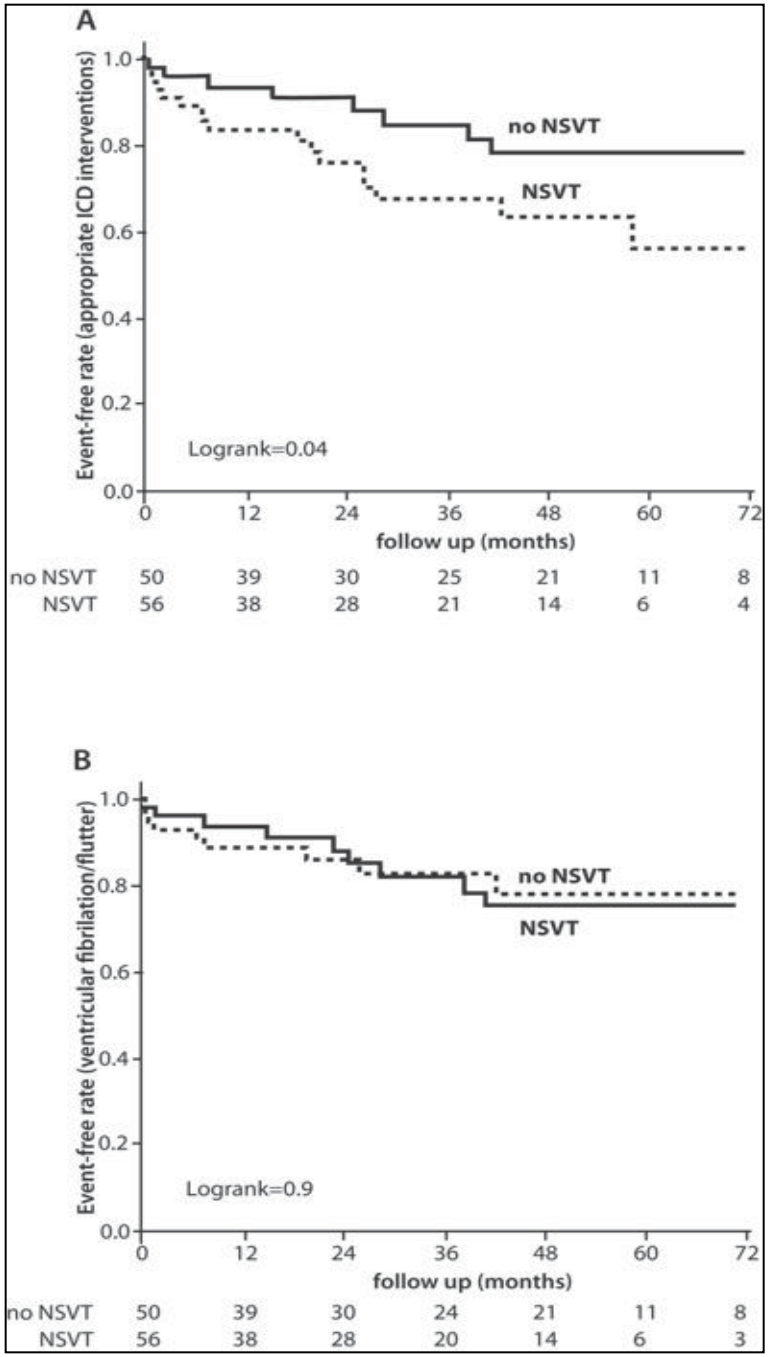
Kaplan-Meier analysis of cumulative survival from appropriate ICD interventions



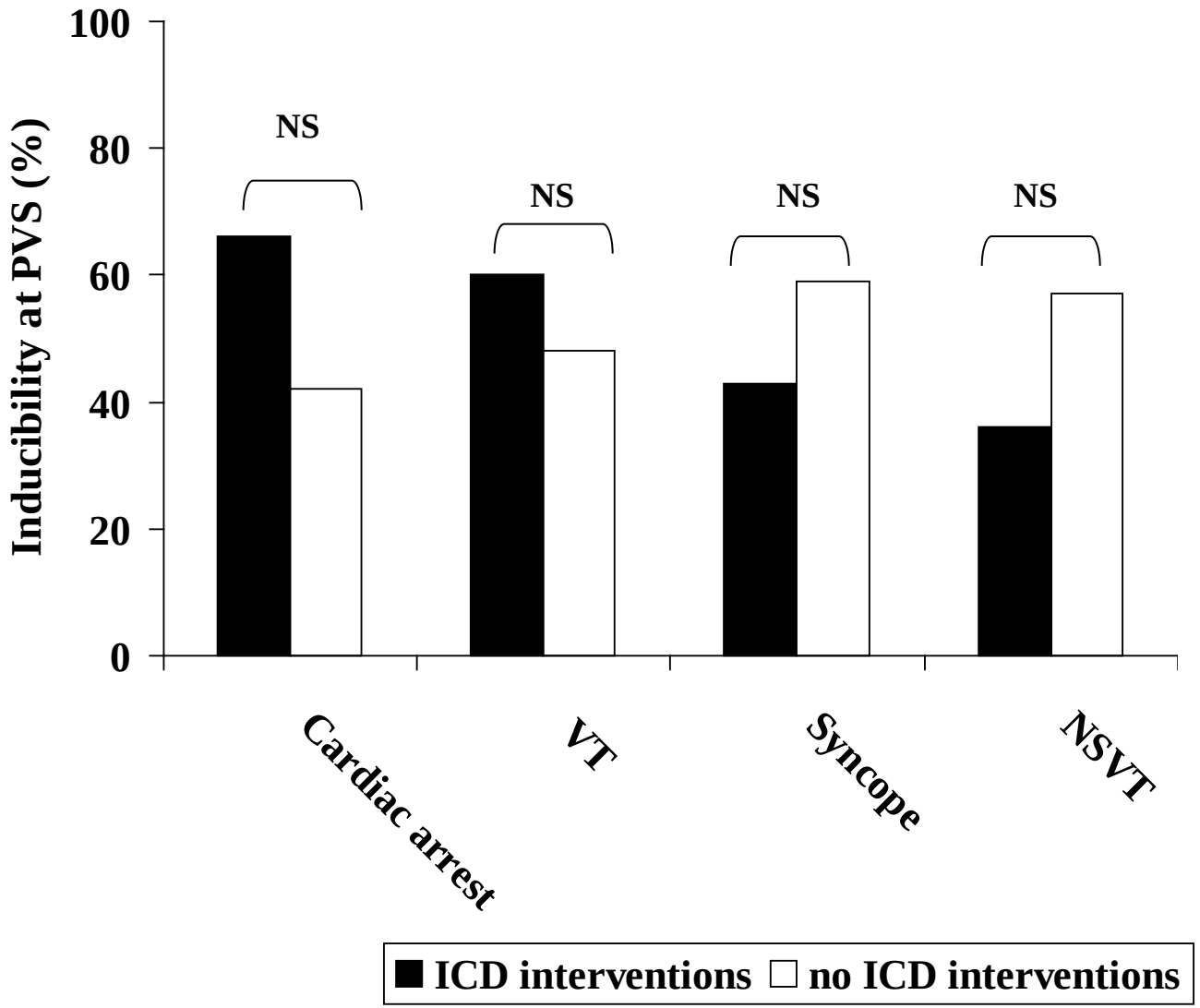
Kaplan-Meier analysis of actual survival vs theoretic survival (ICD shock on VF/Vfl)




A
Event-free rate (appropriate ICD interventions)
1.0
0.8
0.6
0.4
0.2
0.0
no syncope
syncope
Logrank=0.002
0
12
24
36
48
60
72
follow up (months)
no syncope 64 45 33 24 21 11 7
syncope 42 32 25 21 14 6 4
B
Event-free rate (ventricular fibrilation/flutter)
no syncope
syncope
Logrank<0.001
follow up (months)
no syncope 64 45 33 24 21 11 7
syncope 42 32 25 21 14 6 4


A
Event-free rate (appropriate ICD interventions)
1.0
0.8
0.6
0.4
0.2
0.0
no NSVT
NSVT
Logrank=0.04
0
12
24
36
48
60
72
follow up (months)
no NSVT 50 39 30 25 21 11 8
NSVT 56 38 28 21 14 6 4
B
Event-free rate (ventricular fibrilation/flutter)
no NSVT
NSVT
Logrank=0.9
follow up (months)
no NSVT 50 39 30 24 21 11 8
NSVT 56 38 28 20 14 6 3

Inducibility at PES and appropriate ICD interventions



Prognostic Value of Endocardial Voltage Mapping in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

Federico Migliore, MD*; Alessandro Zorzi, MD*; Maria Silvano, MD; Michela Bevilacqua, MD, PhD; Loira Leoni, MD, PhD; Martina Perazzolo Marra, MD, PhD; Mohamed Elmaghawry, MD; Luca Brugnaro, SD; Carlo Dal Lin, MD; Barbara Bauce, MD, PhD; Ilaria Rigato, MD, PhD; Giuseppe Tarantini, MD, PhD; Cristina Basso, MD, PhD; Gianfranco Buja, MD; Gaetano Thiene, MD; Sabino Iliceto, MD; Domenico Corrado, MD, PhD

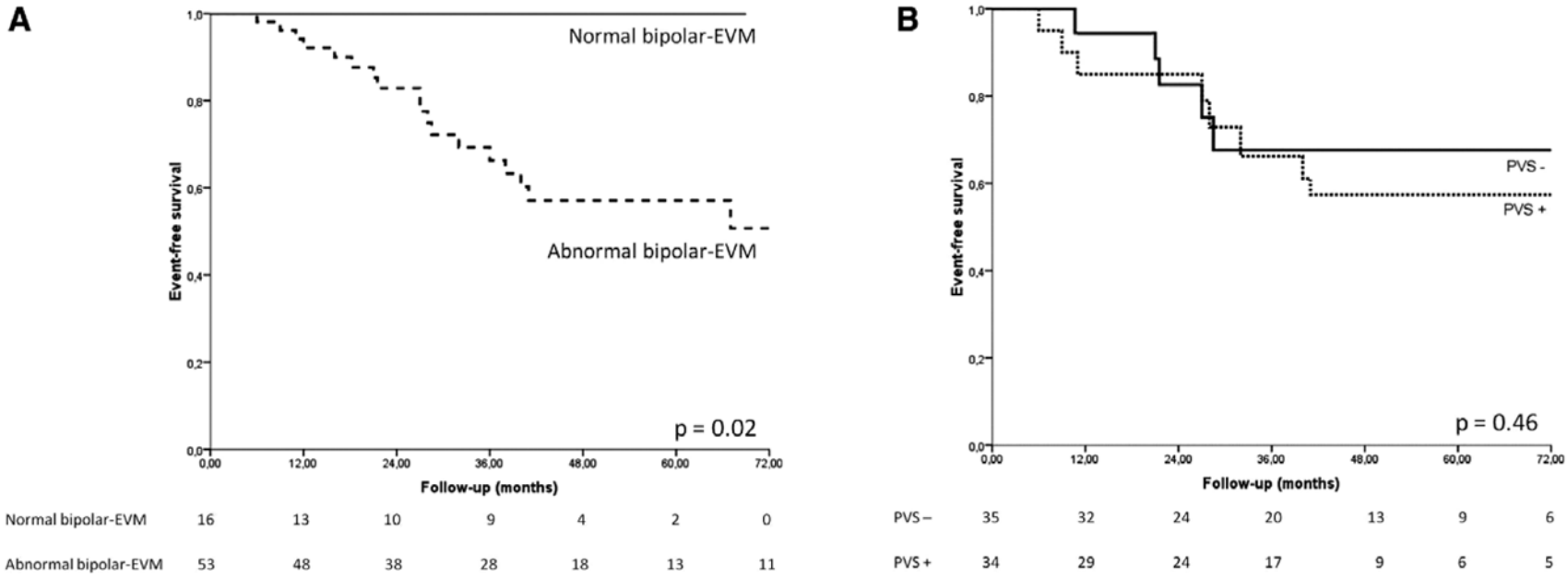
Background—Endocardial voltage mapping (EVM) identifies low-voltage right ventricular (RV) areas, which may represent the electroanatomic scar substrate of life-threatening tachyarrhythmias. We prospectively assessed the prognostic value of EVM in a consecutive series of patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D).

Methods and Results—We studied 69 consecutive ARVC/D patients (47 males; median age 35 years [28–45]) who underwent electrophysiological study and both bipolar and unipolar EVM. The extent of confluent bipolar (<1.5 mV) and unipolar (<6.0 mV) low-voltage electrograms was estimated using the CARTO-incorporated area calculation software. Fifty-three patients (77%) showed ≥1 RV electroanatomic scars with an estimated burden of bipolar versus unipolar low-voltage areas of 24.8% (7.2–31.5) and 64.8% (39.8–95.3), respectively (P=0.009). In the remaining patients with normal bipolar EVM (n=16; 23%), the use of unipolar EVM unmasked ≥1 region of low-voltage electrogram affecting 26.2% (11.6–38.2) of RV wall. During a median follow-up of 41 (28–56) months, 19 (27.5%) patients experienced arrhythmic events, such as sudden death (n=1), appropriate implantable cardioverter defibrillator interventions (n=7), or sustained ventricular tachycardia (n=11). Univariate predictors of arrhythmic outcome included previous cardiac arrest or syncope (hazard ratio=3.4; 95% confidence interval, 1.4–8.8; P=0.03) and extent of bipolar low-voltage areas (hazard ratio=1.7 per 5%; 95% confidence interval, 1.5–2; P<0.001), whereas the only independent predictor was the bipolar low-voltage electrogram burden (hazard ratio=1.6 per 5%; 95% confidence interval, 1.2–1.9; P<0.001). Patients with normal bipolar EVM had an uneventful clinical course.

Conclusions—The extent of bipolar RV endocardial low-voltage area was a powerful predictor of arrhythmic outcome in ARVC/D, independently of history and RV dilatation/dysfunction. A normal bipolar EVM characterized a low-risk subgroup of ARVC/D patients. **(*Circ Arrhythm Electrophysiol*. 2013;6:167-176.)**

Key Words: arrhythmogenic right ventricular cardiomyopathy-dysplasia ■ cardiac arrhythmias ■ electrophysiology ■ electroanatomic voltage mapping ■ risk

EVM vs EPS



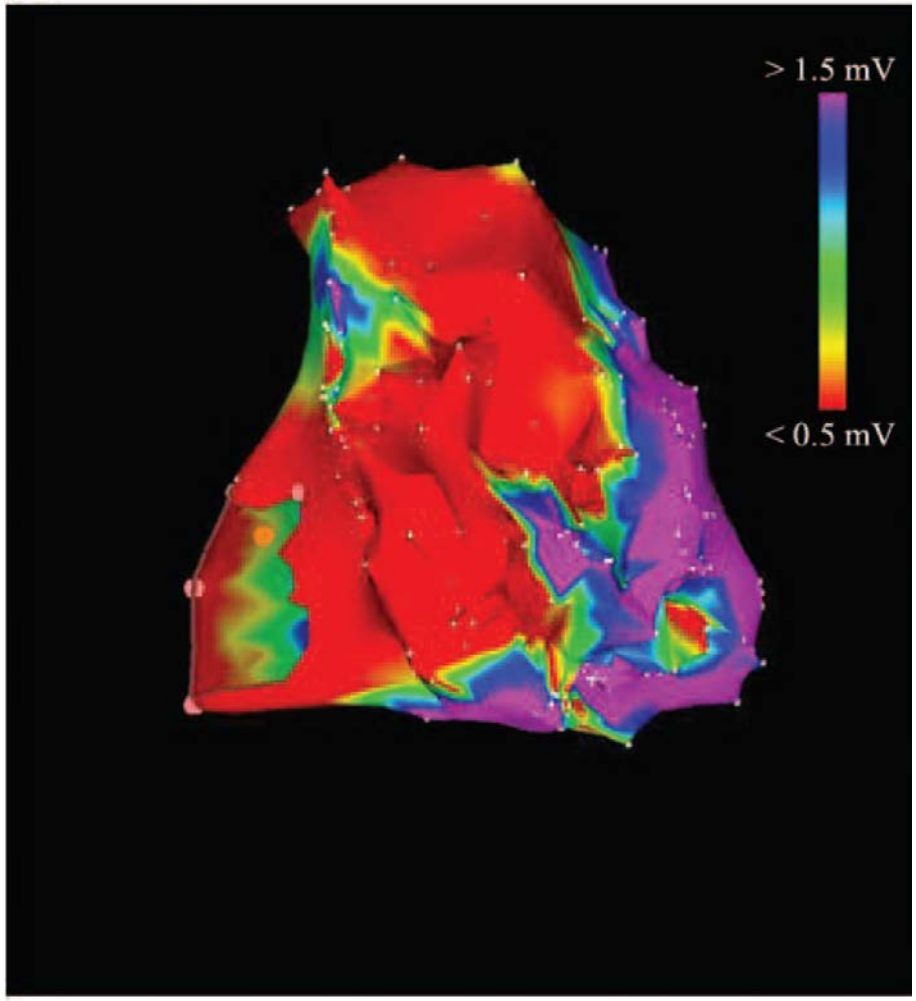
Normal bipolar-EVM	16	13	10	9	4	2	0
Abnormal bipolar-EVM	53	48	38	28	18	13	11

PVS –	35	32	24	20	13	9	6
PVS +	34	29	24	17	9	6	5

Figure 4. Kaplan–Meier analysis of freedom from adverse events stratified by the presence of abnormal bipolar endocardial voltage mapping (EVM; **A**) and programmed ventricular stimulation (PVS) findings (**B**).

Migliore , …Buja et al. Circ Arrhythm Electrophysiol 2013;6:167-176

Amount of ElectroAnatomicScar and arrhythmic outcome



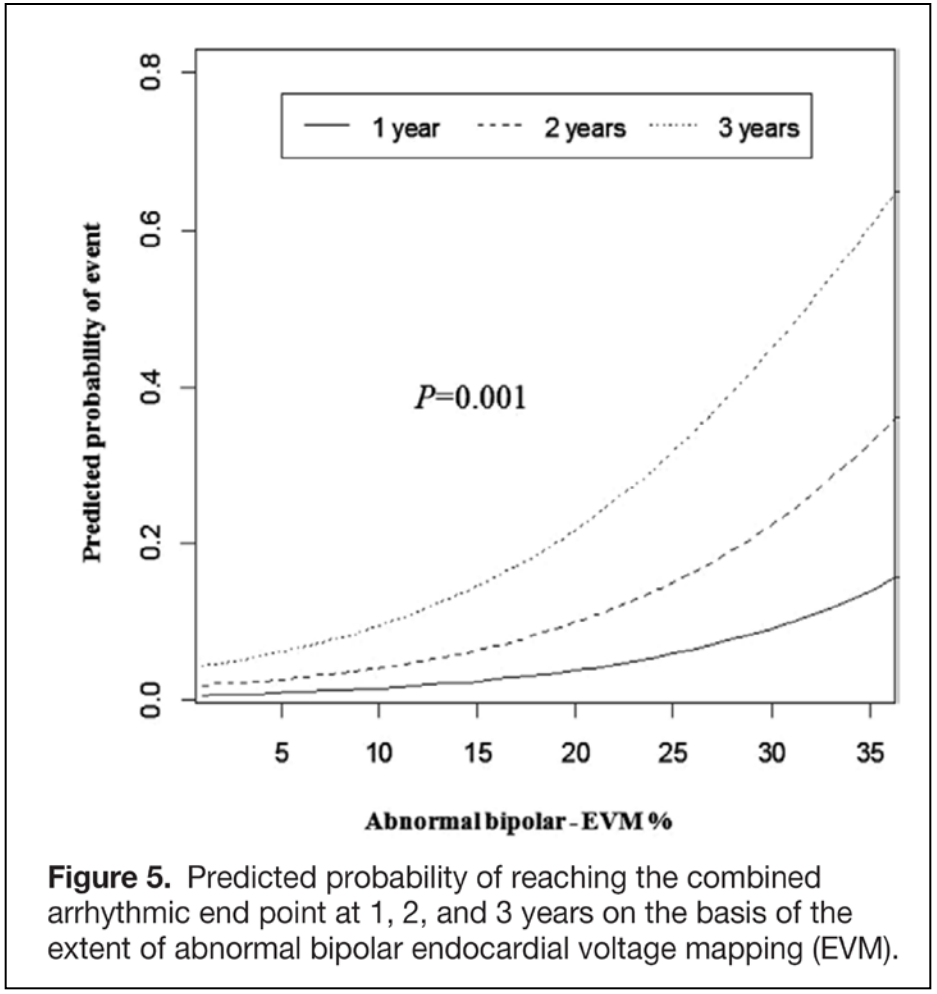
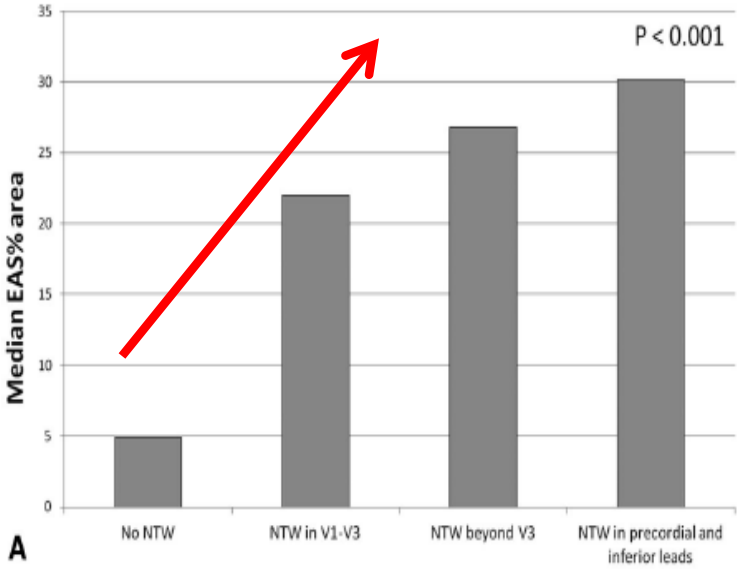


Figure 5. Predicted probability of reaching the combined arrhythmic end point at 1, 2, and 3 years on the basis of the extent of abnormal bipolar endocardial voltage mapping (EVM).

Migliore et al. Circ Arrhythm Electrophysiol 2013;6:167-176

Electrocardiographic Predictors of Electroanatomic Scar Size in Arrhythmogenic Right Ventricular Cardiomyopathy: Implications for Arrhythmic Risk Stratification

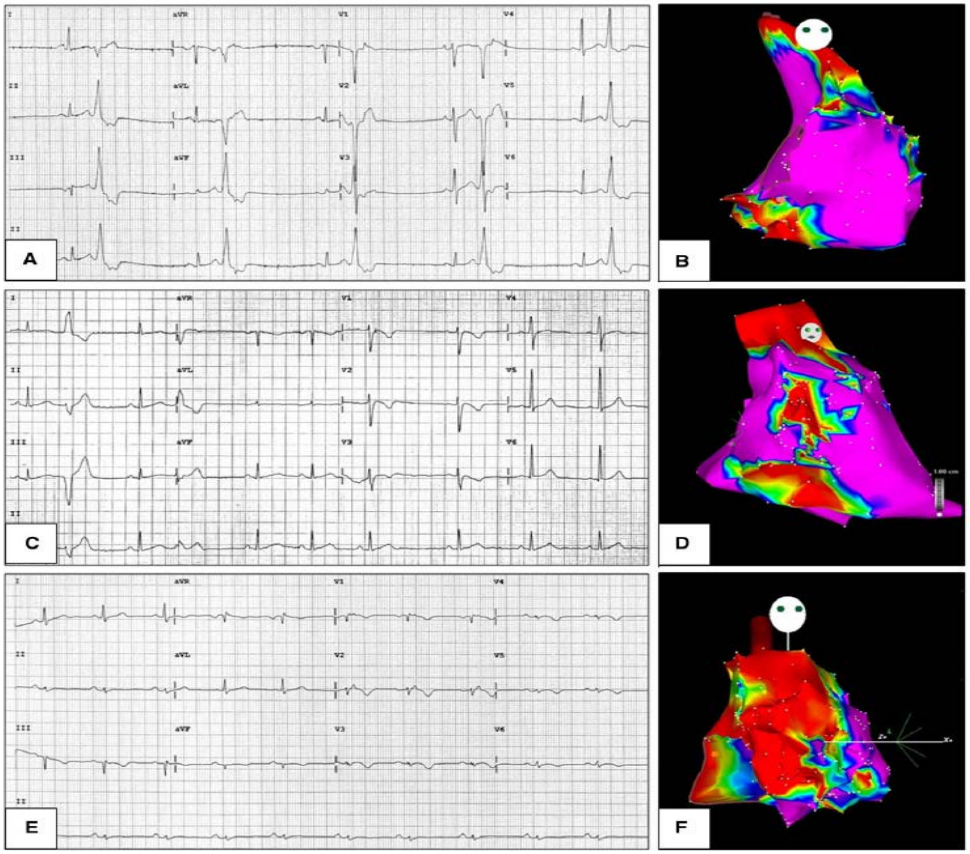
ALESSANDRO ZORZI, M.D.,* FEDERICO MIGLIORE, M.D., PH.D.,*
MOHAMED ELMAGHAWRY, M.D.,*,† MARIA SILVANO, M.D.,*
MARTINA PERAZZOLO MARRA, M.D., PH.D.,* ALICE NIERO, M.D.,* KIM NGUYEN, M.D.,*
ILARIA RIGATO, M.D., PH.D.,* BARBARA BAUCE, M.D, PH.D.,*
CRISTINA BASSO, M.D., PH.D.,‡ GAETANO THIENE, M.D.,‡ SABINO ILICETO, M.D.,*
and DOMENICO CORRADO, M.D., PH.D.*



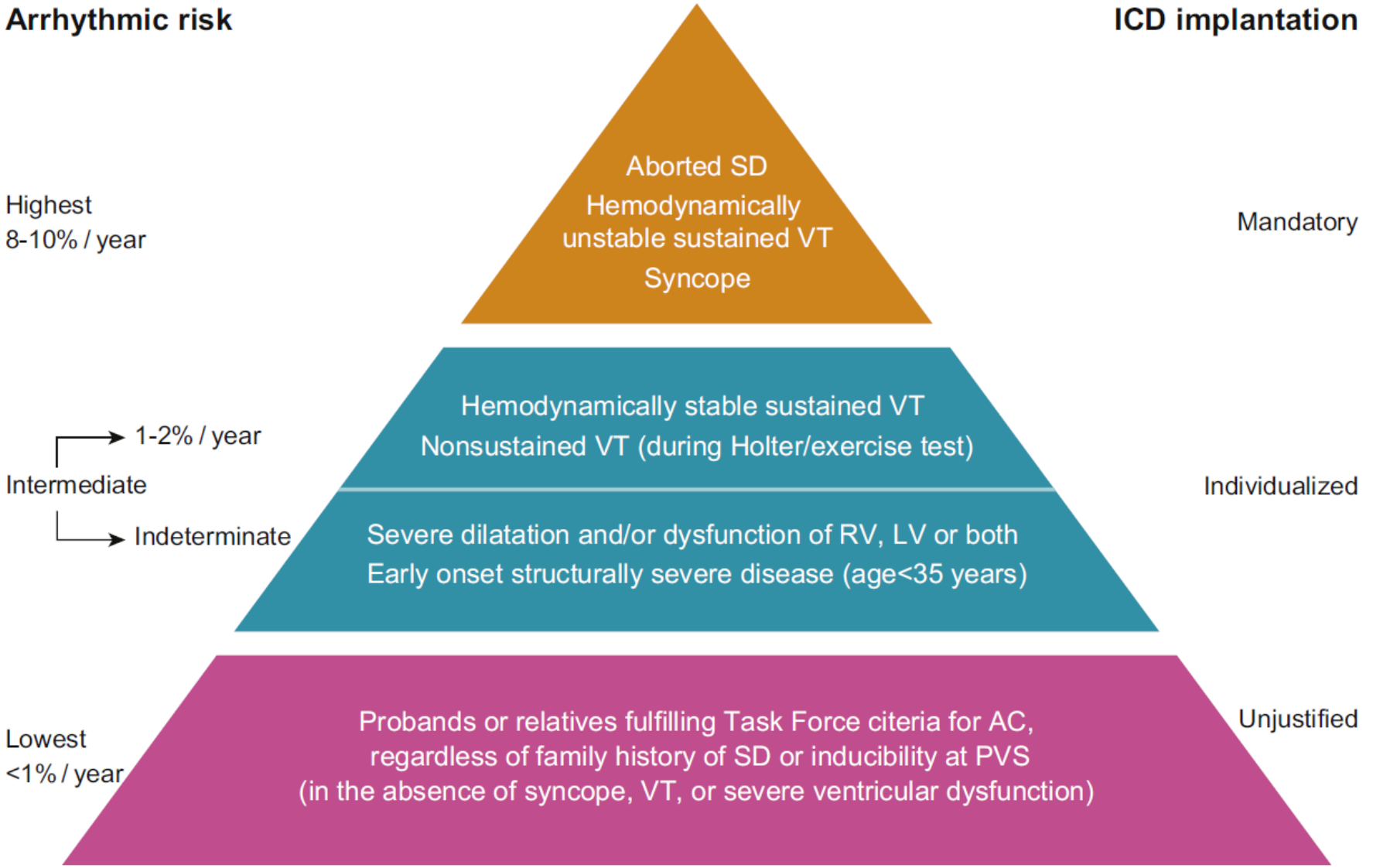
Multivariate Analysis for Predictors of RV-EAS% Area

	B (95% CI)	P
Epsilon waves	2.9 (−5.4–11.2)	0.49
Extent of NTW	4.4 (1.3–7.4)	0.006
RV-EDV (mL/m^2)	0.04 (−0.2–1.4)	0.63
RV-FAC (%)	−0.7 (−1.4–0.2)	0.09

FAC = fractional area change; EDV = end-diastolic volume; NTW = negative T waves; RV = right ventricular.

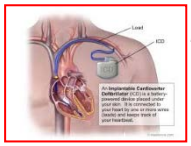


J Cardiovasc Electrophysiol 2013



«…Nevertheless, in spite of the growing amount of data, primary prevention of SCD in ARVC pts. remains mostly an individual decision.»

Corrado D, et al. Heart 2011;97:530-9



ICD- Double-edged sword

BUJA G et al 2008

Table 2. Studies on ICD Therapy in ARVC/D

Author	Year	No. of Patients	Study Type	Males (%)	FU (mo)	Primary Prev. (%)	Mortality Overall (%)	Appropriate ICD Ther. (%)	Life-Saving ICD Ther. (%)	Complications (%)
Breithardt	1994	18	SC	72	17	0	0	50	NR	NR
Link	1997	12	SC	58	22	0	8	67	50	33
Tavernier	2001	9	SC	89	32	0	0	78	44	NR
Corrado	2003	132	MC	70	39	22	3	48	24	14
Wichter	2004	60	SC	82	80	7	13	68	40	45
Rougin	2004	42	MC	52	42	40	2	78	NR	14
Hodgkinson	2005	48	MC	63	31	73	0	70	30	6

BUJA G et al 2008

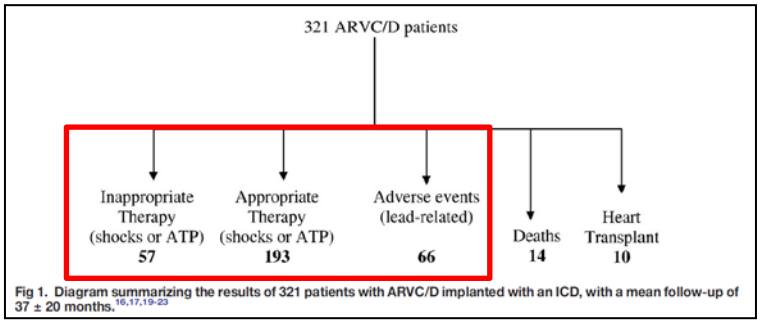


Fig 1. Diagram summarizing the results of 321 patients with ARVC/D implanted with an ICD, with a mean follow-up of 37 ± 20 months.[16,17,19-23]

17.7% 60% 20.5%

(*Circ Arrhythm Electrophysiol.* 2013;6:562-568.)

Implantable Cardioverter Defibrillators in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

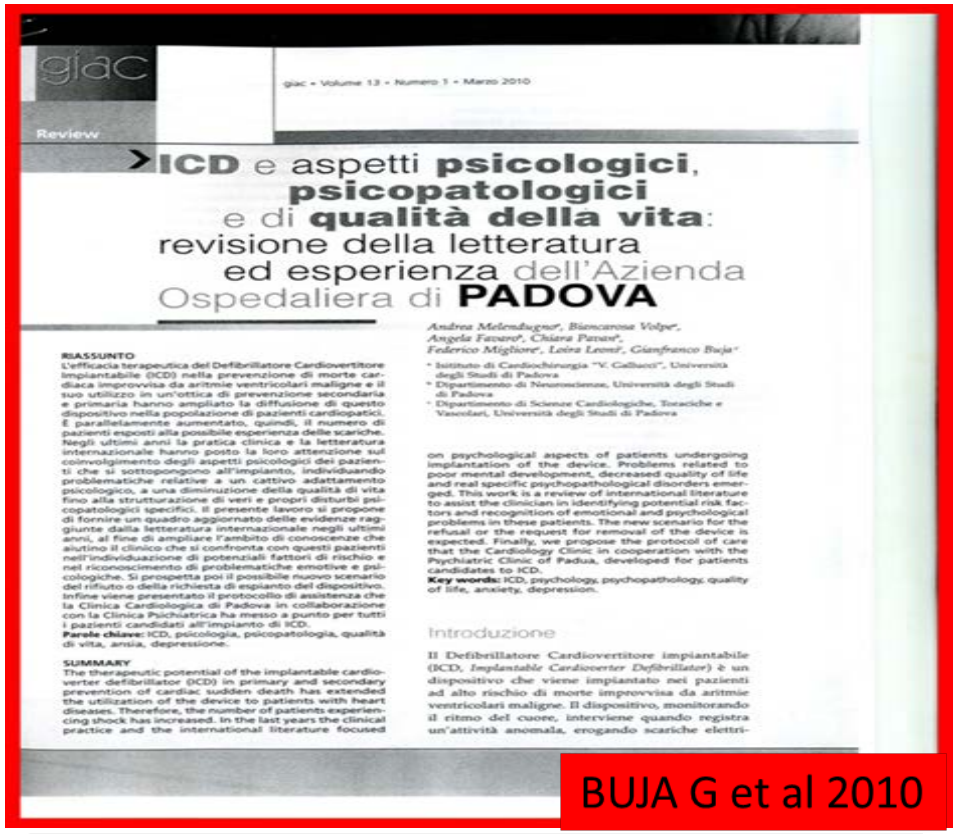
Patient Outcomes, Incidence of Appropriate and Inappropriate Interventions, and Complications

Arend F.L. Schinkel, MD, PhD

	Appropriate Intervention, %	Inappropriate Intervention, %	Complications, %				
			Difficult Lead Placement	Lead Malfunction	Infection	Lead Displacement	Any
Event rate (95% confidence interval)	40.4 (34.8–46.0)	16.5 (12.4–20.6)	18.4 (2.2–34.5)	9.8 (6.0–13.6)	1.4 (0–3.1)	3.3 (0–7.5)	20.3 (13.4–27.1)
Annualized event rate (95% confidence interval)	9.5 (6.8–12.2)	3.7 (1.8–5.7)	5.3 (0–14.0)	2.4 (0.5–4.3)	0.3 (0–1.1)	0.6 (0–2.2)	4.4 (1.2–7.6)

ICD-Psycopathologic adverse event-Quality of Life

Pts. 321
Mean age 40 yo



giac • Volume 13 • Numero 1 • Marzo 2010

Review

ICD e aspetti psicologici, psicopatologici e di qualità della vita: revisione della letteratura ed esperienza dell'Azienda Ospedaliera di PADOVA

Andrea Melendugno[a], Biancarosa Volpe[a], Angela Fazaro[b], Chiara Pavan[b], Federico Migliore[c], Loira Leoni[c], Gianfranco Buja[c]

[a] Istituto di Cardiochirurgia "V. Gallucci", Università degli Studi di Padova
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RIASSUNTO
L'efficacia terapeutica del Defibrillatore Cardiovertitore Impiantabile (ICD) nella prevenzione di morte cardiaca improvvisa da aritmie ventricolari maligne e il suo utilizzo in un'ottica di prevenzione secondaria e primaria hanno ampliato la diffusione di questo dispositivo nella popolazione di pazienti cardiopatici. E parallelamente aumentato, quindi, il numero di pazienti esposti alla possibile esperienza delle scariche. Negli ultimi anni la pratica clinica e la letteratura internazionale hanno posto la loro attenzione sul coinvolgimento degli aspetti psicologici dei pazienti che si sottopongono all'impianto, individuando problematiche relative a un cattivo adattamento psicologico, a una diminuzione della qualità di vita fino alla strutturazione di veri e propri disturbi psicopatologici specifici. Il presente lavoro si propone di fornire un quadro aggiornato delle evidenze raggiunte dalla letteratura internazionale negli ultimi anni, al fine di ampliare l'ambito di conoscenze che aiutino il clinico che si confronta con questi pazienti nell'individuazione di potenziali fattori di rischio e nel riconoscimento di problematiche emotive e psicologiche. Si prospetta poi il possibile nuovo scenario del rifiuto o della richiesta di espianto del dispositivo. Infine viene presentato il protocollo di assistenza che la Clinica Cardiologica di Padova in collaborazione con la Clinica Psichiatrica ha messo a punto per tutti i pazienti candidati all'impianto di ICD.
Parole chiave: ICD, psicologia, psicopatologia, qualità di vita, ansia, depressione.

SUMMARY
The therapeutic potential of the implantable cardioverter defibrillator (ICD) in primary and secondary prevention of cardiac sudden death has extended the utilization of the device to patients with heart diseases. Therefore, the number of patients experiencing shock has increased. In the last years the clinical practice and the international literature focused on psychological aspects of patients undergoing implantation of the device. Problems related to poor mental development, decreased quality of life and real specific psychopathological disorders emerged. This work is a review of international literature to assist the clinician in identifying potential risk factors and recognition of emotional and psychological problems in these patients. The new scenario for the refusal or the request for removal of the device is expected. Finally, we propose the protocol of care that the Cardiology Clinic in cooperation with the Psychiatric Clinic of Padua, developed for patients candidates to ICD.
Key words: ICD, psychology, psychopathology, quality of life, anxiety, depression.

Introduzione

Il Defibrillatore Cardiovertitore impiantabile (ICD, *Implantable Cardioverter Defibrillator*) è un dispositivo che viene impiantato nei pazienti ad alto rischio di morte improvvisa da aritmie ventricolari maligne. Il dispositivo, monitorando il ritmo del cuore, interviene quando registra un'attività anomala, erogando scariche elettri-

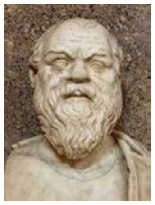
BUJA G et al 2010

- Unable to work (2,1%)
- Temporary restriction driving (47%)
- Ban driving (1,2%)
- Refuse, psychological distress(anxiety, fears) (18%)
- Economic impact (4,2%)
- Car accident ICD therapy-related (4 pts; 0.4%/pt/year)

1 SUICIDE

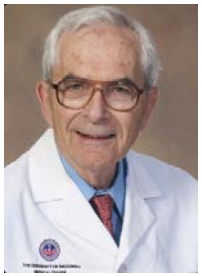
ARVC

Pedigree of the family

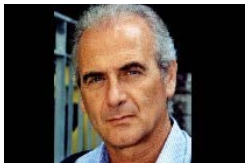


«A life without research is not worthy to be lived»
Socrate 399 b.c.

FATHER (S)




AFFECTED RELATIVES



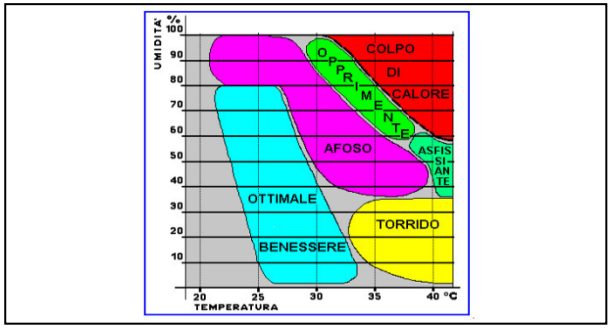

THANK YOU VERY MUCH FOR YOUR ATTENTION

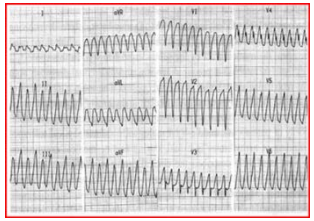
Seasonal variation in the frequency of sudden cardiac death and ventricular tachyarrhythmia in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy: The effect of meteorological factors

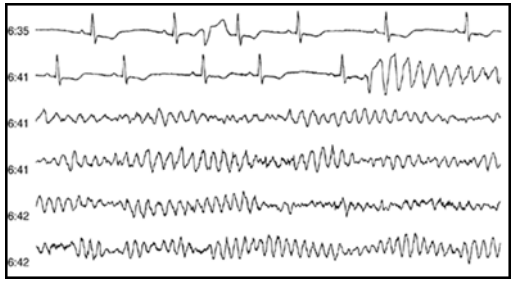
Fa-Po Chung, MD,[*] Hsin-Ru Li, MD,[*] Eric Chong, MBBS, MRCP, FACC, FESC,[*†] Chih-Hsin Pan, MD,[*‡] Yenn-Jiang Lin, MD,[*§] Shih-Lin Chang, MD,[*§] Li-Wei Lo, MD,[*§] Yu-Feng Hu, MD,[*§] Ta-Chuan Tuan, MD,[*§] Tze-Fan Chao, MD,[*§] Jo-nan Liao, MD,[*] Wen-Yu Lin, MD,[‖] Kai-Ping Shaw, MD, PhD,[*‡] Shih-Ann Chen, MD[*§]

From the [*]Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, [†]Department of Cardiology, Jurong Health Pte Ltd, Singapore, [‡]Institute of Forensic Medicine, Ministry of Justice, Taipei, Taiwan, [§]Institute of Clinical Medicine and Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan, and [‖]Department of Cardiology, Tri-service General Hospital, Taipei, Taiwan.

(Heart Rhythm 2013;10:1859–1866)

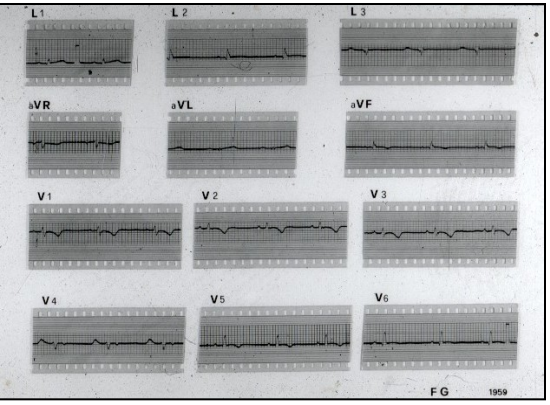




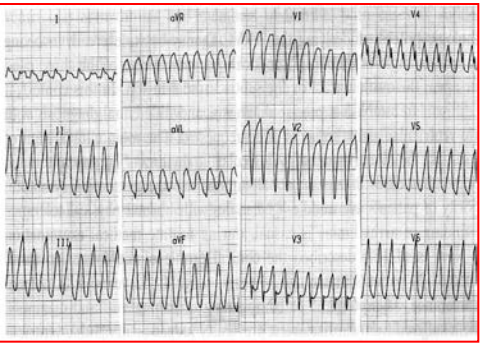


ARVC-The road map of the science

1980



First Pt with ?-PD
Uhl' Sdr ? Cardiomyopathy ?



NAVA A, BUJA G, MARTINI B

1982

F. Marcus
Circulation
Right Ventricular
Dysplasia

1984

RV-only

1988

1994
first-gene
locus(14q
23-24) PD

1998

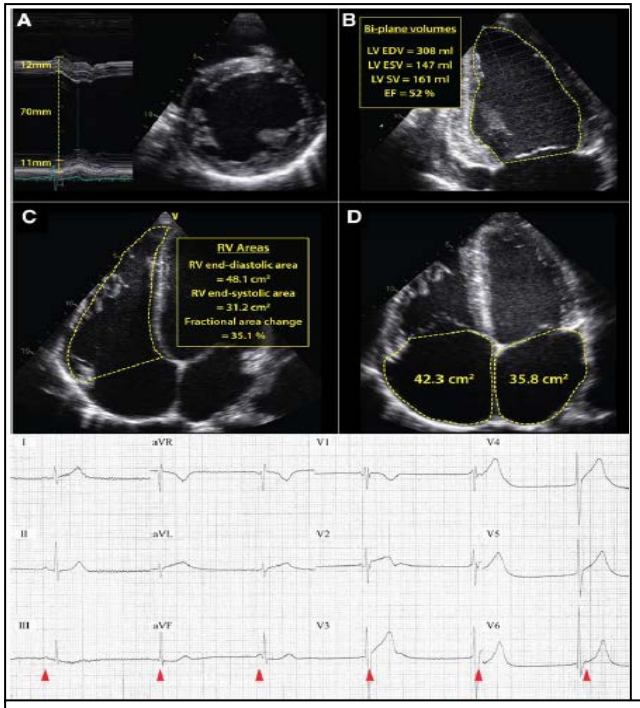
1994-Naxos
L.Rossi

2012

AC
"RV-LV"

Basso C et al Circulation
Cardiomyopathy, Distrophy, Dysplasia, Myocarditis ???

Sport and right ventricle



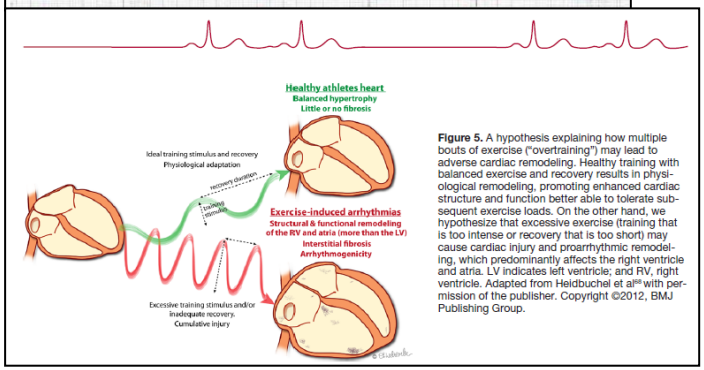


Figure 5. A hypothesis explaining how multiple bouts of exercise ("overtraining") may lead to adverse cardiac remodeling. Healthy training with balanced exercise and recovery results in physiological remodeling, promoting enhanced cardiac structure and function better able to tolerate subsequent exercise loads. On the other hand, we hypothesize that excessive exercise (training that is too intense or recovery that is too short) may cause cardiac injury and proarrhythmic remodeling, which predominantly affects the right ventricle and atria. LV indicates left ventricle; and RV, right ventricle. Adapted from Heidbuchel et al[88] with permission of the publisher. Copyright ©2012, BMJ Publishing Group.

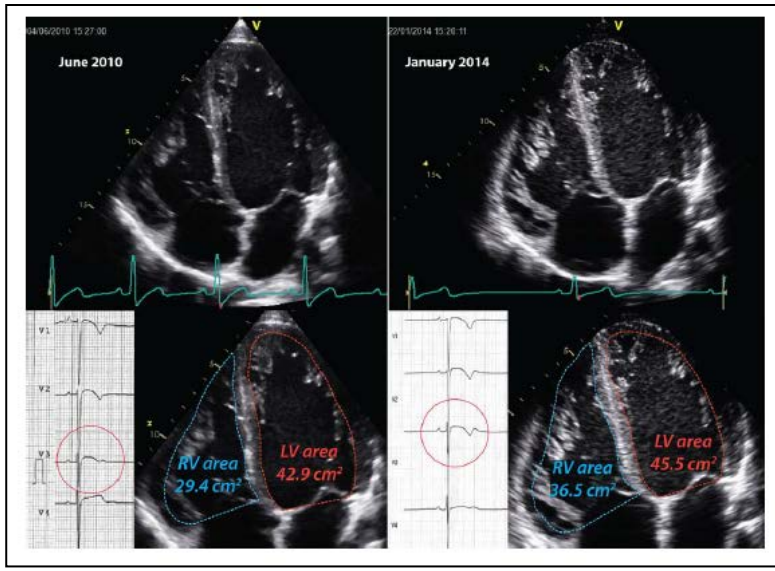


Figure 4. Relative increase in right ventricular dimensions in an elite cyclist with arrhythmias. Case 2 was assessed during a period of relatively low training in June 2010 (left) and then 18 months after a return to professional competition (right). Apical 4-chamber echocardiographic views are used to illustrate the increase in cardiac dimensions with a greater increase the area of the right ventricle (RV) than the left ventricle (LV). Also notable is the mild global increase in wall thickness and prominent trabeculations of both ventricles. At times of increased training, T-wave inversion on ECG was observed to extend to precordial lead V3.

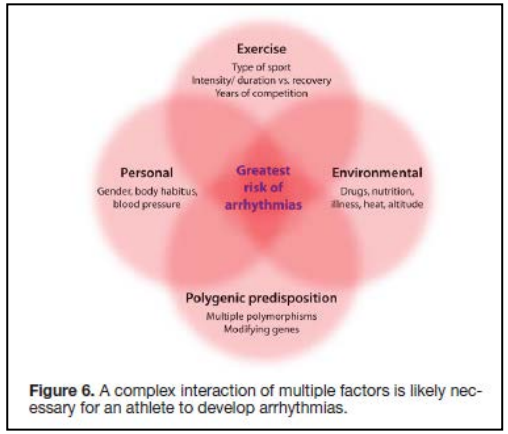


Figure 6. A complex interaction of multiple factors is likely necessary for an athlete to develop arrhythmias.

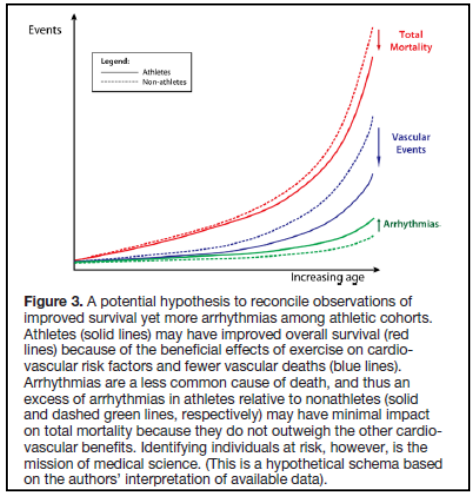


Figure 3. A potential hypothesis to reconcile observations of improved survival yet more arrhythmias among athletic cohorts. Athletes (solid lines) may have improved overall survival (red lines) because of the beneficial effects of exercise on cardiovascular risk factors and fewer vascular deaths (blue lines). Arrhythmias are a less common cause of death, and thus an excess of arrhythmias in athletes relative to nonathletes (solid and dashed green lines, respectively) may have minimal impact on total mortality because they do not outweigh the other cardiovascular benefits. Identifying individuals at risk, however, is the mission of medical science. (This is a hypothetical schema based on the authors' interpretation of available data).

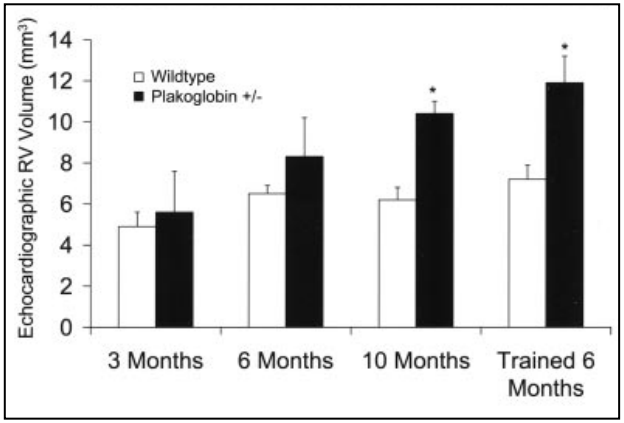
Age- and Training-Dependent Development of Arrhythmogenic Right Ventricular Cardiomyopathy in Heterozygous Plakoglobin-Deficient Mice

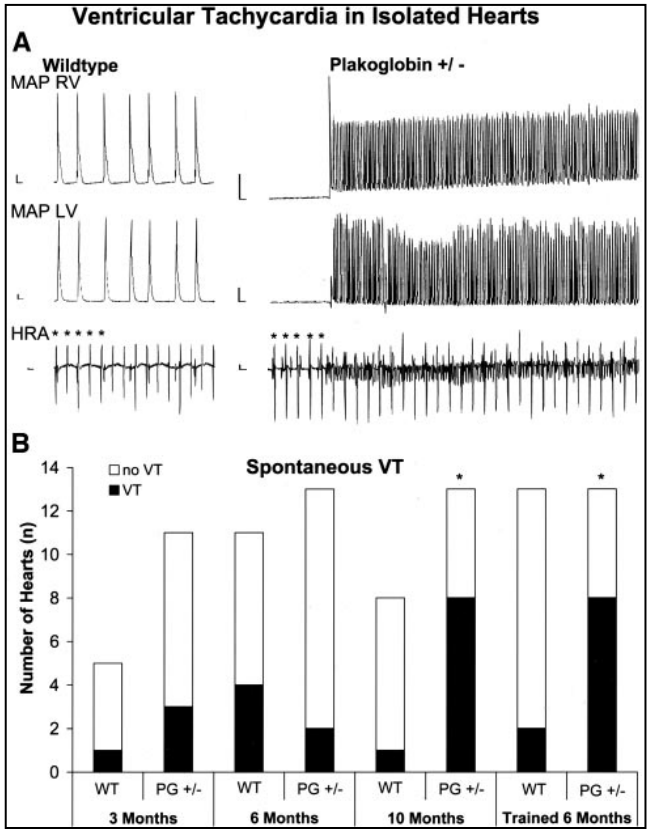
Paulus Kirchhof, MD; Larissa Fabritz, MD; Melanie Zwiener, VetD; Henning Witt, PhD; Michael Schäfers, MD; Stephan Zellerhoff, MD; Matthias Paul, MD; Timur Athai, BS; Karl-Heinz Hiller, PhD; Hideo A. Baba, MD; Günter Breithardt, MD; Patricia Ruiz, PhD; Thomas Wichter, MD; Bodo Levkau, MD

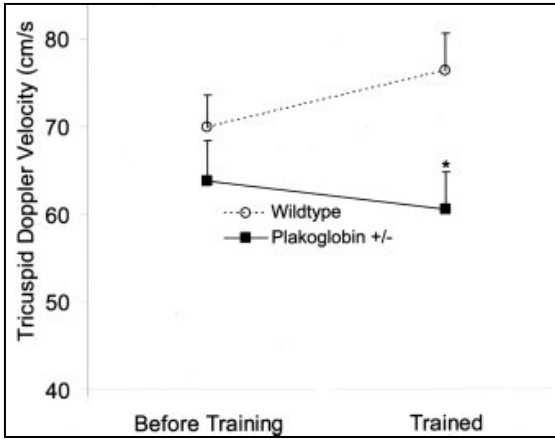
(*Circulation*. 2006;114:1799-1806.)

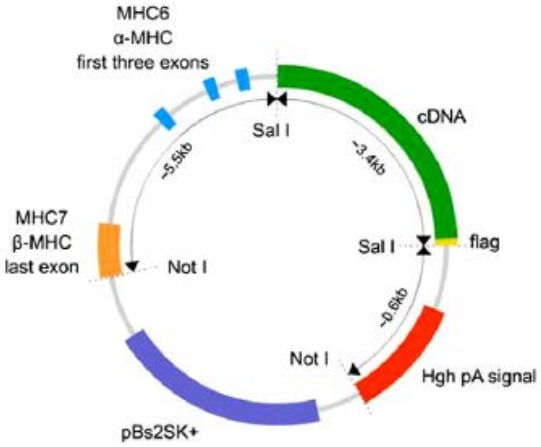
TRAINING

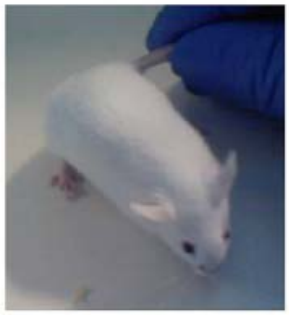
REST











N271S mouse homologue of the human N266S mutation

Fig. 7. Desmoglein 2 transgenic mice.

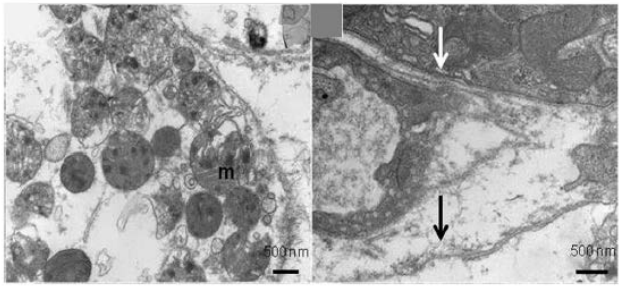


Fig. 11. At electron microscopy, cardiomyocyte death in the desmoglein 2 transgenic mice presents with features of necrosis.

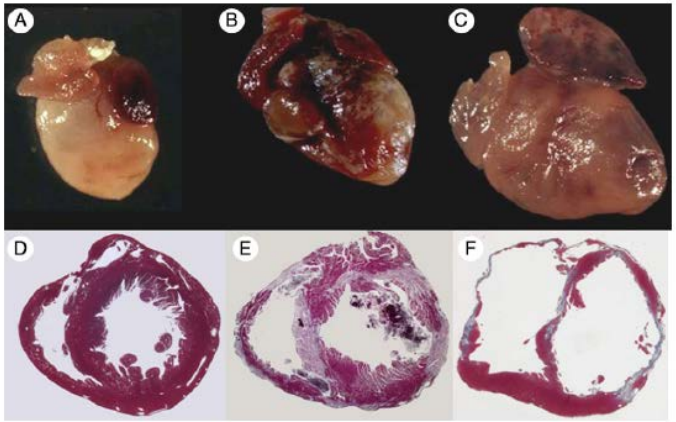
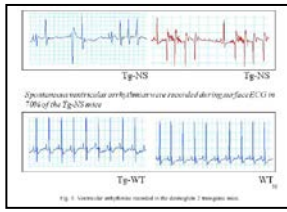


Fig. 10. Appearance with time of fibrosis (5 weeks, B and E) and ventricular aneurysms (10 weeks, C and F) in the desmoglein 2 transgenic mice heart.



SUDDEN CARDIAC DEATH

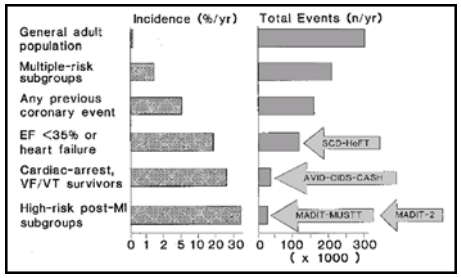
Epidemiology

- Incidence: 300,000 deaths/year in USA
- Risk for general population aged 35 or older: 0.1-0.2% per year
- Marked increase in risk between the ages of 40 to 65 years
- Risk for adolescents-young adults (10-30 y.o.): 0.001% per year.

- **In Italy:**
  - Incidence: 70,000 deaths/year.
  - 0.36 to 1.28 per 1.000 person/year.

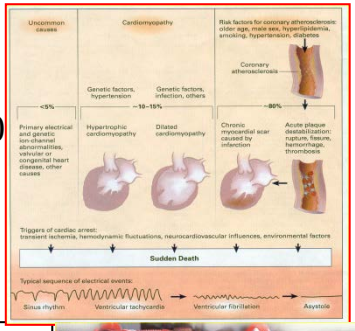
  → one SCD every 7 minutes.

«THE NEW CULTURE OF SUDDEN CARDIAC DEATH»

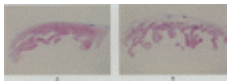


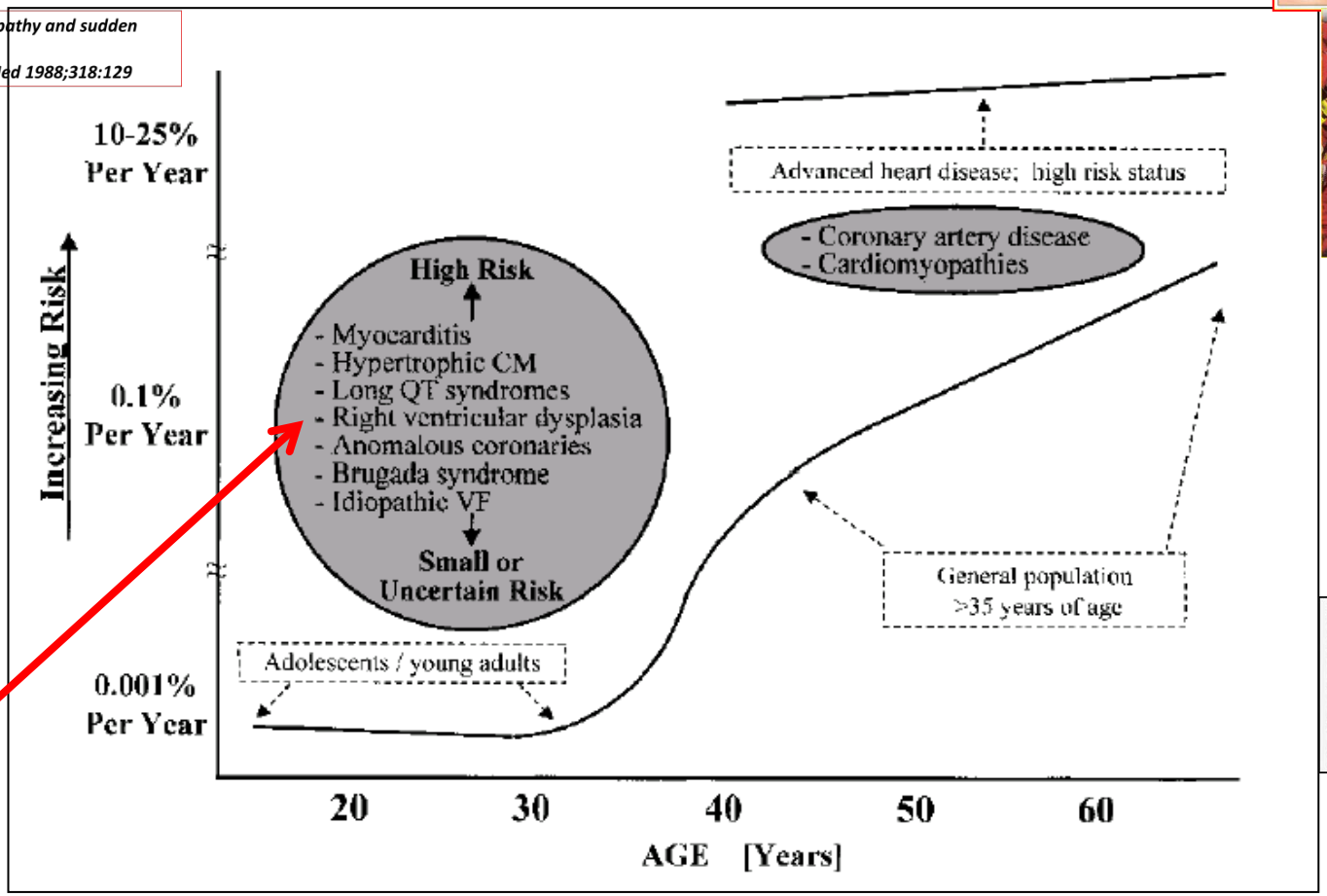
RJ Myerburg
JCE 2001;12:369

HV Huikuri
NEJM 2001;345:20



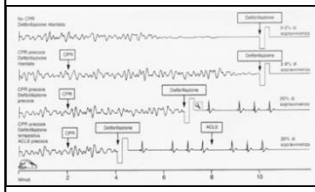
Right Ventricular Cardiomyopathy and sudden death in young people
Thiene G, et al. New Engl J Med 1988;318:129





ARVC

AED Out-of-H

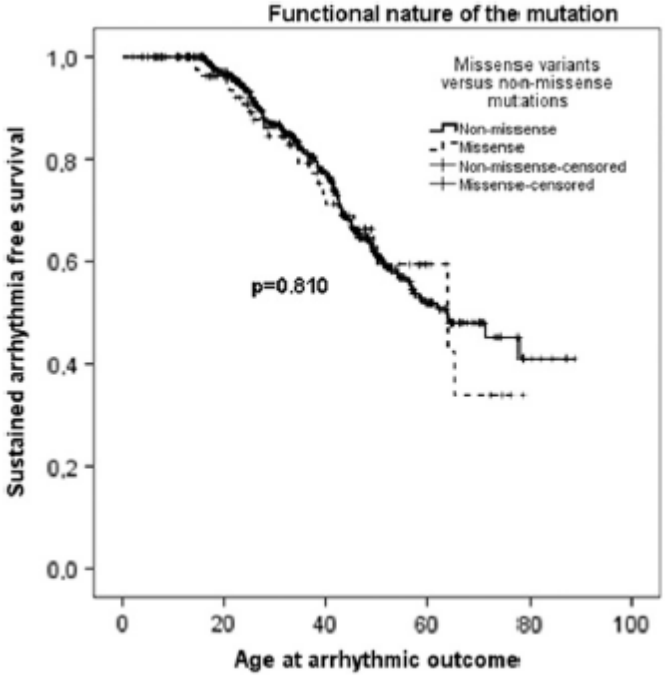


Myerburg RJ J Cardiovasc Electrophysiol 2001; 12: 369.

CLINICAL ABSTRACTS

PREDICTION OF PATHOGENICITY OF MISSENSE VARIANTS IN ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

JA Groeneweg et al, Circulation 2014



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Heart Rhythm Disorders

The Impact of Implantable Cardioverter-Defibrillator Therapy on Survival in Autosomal-Dominant Arrhythmogenic Right Ventricular Cardiomyopathy (ARVD5)

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St. John's and Toronto, Canada; Berlin, Germany; and London, England

OBJECTIVES We sought to determine the impact of implantable cardioverter-defibrillator (ICD) therapy in patients with familial arrhythmogenic right ventricular cardiomyopathy (ARVC).

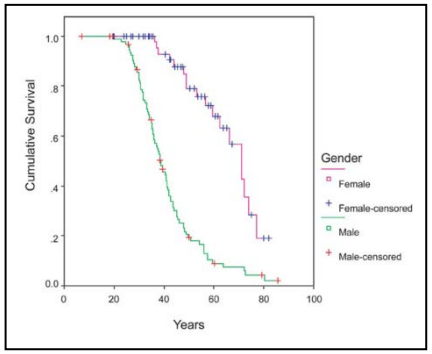
BACKGROUND Arrhythmogenic right ventricular cardiomyopathy is a cause of sudden cardiac death, which may be prevented by ICD.

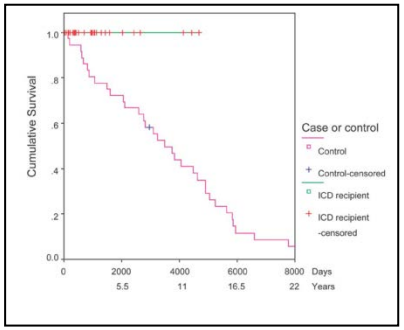
METHODS We studied 11 families in which a 3p25 deoxyribonucleic acid (DNA) haplotype at locus ARVD5 segregated with disease and compared mortality in subjects who received an ICD with that in control subjects who were matched for age, gender, ARVC status, and family. Subjects (n = 367) at 50% a priori risk of inheriting ARVC were classified as high risk (HR) (n = 197), low risk (n = 92), or unknown (n = 78) on the basis of clinical events, DNA haplotyping, and/or pedigree position. Forty-eight HR subjects (30 males, [median age 32 years] and 18 females [median age 41 years]) were followed after ICD (secondary to ventricular tachycardia [VT] in 27%). Survival was compared with 58 HR control subjects who were alive at the same age to-the-day at which the ICD subject received the device.

RESULTS In the HR group, 50% of males were dead by 39 years and females by 71 years: relative risk of death was 5.1 (95% confidence interval 3 to 8.5) for males. The five-year mortality rate after ICD in males was zero compared with 28% in control subjects ($p = 0.009$). Within five years, the ICD fired for VT in 70% and for VT >240 beats/min in 30%, with no difference in discharge rate when analyzed by ICD indication.

CONCLUSIONS The unknown mutation at the ARVD5 locus causing ARVC results in high mortality. Risk stratification using genetic haplotyping and ICD therapy produced improved survival for males. (J Am Coll Cardiol 2005;45:400–8) © 2005 by the American College of Cardiology Foundation

* 50% of males dead by 39 years





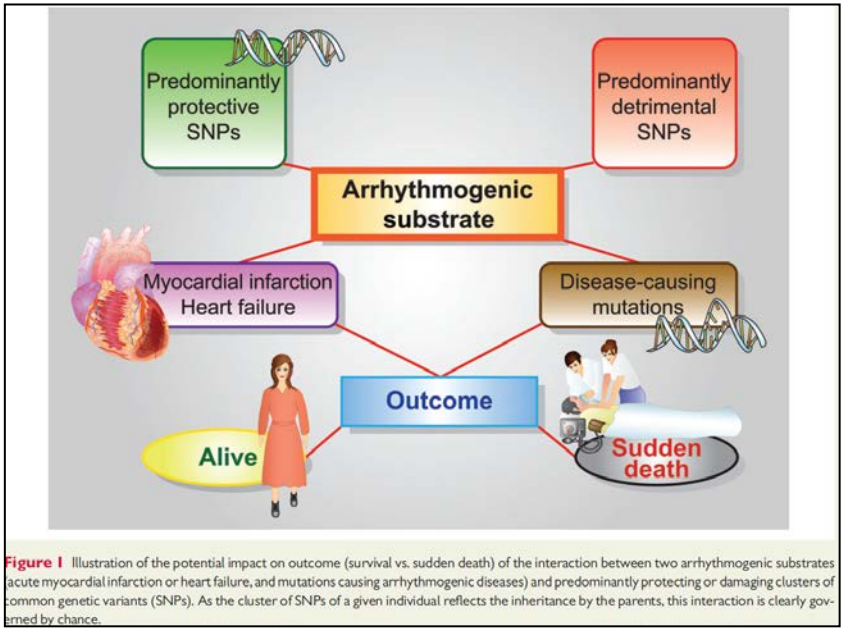


Figure 1 Illustration of the potential impact on outcome (survival vs. sudden death) of the interaction between two arrhythmogenic substrates (acute myocardial infarction or heart failure, and mutations causing arrhythmogenic diseases) and predominantly protecting or damaging clusters of common genetic variants (SNPs). As the cluster of SNPs of a given individual reflects the inheritance by the parents, this interaction is clearly governed by chance.

Clinical Profile and Long-term Follow-up of 37 Families With Arrhythmogenic Right Ventricular Cardiomyopathy

Nava A, .. Buja G et al. JACC 2000;36:2226

A)Probands affected from 37 families (11 with genetic study)

B)Population: 365 subjects
- 151 affected
- 157 non affected
- 17 health carriers
- 40 uncertain

C) 28 Families Linkage analysis
- 6 families 14q23-q24
- 4 families 14q42-q43
- 4 families 1q32.1-q32.3q
- 4 families ?

FU: 8.5±4.6 years=-1 SCD (0.08/pt year mortality)
-15 overt ARVC