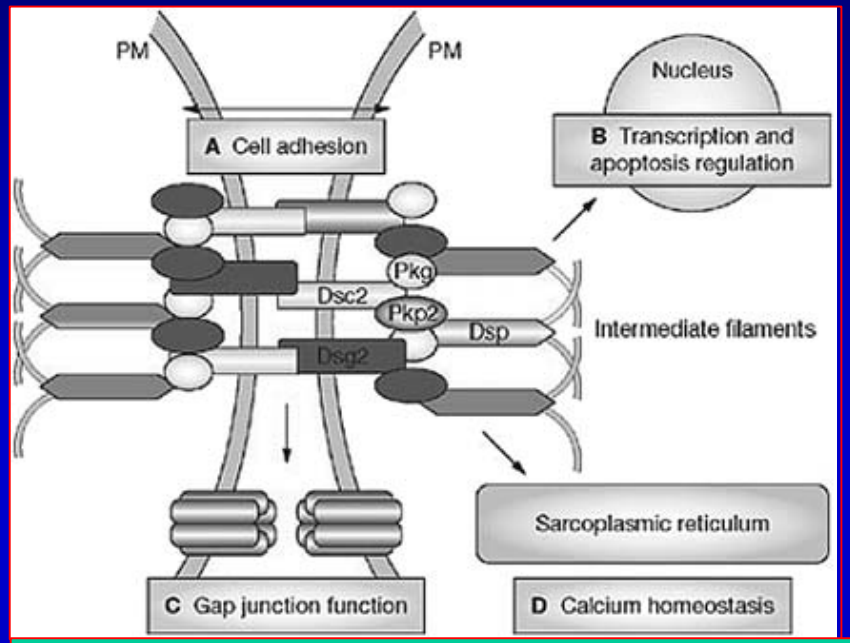
Treatment strategies in arrhythmogenic right ventricular cardiomiopathy

MY THANKS to Prof Gaita

MY THANKS to Prof Leclerque

ARVC: pathogenesis and epidemiology



M:F=2:1 - 20-40 y
1/2000 -1/5000
60% familial /genetic +
Incidence of SD 0.08-3,6 %/y
No SD in pts < 12y or > 60 y

Inherited, desmosomal cardiomiopathy - distrophy
Autosomical dominant, variable penetrance
Gap junction remodeling for defect of cell-adhesion desmosomial protein
VF/SD as clinical manifestation of «hot phase» of inflammation
Stable VT as clinical evidence of arrhytmogenic «scar»

Variable clinical expression/myocardial involvement

TABLE 2 **Proposed Modification of the Task Force Criteria for Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia.**

	Major Criteria	Minor Criteria
Family history	ARVD confirmed in a first degree relative who meets current Task Force Criteria	History of ARVD in a first degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force Criteria
	ARVD confirmed pathologically at autopsy or surgery in a first-degree relative	Premature sudden death (<35 years of age) due to suspected ARVD in a first degree relative
	Identification of a pathogenetic mutation categorized as associated or probably associated with ARVD in the patient under evaluation	ARVD confirmed pathologically or by current Task Force Criteria in second-degree relative

TF 2010 – Circulation
Major and minor criteria

§

Global or regional dysfunction: Echo-RM
Tissue characterization of wall
Repolarization abnormality
Depolarization/conduction abnormality
Arrhythmias
Family history

abnormalities		
By 2D echo	Regional RV akinesia, dyskinesia, or aneurism and 1 of the following (end diastole): PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m²) PSAX RVOT ≥36 mm(corrected for body size [PSAX/BSA] ≥21 mm/m²) Fractional area change ≤33%	Regional RV akinesia, dyskinesia and 1 of the following (end diastole): PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] >16 to <19 mm/m²) PSAX RVOT ≥32 to <36 mm(corrected for body size [PSAX/BSA] ≥18 to <21 mm/m²) Fractional area change >33% to ≤40%
By MRI	Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: Ratio of RV end-diastolic volume to BSA ≥110 mL/m² (male) or ≥100 mL/mq (female) RV ejection fraction ≤40%	Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/mq(male) or ≥90 to <100 mL/m² (female) RV ejection fraction >40% to ≤45%
By RV angiography	Regional RV akinesia, dyskinesia, or aneurysm	Regional RV akinesia, dyskinesia, or aneurysm

ARVD indicates arrhythmogenic right ventricular dysplasia; BSA, body surface area; LBBB, left bundle branch block; PSAX, parasternal short-axis view; PLAX, parasternal long-axis view; RV, right ventricle; RVOT, RV outflow tract; SAECG, signal-averaged electrocardiogram.
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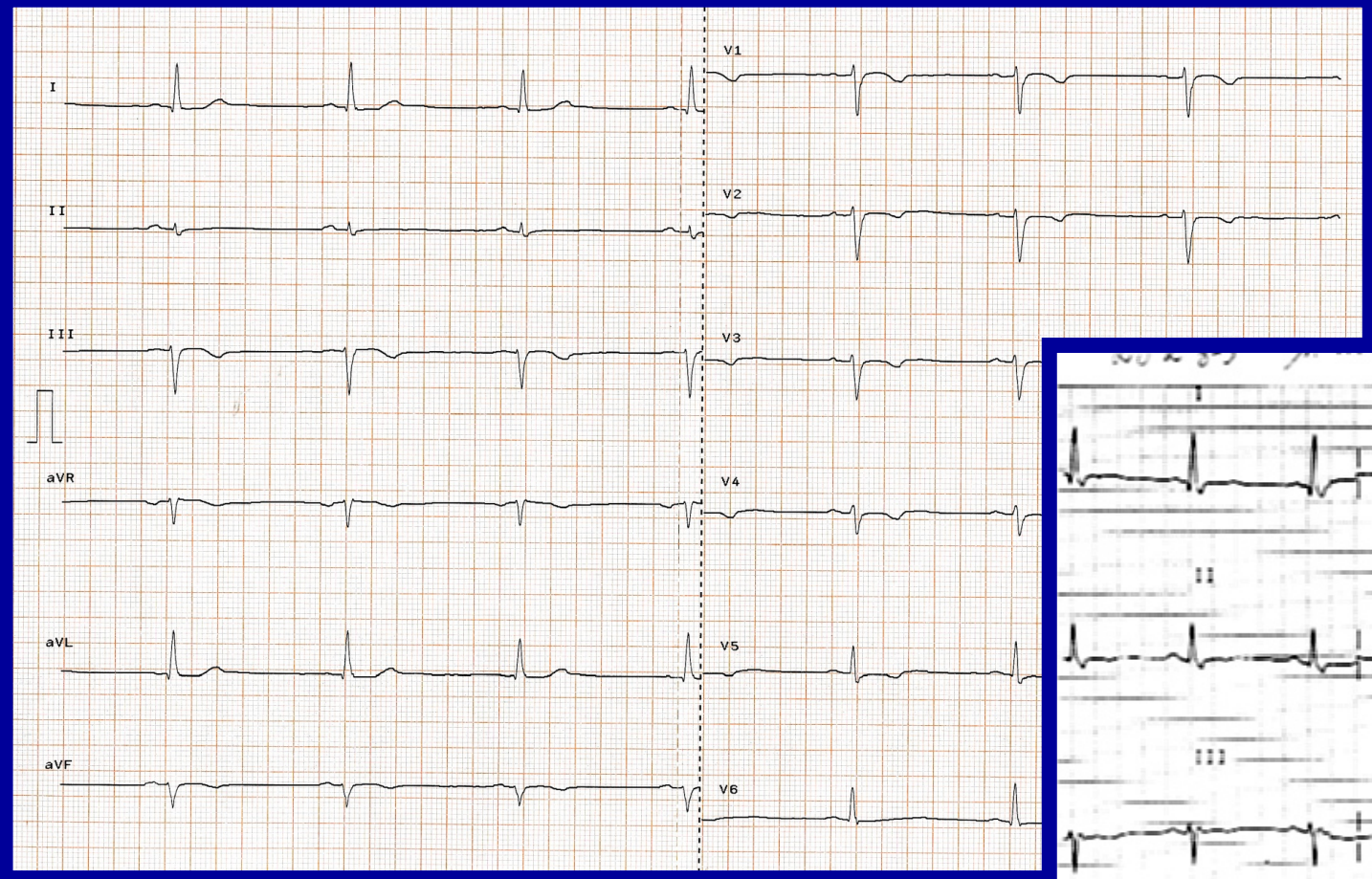
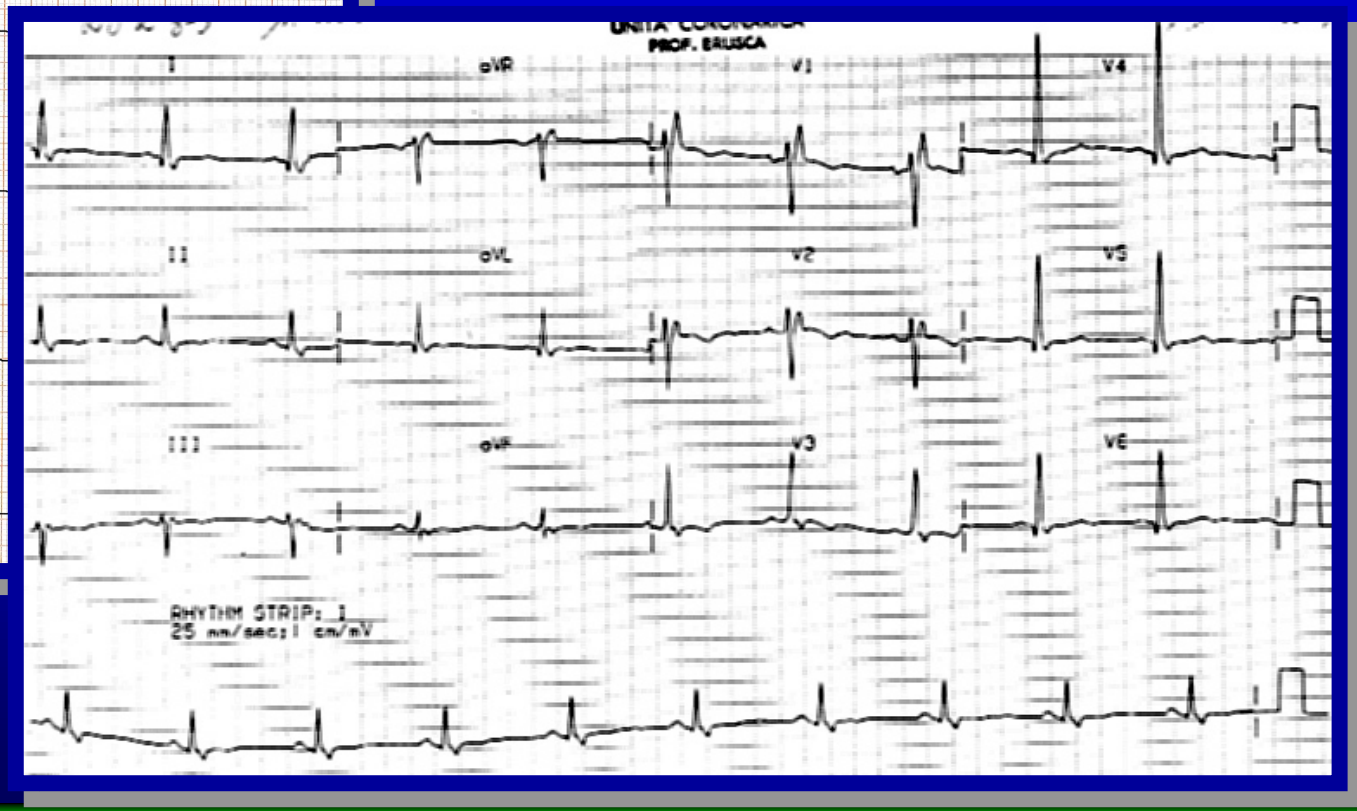
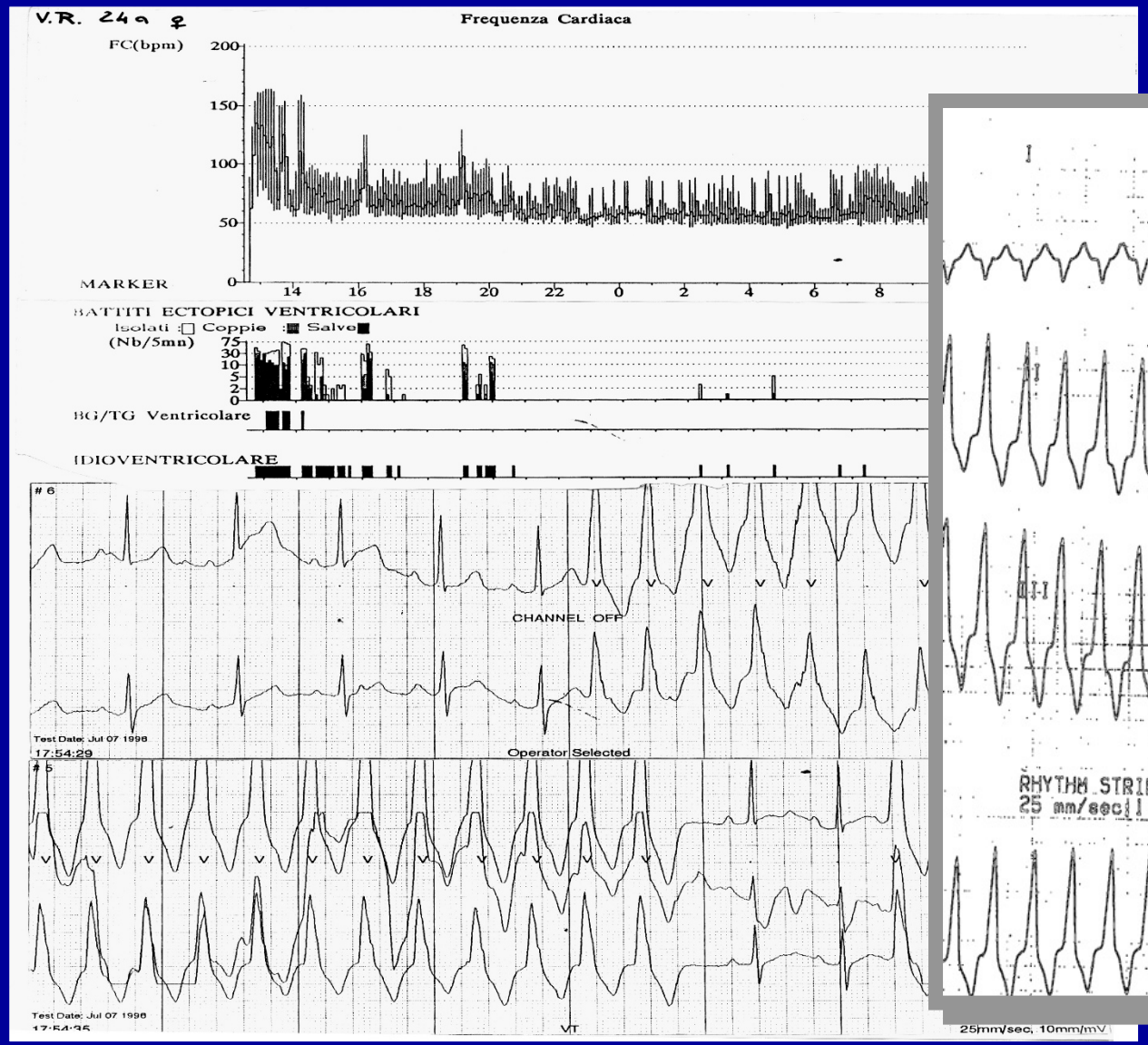
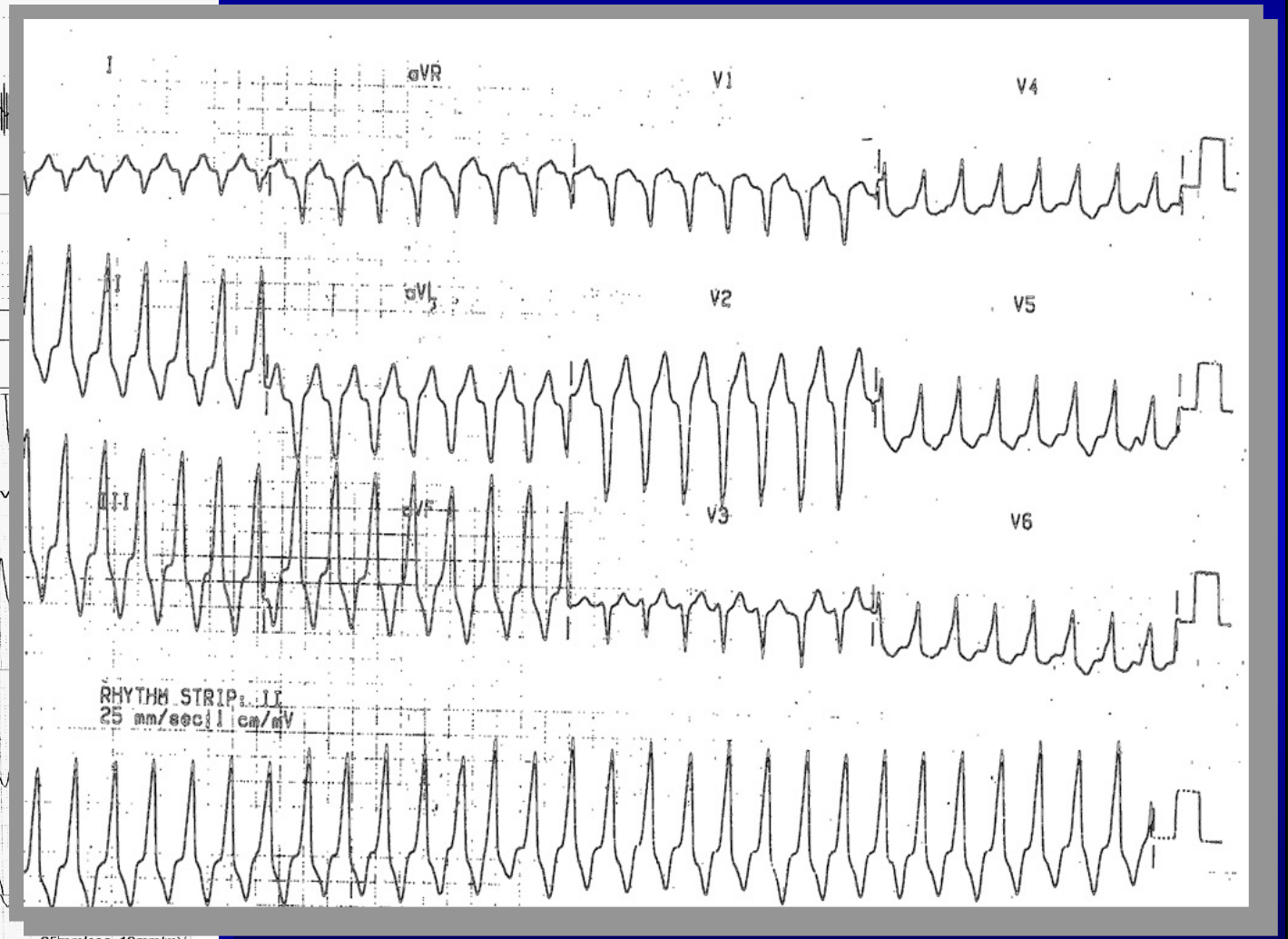
ARVC: ECG


I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6

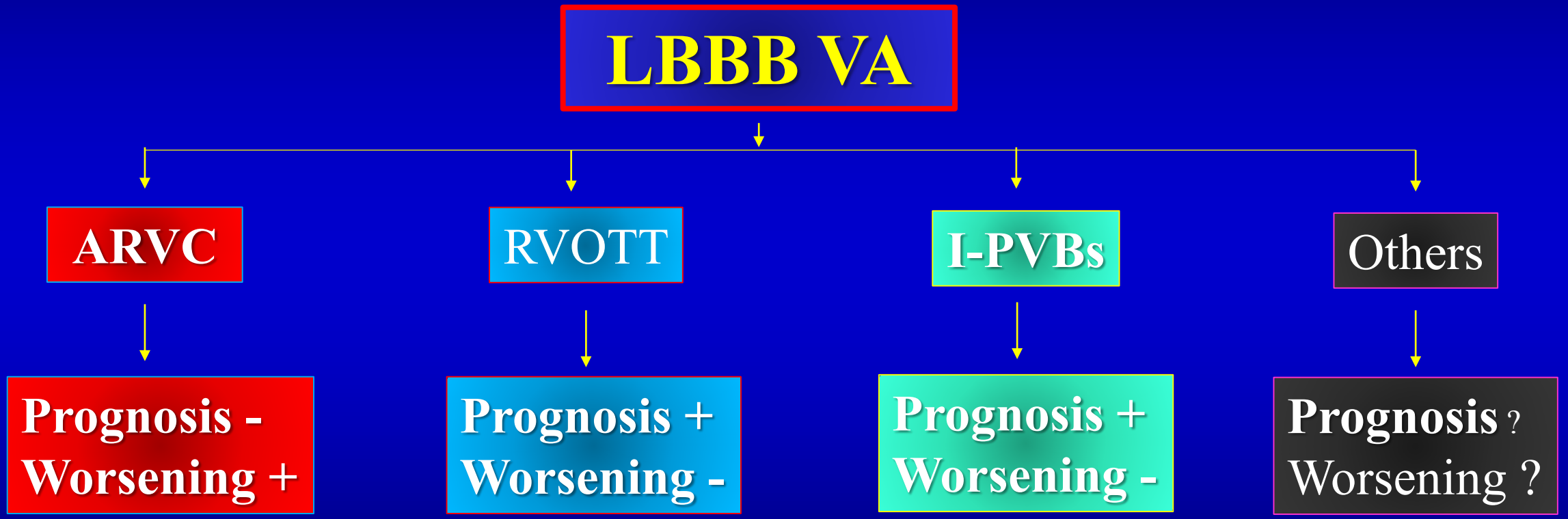

PROF. BALUSCA
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
RHYTHM STRIP: I
25 mm/sec; 1 cm/mV

ARVC: Ventricular Tachycardia





ARVC: DD for LBBB Arrhythmias



ARVC THERAPY GOALS

- Reduction of mortality
- Primary prevention in gene carriers
- Prevention of the desease progression
- Improve arrhythmic symptoms and QoL
- Improve heart failure symptoms and QoL

ARVC THERAPY: How to reach goals

Heart Failure Management

Reduce symptoms

Prevention of SD/

Reduce symptoms

Beta blockers

Life-style changes ?

Conventional HF th

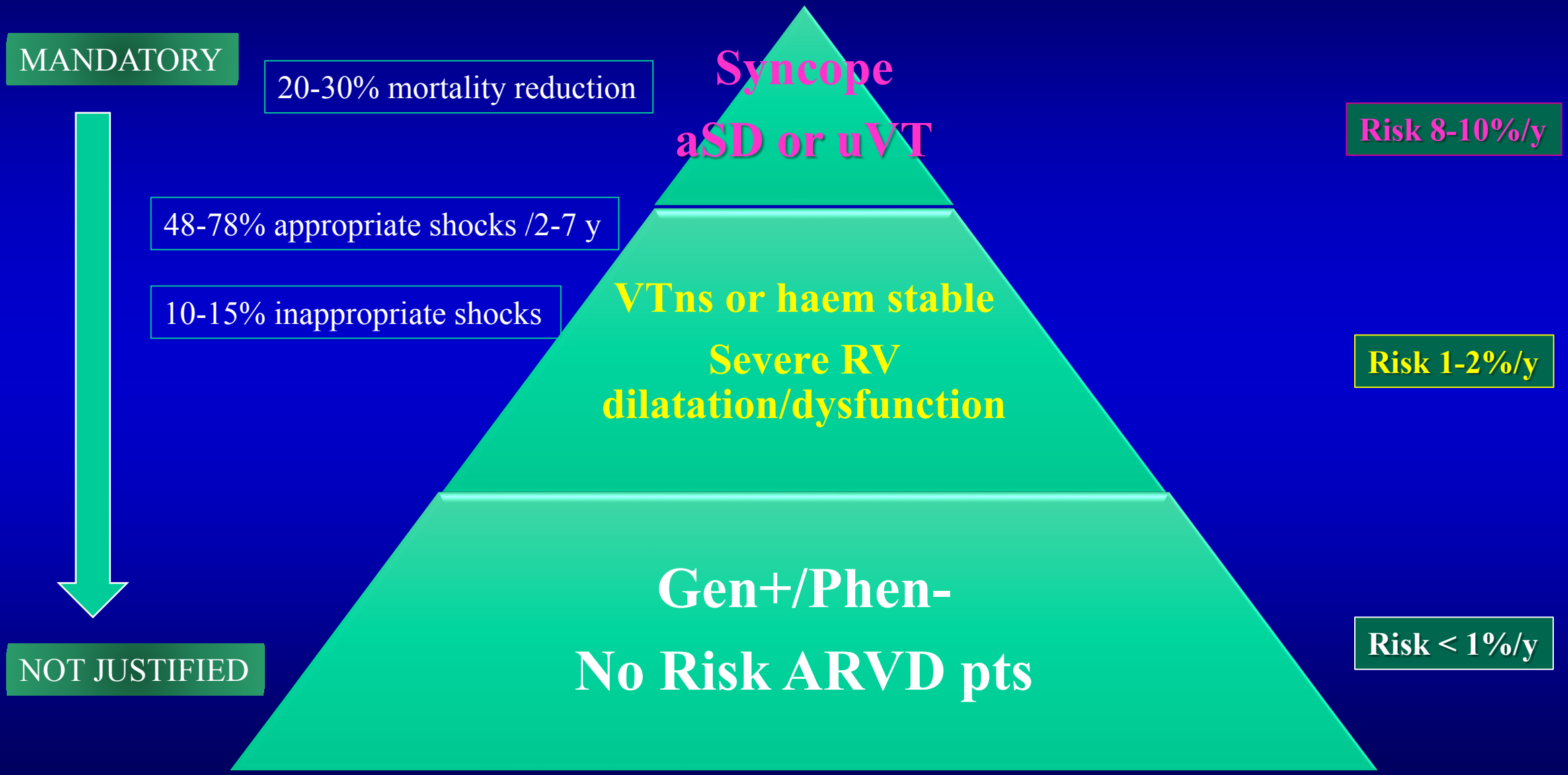
Non pharmacological HF Th

LIFE-STYLE CHANGES

HIGH RISK	INTER RISK	LOW RISK	GEN+/PHEN-
ICD	AAD & BB	FOLLOW UP	FOLLOW UP
BB & AAD	ABLATION	BETA BLOCKER	
ABLATION	ICD		

HEART TRANSPLANTATION

ARVC Therapy: indication for ICD



ANTIARRHYTHMIC DRUGS

- **Non prospective randomized study of comparison → empiric choise**

- Witcher 1992: 81 pts with baseline inducible VT; choise of AAD PVS guided: SOTALOL 320-480 mg >>Amio >> Betablocker
- Witcher 2005: 191 pts confirm sotalol efficacy 68%

- Corrado 2003: 132 pts with ICD: no significant influence on ICD appropriate shock between treated and non treated (amio, sota, fleca, BB)
- Marcus 2009: 95 pts with ICD: AMIO is the only AAD protective to ICD intervention

BETA BLOCKERs

- Efficacy in prevent VA but not for VT inducibility
- Reduction of VA effort-related
- Possible reduction of mechanical myocardial stress → disease modifying action ? (not with nitrates or diuretics)
- Not clinical data on healthy carriers (clinical close FU)
- With ACE-I, diuretics and spironolactone in the HF treatment

OTHERS

- Conventional HF drugs in pts with ventricular disfunction
- Anticoagulation for ventricular enlargement/dysfunction is not certain (0,5%/y thromboembolic complication)
- Anticoagulation if AF as other cardiomiopathy
- Catheter ablation: for stable VT due to a scar-related macro-reentry; is a palliative therapy

OUR EXPERIENCE

- 68 pts (69% m, 31 ± 19y)
- FU: 2-29 Y (17 ± 8 y)
- TF 1994 criteria (post-hoc validation on TF 2010)
- BB and avoid physical effort for all pts
- If VT inducibility in BB started AAD

- If VT ind on AAD → ICD
- To reduce symptoms AAD and ablation
- If aSD → direct ICD

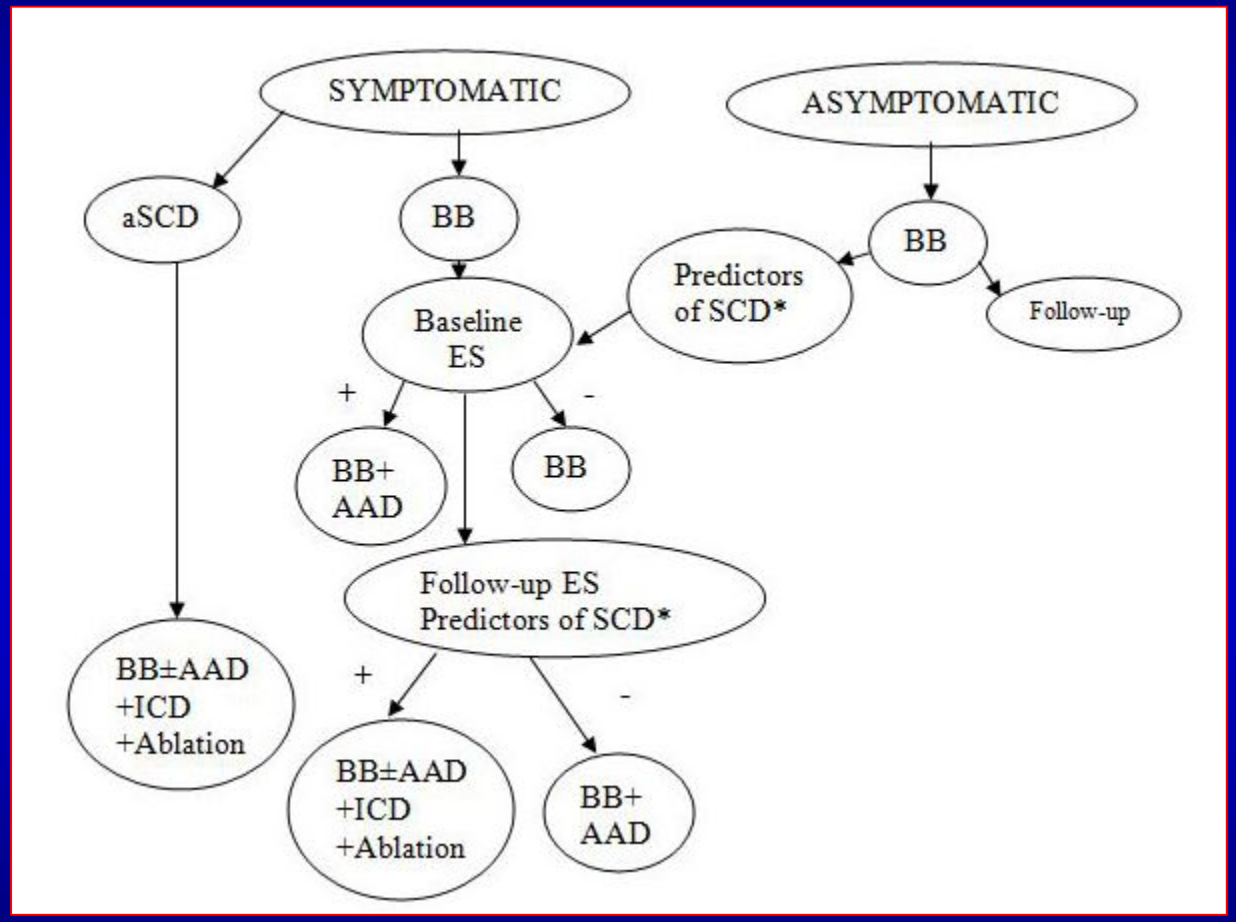
J Cardiovasc Med 2016, 17: 418-24

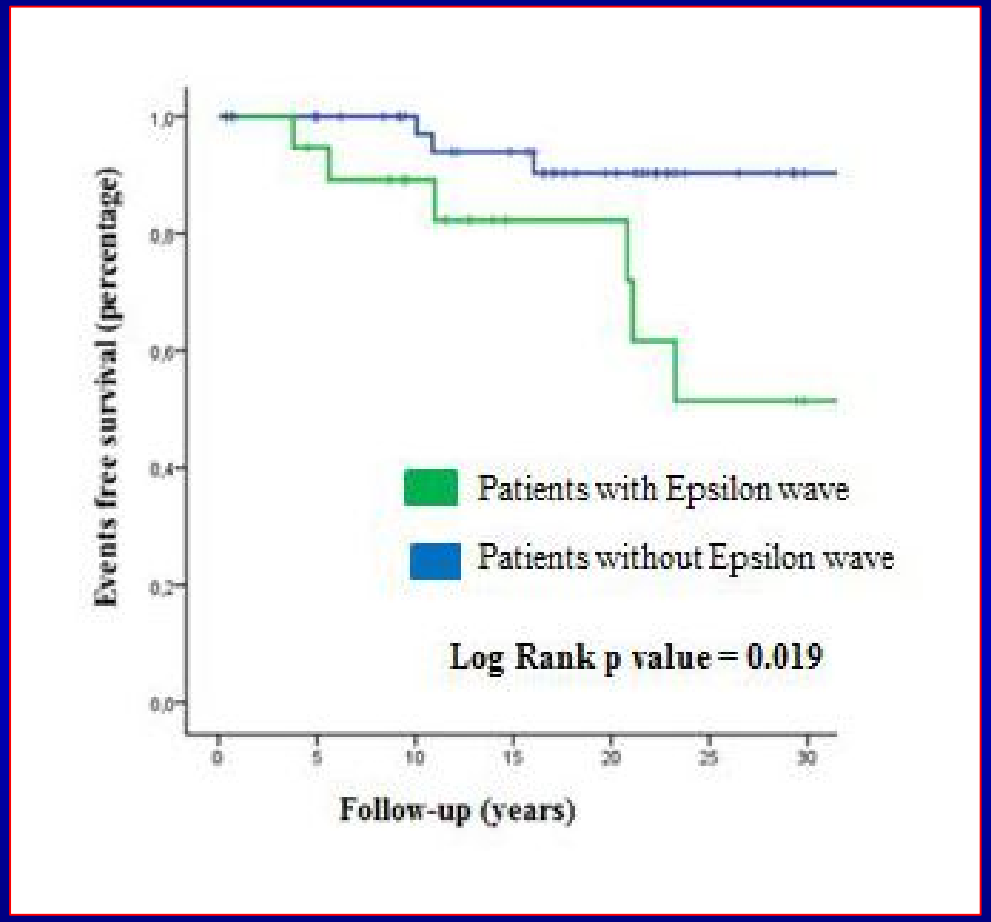
OUR EXPERIENCE: FU of 17±8y

- 61 pts (89%) had PVS: 64% inducibility
- 33 pts had II PVS in BB+AAD: 63% inducibility
- 24 pts received ICD
- 1 ICD for aSD
- 17 pts had VT ablation
- 3 heart transplantations
- 16 pts had also FA

- 12 pts died
- 3 SD: 18y m, waiting ICD implantation in sotalol,
  - 61y f, spontneously stopped amio e nado
  - 46y f, VF but ICD lead fracture
- 4 end-stage HF
- 5 non cardiac death
- 7 aSD: 1 for sVT during hospitalitation for VT ablation, 6 in ICD carriers
- 21% inappropriate shocks, 7 devices related complications

OUR EXPERIENCE





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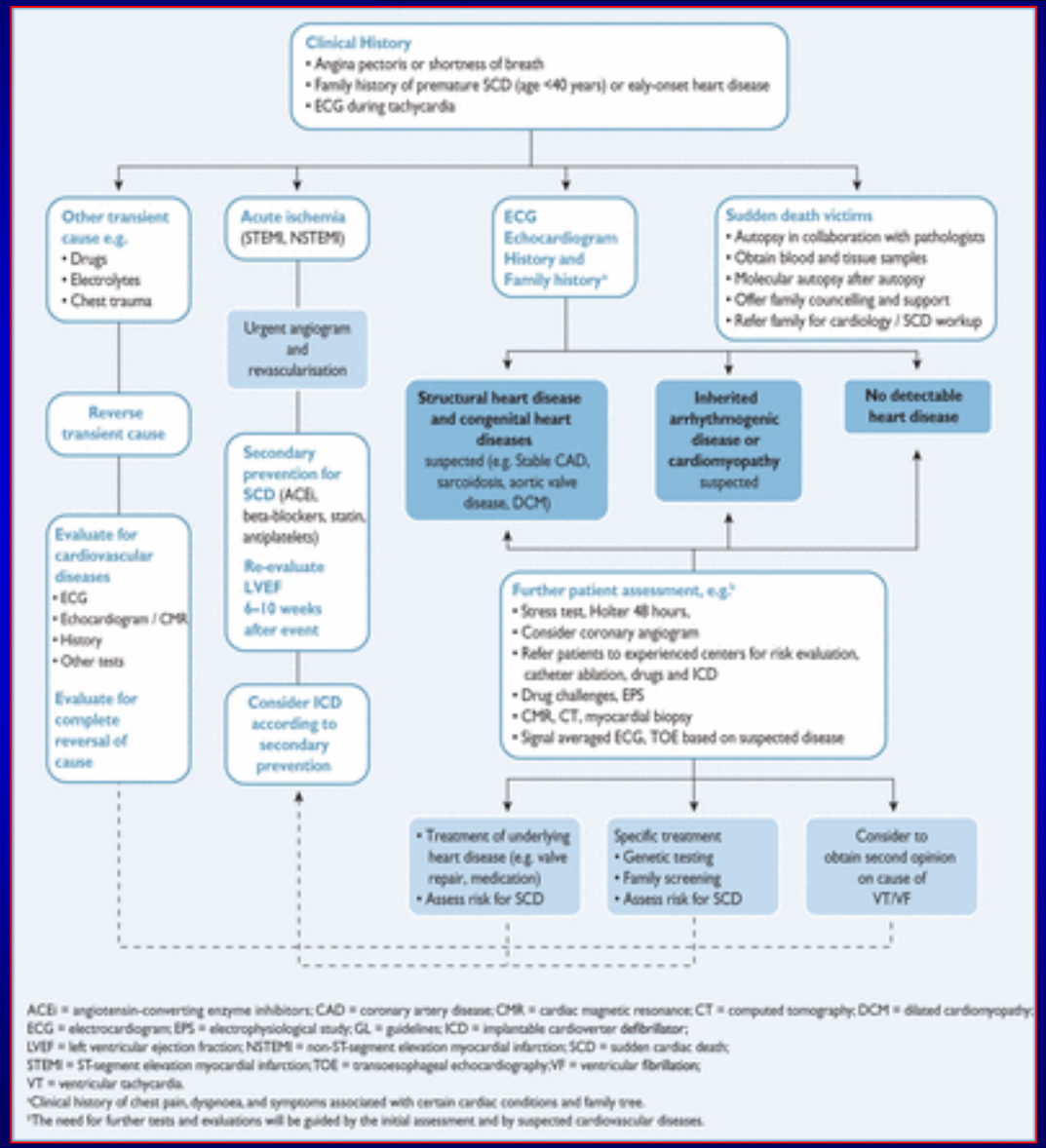
ESC Guidelines on ventricular arrhythmias 2015



ACEi = angiotensin-converting enzyme inhibitors; CAD = coronary artery disease; CMR = cardiac magnetic resonance; CT = computed tomography; DCM = dilated cardiomyopathy; ECG = electrocardiogram; EPS = electrophysiological study; GL = guidelines; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; NSTEMI = non-ST-segment elevation myocardial infarction; SCD = sudden cardiac death; STEMI = ST-segment elevation myocardial infarction; TOE = transoesophageal echocardiography; VF = ventricular fibrillation; VT = ventricular tachycardia.

[a]Clinical history of chest pain, dyspnoea, and symptoms associated with certain cardiac conditions and family tree.

[b]The need for further tests and evaluations will be guided by the initial assessment and by suspected cardiovascular diseases.

Recommendations	Class[a]	Level[b]	Ref.[c]
Avoidance of competitive sports[d] is recommended in patients with ARVC.	I	C	388
Beta-blockers titrated to the maximally tolerated dose are recommended as the first-line therapy to improve symptoms in patients with frequent PVC and NSVT.	I	C	This panel of experts
ICD implantation is recommended in patients with a history of aborted SCD and haemodynamically poorly tolerated VT.	I	C	389
Amiodarone should be considered to improve symptoms in patients with frequent PVC or NSVT who are intolerant of or have contraindications to beta-blockers.	IIa	C	390,391
Catheter ablation, performed in experienced centres, should be considered in patients with frequent symptomatic PVC or VT unresponsive to medical therapy to improve symptoms and prevent ICD shocks, respectively.	IIa	B	183,202,207,392,393
ICD implantation should be considered in ARVC patients who have haemodynamically well-tolerated sustained VT, balancing the risk of ICD therapy, including long-term complications, and the benefit for the patient.	IIa	B	387,394,395
ICD implantation may be considered in patients with one or more recognized risk factors for VA in adult patients with a life expectancy >1 year following detailed clinical assessment that takes into account the lifelong risk of complications and the impact of an ICD on lifestyle, socioeconomic status and psychological health.	IIb	C	This panel of experts
Invasive EPS with PVS may be considered for stratification of SCD risk.	IIb	C	113,114

CONCLUSION

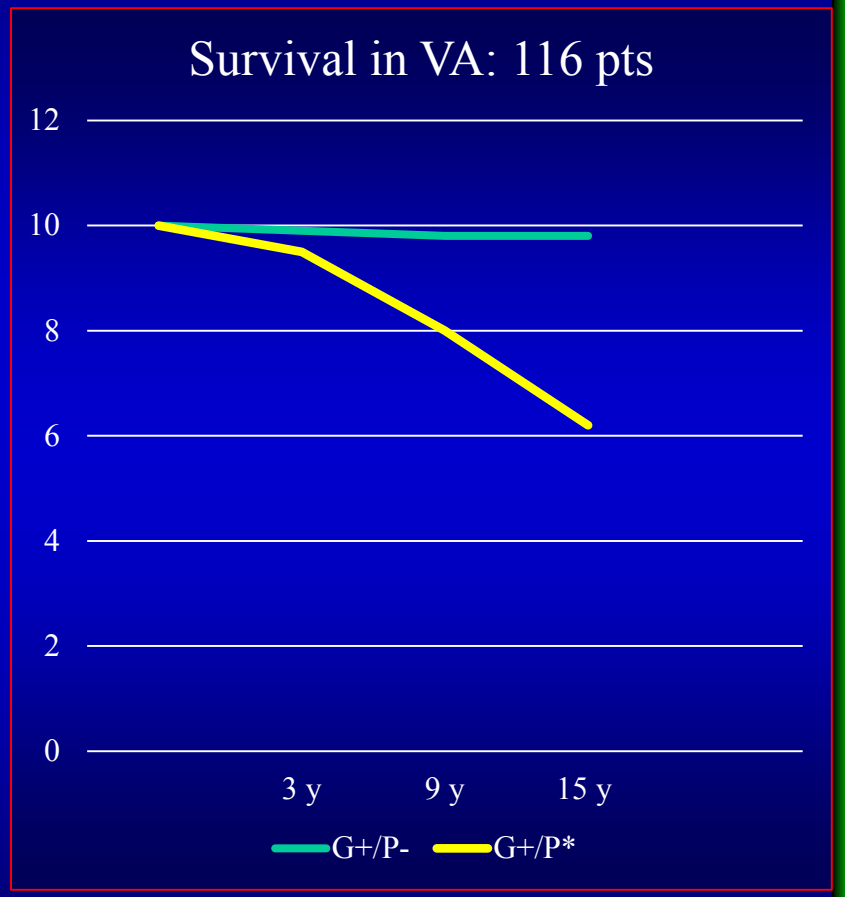
- Nowadays the diagnosis of ARVD remain a poliparametric research of major and minor, morphogical and arrythmic criteria

- Empiric pharmacological antiarrythmic therapy (A, S, BB, IC)
- ICD and ablation have well definite indication
- Conventional drugs for HF

- Not clear how to prevent the gene carrier (G+/P-)
- Great relevance in clinical/instrumental risk stratification
- Close follow-up to intercept the disease evolution

ARVD: Risk Stratification Genetics

ARVD/C locus name	MIM	Gene	Chromosome	Inheri tance	Pene trance	Detection rate
ARVD/C-1	107970	*TGFß -3*	14q23-24	AD	high	
ARVD/C-2	600996	*RYR-2*	1q42-43	AD	high	
ARVD/C-3	602086	*Not identified*	14q12-22	AD		
ARVD/C-4	602087	*Not identified*	2q32.1-32.3	AD		
ARVD/C-5	604400	*LAMR1 TMEM43*	3p23	AD		Unknown
ARVD/C-6	604401	*PTPLA*	10p12-14	AD		
ARVD/C-7	609160	*DES ZASP*	10q22	AD		
ARVD/C-8	607450	*Desmoplakin (DSP)*	6p24	AD	~50%	6-16%
ARVD/C-9	609040	*Plakophilin-2 (PKP2)*	12p11	AD/AR	~30%	11-43%
ARVD/C-10	610193	*Desmoglein-2 (DSG-2)*	18q12.1 - q12.2	AD		10-12%
ARVD/C-11	610476	*Desmocollin (DSC-2)*	18q12.1	AD		1-5%
Naxos	601214	*Plakoglobin (JUP)*	17q21	AR	100%	



Zorzi et al, Europace, 2016,

CRM comparison of diagnostic criteria