

ESC Congress 2018, Munich (DE), Aug 24-29, 2018

Symposium: **ARVC: from pathology to prognosis**



Treatment of ARVC ...
... Current Standards and Future Perspectives

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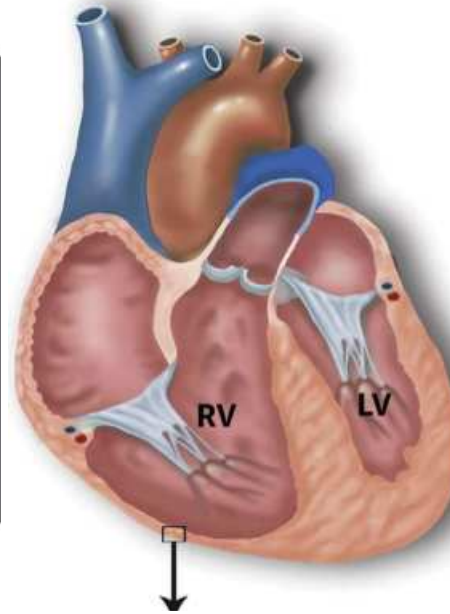
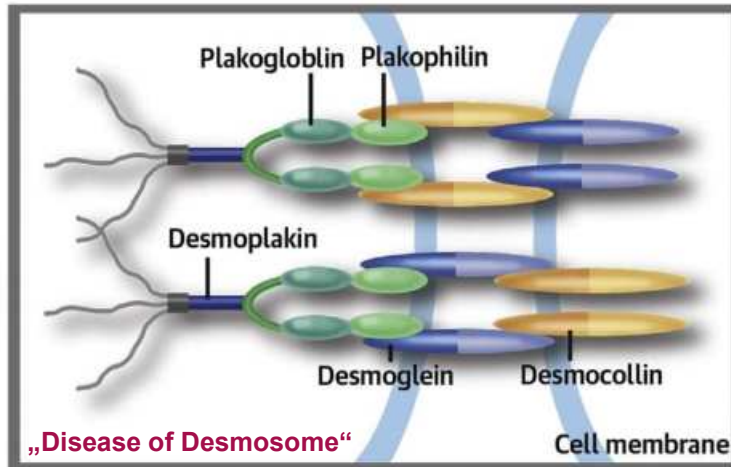
Thomas Wichter, MD, FESC
Treatment of VT in ARVC

No Conflict of Interest
Nothing to Disclose

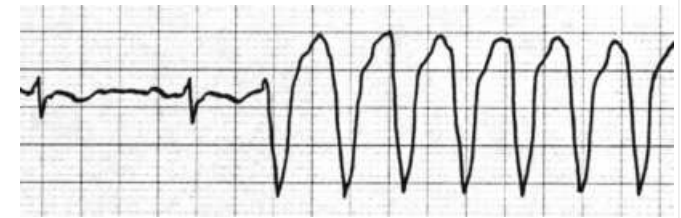
Diagnostic Criteria of ARVC

International ARVC Task Force (2010)

Genetics and Family History



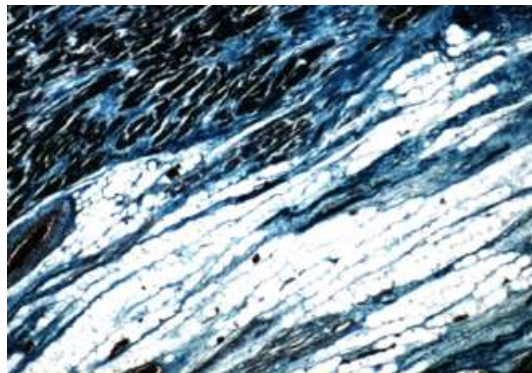
Ventricular Arrhythmias (LBBB-VT)



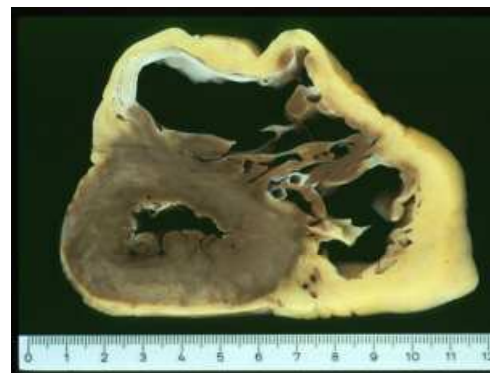
ECG: Depolarization + Repolarization



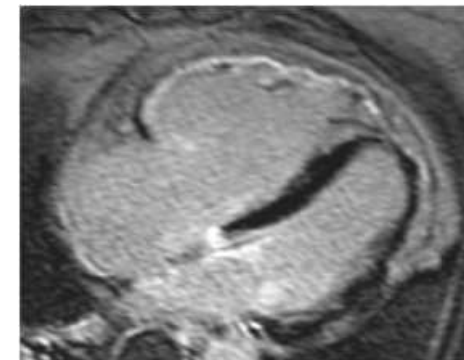
Tissue Characterization



Pathology



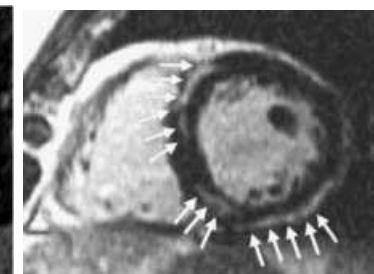
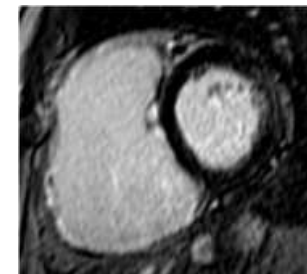
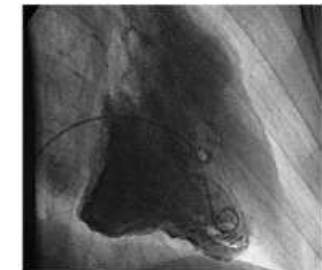
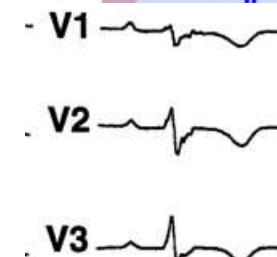
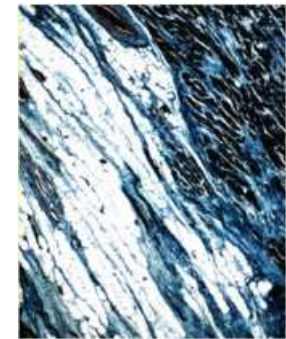
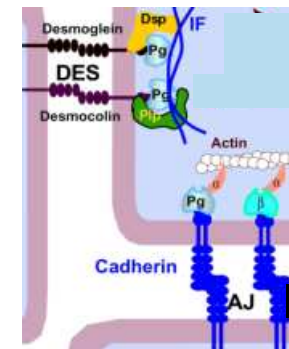
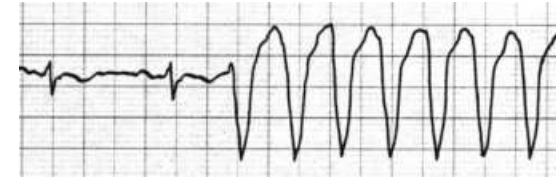
RV-/LV- Wall Motion + Structure



What is ARVC ?

Be aware of clinical features

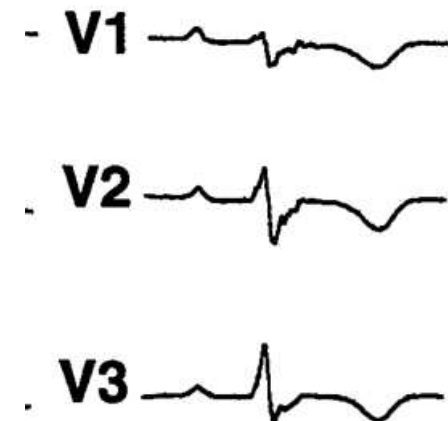
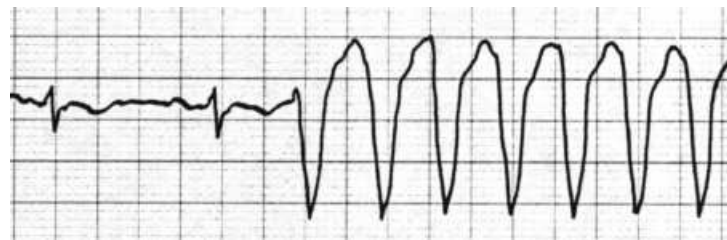
- Young, apparently healthy pts
- Ventricular arrhythmias (LBBB pattern)
- Exercise provokable arrhythmias
- High prevalence in athletes
- Family history (ARVC, unexplained SCD)
 - Genetic background (desmosomal proteins)
- Right precordial ECG abnormalities
 - T-wave inversion, QRS prolongation, ϵ -waves
- RV-enlargement / RV-dysfunction
- LV involvement frequent (even dominant)



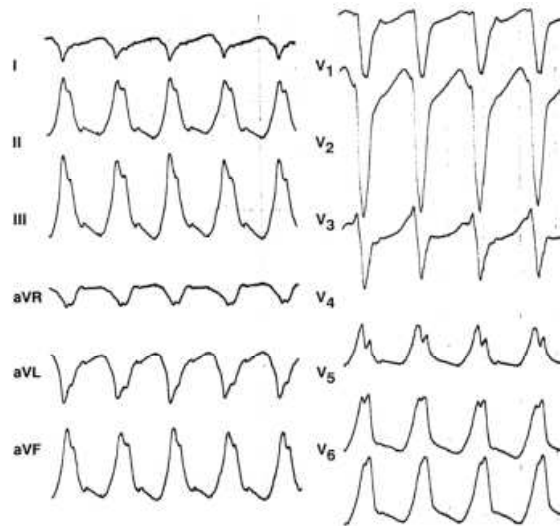
Treatment of VT in ARVC

ARVC: Clinical Features

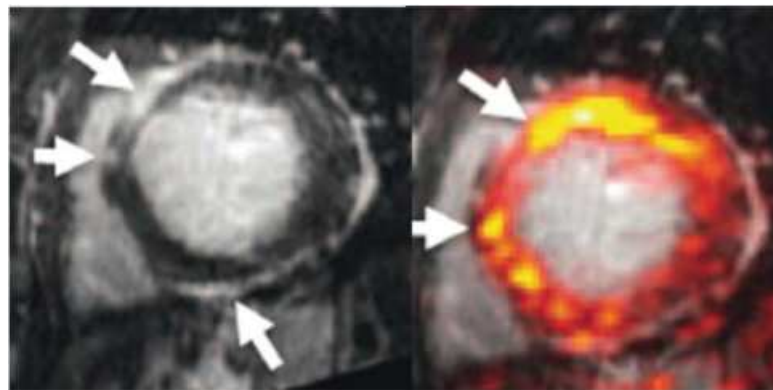
- Young, apparently healthy pts
- Ventricular arrhythmias of LBBB morphology
- Exercise provokable arrhythmias
- High prevalence in athletes
- Family history (ARVC, unexplained sudden death or VT)
- RV-enlargement or RV-dysfunction
- Right precordial ECG abnormalities
 - T-wave inversion, broad S-wave upstroke,
 - QRS prolongation, Epsilon potential



Reassess: Is it really ARVC? ... or is it rather a phenocopy... ?



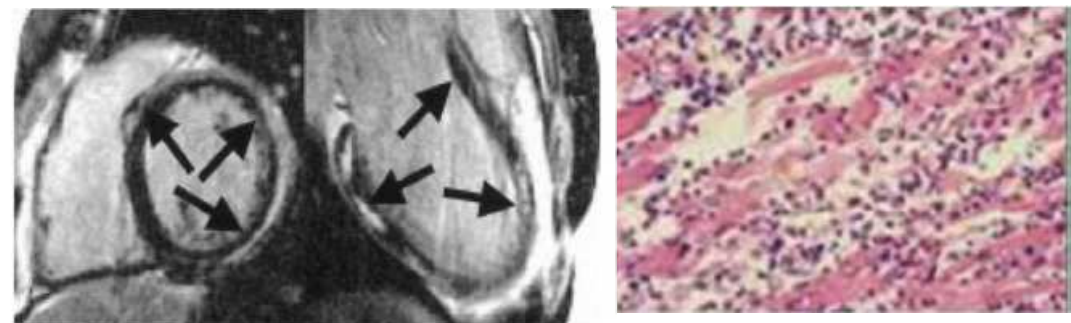
Idiopathic RVO-VT



Cardiac Sarcoidosis



Restrictive CM



Myocarditis (acute / chronic)

**Make the
correct diagnosis
for specific therapy !**

ARVC: a rare disease....

Underdiagnosed?

- ... Increased risk of sudden death due to undertreatment

Overdiagnosed?

- ... Disease „labeling“ (incl. family members)
potential consequences for social life, sports activity, insurances, etc.
- ... Unjustified ICD indications (incl. complications, inappr. shocks)

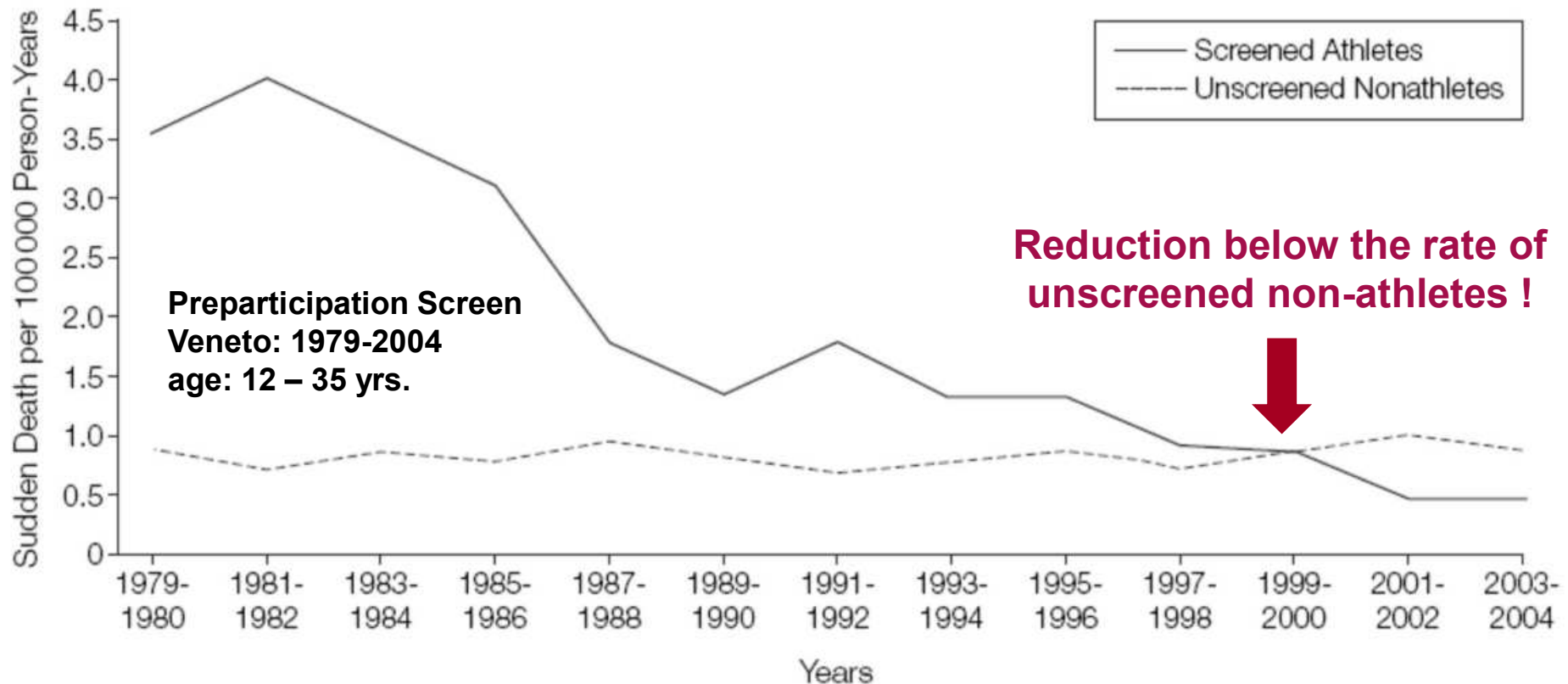
Misdiagnosed?

- ... other diseases mimicking ARVC remain unrecognized
(myocarditis, sarcoidosis, cardiomyopathies, etc.)
- ... specific treatment options not applied

What awareness can do ...

Preparticipation Screening of Athletes

4-fold Reduction of Sudden Death in Athletes in Italy by Disqualification of diagnosed HCM and ARVC pts



2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

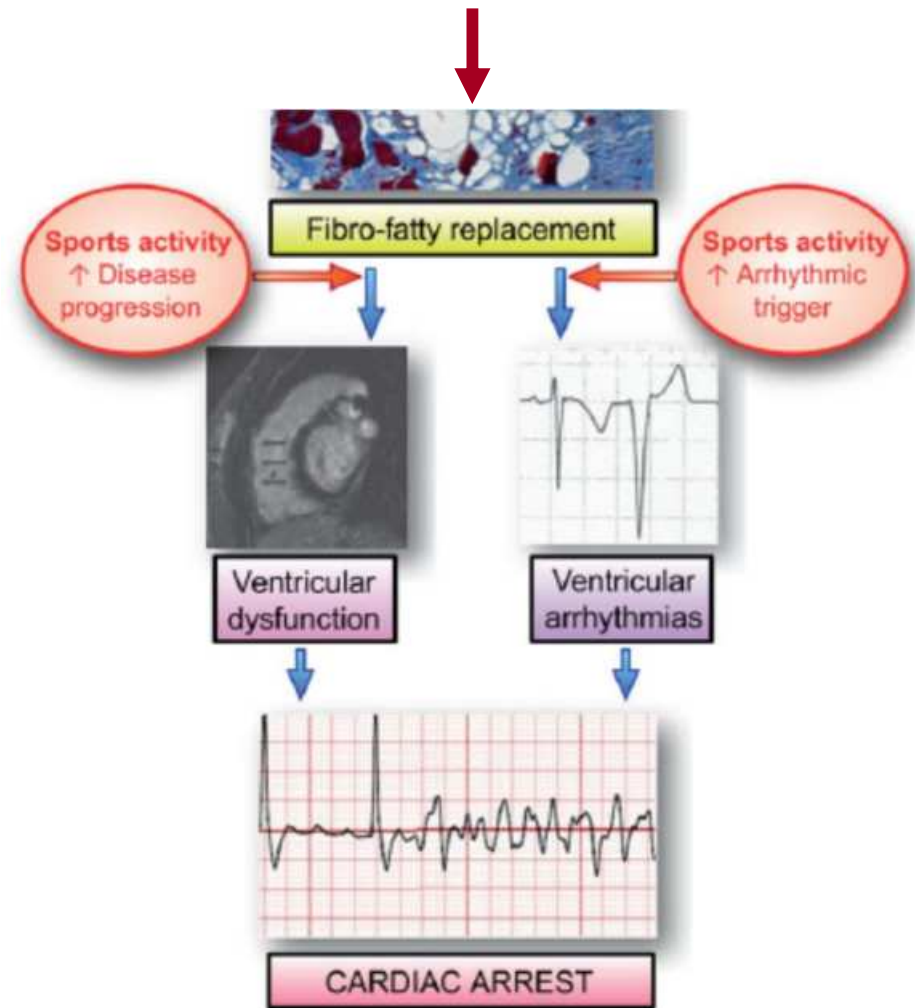
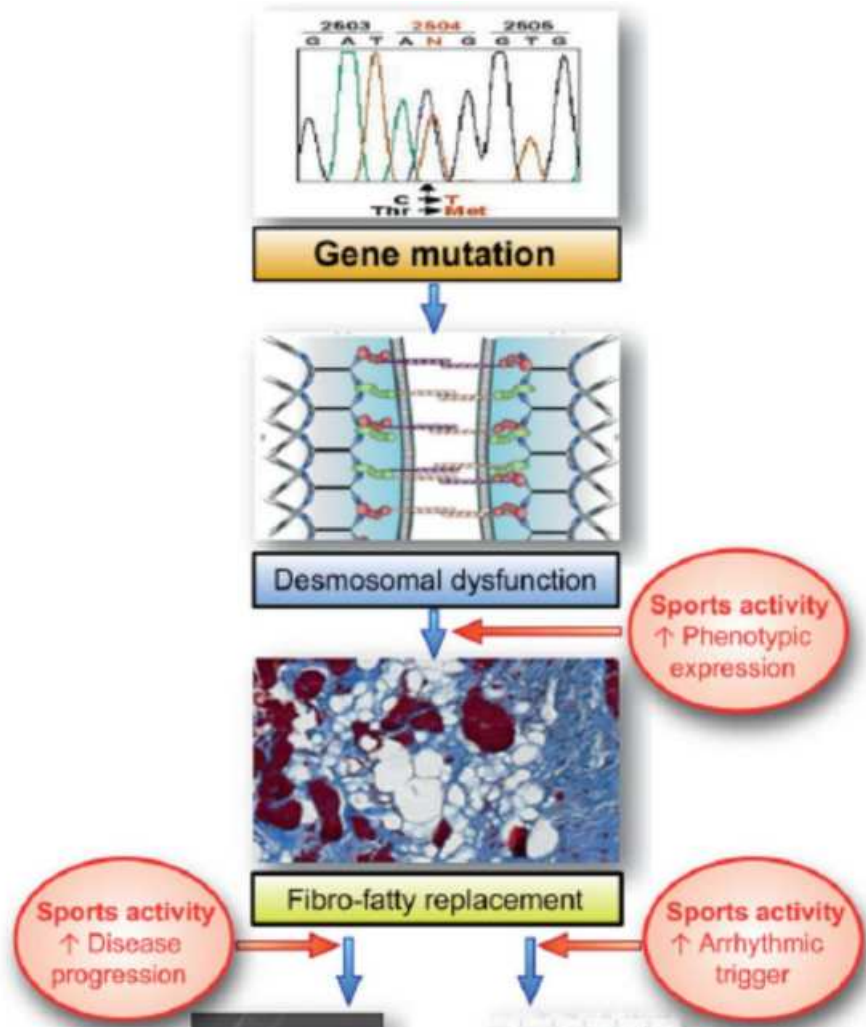
Sports Recommendation in ARVC

Recommendations	Class ^a	Level ^b
Avoidance of competitive sports ^d is recommended in patients with ARVC.	I	C

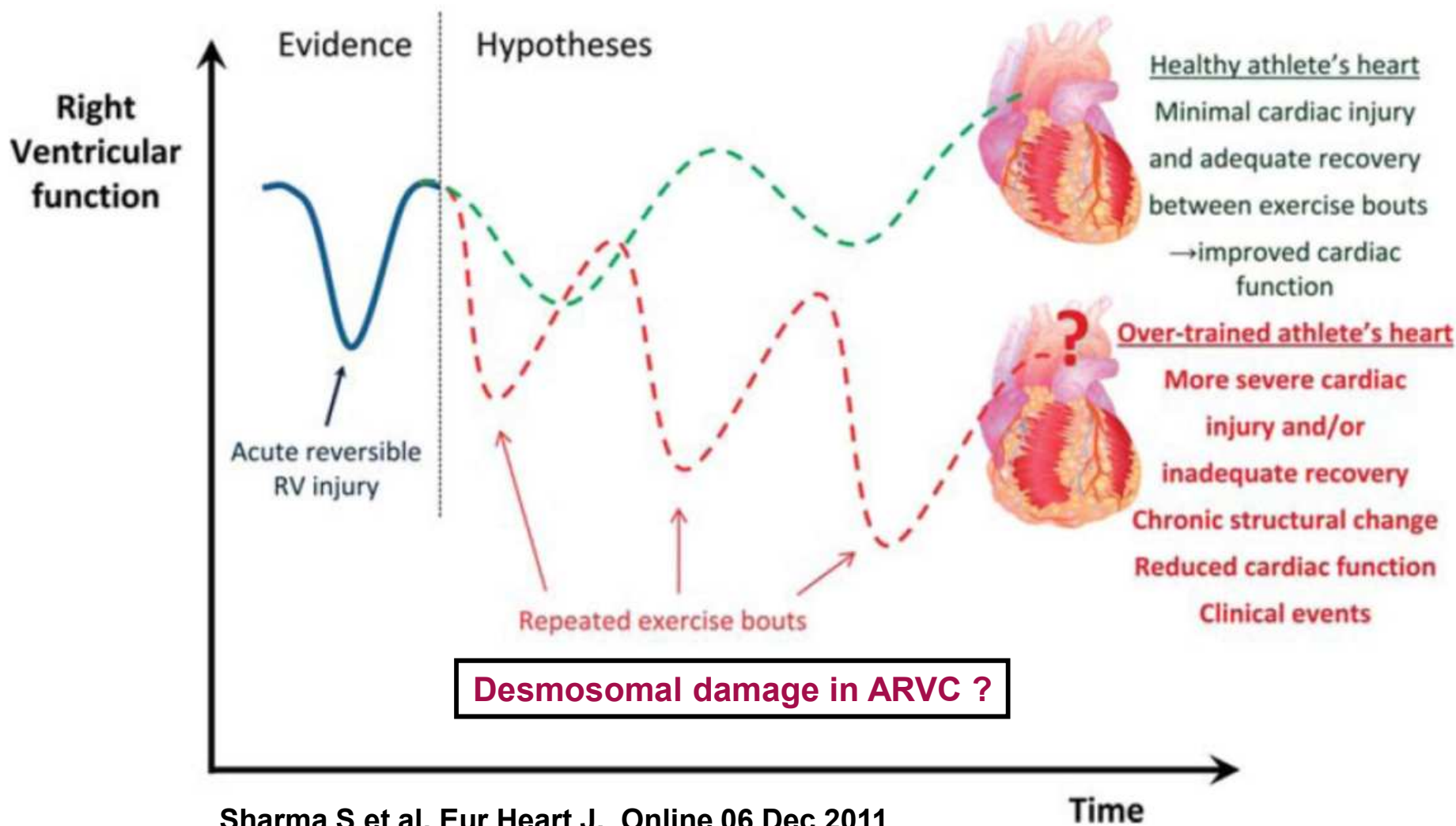
^d ESC guidelines define competitive sport as amateur or professional engagement in exercise training on a regular basis and participation in official competitions

Pathophysiology of ARVC

Role of Exercise + Training



Exercise and RV-Dysfunction



ARVC Mouse Model (JUP -/+): Impact of Exercise + Training

Plakoglobin deficient (- / +) mouse model



Treadmill - Training
139 ± 16 km distance / week

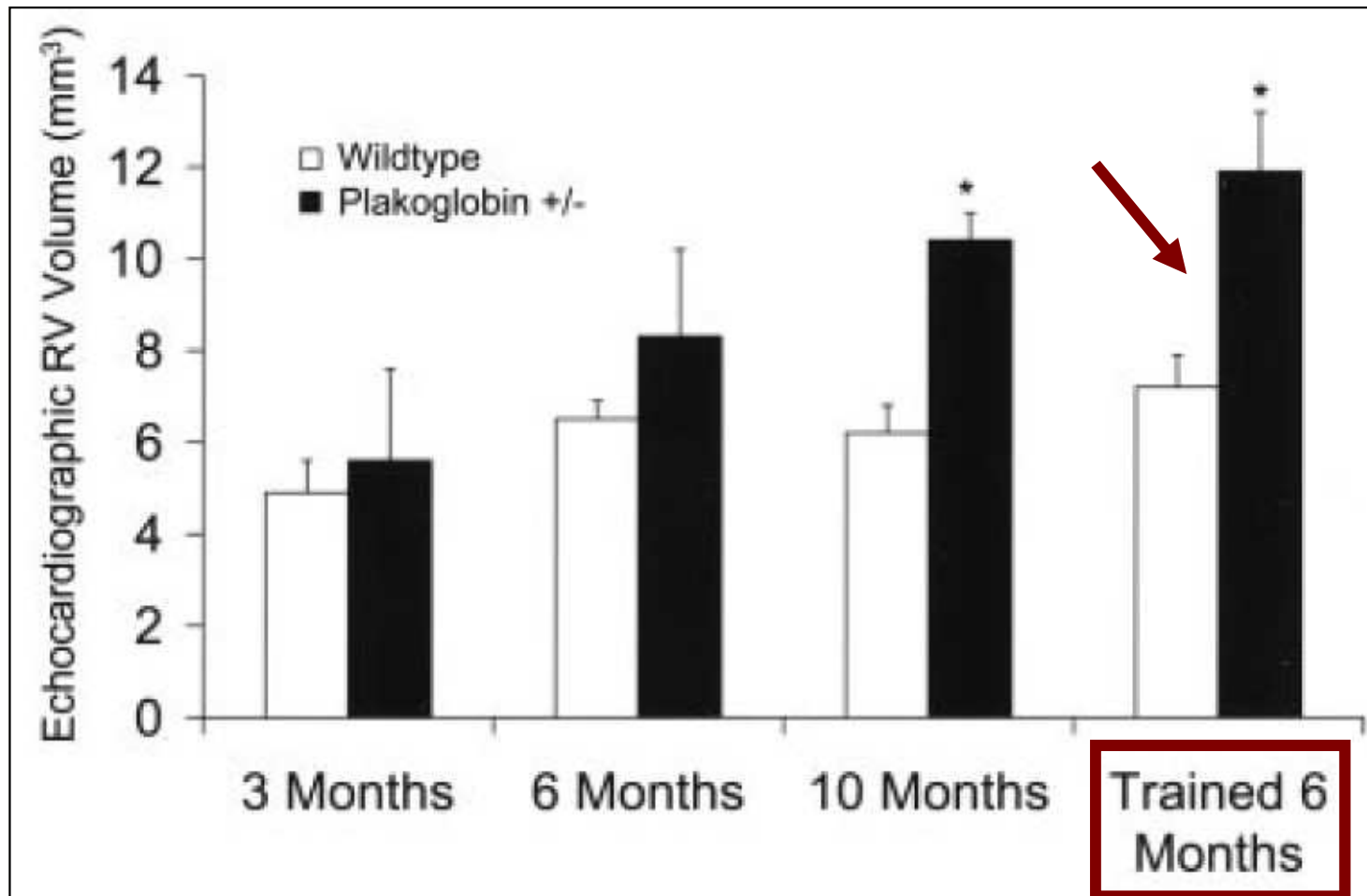


Swim - Training
10 – 90 min/ day

ARVC Mouse Model (JUP -/+)

Exercise accelerates ...

RV enlargement, RV-dysfunction, arrhythmias



Kirchhof P, et al.
Circulation. 2006. 114:1799-1806

Echo measurements confirmed by CMR. No changes in LV or LA size or function

ARVC Mouse Model (JUP +/-)

„Upstream“ Therapy

PRE-CLINICAL RESEARCH

Load-Reducing Therapy Prevents Development of Arrhythmogenic Right Ventricular Cardiomyopathy in Plakoglobin-Deficient Mice

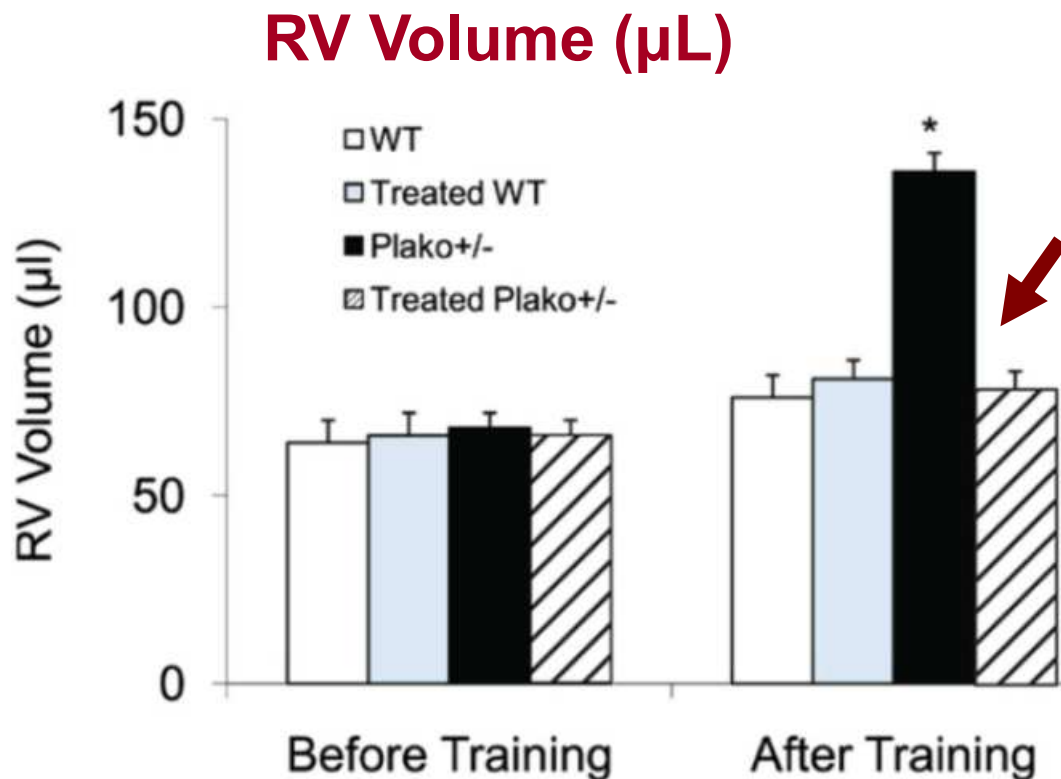
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Muenster, Berlin, Osnabrück, Essen, and Heidelberg, Germany; and Amsterdam and Utrecht, the Netherlands

ARVC Mouse Model (JUP -/+)

Preload-Reducing Therapy

prevents training-induced RV-enlargement and VT



Mouse model Pg +/- :

- littermate pairs:
14 Pg +/- and 5 WT
- 3 months old
- 7 wk training (swim)

Load-reducing therapy: (diuretics, nitrates / molsidomine)

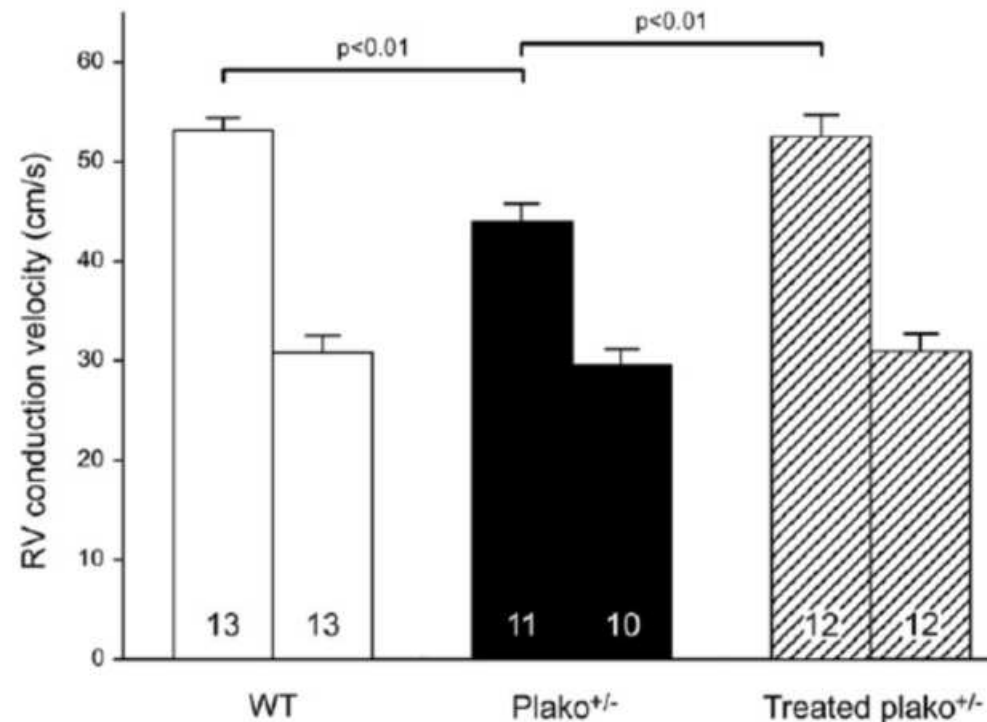
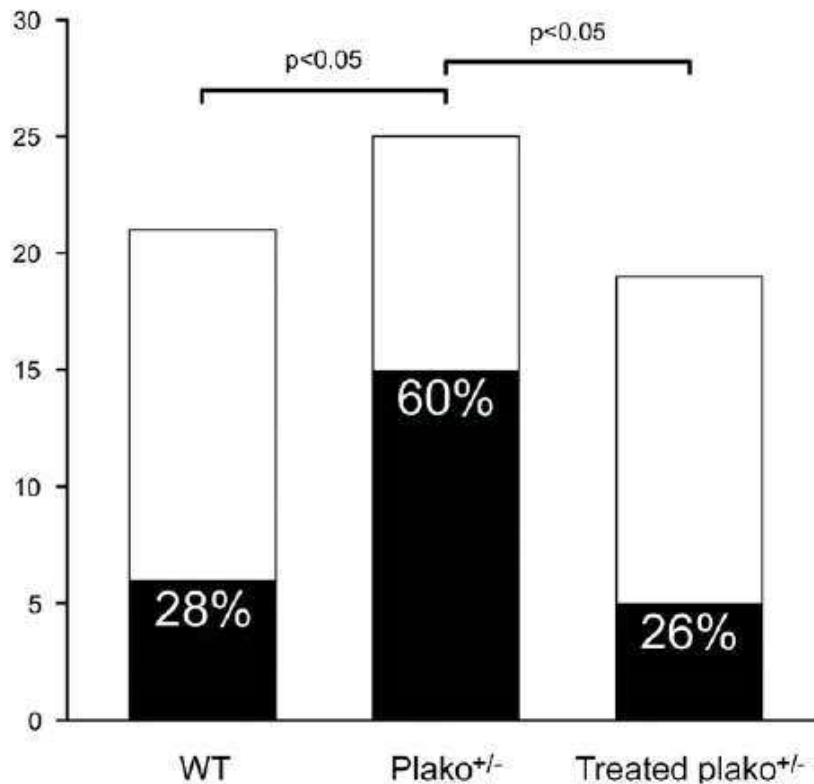
- prevents RV-dilatation
- reduced VT induction
- prevents conduction slowing

Treatment of VT in ARVC

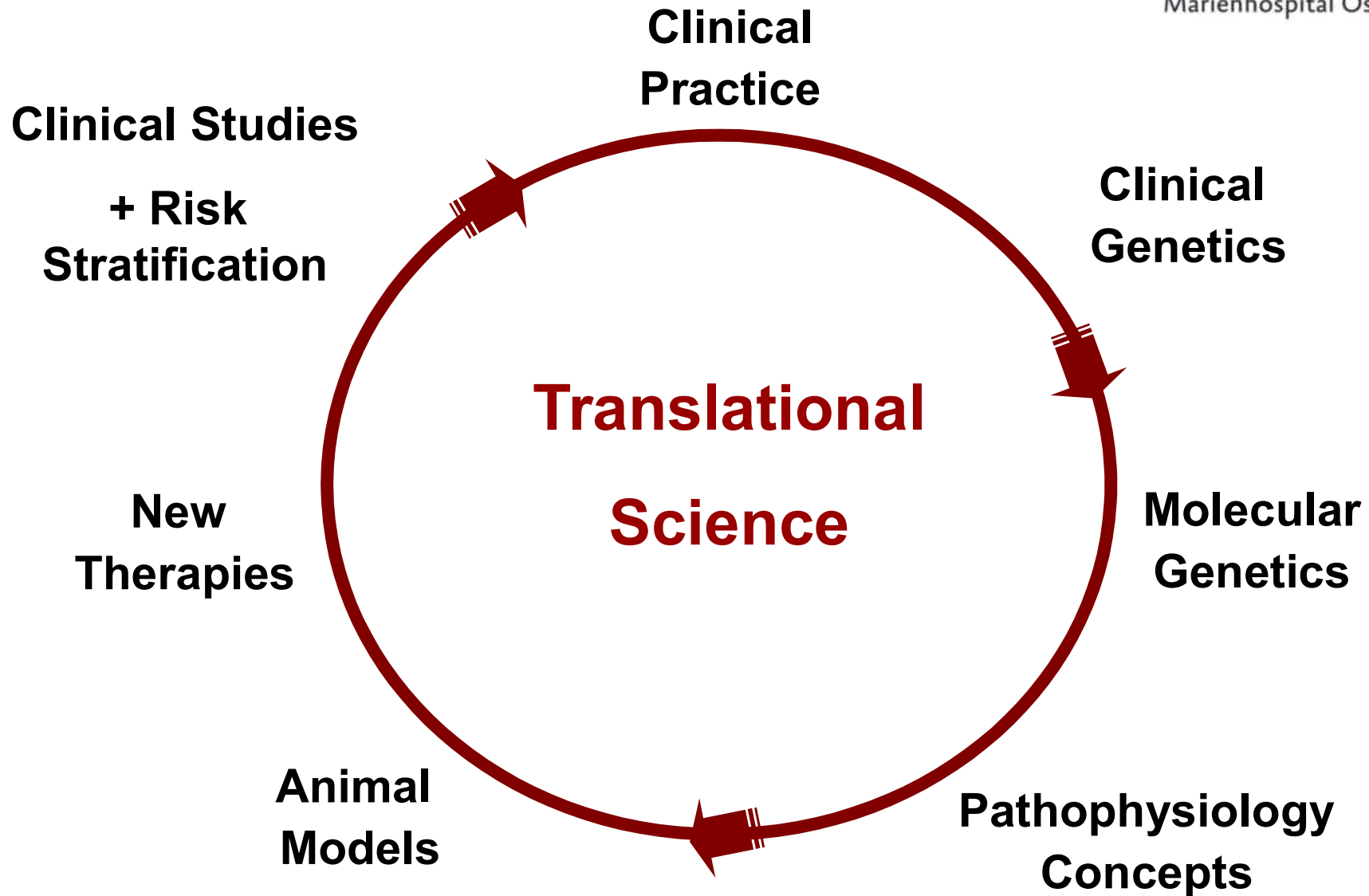
Load-reducing therapy

in Plako +/- mice prevents training induced ...

Inducibility of macro-reentrant VT Longit. RV conduction slowing



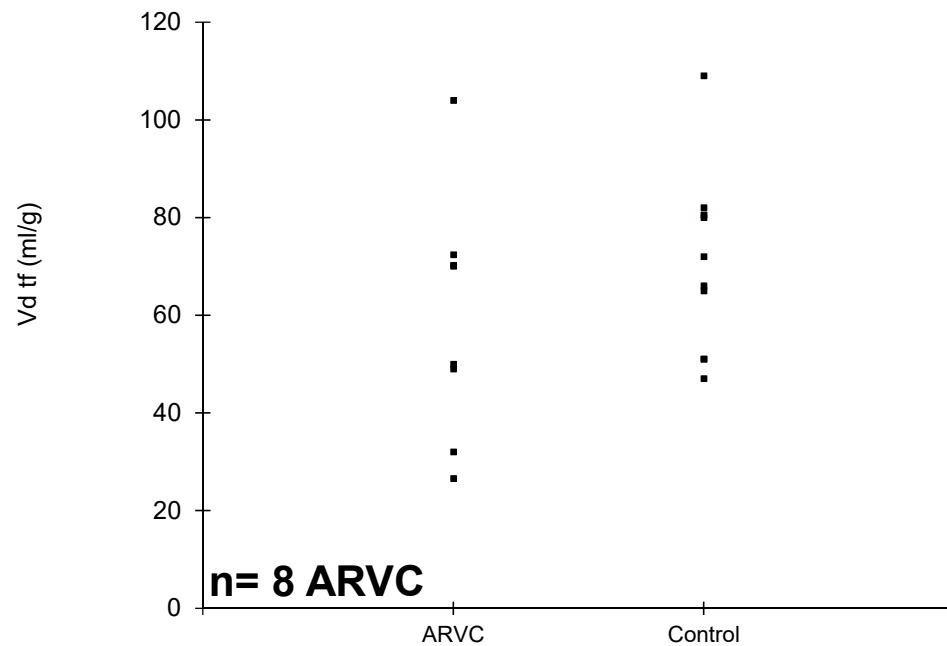
ARVC – from bedside to lab



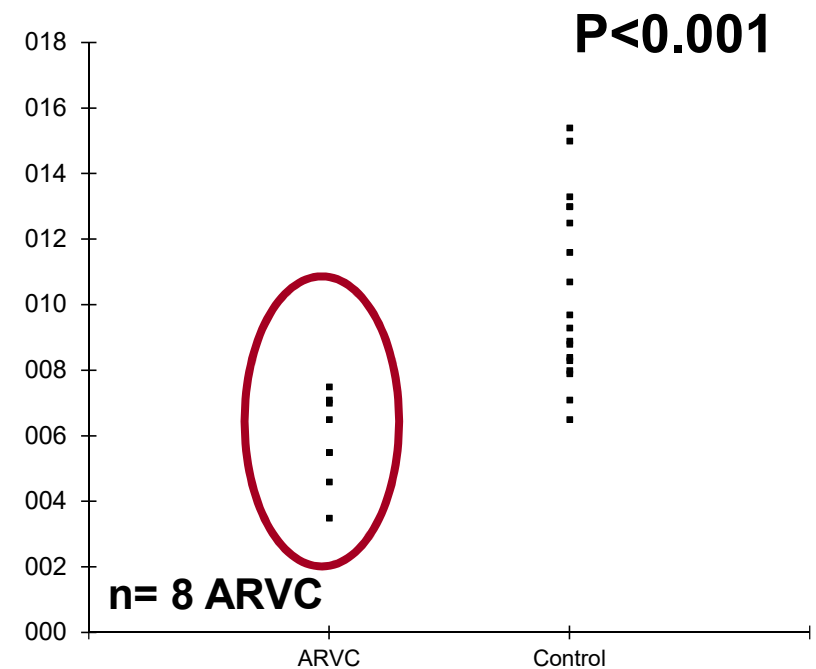
Adrenergic Dysfunction in ARVC: Quantitative Assessment by PET

Downregulation of adrenergic β -receptors

Presynaptic Norepinephrine Reuptake
volume of distribution: V_d ^{11}C -HED



Postsynaptic β -Receptor Density
max. binding capacity: B_{max} ^{11}C -CGP₁₂₁₇₇



ARVC: Sports Type and Level

Niels-Stensen-Kliniken 
Marienhospital Osnabrück



European Heart Journal (2015) **36**, 1735–1743
doi:10.1093/eurheartj/ehv110

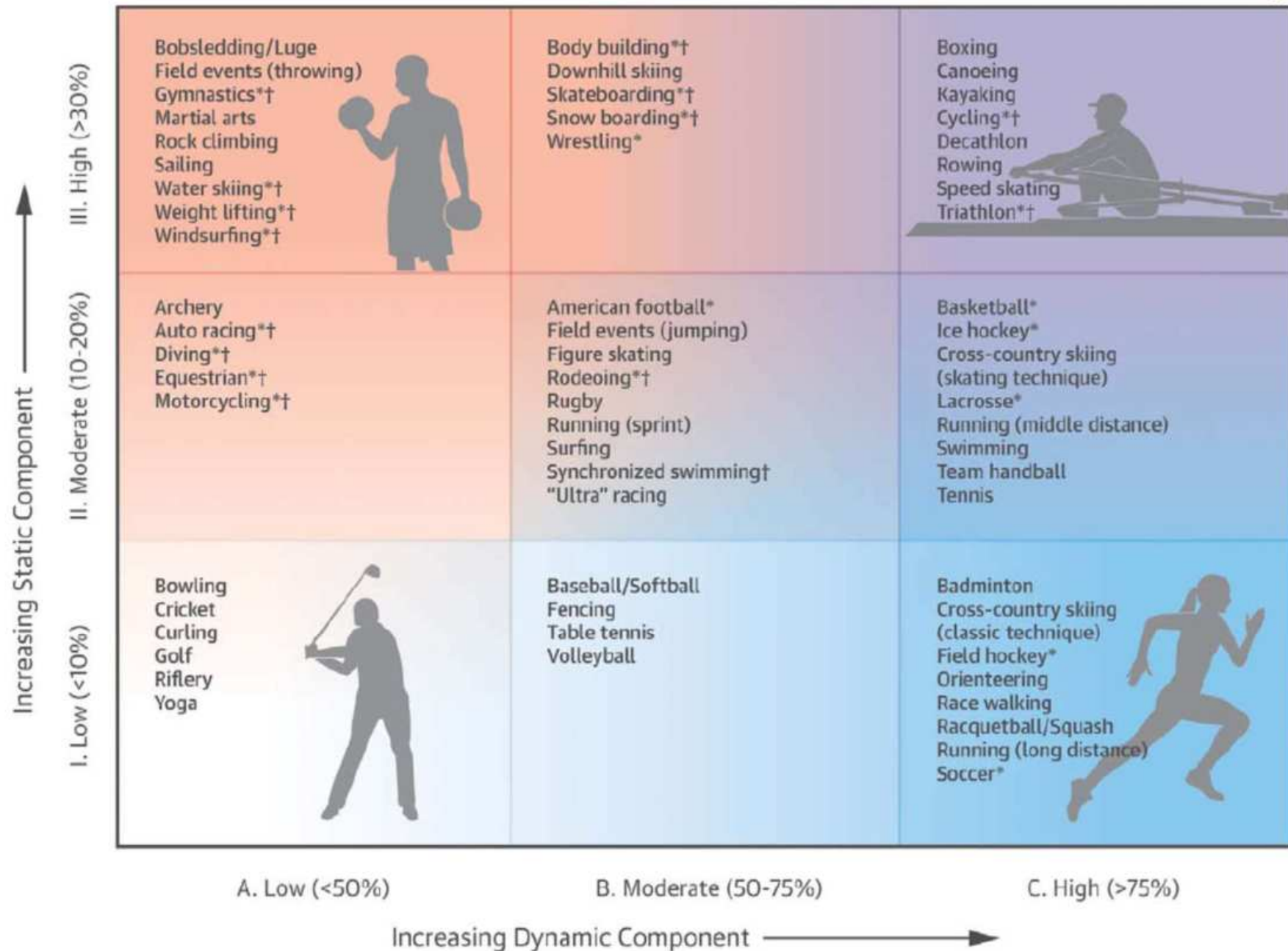
CLINICAL RESEARCH
Arrhythmia/electrophysiology

Association of competitive and recreational sport participation with cardiac events in patients with arrhythmogenic right ventricular cardiomyopathy: results from the North American multidisciplinary study of arrhythmogenic right ventricular cardiomyopathy

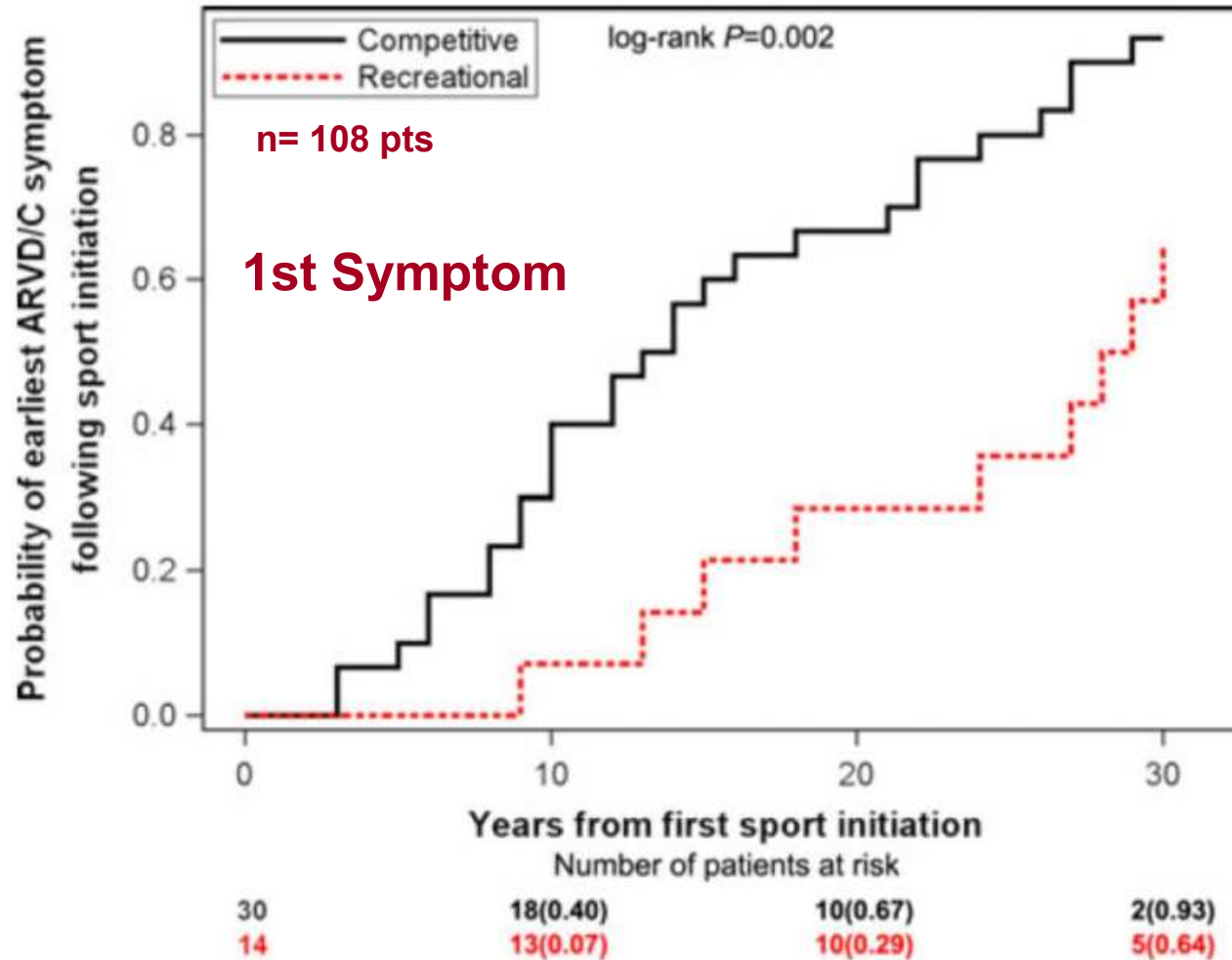
Anne-Christine Ruwald^{1,2*}, Frank Marcus³, N.A. Mark Estes III⁴, Mark Link⁴, Scott McNitt¹, Bronislava Polonsky¹, Hugh Calkins⁵, Jeffrey A. Towbin⁶, Arthur J. Moss¹, and Wojciech Zareba¹

Eur Heart J. 2015;36:1735-43

Sport Types and Levels



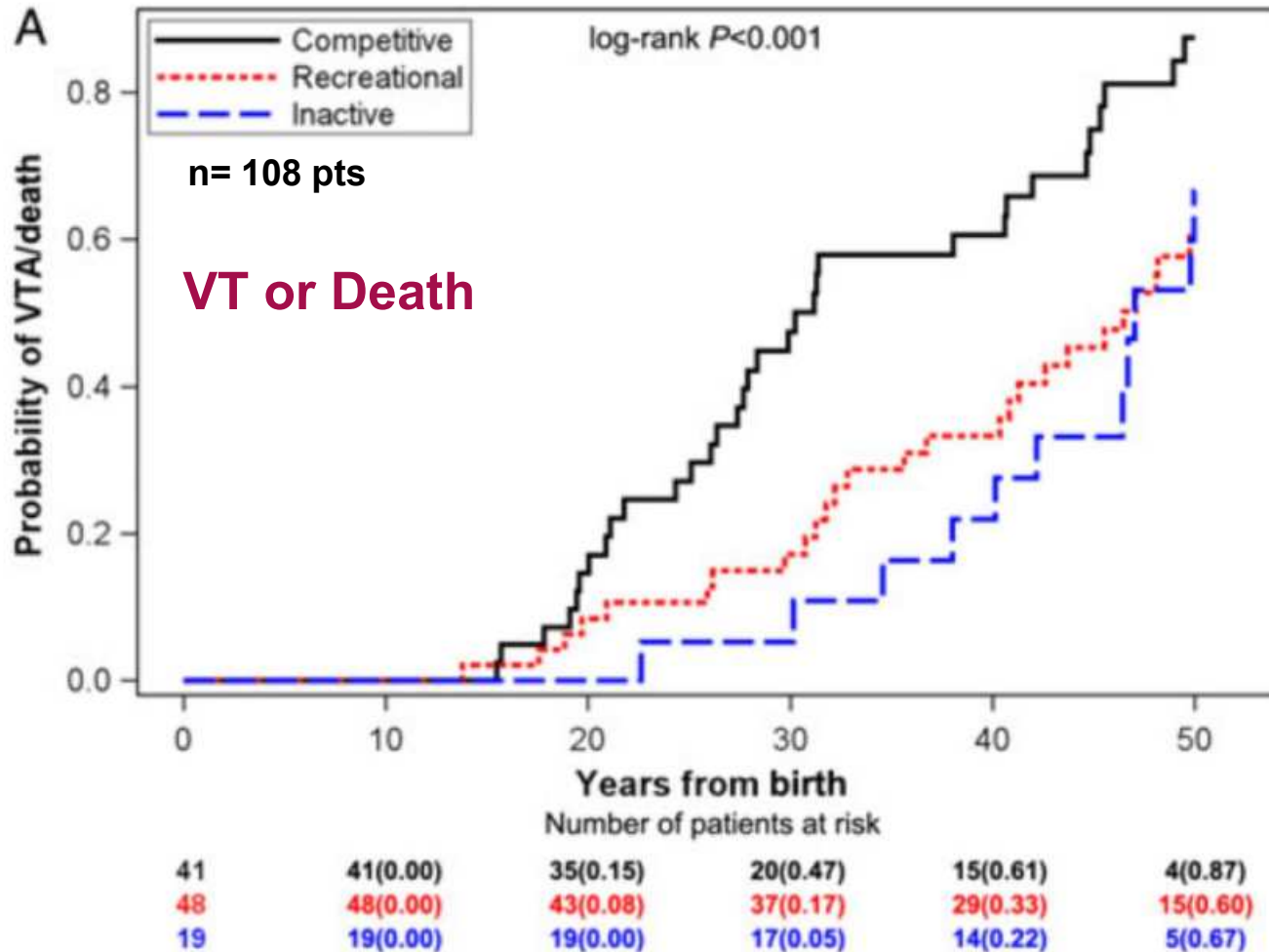
ARVC: Sports Level + Timing to Symptom Onset



Competitive vs. recreational sports:

- Time to 1st symptom is shorter
- Manifestation of ARVC is earlier
- Disease acceleration with competitive sports

ARVC: Sports Level and Prognosis (VT or Death)



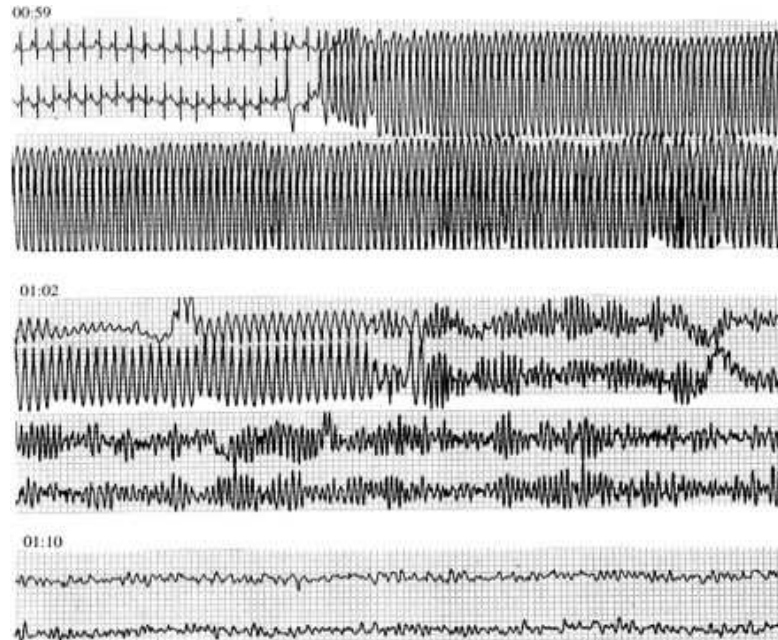
Competitive vs. recreational sports vs. inactive pts:

- Competitive sports triggers arrhythmias
- Recreational sports is not different vs. inactive lifestyle
- Competitive sports discouraged !
- Recreational sports allowed ?

Treatment of VT in ARVC

Natural Course of ARVC

- Risk of VF or fast VT: **early (concealed) phase**
(arrhythmias may precede morphological abnormalities)
- Recurrent monomorphic VT: **overt phase**
- Chronic biventricular heart failure: **end-stage**

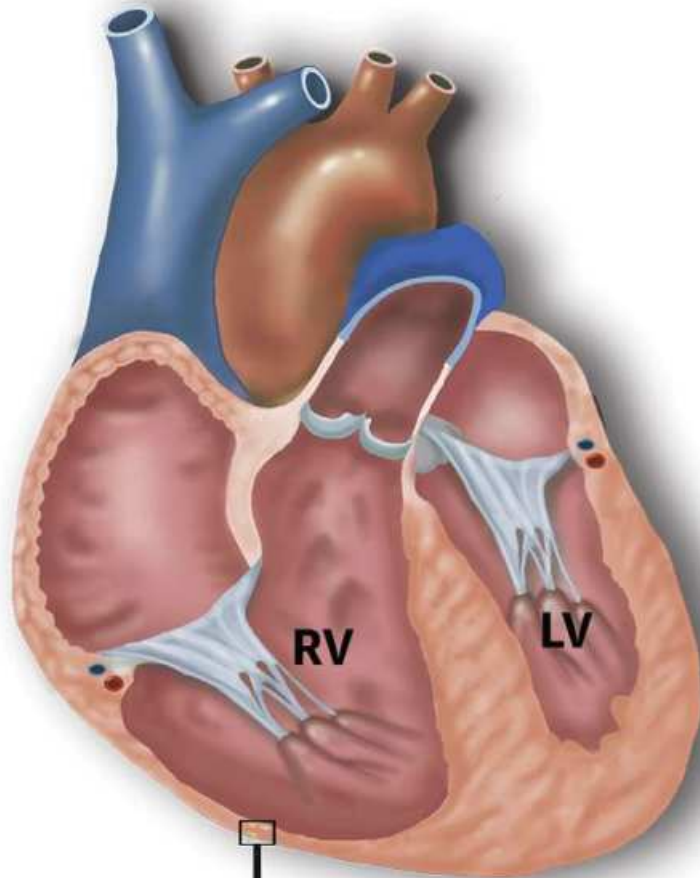


Aziz et al., Circulation. 2000;101;825-827

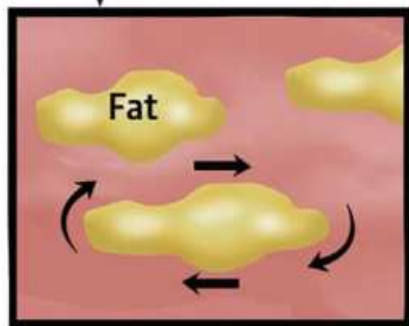
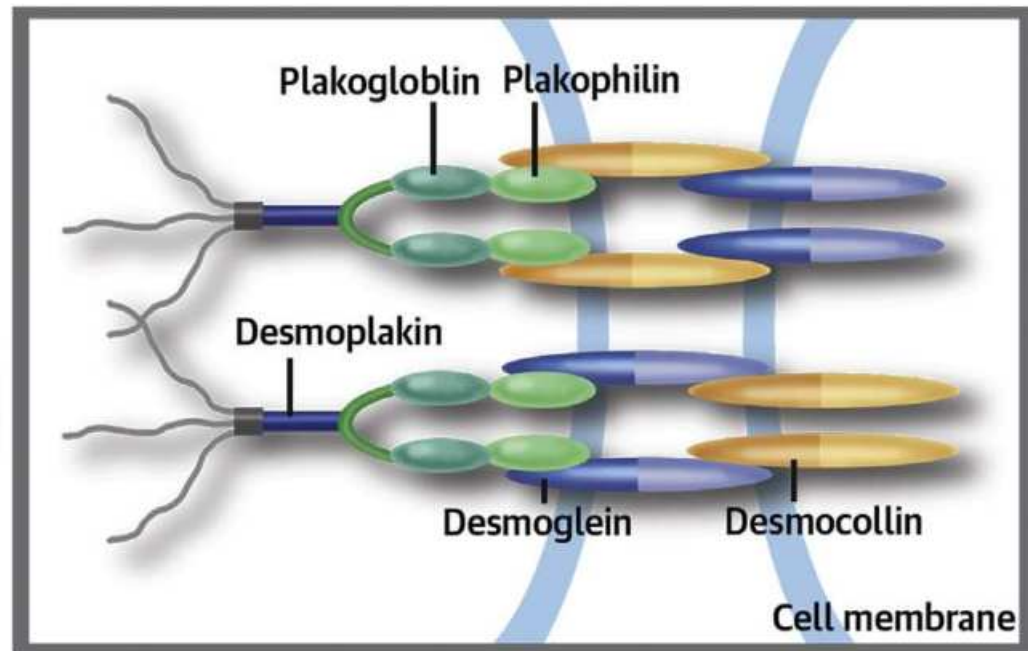


Wichter T et al., 2005

Pathophysiology of ARVC

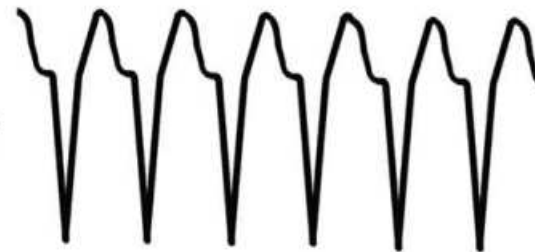


Abnormalities in the following proteins cause ARVC



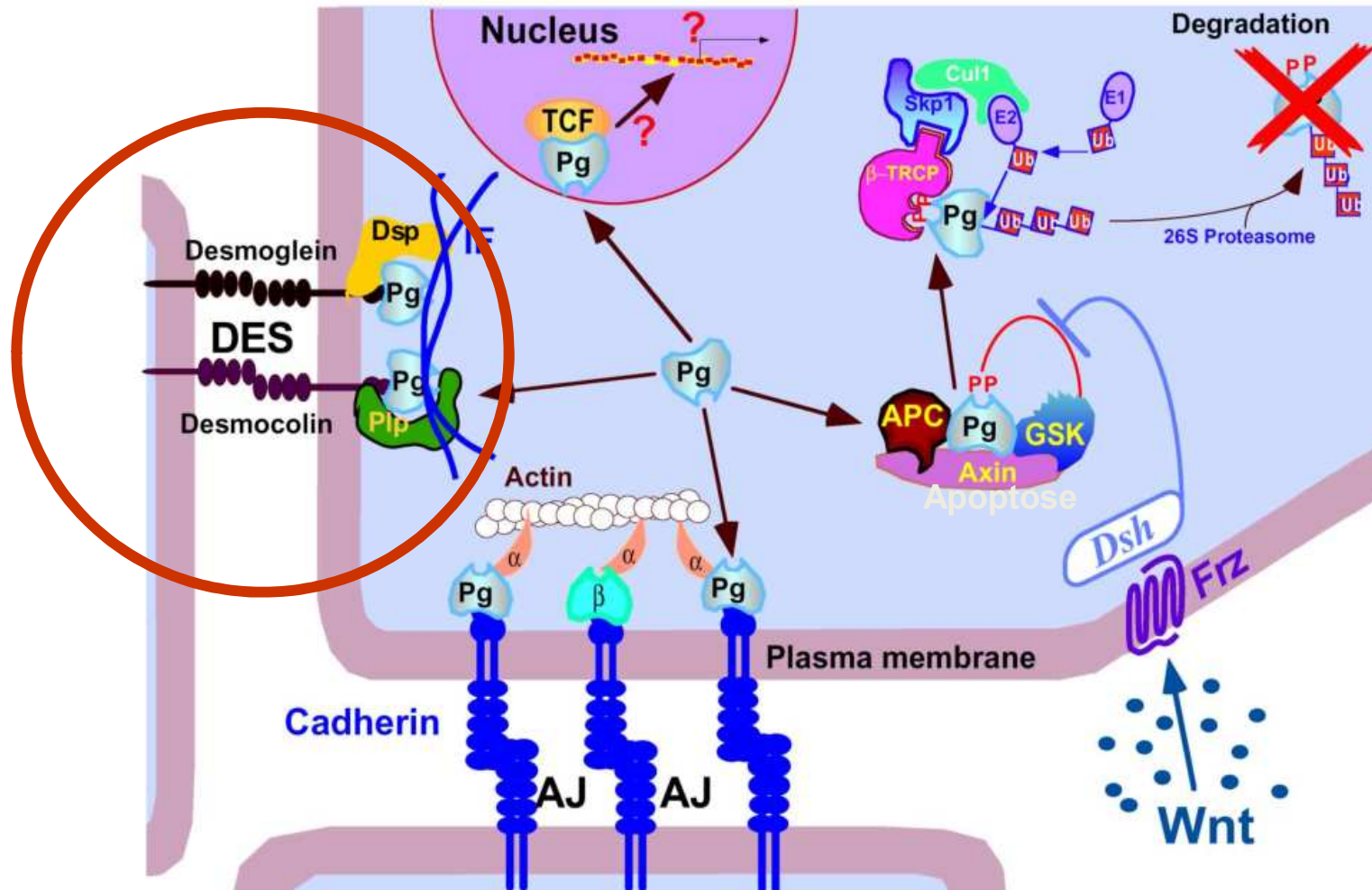
RV wall

Re-entrant VT



Pathophysiology of ARVC

Disease of the Desmosome

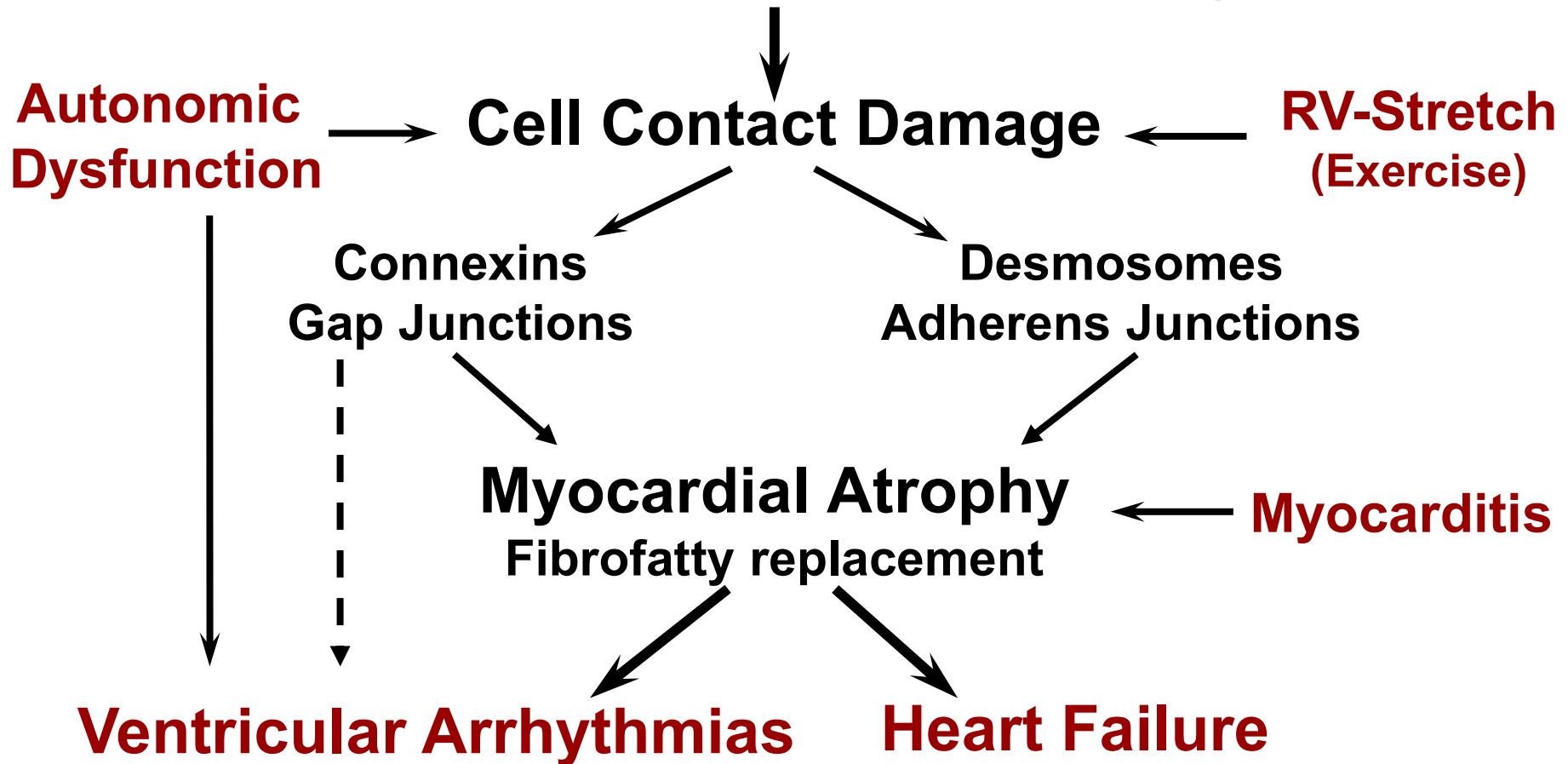




ARVC

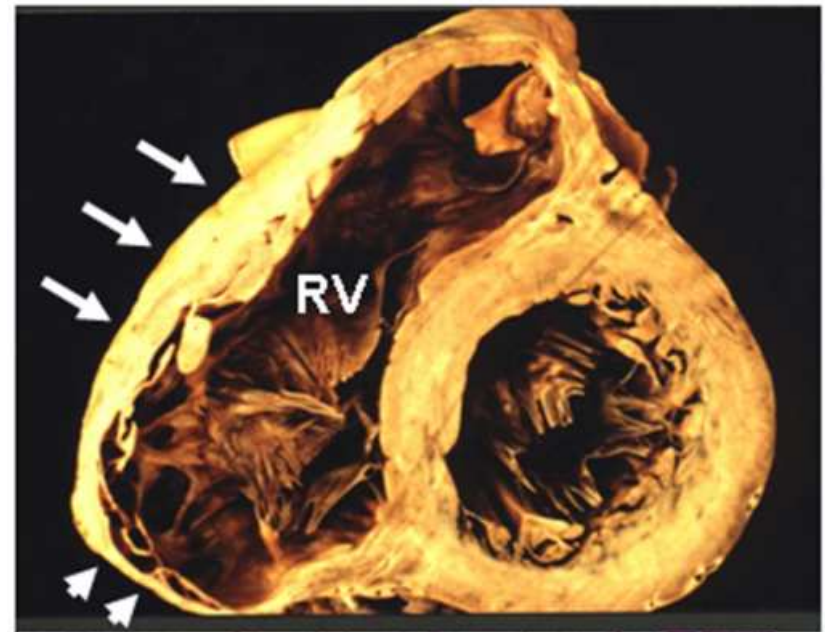
Genetic Disposition

Double/compound mutations, modifier genes



From Risk Stratification to Treatment of ARVC

- **Improve symptoms and quality of life**
 - VT recurrences and palpitations
 - Appropriate and inappropriate ICD discharges
 - Heart failure symptoms and exercise capacity
- **Prevent disease progression**
 - Relevant arrhythmias
 - RV and LV dysfunction
 - Heart failure
- **Reduce mortality**
 - Arrhythmic death
 - Death from heart failure

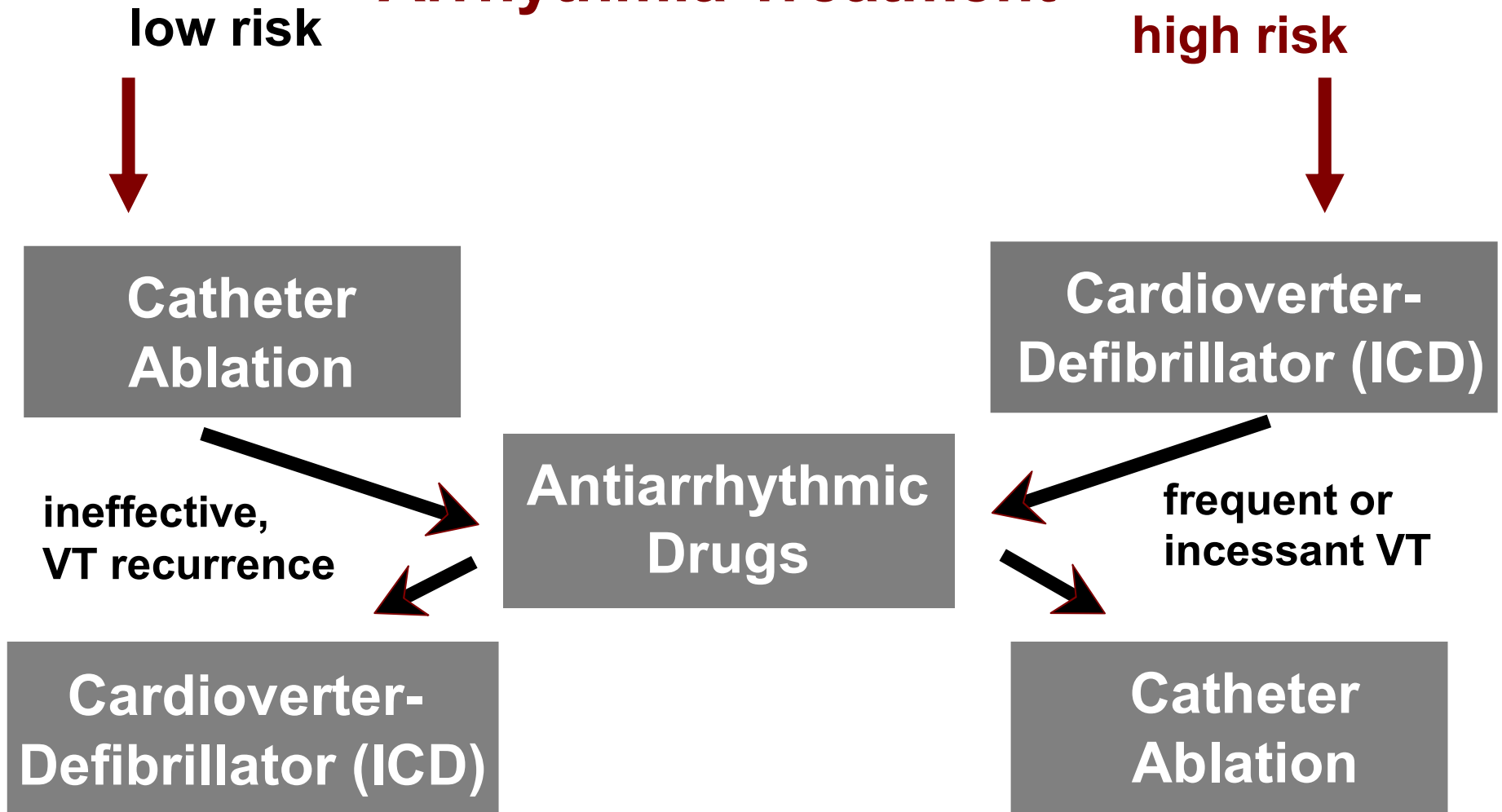


Wichter T et al., 2005

Management of ARVC

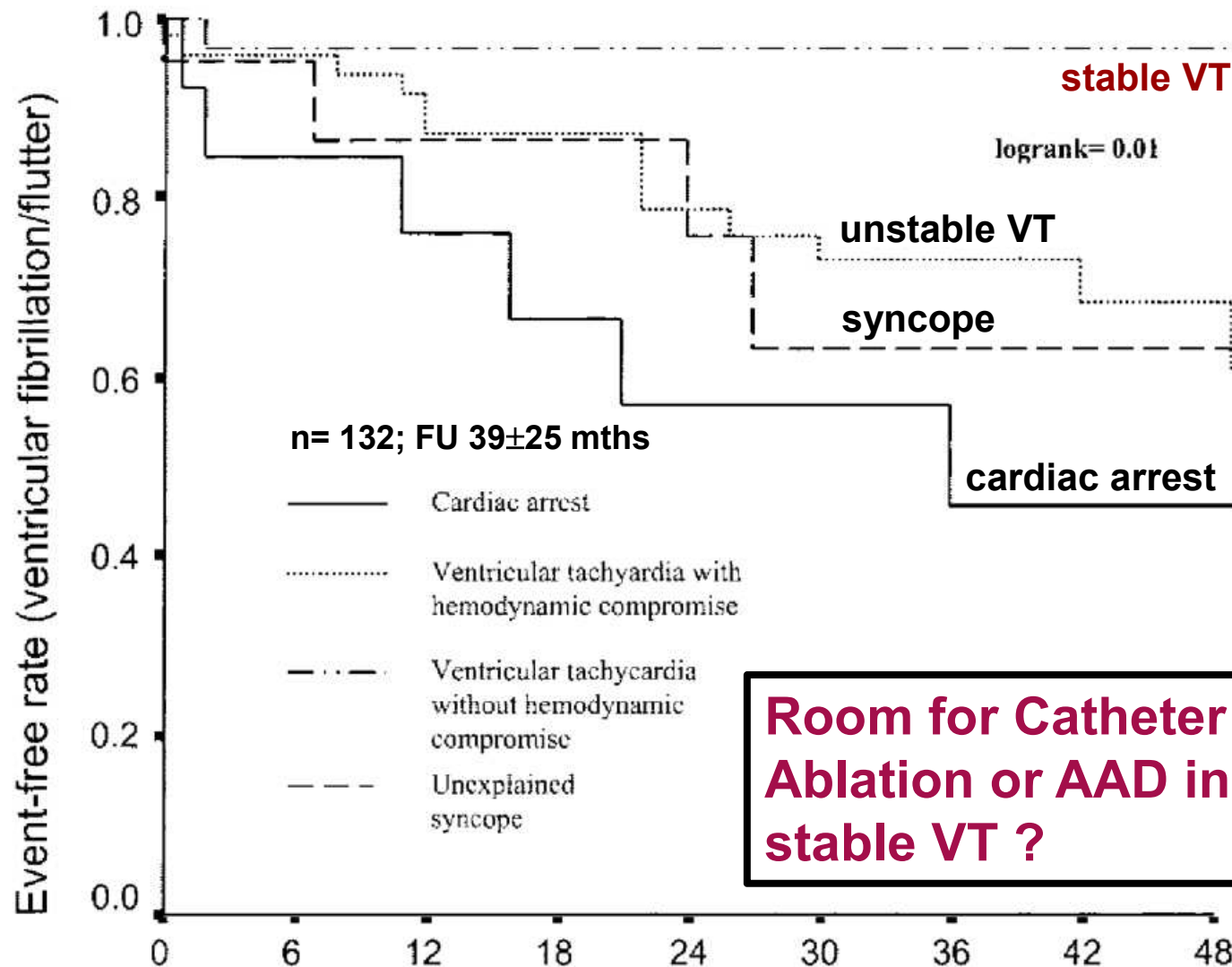


Arrhythmia Treatment



Risk Stratification in ARVC

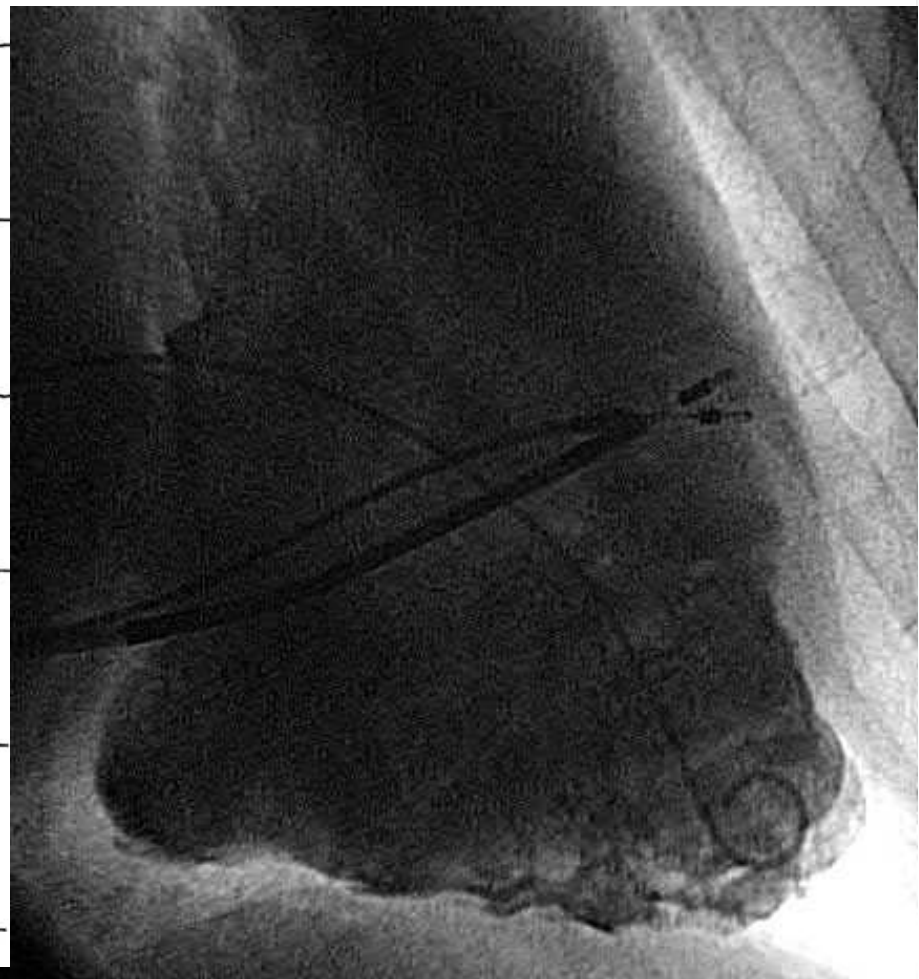
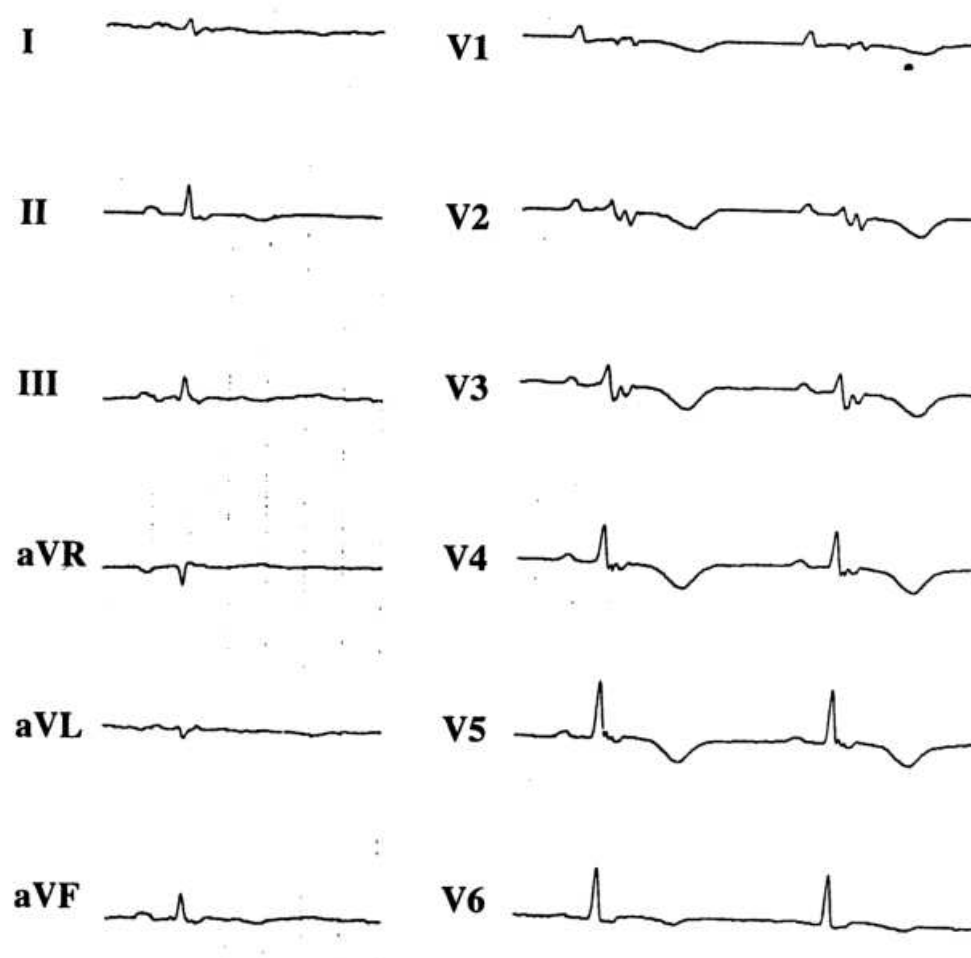
VF / V-flutter after ICD implant



In pts with **stable VT**, there was frequent VT-recurrence but **very rare occurrence of VF or V-flutter**

Severe RV Dysfunction in ARVC

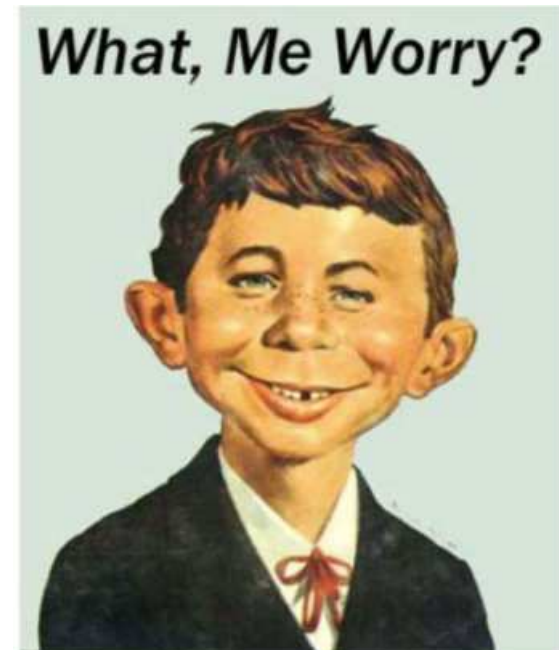
History of VT, sympt. heart failure, LV involvement, T-wave inversion, fragmented QRS, QRS amplitude ratio



Risk Stratification in ARVC

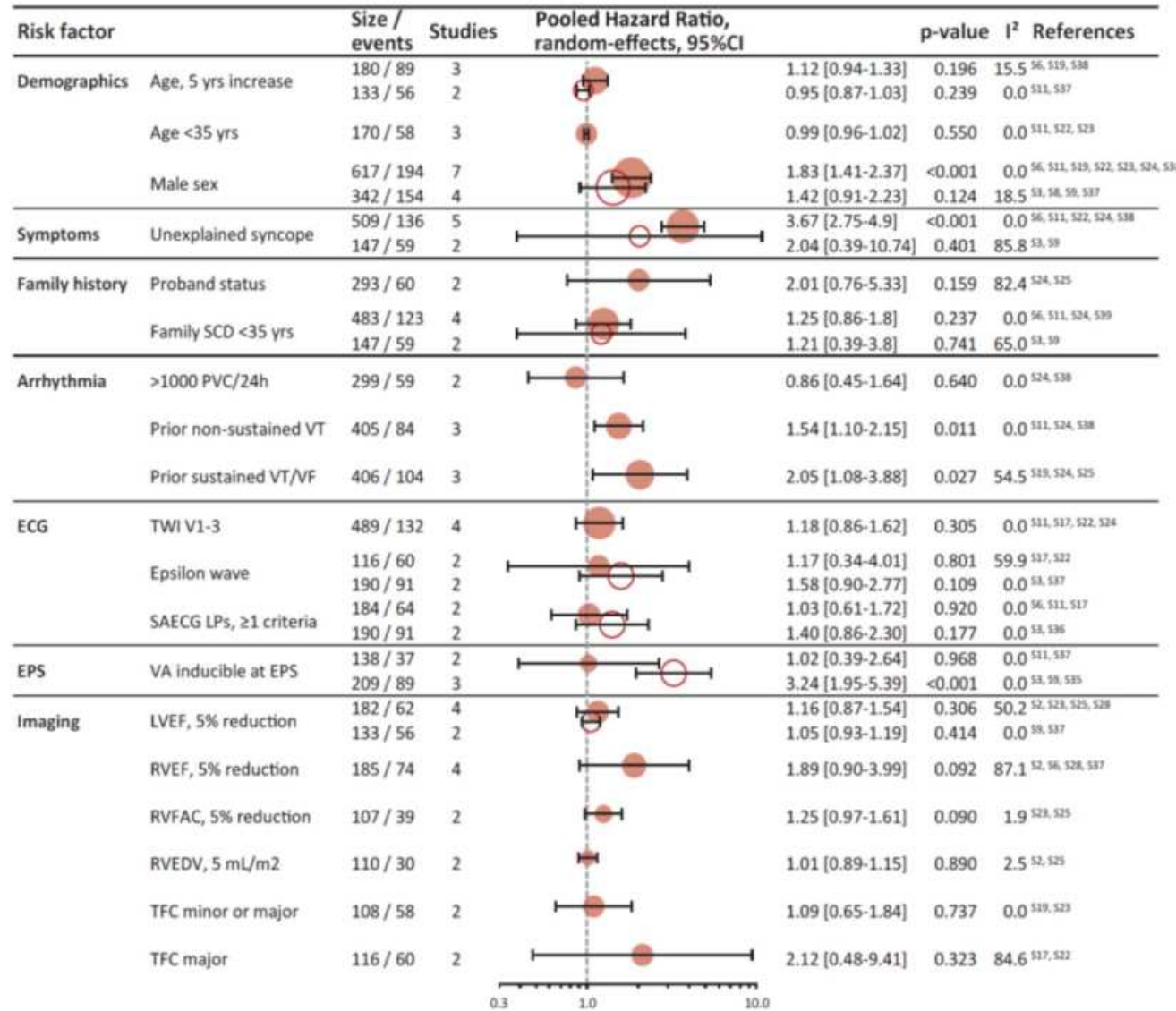
What Risk ?

- Sudden death
- Ventricular tachycardia (VT), Syncope
- ICD shock delivery / clusters
- Heart failure (right, left, biventricular)
- Cardiac transplantation
- Hospitalization (VT, CHF)
- Exercise capacity ↓
- Quality of life ↓ (sports restriction)
- Disease manifestation in mutation carriers
- „Disease labeling“ of asymptomatic mutation carriers



ARVC: Risk Stratification

Meta analysis: no single discriminating factor



● = cohort with definite ARVC patients only (TFC ≥4) ○ = cohort with at least borderline ARVC patients (TFC ≥3)

Age at onset

Syncope unexplained

Proband status

Arrhythmias

- nsVT
- sust. VT / VF

ECG abnormalities

Inducibility at EPS

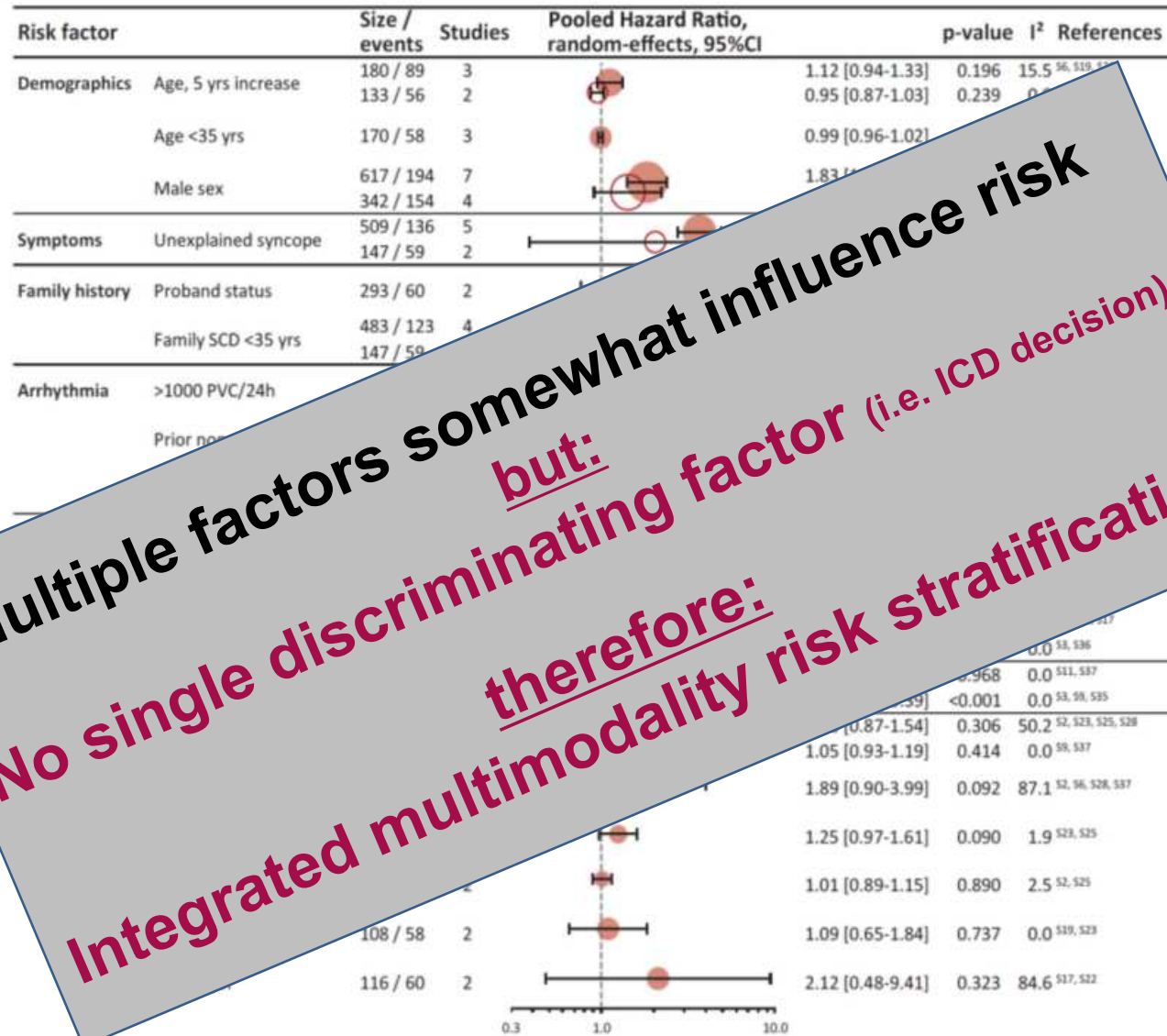
Imaging

- LV dysfunction
- RV dysfunction
- Chamber dilatation

Bosman et al.
Heart Rhythm.
2018;15:1097

ARVC: Risk Stratification

Meta analysis: no single discriminating factor



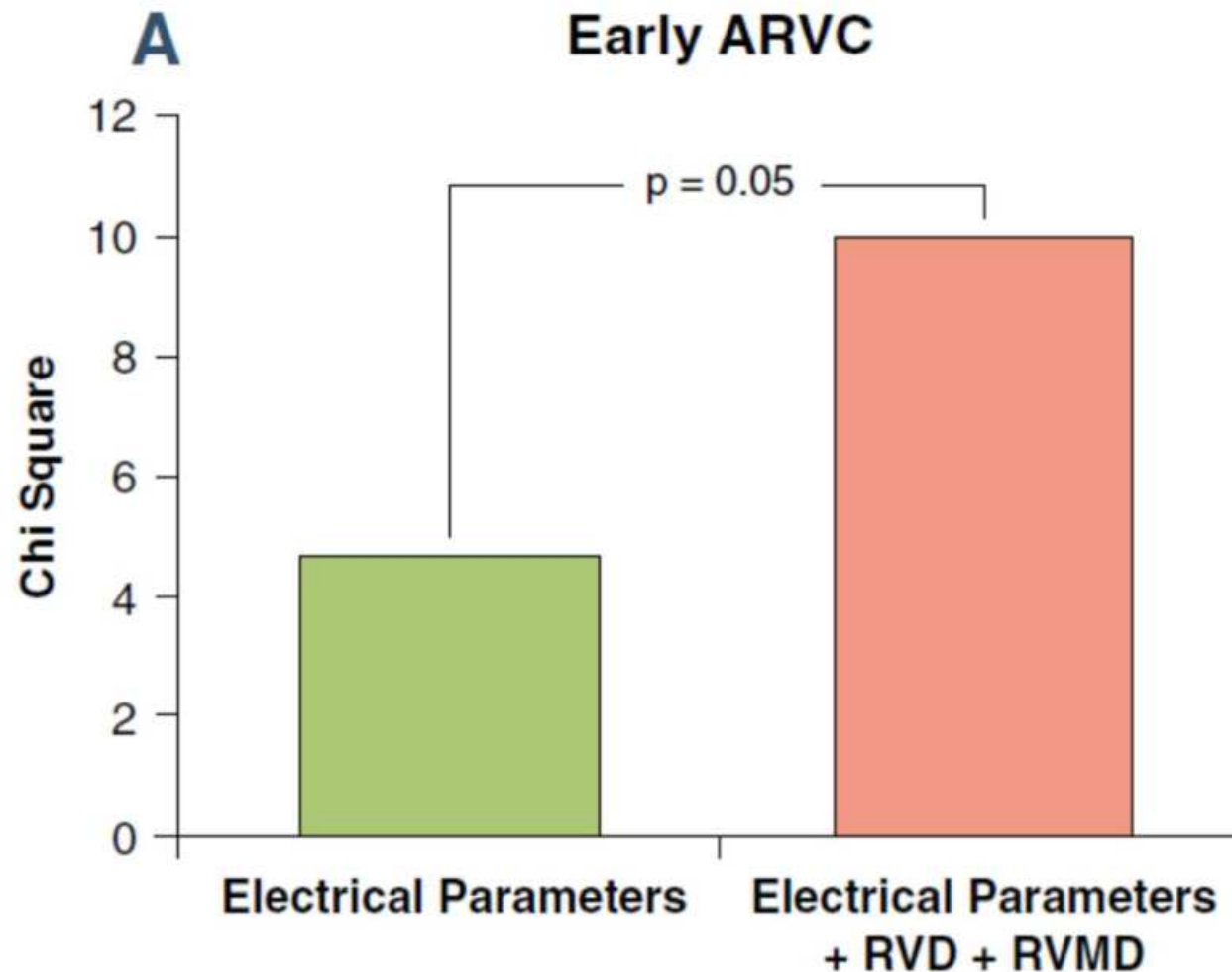
Multiple factors somewhat influence risk
but:
No single discriminating factor (i.e. ICD decision)
therefore:
Integrated multimodality risk stratification

- Age at onset
- Syncope unexplained
- Proband status
- Arrhythmias
- nsVT
- ust. VT / VF
- ECG abnormalities
- Inducibility at EPS
- Imaging
 - LV dysfunction
 - RV dysfunction
 - Chamber dilatation

● = cohort with definite ARVC patients only (TFC ≥4) ○ = cohort with at least borderline ARVC patients (TFC ≥3)

ARVC: Risk Stratification

Combined ECG and Imaging parameters provide best assessment of arrhythmic risk



**Integrated
multimodality
approach !**

ARVC: Risk Stratification

Indications for ICD implantation

2015 ESC Guideline for Management of Ventricular Arrhythmias



European Heart Journal (2015) 36, 2793–2867
 doi:10.1093/eurheartj/ehv316

ESC GUIDELINES

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)

Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC)

Authors/Task Force Members: Silvia G. Priori^{*}(Chairperson) (Italy), Carina Blomström-Lundqvist[†](Co-chairperson) (Sweden), Andrea Mazzanti[†] (Italy), Nico Blom[‡] (The Netherlands), Martin Borggrefe (Germany), John Camm (UK), Perry Mark Elliott (UK), Donna Fitzsimons (UK), Robert Hatala (Slovakia), Gerhard Hindricks (Germany), Paulus Kirchhof (UK/Germany), Keld Kjeldsen (Denmark), Karl-Heinz Kuck (Germany), Antonio Hernandez-Madrid (Spain), Nikolaos Nikolaou (Greece), Tone M. Norekvål (Norway), Christian Spaulding (France), and Dirk J. Van Veldhuisen (The Netherlands)

Risk factors: unexplained syncope, frequent NSVT, family history of premature SD, extensive RV disease, marked QRS prolongation, LGE on MRI (including LV involvement), LV dysfunction and VT induction during EPS.

Recommendations	Class ^a	Level ^b
ICD implantation is recommended in patients with a history of aborted SCD and haemodynamically poorly tolerated VT.	I	C
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
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
Invasive EPS with PVS may be considered for stratification of SCD risk.	IIb	C

ARVC – Risk Stratification

Arrhythmic risk

ICD implantation

Highest
8-10% / year

Aborted SD
Hemodynamically
unstable sustained VT
Syncope

Mandatory

Intermediate
1-2% / year

Hemodynamically stable sustained VT
Nonsustained VT (during Holter/exercise test)

Individualized

Indeterminate

Severe dilatation and/or dysfunction of RV, LV or both
Early onset structurally severe disease (age < 35 years)

Lowest
< 1% / year

Probands or relatives fulfilling Task Force criteria for AC,
regardless of family history of SD or inducibility at PVS
(in the absence of syncope, VT, or severe ventricular dysfunction)

Unjustified

Management of ARVC

Niels-Stensen-Kliniken 
Marienhospital Osnabrück

European Heart Journal Advance Access published July 27, 2015



European Heart Journal
doi:10.1093/eurheartj/ehv162

CURRENT OPINION

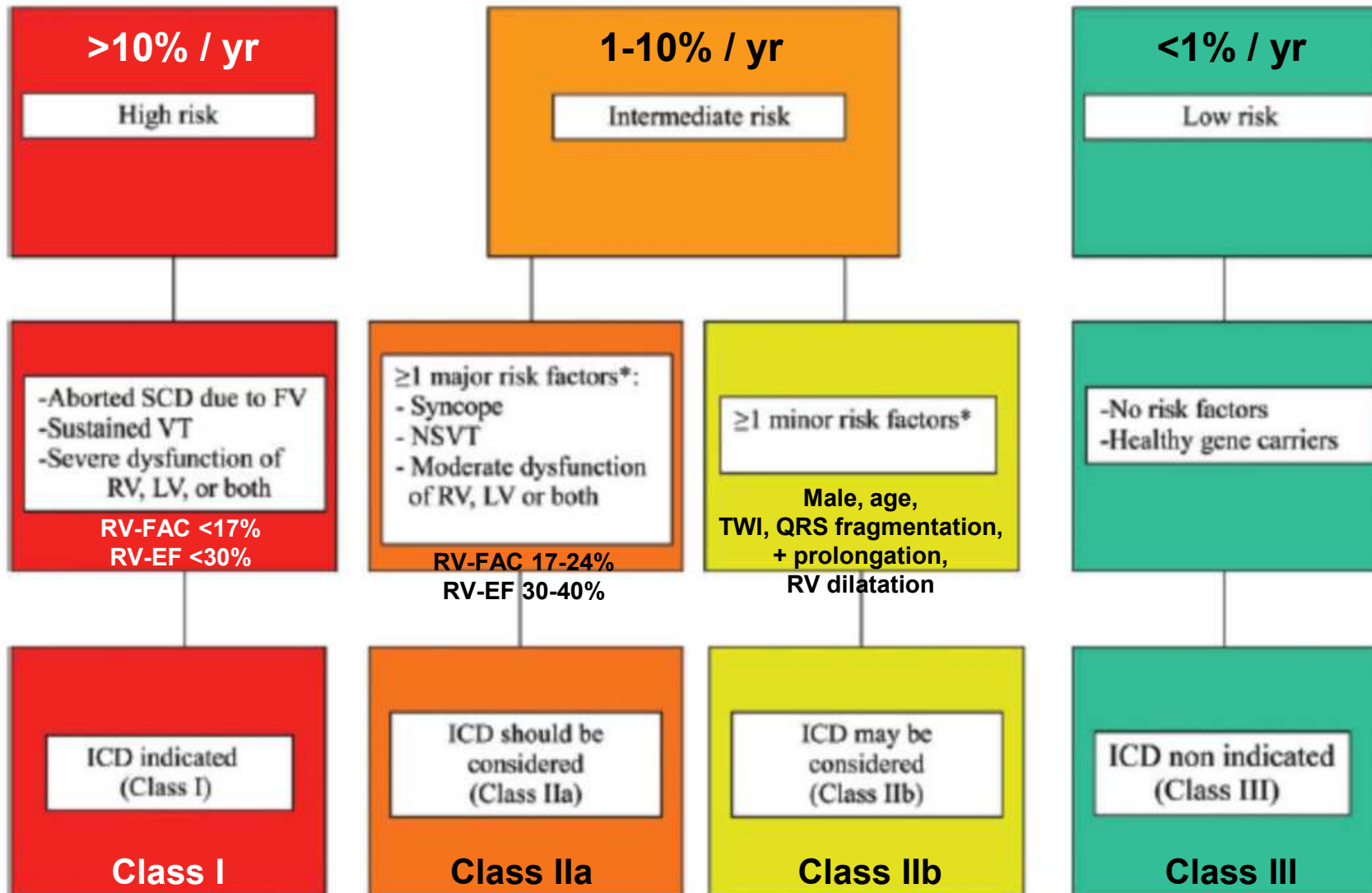
Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement

Domenico Corrado^{1*}, Thomas Wichter², Mark S. Link³, Richard Hauer⁴, Frank Marchlinski⁵, Aris Anastasakis⁶, Barbara Bauce¹, Cristina Basso¹, Corinna Brunckhorst⁷, Adalena Tsatsopoulou⁸, Harikrishna Tandri⁹, Matthias Paul¹⁰, Christian Schmied⁷, Antonio Pelliccia¹¹, Firat Duru⁷, Nikos Protonotarios⁸, NA Mark Estes III³, William J. McKenna¹², Gaetano Thiene¹, Frank I. Marcus¹³, and Hugh Calkins⁹

Eur Heart J. 2015;36: online July 27

ICD Indication in ARVC

2015 Task Force Consensus on ARVC Treatment

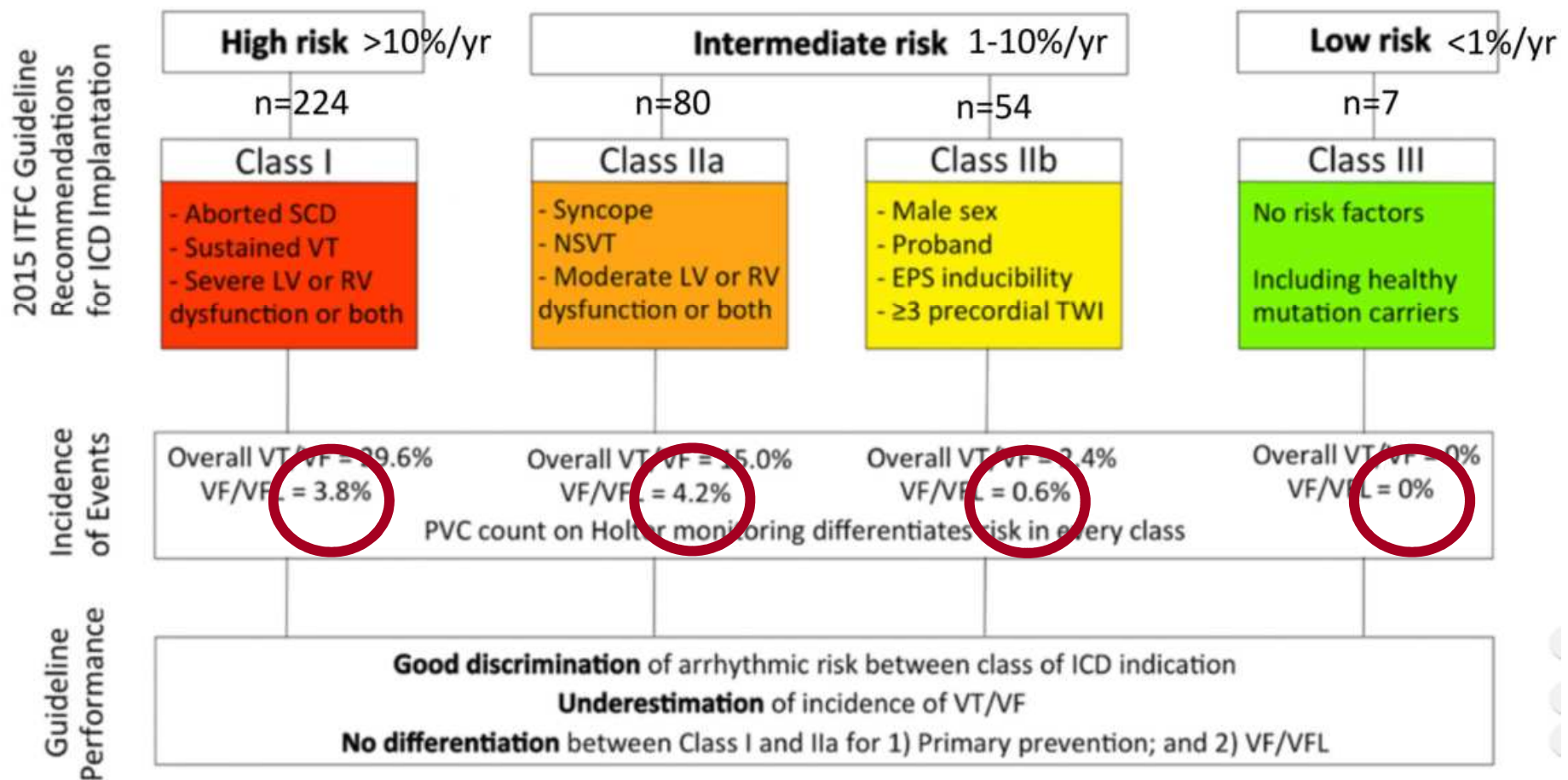


ARVC: Risk Stratification

Indications for ICD implantation

2015 ESC Guideline for Management of Ventricular Arrhythmias

Validation of 2015 Task Force



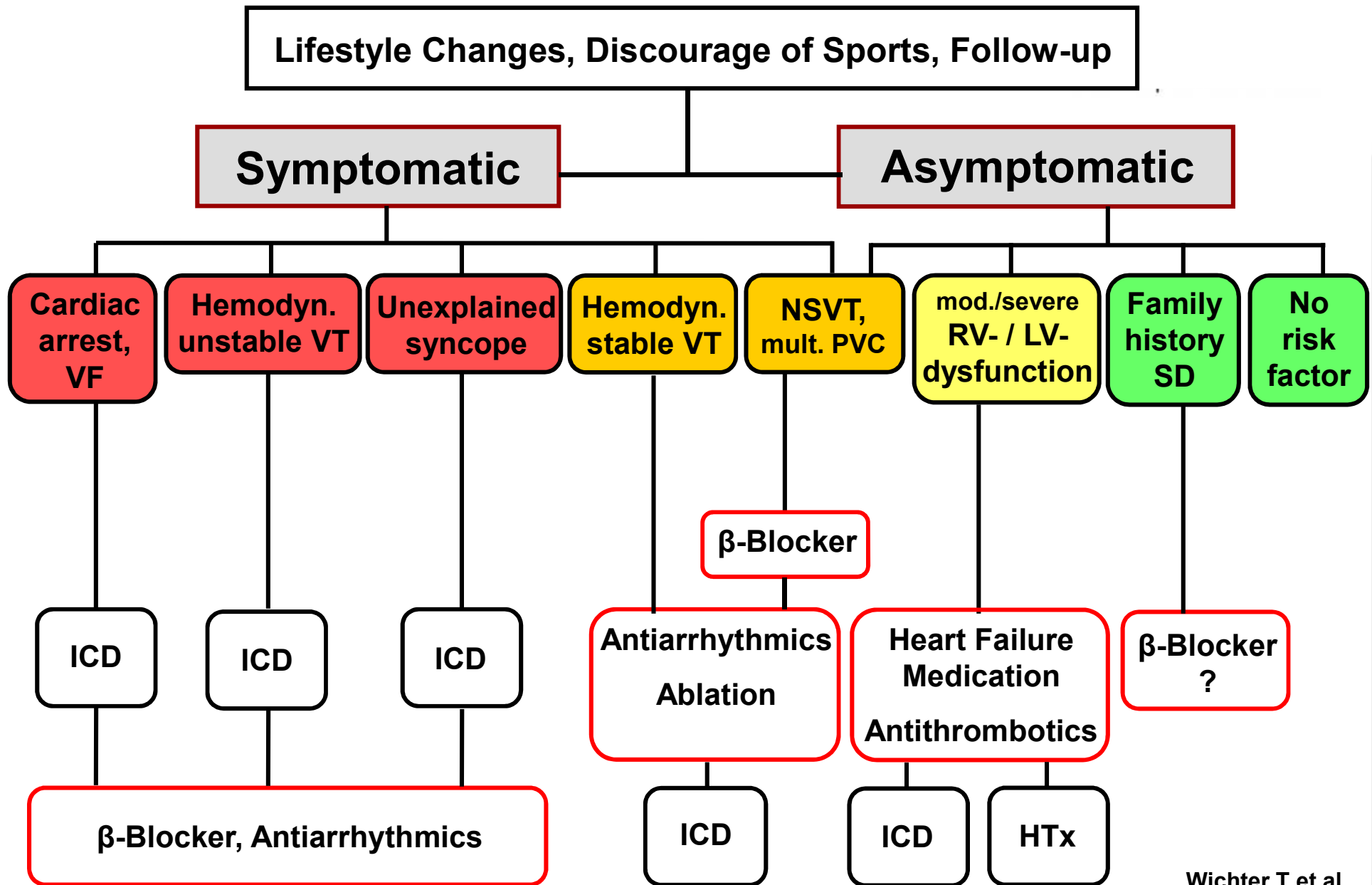
ARVC: Risk Calculator (work in progress)

Collaboration of 14 centers

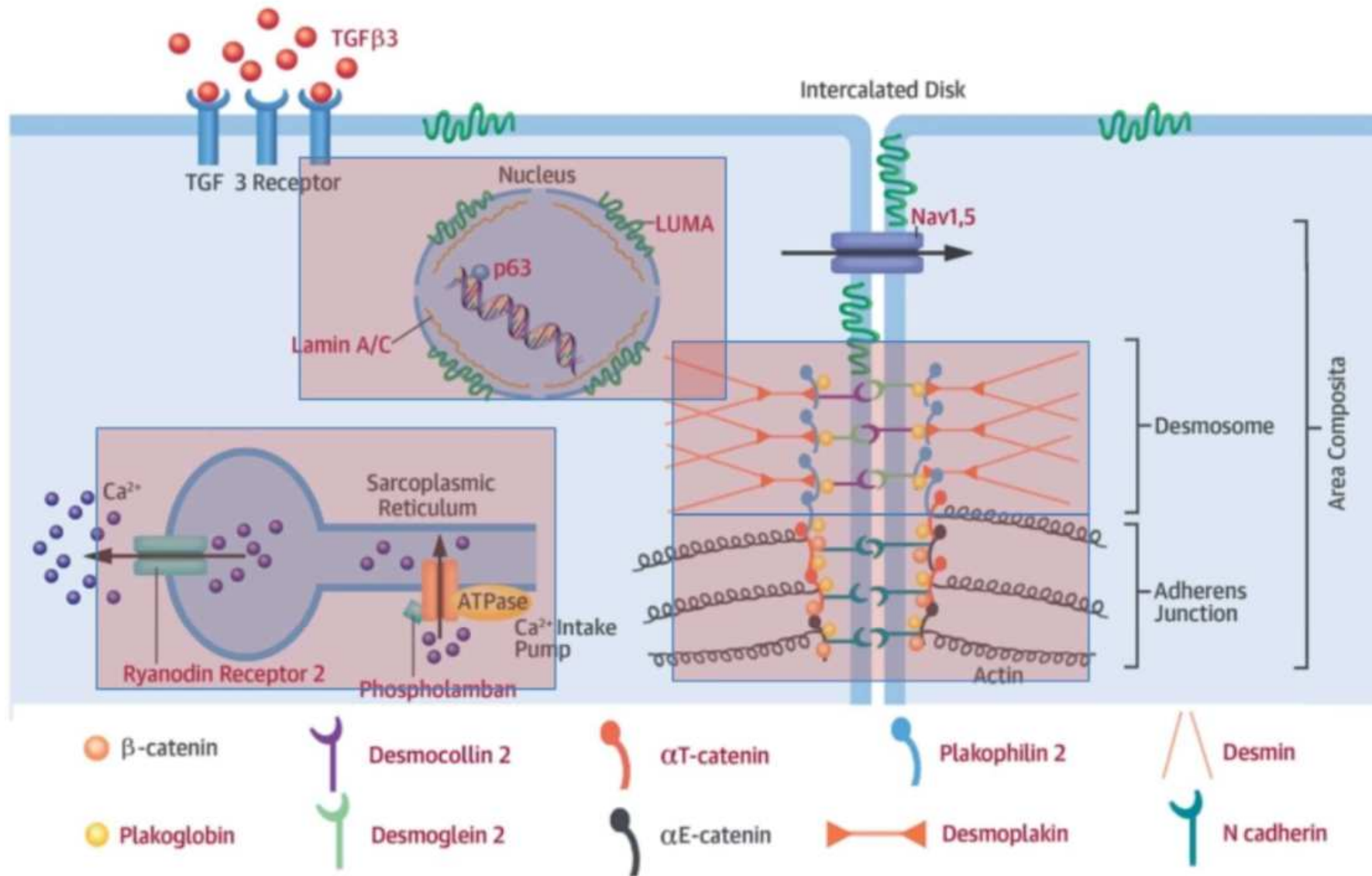
Weighing risk factors from MV analysis

Predictor	Univariate		Multivariable Final prediction model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Male Sex	1.74 (1.26-2.40)	< 0.01	1.46 (0.93-2.28)	0.10
Age (per year increase)	0.98 (0.97-0.99)	< 0.01	0.97 (0.96-0.99)	< 0.01
Recent syncope (<6 months prior to and <1 year after diagnosis)	2.66 (1.74-4.08)	< 0.01	2.20 (1.20-4.02)	0.01
Prior Non-sustained VT	3.17 (2.13-4.71)	< 0.01	1.97 (1.20-3.21)	0.01
24 h. PVC count (ln)*	1.36 (1.21-1.53)	< 0.01	1.20 (1.05-1.37)	0.01
Leads with T-wave inversion anterior + inferior (per lead increase)	1.19 (1.10-1.28)	< 0.01	1.10 (0.99-1.21)	0.08
Right ventricular ejection fraction (per % decrease)	1.04 (1.03-1.06)	< 0.01	1.02 (1.01-1.05)	0.03
Survival probability at 1 year ($S_0(t)$)	0.93			

Treatment of ARVC



ARVC: Target-Directed Therapies ?



Gandjbakhch, E. et al. J Am Coll Cardiol. 2018;72(7):784-804.

Treatment of ARVC: Summary and Recommendations

- **Correct ARVC diagnosis** (detailed clinical evaluation / FU)
- **Confirmatory genetic testing is controversial** (may be misleading)
- **Restriction of competitive sports** (recreational sports allowed?)
- **Preparticipation screening reduces SCD in athletes**
- **Beta-blockers generally recommended** (although not proven)
- **Catheter Ablation (and AAD) to suppress symptomatic VT**
- **ICD implantation is indicated in high risk pts** (class I, IIa)
- **Risk stratification requires further refinement** (calculator?)
- **Most recommendations at „consensus“ level „C“**
- **Complex treatment decisions remain highly individual**
- **Target-directed therapies are yet to come**

ESC Congress 2018, Munich (DE), Aug 24-29, 2018

Symposium: **ARVC: from pathology to prognosis**



Treatment of ARVC ...
... Current Standards and Future Perspectives

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