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

Niels-Stensen-Kliniken
Marienhospital Osnabrück

Symposium: ARVC: from pathology to prognosis

Treatment of ARVC …

… Current Standards and Future Perspectives

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Professor of Medicine (Cardiology)

Dept. of Internal Medicine / Cardiology
Heart Center Osnabrück / Bad Rothenfelde

Niels-Stensen-Kliniken, Marienhospital
Osnabrück, Germany (DE)

No Conflict of Interest
Nothing to Disclose

Diagnostic Criteria of ARVC

International ARVC Task Force (2010)

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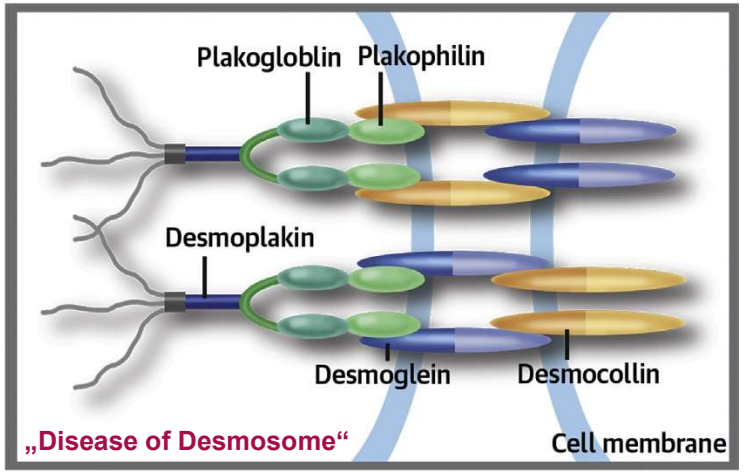
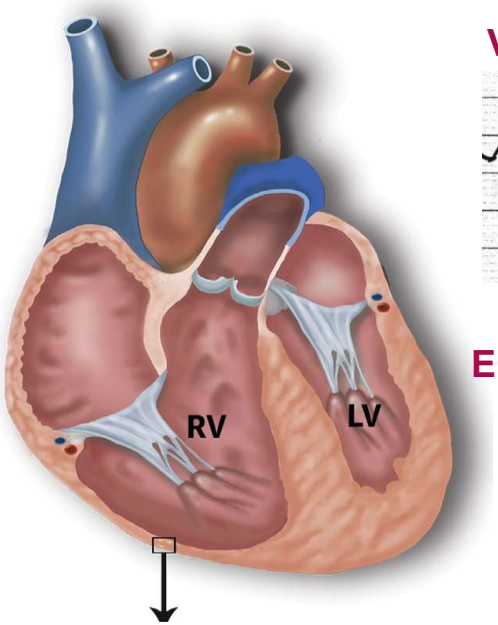
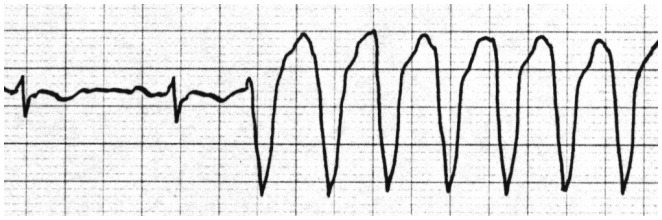
Genetics and Family History

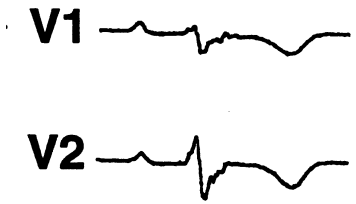




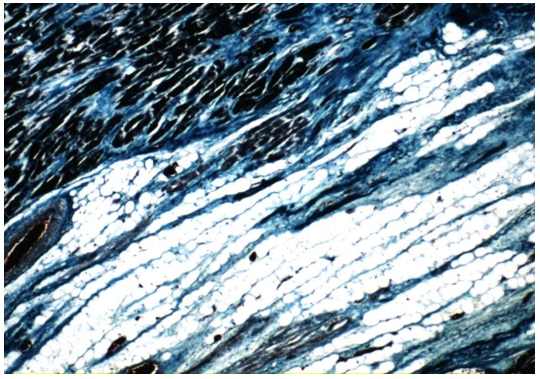
Ventricular Arrhythmias (LBBB-VT)



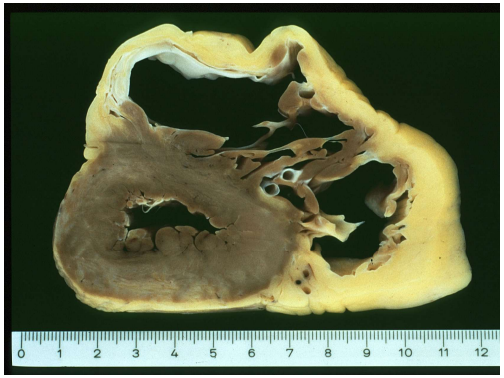
ECG: Depolarization + Repolarization



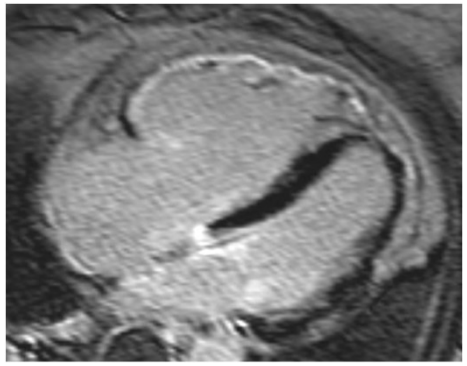
Tissue Characterization



Pathology



RV-/LV- Wall Motion + Structure



What is ARVC ?

Be aware of clinical features

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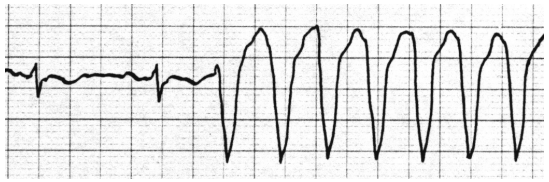
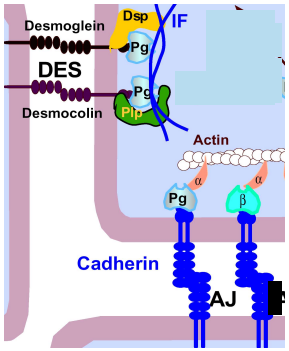
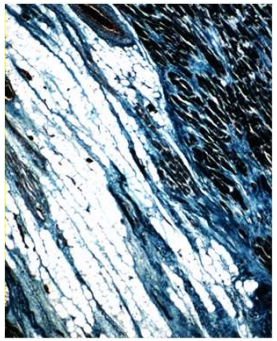
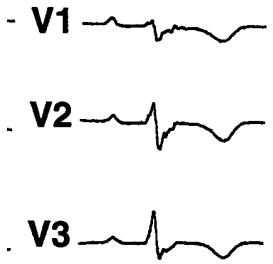
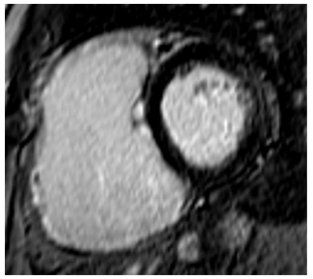
- Young, apparently healthy pts
- Ventricular arrhythmias (LBBB pattern)
- Exercise provocable arrhythmias
- High prevalence in athletes
- Family history (ARVC, unexplained SCD)
  - Genetic background (desmosomal proteins)
- Right precordial ECG abnormalities
  - T-wave inversion, QRS prolongation, ε-waves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

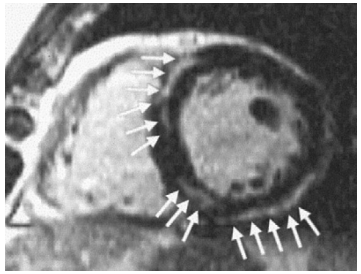












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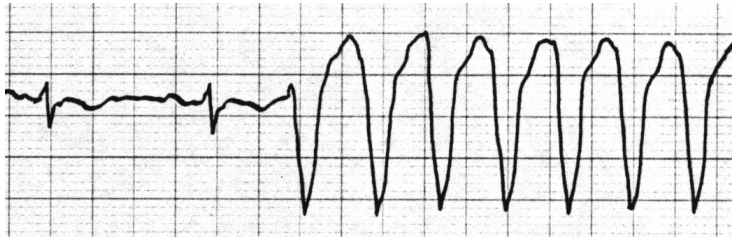
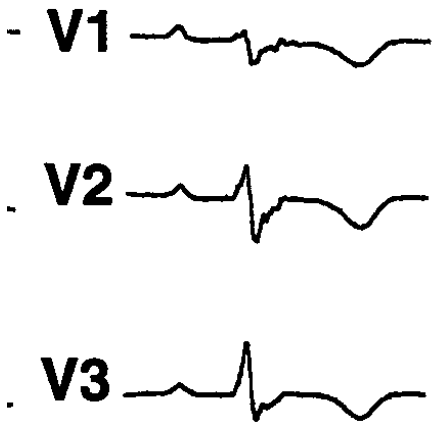
ARVC: Clinical Features

- Young, apparently healthy pts
- Ventricular arrhythmias of LBBB morphology
- Exercise provocable 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… ?

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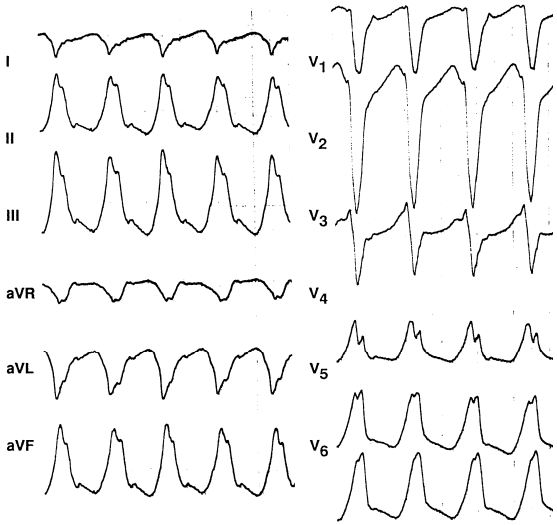
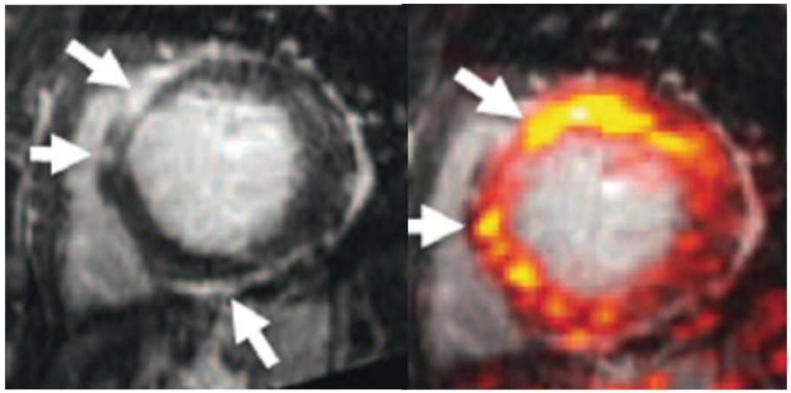
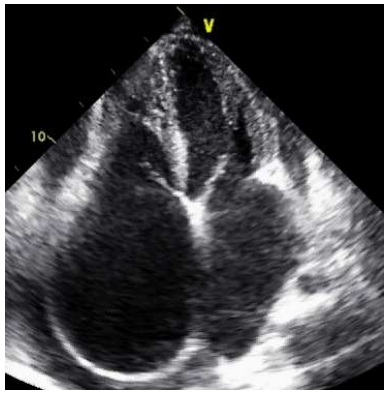


Idiopathic RVO-VT

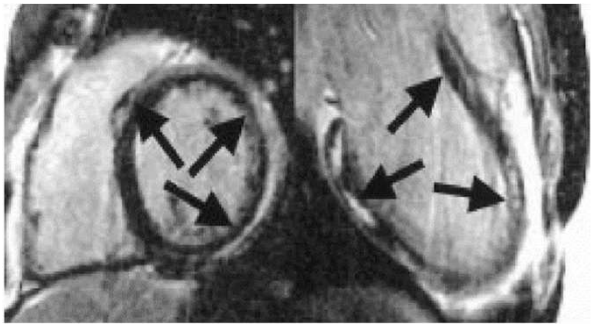


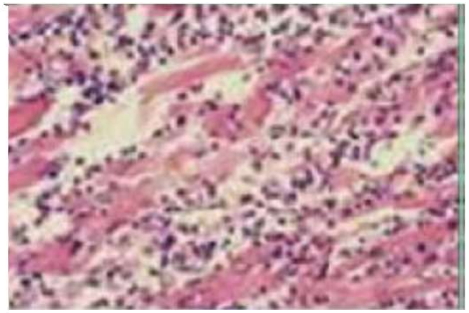
Cardiac Sarcoidosis



Restrictive CM

Make the correct diagnosis
for specific therapy !





Myocarditis (acute / chronic)

ARVC: a rare disease….

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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 …

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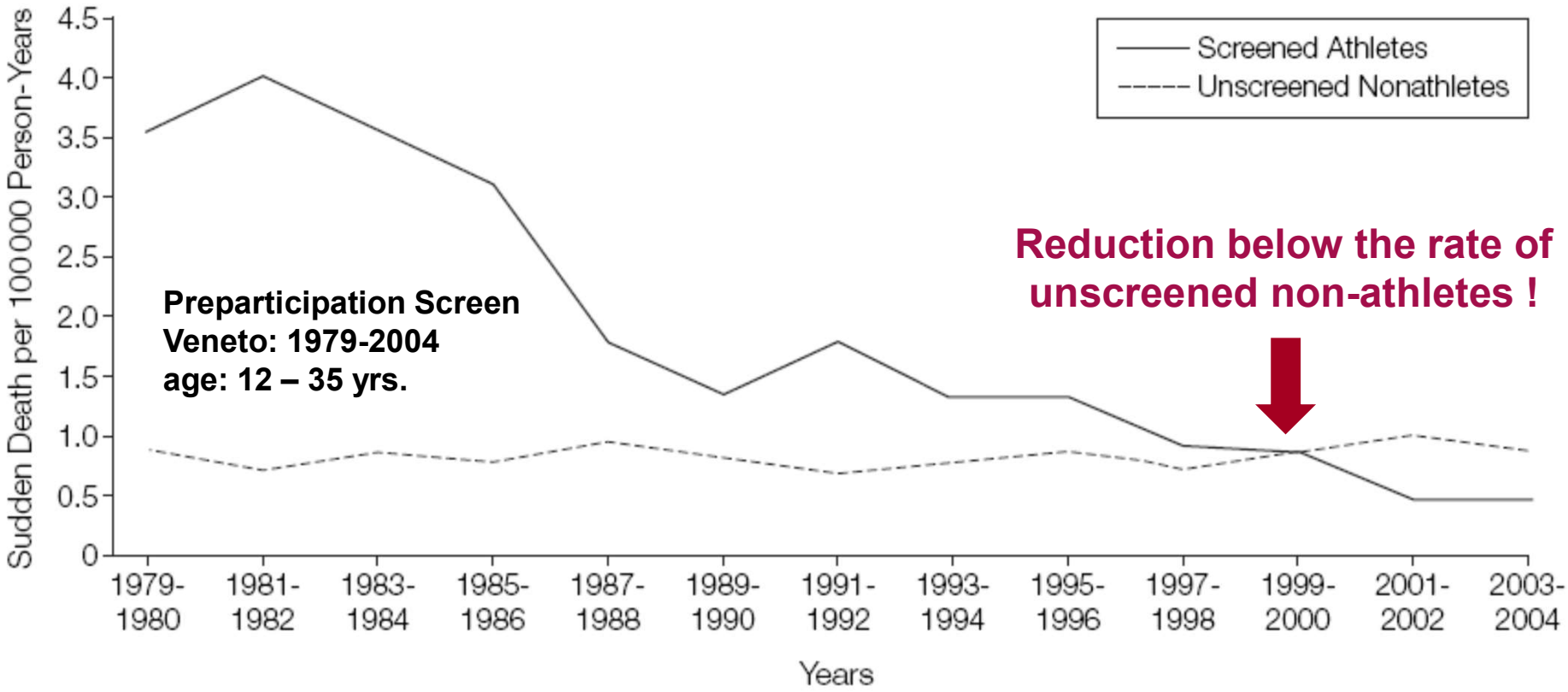
Preparticipation Screening of Athletes

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



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

European Heart Journal
doi:10.1093/eurheartj/ehv316

ESC GUIDELINES

brück

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

Priori S et al., Eur Heart J. 2015;36:online Aug 29, 2015

Pathophysiology of ARVC

Role of Exercise + Training

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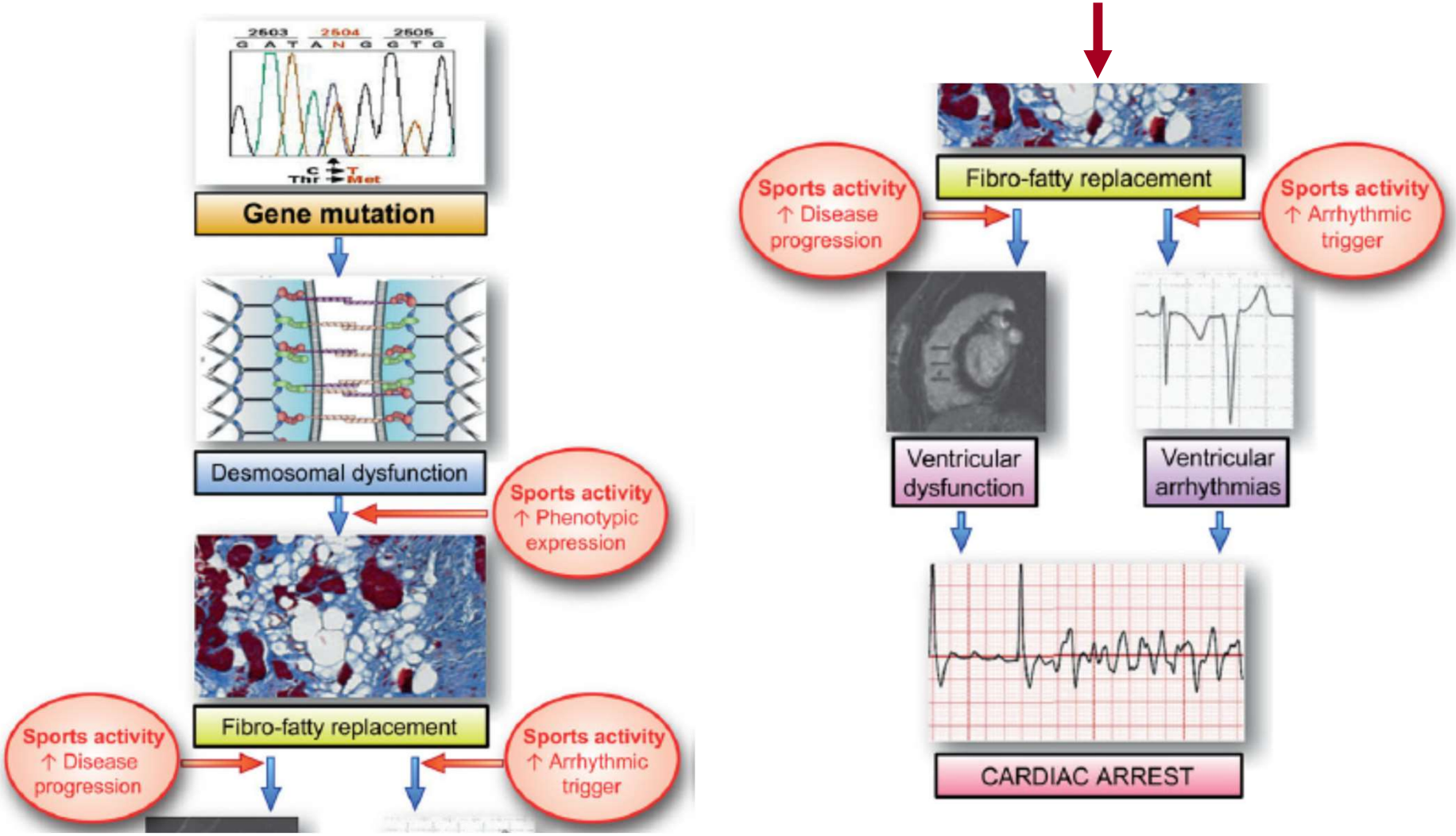

Corrado D et al. Eur Heart J. 2015; May 12

Exercise and RV-Dysfunction

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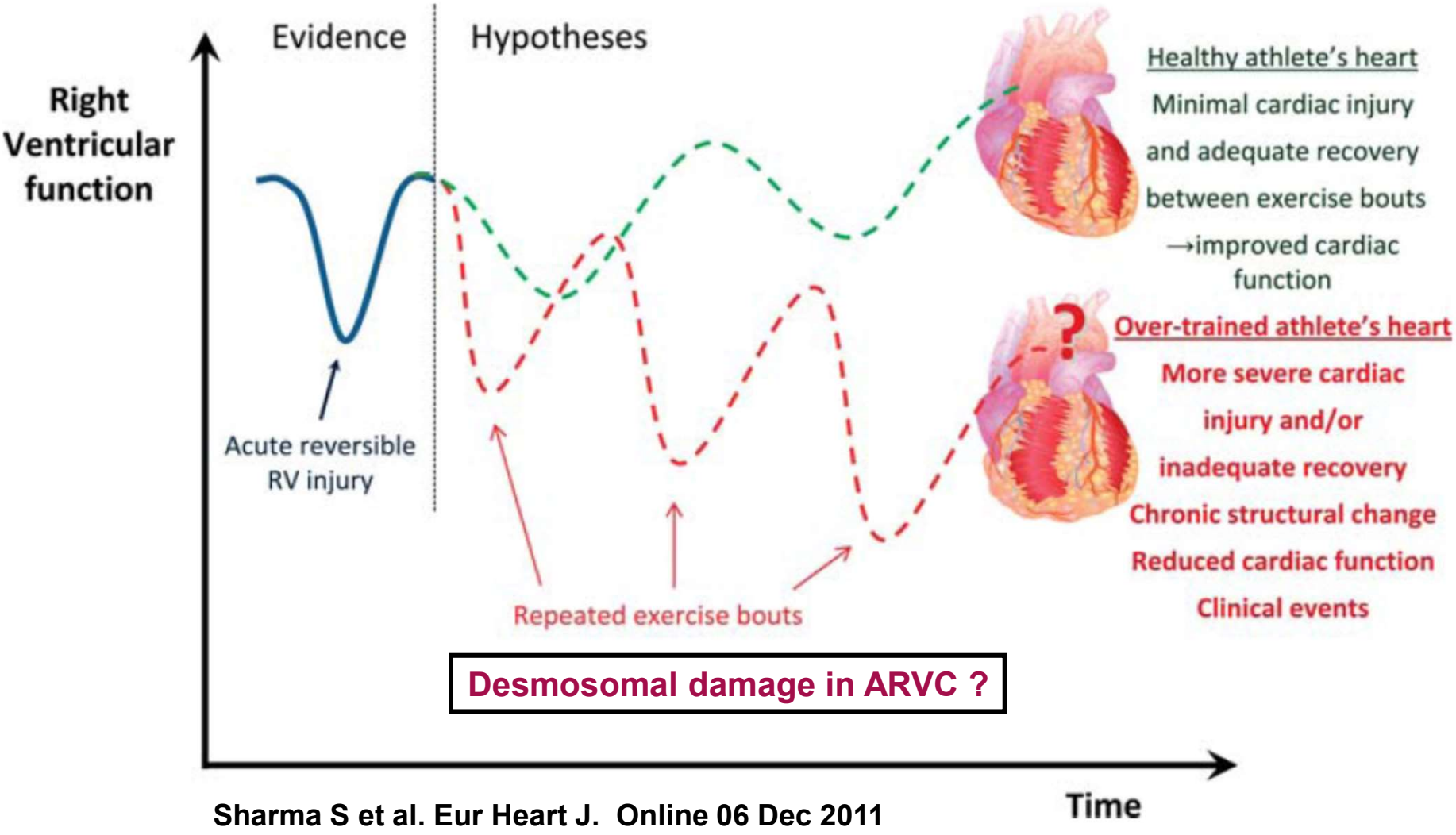

Desmosomal damage in ARVC ?

Sharma S et al. Eur Heart J. Online 06 Dec 2011

ARVC Mouse Model (JUP -/+) :

Impact of Exercise + Training

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Plakoglobin deficient (- / +) mouse model

Treadmill - Training
139 ± 16 km distance / week

Swim - Training
10 – 90 min/ day

ARVC Mouse Model (JUP -/+)

Exercise accelerates …

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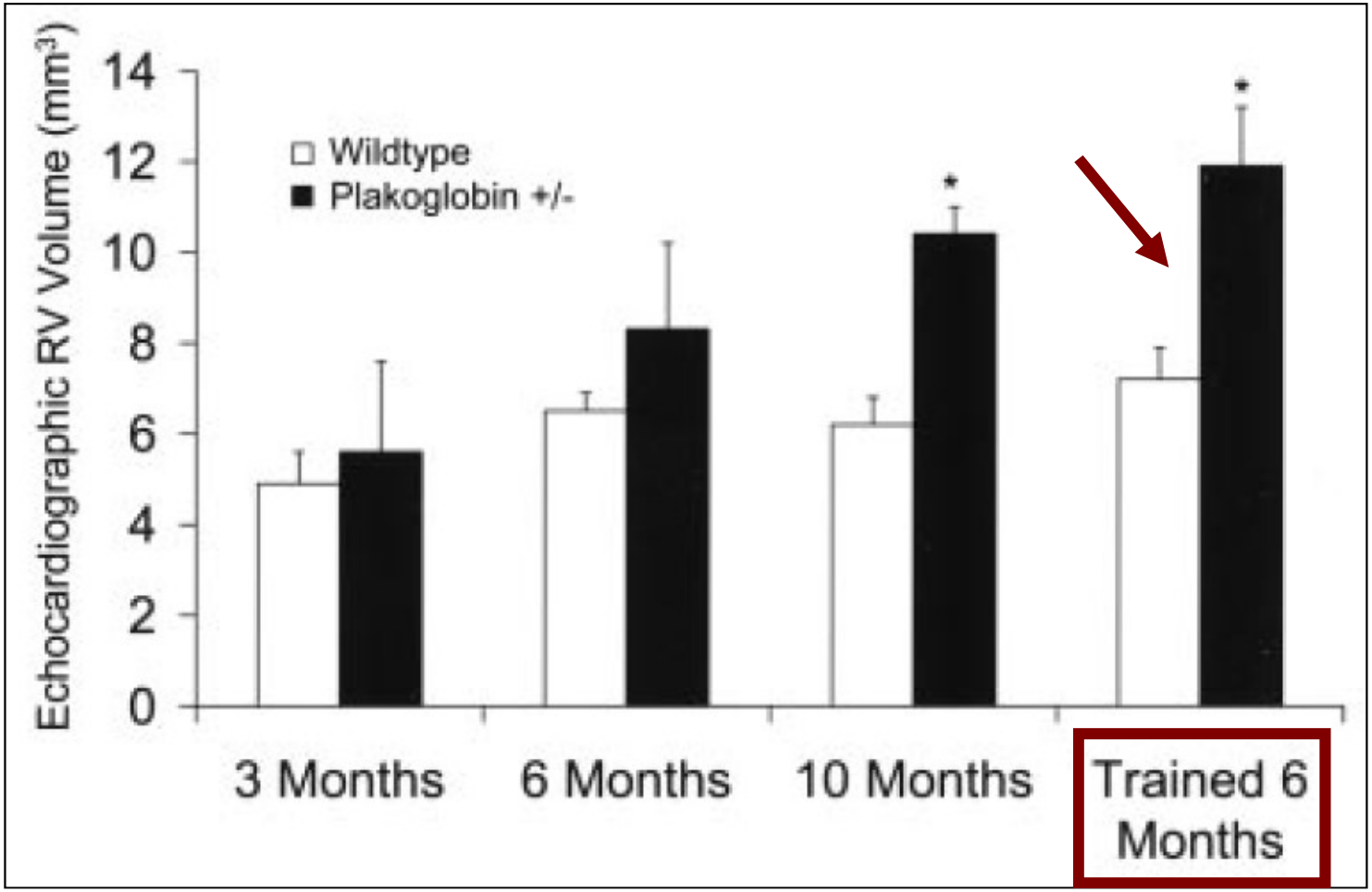
RV enlargement, RV-dysfunction, arrhythmias



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

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Journal of the American College of Cardiology

Published by Elsevier Inc.

Fabritz L et al. JACC. 2011;57:740-50

Vol. 57, No. 6, 20
ISSN 0735-1097/$36.
doi:10.1016/j.jacc.2010.09.0

PRE-CLINICAL RESEARCH

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

Larissa Fabritz, MD,* Mark G. Hoogendijk, MD,† Brendon P. Scicluna, MSc,†
Shirley C. M. van Amersfoorth, MSc,† Lisa Fortmueller, DVM,* Susanne Wolf, DVM,*
Sandra Laakmann, DVM,* Nina Kreienkamp,* Ilaria Piccini, PHD,* Günter Breithardt, MD,*
Patricia Ruiz Noppinger, PHD,‡ Henning Witt, PHD,‡ Klaus Ebnet PHD,§ Thomas Wichter MD,‖
Bodo Levkau, MD,¶ Werner W. Franke, PHD,# Sebastian Pieperhoff, PHD,#
Jacques M. T. de Bakker, PHD,†** Ruben Coronel, MD, PHD,† Paulus Kirchhof, MD*

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

ARVC Mouse Model (JUP -/+)

Preload-Reducing Therapy

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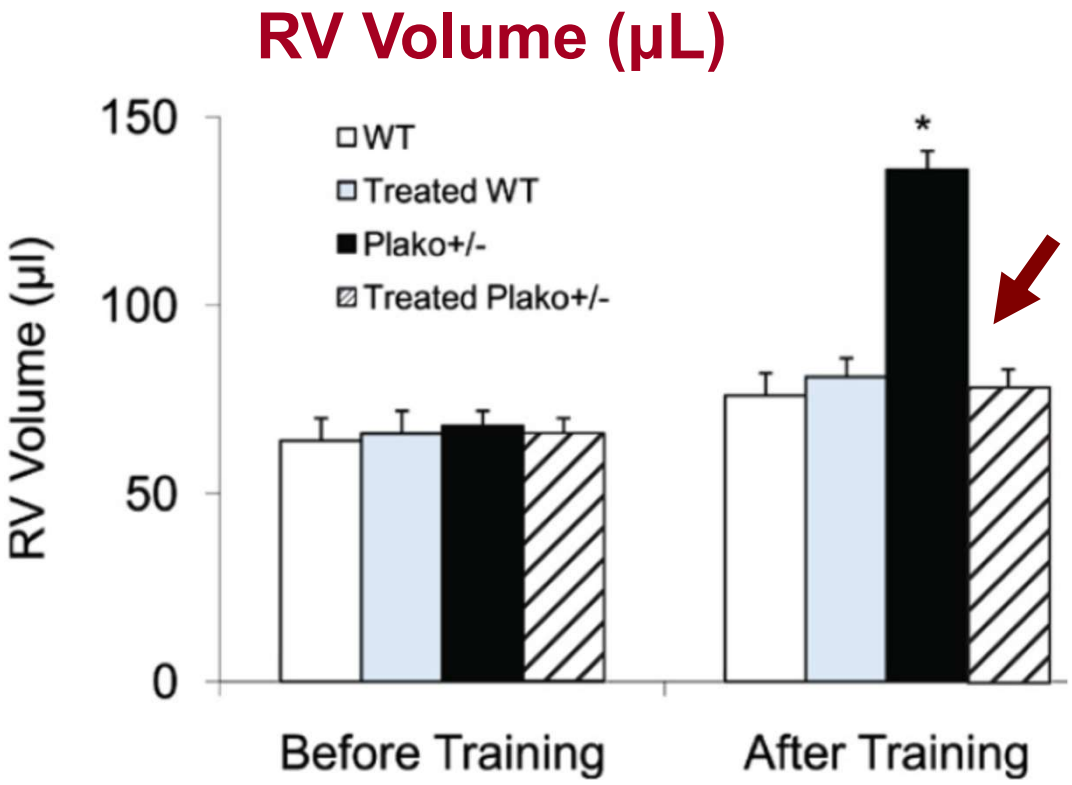
prevents training-induced RV-enlargement and VT



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

Fabritz L et al. JACC. 2011;57:740-50

Treatment of VT in ARVC

Load-reducing therapy

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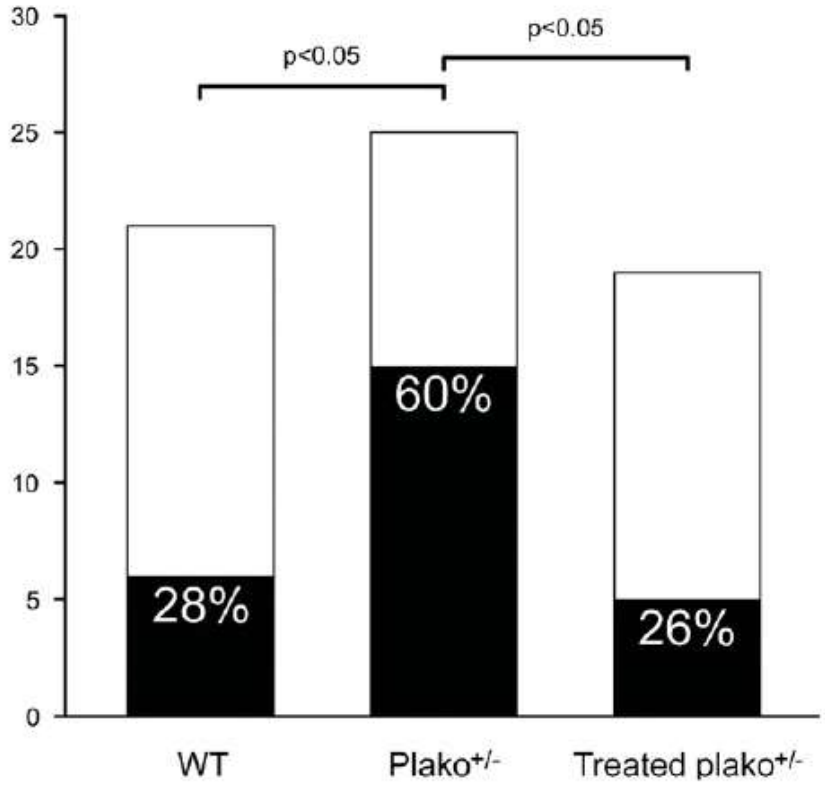
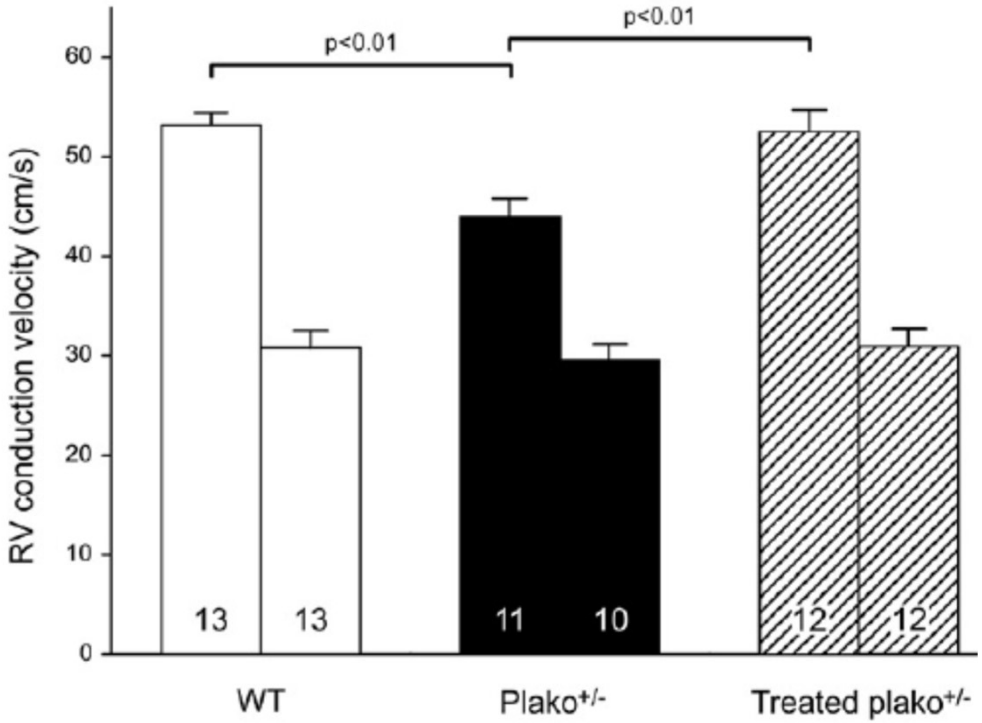
in Plako +/- mice prevents training induced …

Inducibility of macro-reentrant VT



Longit. RV conduction slowing



Fabritz L et al. JACC. 2011;57:740-50

ARVC – from bedside to lab

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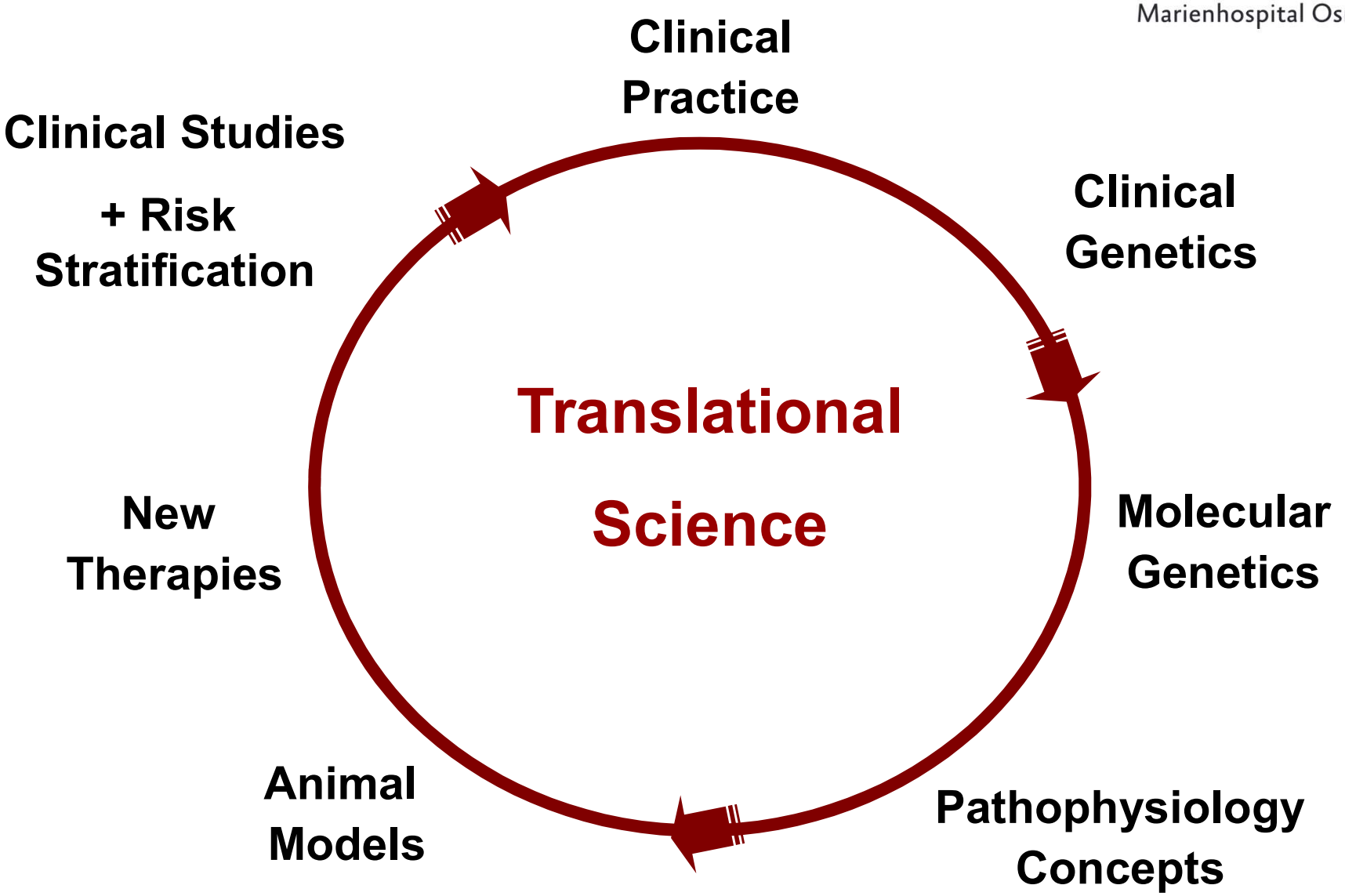

Adrenergic Dysfunction in ARVC:

Quantitative Assessment by PET

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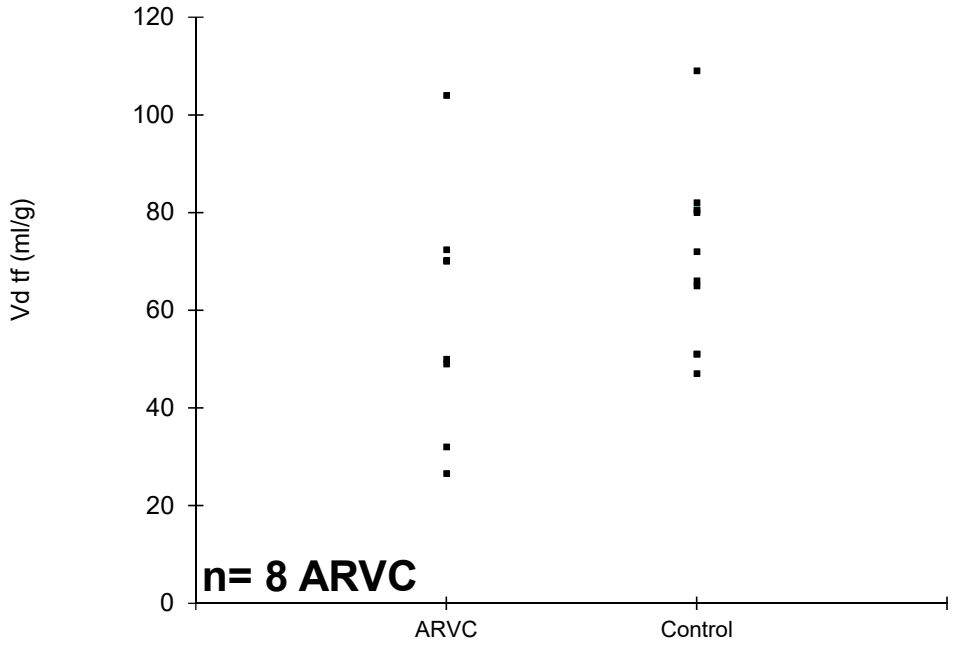
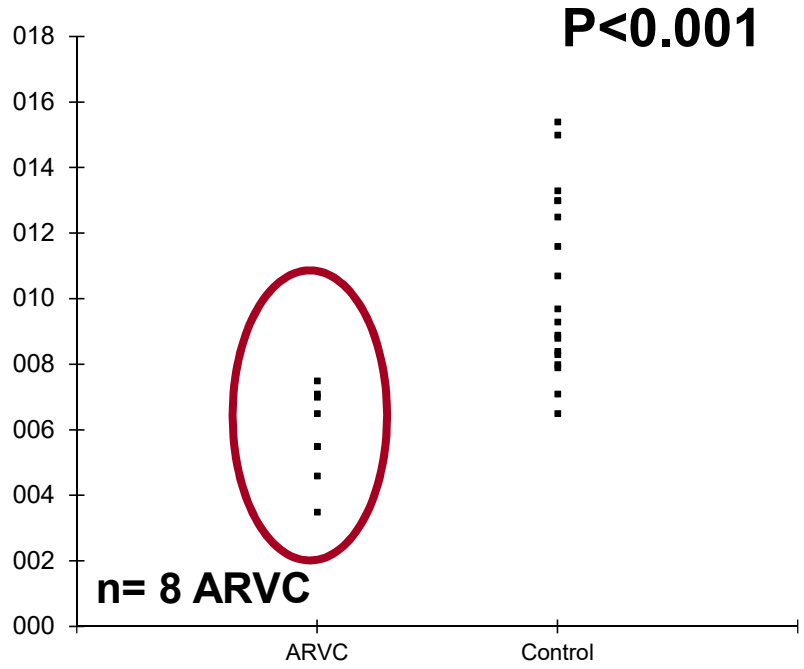
Downregulation of adrenergic ß-receptors

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



Postsynaptic ß-Receptor Density
max. binding capacity: Bmax ^{11}C-CGP$_{12177}$



Wichter T, Schäfers M, et al., Circulation. 2000;101:1552-1558

ARVC: Sports Type and Level

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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 Marcus[3], N.A. Mark Estes III[4], Mark Link[4], Scott McNitt[1], Bronislava Polonsky[1], Hugh Calkins[5], Jeffrey A. Towbin[6], Arthur J. Moss[1], and Wojciech Zareba[1]

Eur Heart J. 2015;36:1735-43

Sport Types and Levels

Increasing Static Component ↑ / Increasing Dynamic Component →	A. Low (<50%)	B. Moderate (50-75%)	C. High (>75%)
III. High (>30%)	Bobsledding/Luge Field events (throwing) Gymnastics*† Martial arts Rock climbing Sailing Water skiing*† Weight lifting*† Windsurfing*†	Body building*† Downhill skiing Skateboarding*† Snow boarding*† Wrestling*	Boxing Canoeing Kayaking Cycling*† Decathlon Rowing Speed skating Triathlon*†
II. Moderate (10-20%)	Archery Auto racing*† Diving*† Equestrian*† Motorcycling*†	American football* Field events (jumping) Figure skating Rodeoing*† Rugby Running (sprint) Surfing Synchronized swimming† "Ultra" racing	Basketball* Ice hockey* Cross-country skiing (skating technique) Lacrosse* Running (middle distance) Swimming Team handball Tennis
I. Low (<10%)	Bowling Cricket Curling Golf Riflery Yoga	Baseball/Softball Fencing Table tennis Volleyball	Badminton Cross-country skiing (classic technique) Field hockey* Orienteering Race walking Racquetball/Squash Running (long distance) Soccer*

ACC-AHA Scientific Statement. Levine BD. Circulation. 2015; 132:262

ARVC: Sports Level + Timing to Symptom Onset

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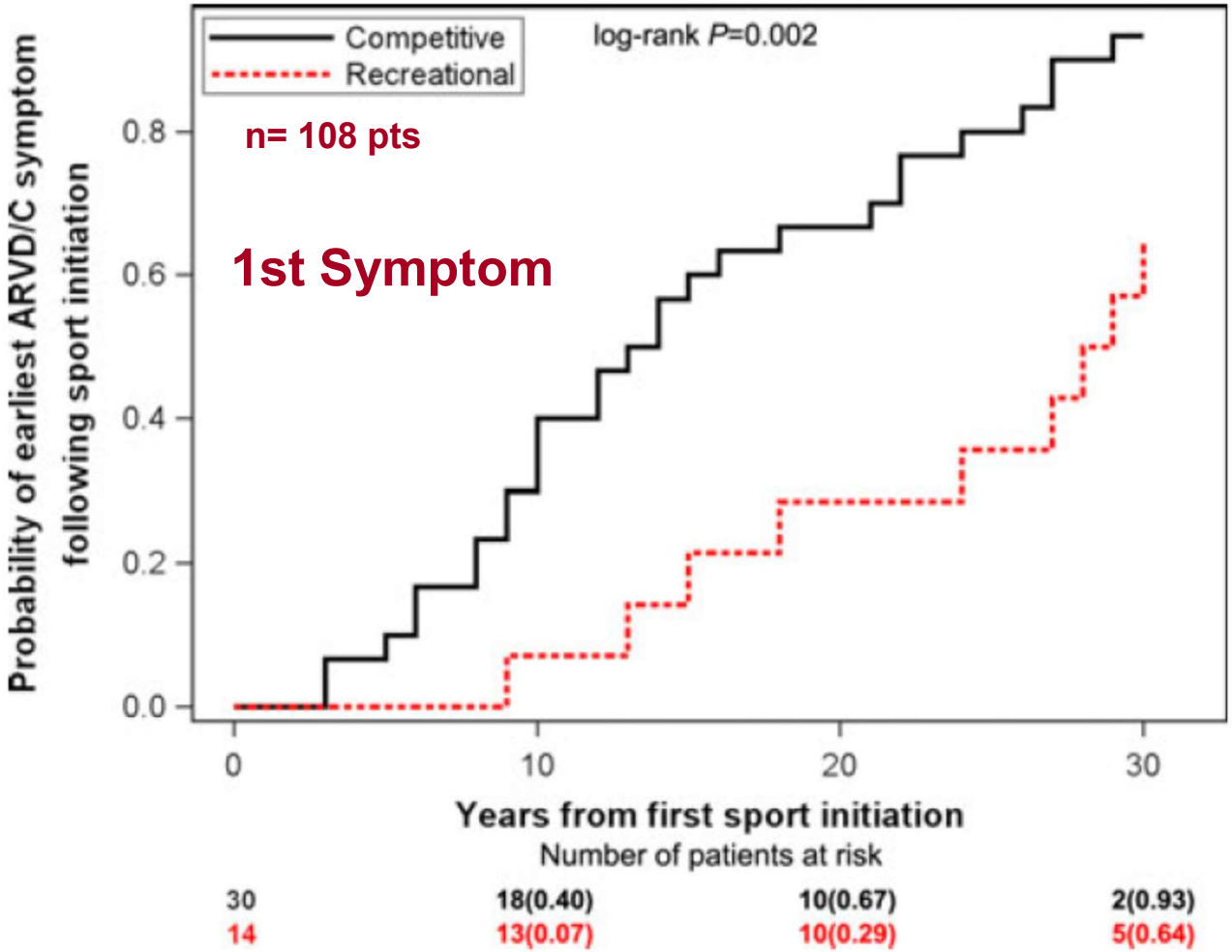

Competitive vs. recreational sports:

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

Eur Heart J. 2015;36:1735-43

ARVC: Sports Level and Prognosis (VT or Death)

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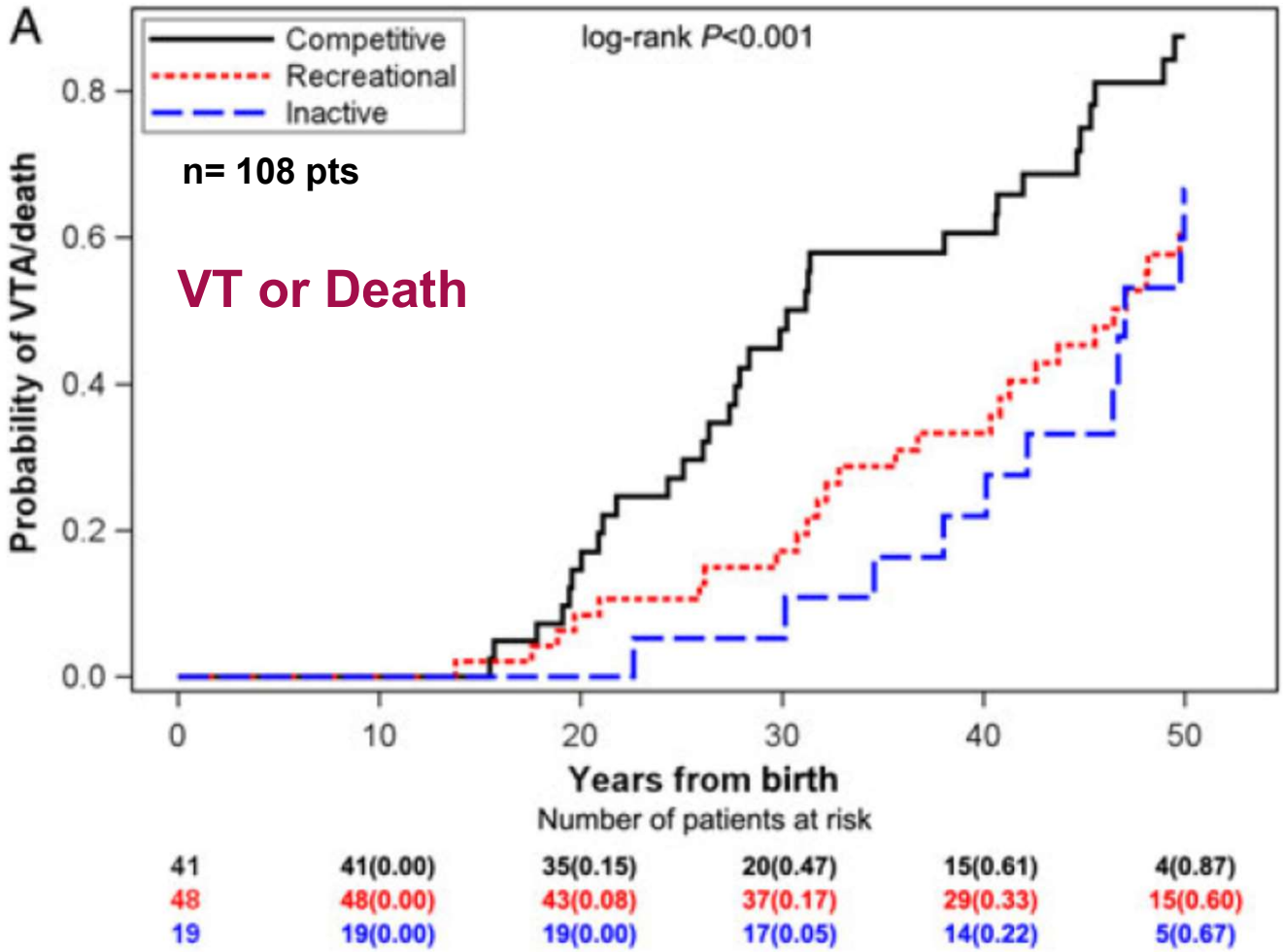

Competitive vs. recreational sports vs. inactive pts:

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

Eur Heart J. 2015;36:1735-43

Natural Course of ARVC

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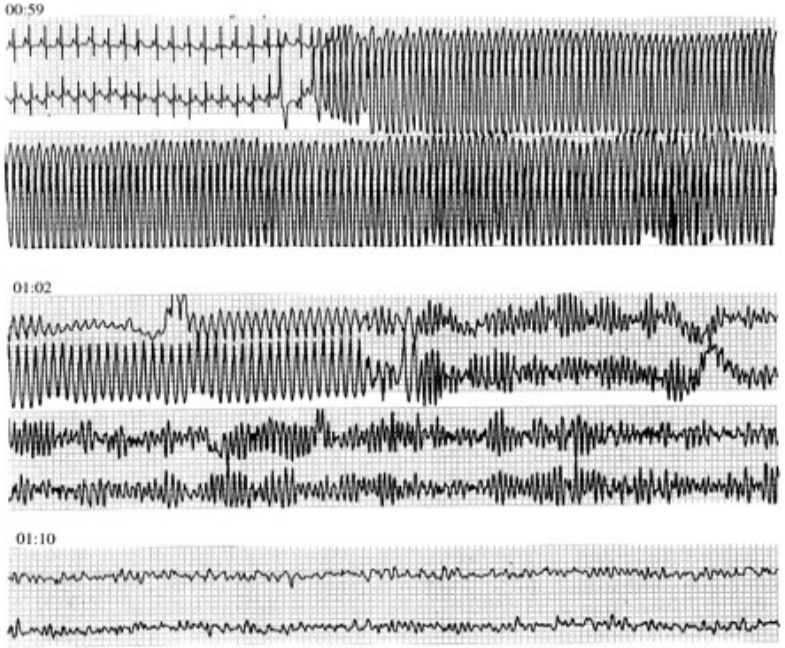
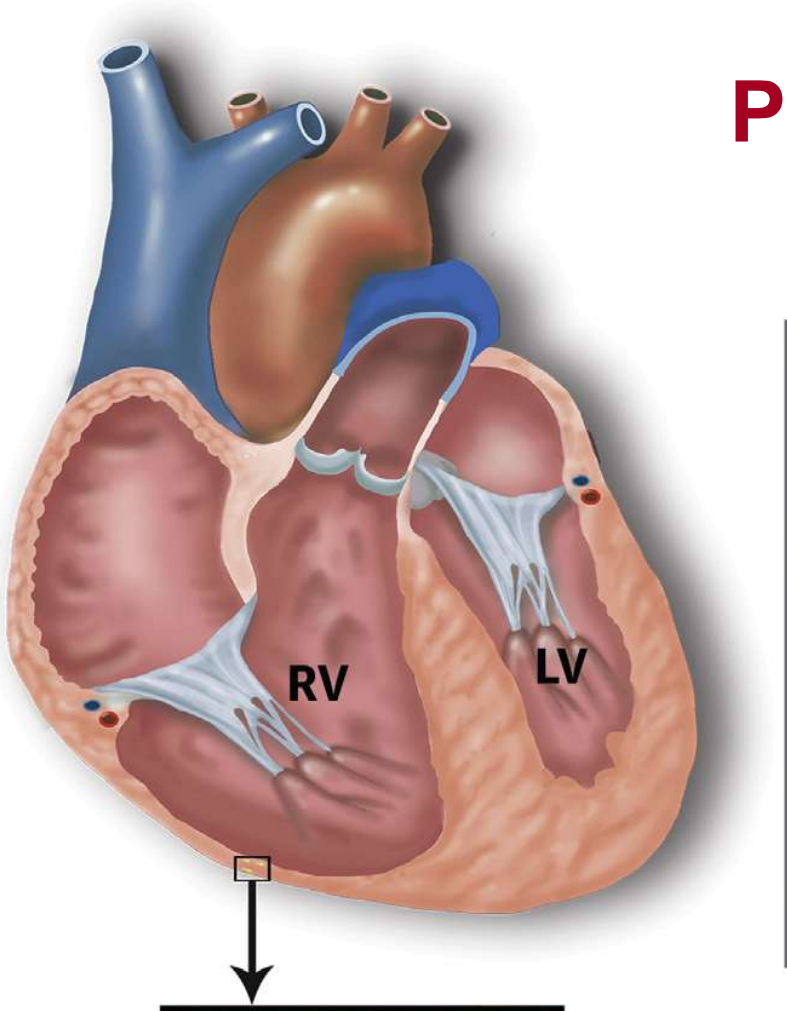
- **Risk of VF or fast VT: early (concealed) phase**
  (arrhythmias may precede morphological abnormalities)
- **Recurrent monomorphic VT: overt phase**
- **Chronic biventricular heart failure: end-stage**

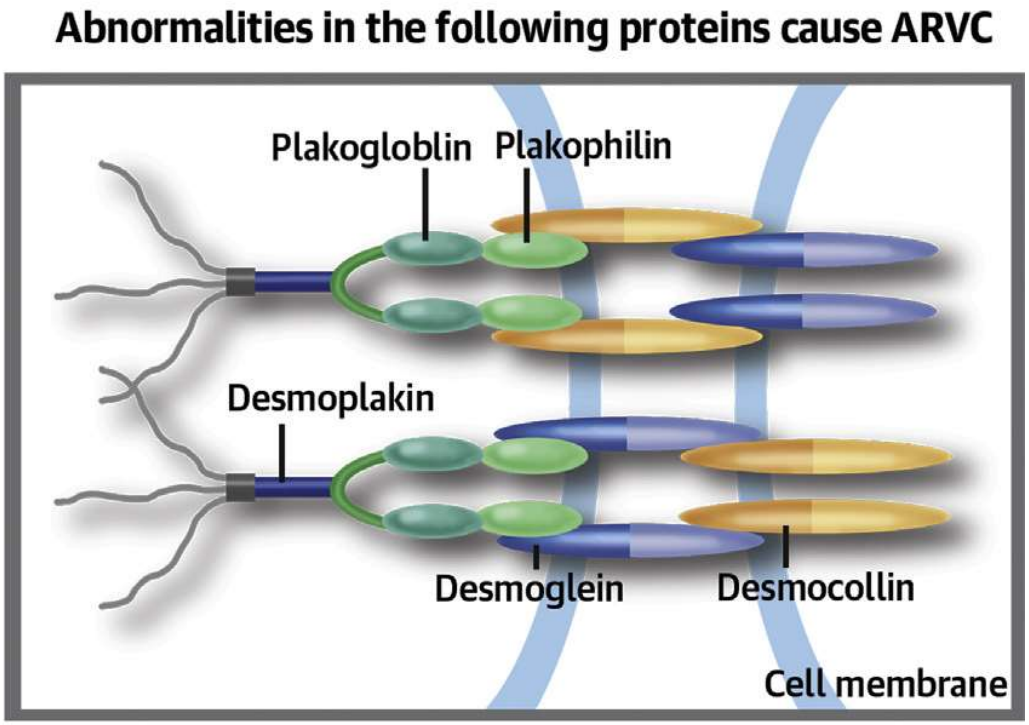


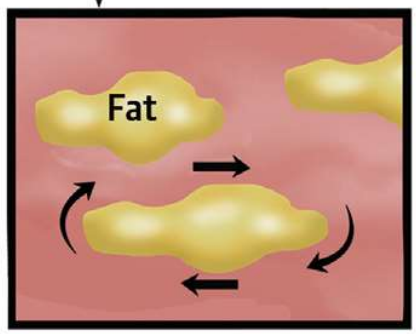
Aziz et al., Circulation. 2000;101;825-827

Wichter T et al., 2005

Pathophysiology of ARVC







RV wall

Re-entrant VT

Link, MS et al. JACC. 2014;64:119-125

Pathophysiology of ARVC

Disease of the Desmosome

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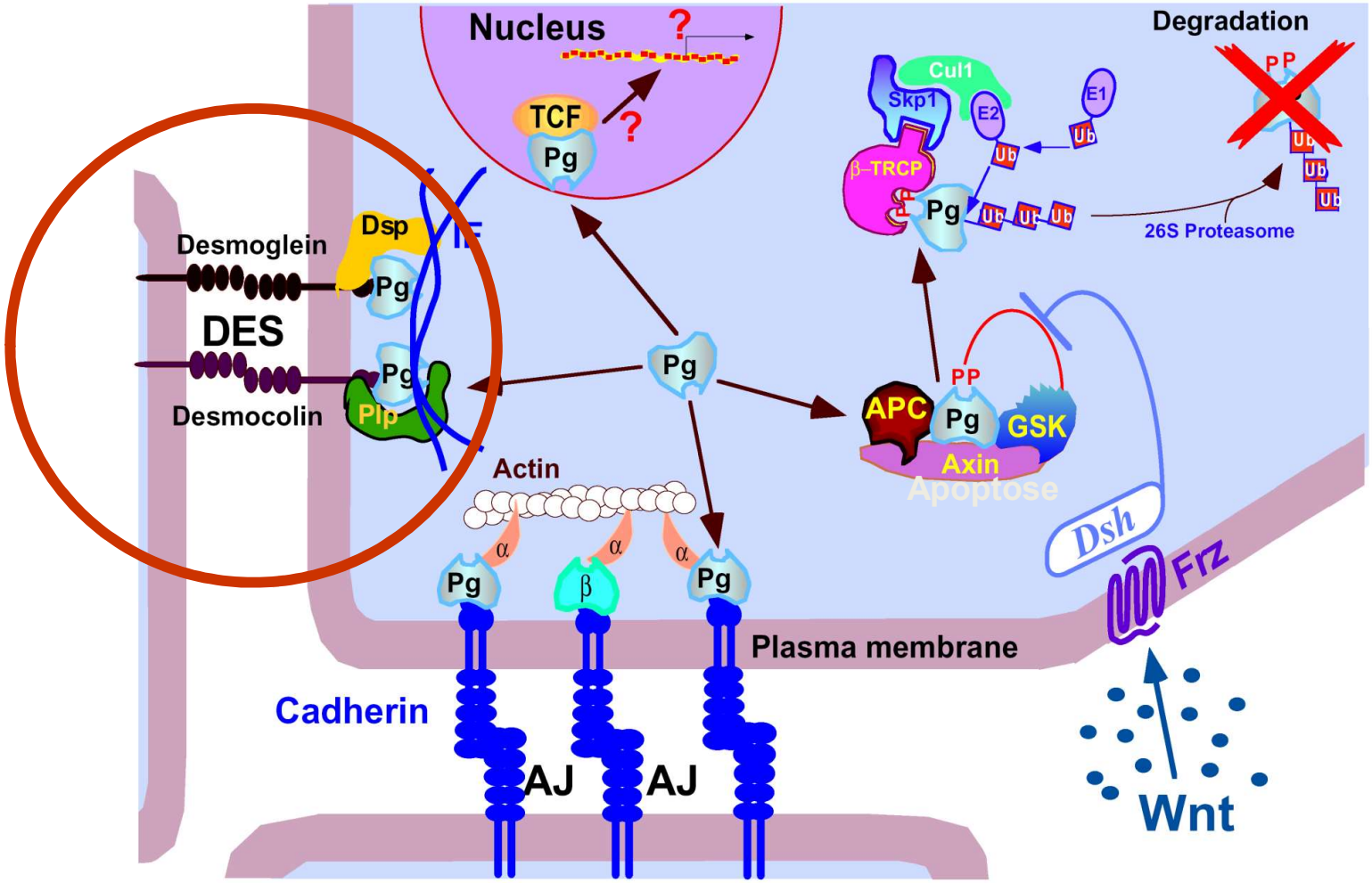
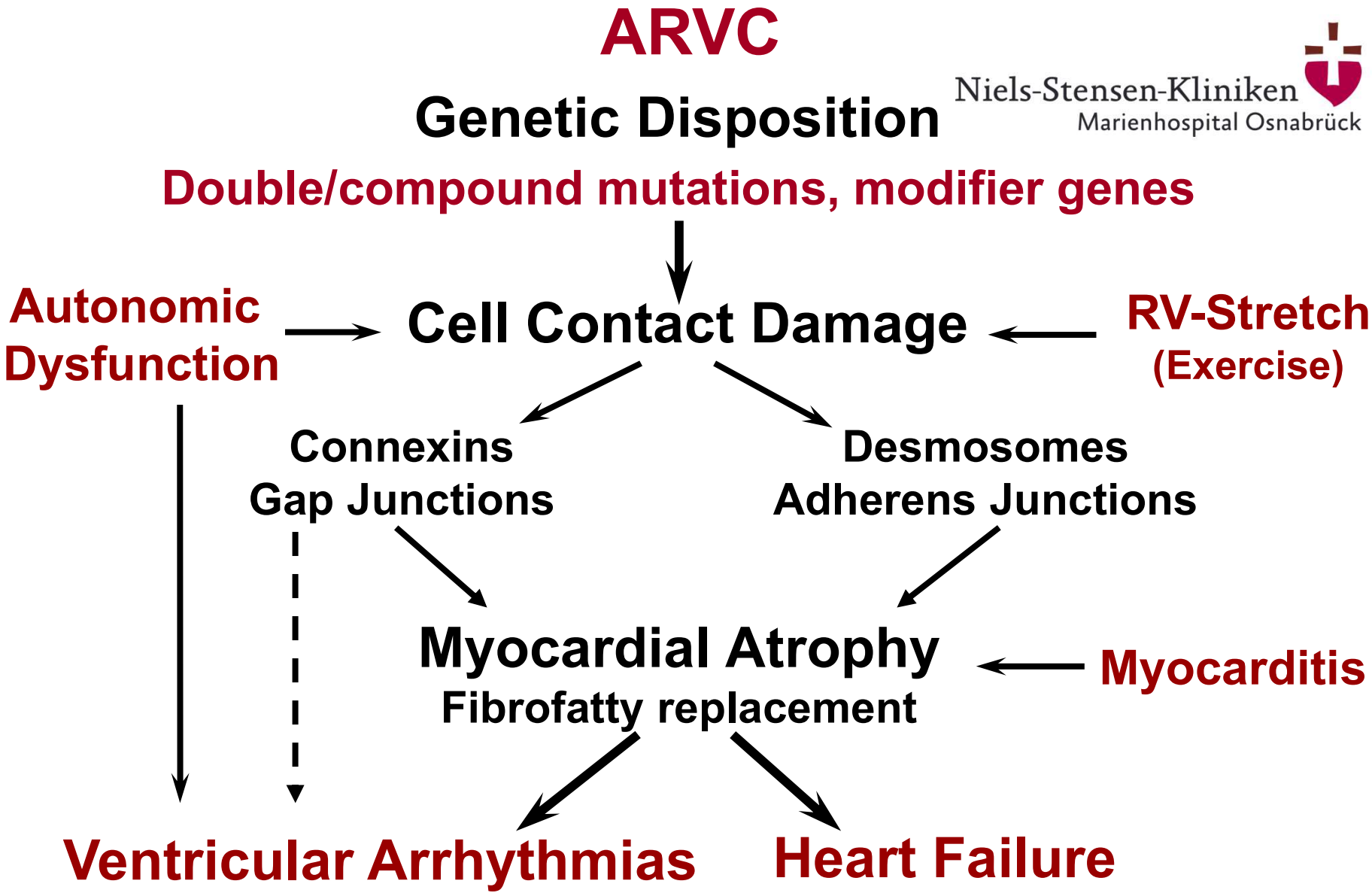


Zhurinsky J et al. J Cell Sci 113:3127-39 (2000)

Pathophysiology of ARVC



Wichter T et al. in Marcus FI, Nava A, Thiene G (eds.), Springer Verlag. 2008, page 147

From Risk Stratification to Treatment of ARVC

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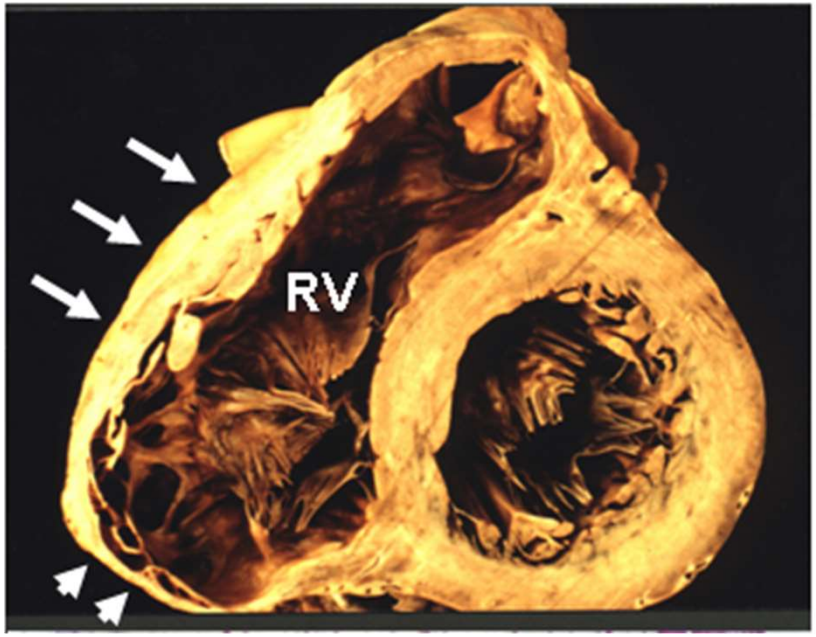
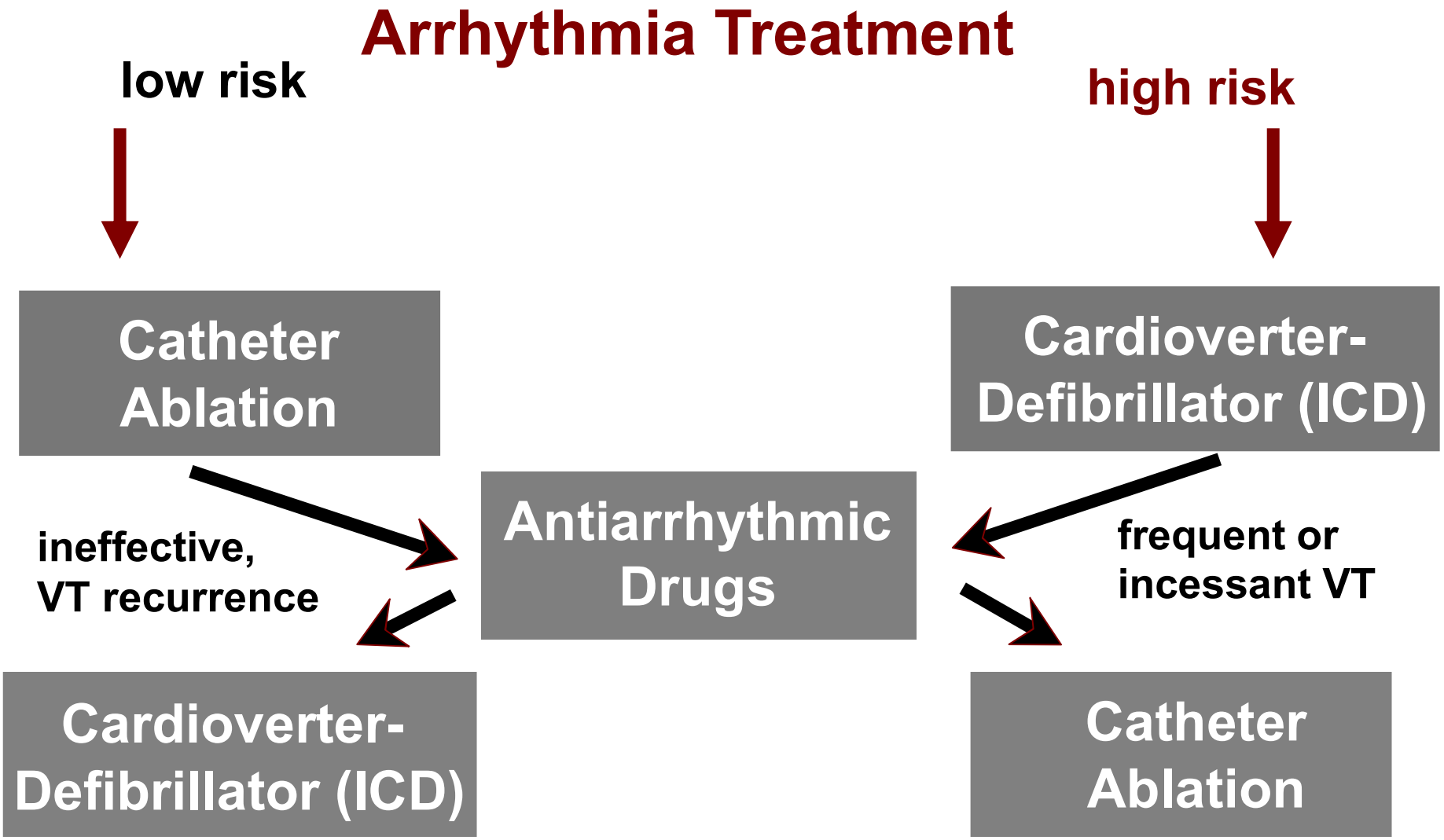
- **Improve symptoms and quality of life**
  - VT recurrences and palpitations
  - Appropriate and inappropriate ICD discharges
  - Heart failure symptoms and exercise capacity
- **Prevent disease progression**
  - Relevant arrhythmias
  - RV and LV dysfunction
  - Heart failure
- **Reduce mortality**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



Wichter T et al., 2005

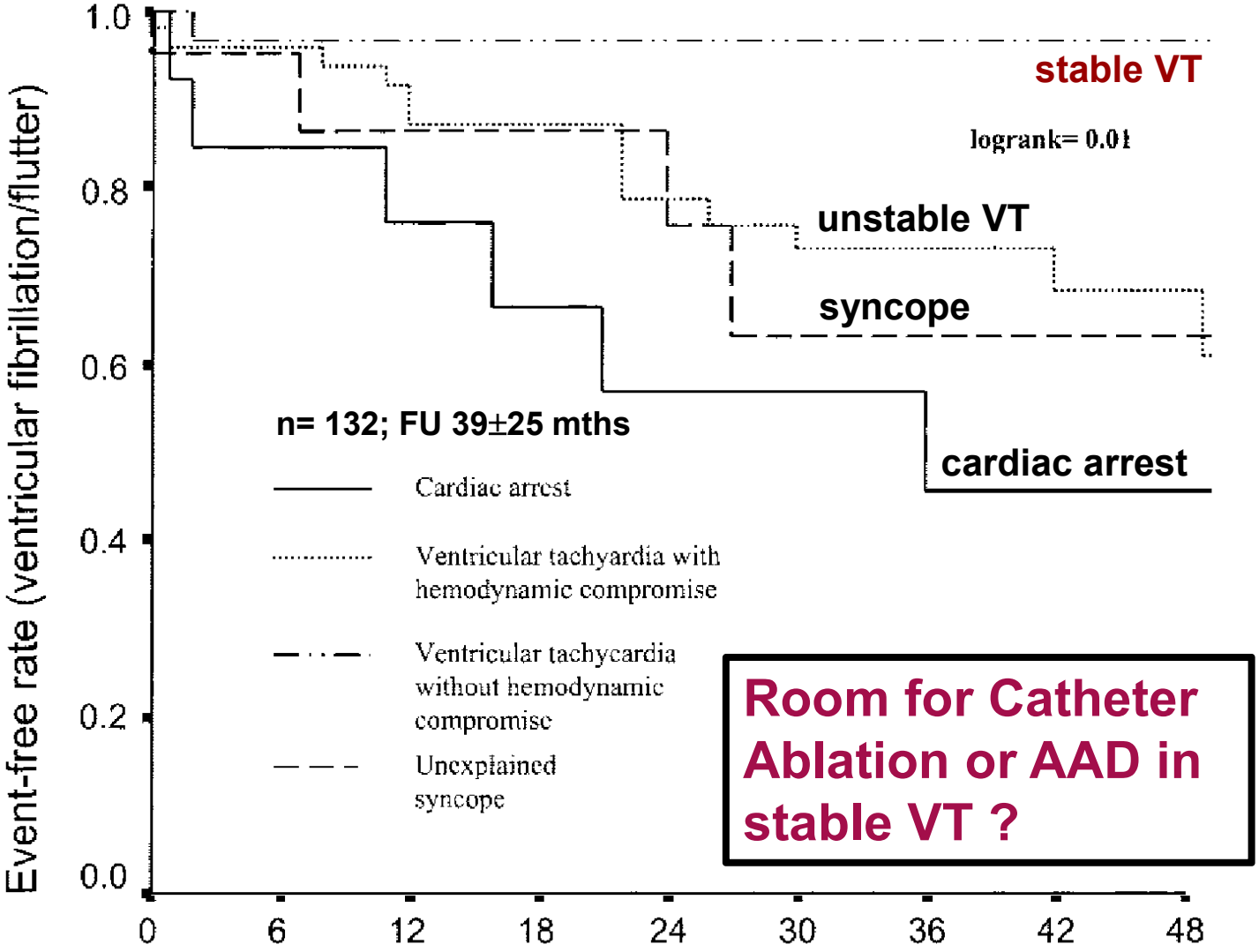
Management of ARVC



Wichter T et al. in Marcus FI, Nava A, Thiene G (eds.), Springer Verlag. 2008, page 172

Risk Stratification in ARVC

VF / V-flutter after ICD implant



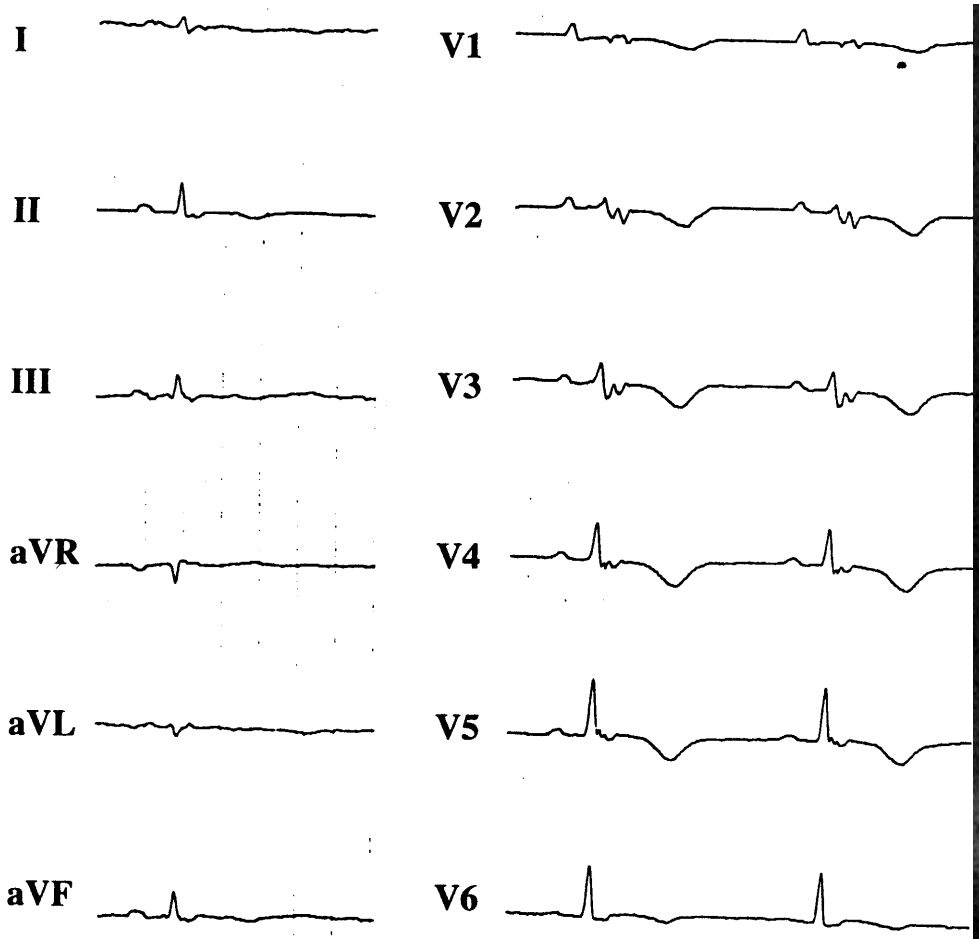
Room for Catheter Ablation or AAD in stable VT ?

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

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

Severe RV Dysfunction in ARVC

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



Wichter T et al., 2005

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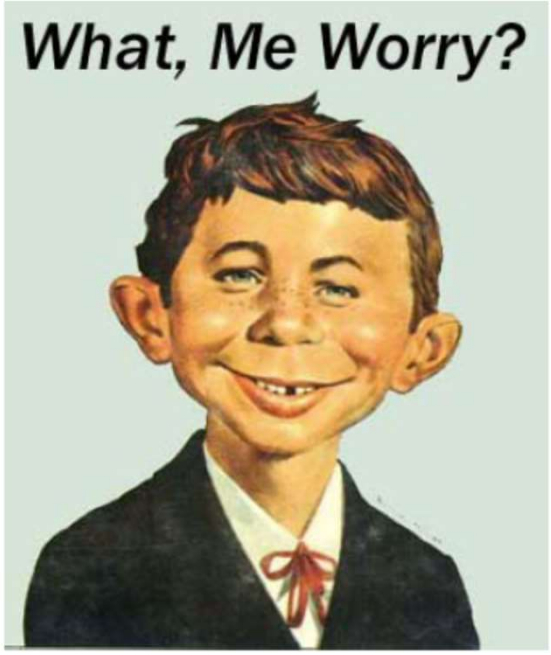
Marienhospital Osnabrück

What Risk ?

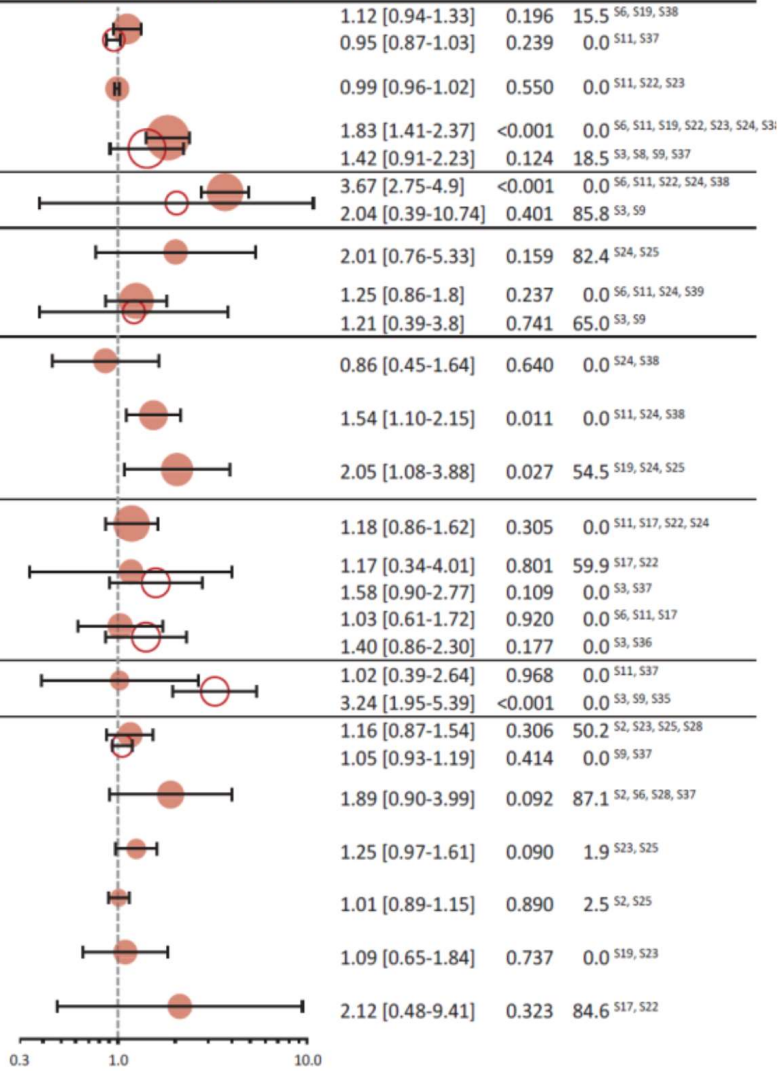
- Sudden death
- Ventricular tachycardia (VT), Syncope
- ICD shock delivery / clusters
- Heart failure (right, left, biventricular)
- Cardiac transplantation
- Hospitalization (VT, CHF)
- Exercise capacity ⬇
- Quality of life ⬇ (sports restriction)
- Disease manifestation in mutation carriers
- „Disease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



ARVC: Risk Stratification

Meta analysis: no single discriminating factor

Risk factor		Size / events	Studies	Pooled Hazard Ratio, random-effects, 95%CI	p-value	I^2	References
Demographics	Age, 5 yrs increase	180 / 89	3	1.12 [0.94-1.33]	0.196	15.5	S6, S19, S38
		133 / 56	2	0.95 [0.87-1.03]	0.239	0.0	S11, S37
	Age <35 yrs	170 / 58	3	0.99 [0.96-1.02]	0.550	0.0	S11, S22, S23
	Male sex	617 / 194	7	1.83 [1.41-2.37]	<0.001	0.0	S6, S11, S19, S22, S23, S24, S3
		342 / 154	4	1.42 [0.91-2.23]	0.124	18.5	S3, S8, S9, S37
Symptoms	Unexplained syncope	509 / 136	5	3.67 [2.75-4.9]	<0.001	0.0	S6, S11, S22, S24, S38
		147 / 59	2	2.04 [0.39-10.74]	0.401	85.8	S3, S9
Family history	Proband status	293 / 60	2	2.01 [0.76-5.33]	0.159	82.4	S24, S25
	Family SCD <35 yrs	483 / 123	4	1.25 [0.86-1.8]	0.237	0.0	S6, S11, S24, S39
		147 / 59	2	1.21 [0.39-3.8]	0.741	65.0	S3, S9
Arrhythmia	>1000 PVC/24h	299 / 59	2	0.86 [0.45-1.64]	0.640	0.0	S24, S38
	Prior non-sustained VT	405 / 84	3	1.54 [1.10-2.15]	0.011	0.0	S11, S24, S38
	Prior sustained VT/VF	406 / 104	3	2.05 [1.08-3.88]	0.027	54.5	S19, S24, S25
ECG	TWI V1-3	489 / 132	4	1.18 [0.86-1.62]	0.305	0.0	S11, S17, S22, S24
	Epsilon wave	116 / 60	2	1.17 [0.34-4.01]	0.801	59.9	S17, S22
		190 / 91	2	1.58 [0.90-2.77]	0.109	0.0	S3, S37
	SAECG LPs, ≥1 criteria	184 / 64	2	1.03 [0.61-1.72]	0.920	0.0	S6, S11, S17
		190 / 91	2	1.40 [0.86-2.30]	0.177	0.0	S3, S36
EPS	VA inducible at EPS	138 / 37	2	1.02 [0.39-2.64]	0.968	0.0	S11, S37
		209 / 89	3	3.24 [1.95-5.39]	<0.001	0.0	S3, S9, S35
Imaging	LVEF, 5% reduction	182 / 62	4	1.16 [0.87-1.54]	0.306	50.2	S2, S23, S25, S28
		133 / 56	2	1.05 [0.93-1.19]	0.414	0.0	S9, S37
	RVEF, 5% reduction	185 / 74	4	1.89 [0.90-3.99]	0.092	87.1	S2, S6, S28, S37
	RVFAC, 5% reduction	107 / 39	2	1.25 [0.97-1.61]	0.090	1.9	S23, S25
	RVEDV, 5 mL/m2	110 / 30	2	1.01 [0.89-1.15]	0.890	2.5	S2, S25
	TFC minor or major	108 / 58	2	1.09 [0.65-1.84]	0.737	0.0	S19, S23
	TFC major	116 / 60	2	2.12 [0.48-9.41]	0.323	84.6	S17, S22



● = 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

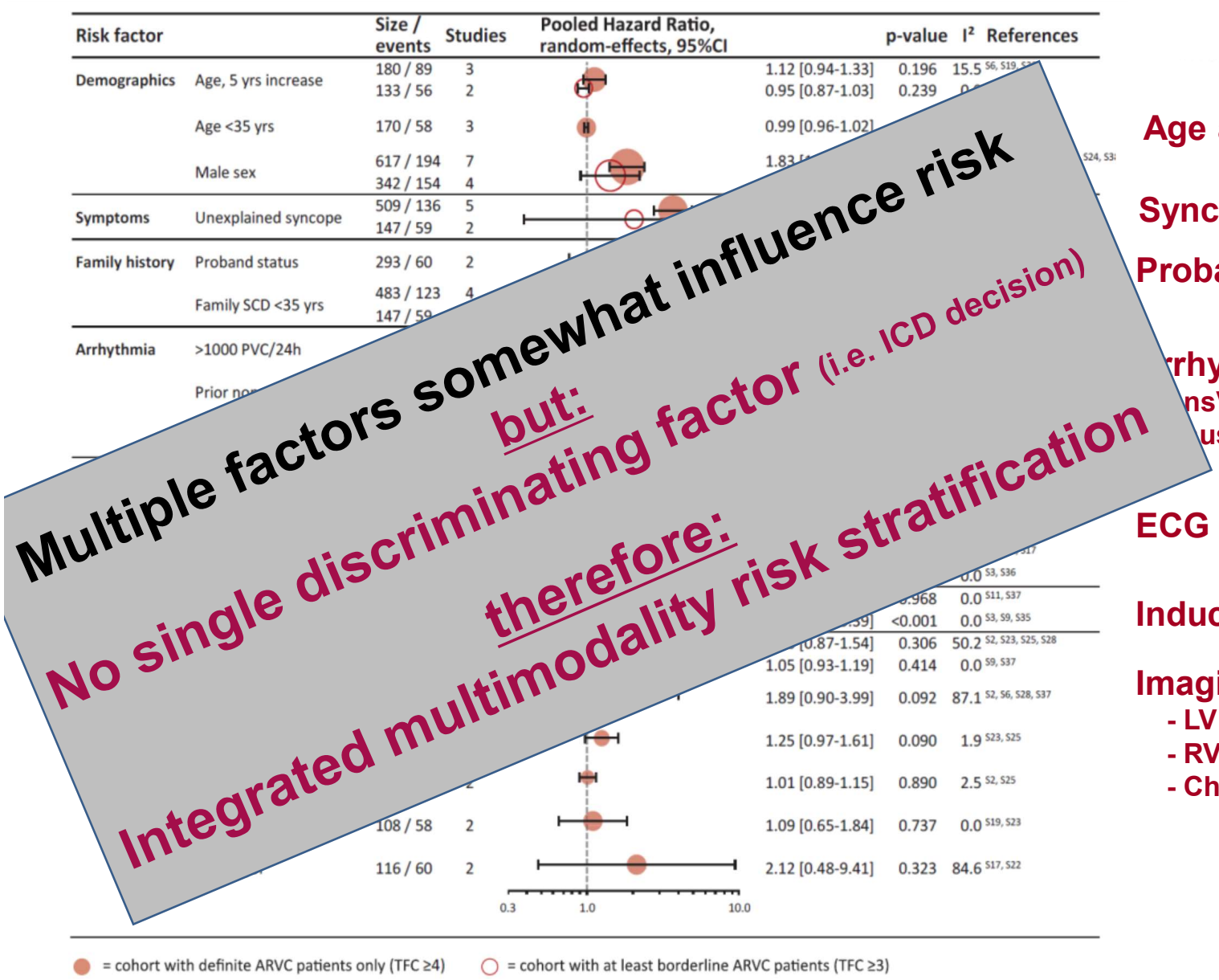
Inducibility at EPS

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

rrhythmias
- nsVT
- ust. VT / VF

ECG abnormalities

Inducibility at EPS

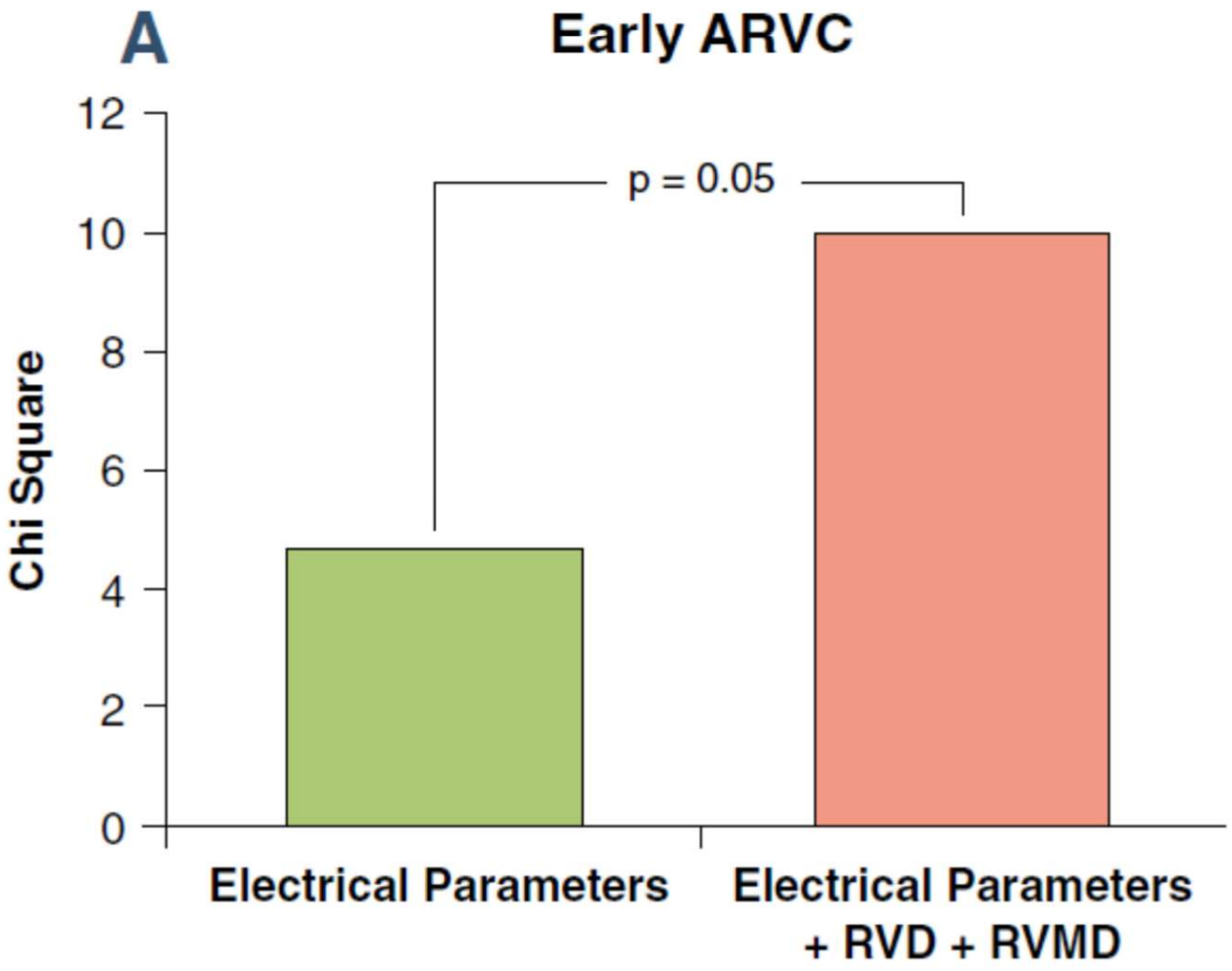
Imaging
- LV dysfunction
- RV dysfunction
- Chamber dilatation

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

ARVC: Risk Stratification

Combined ECG and Imaging parameters provide best assessment of arrhythmic risk

Niels-Stensen-Kliniken
Marienhospital Osnabrück



Integrated multimodality approach !

Leren et al. JACC-CVI. 2017; 10: 503-13

ARVC: Risk Stratification

Indications for ICD implantation

2015 ESC Guideline for Management of Ventricular Arrhythmias

Niels-Stensen-Kliniken
Marienhospital Osnabrück

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)

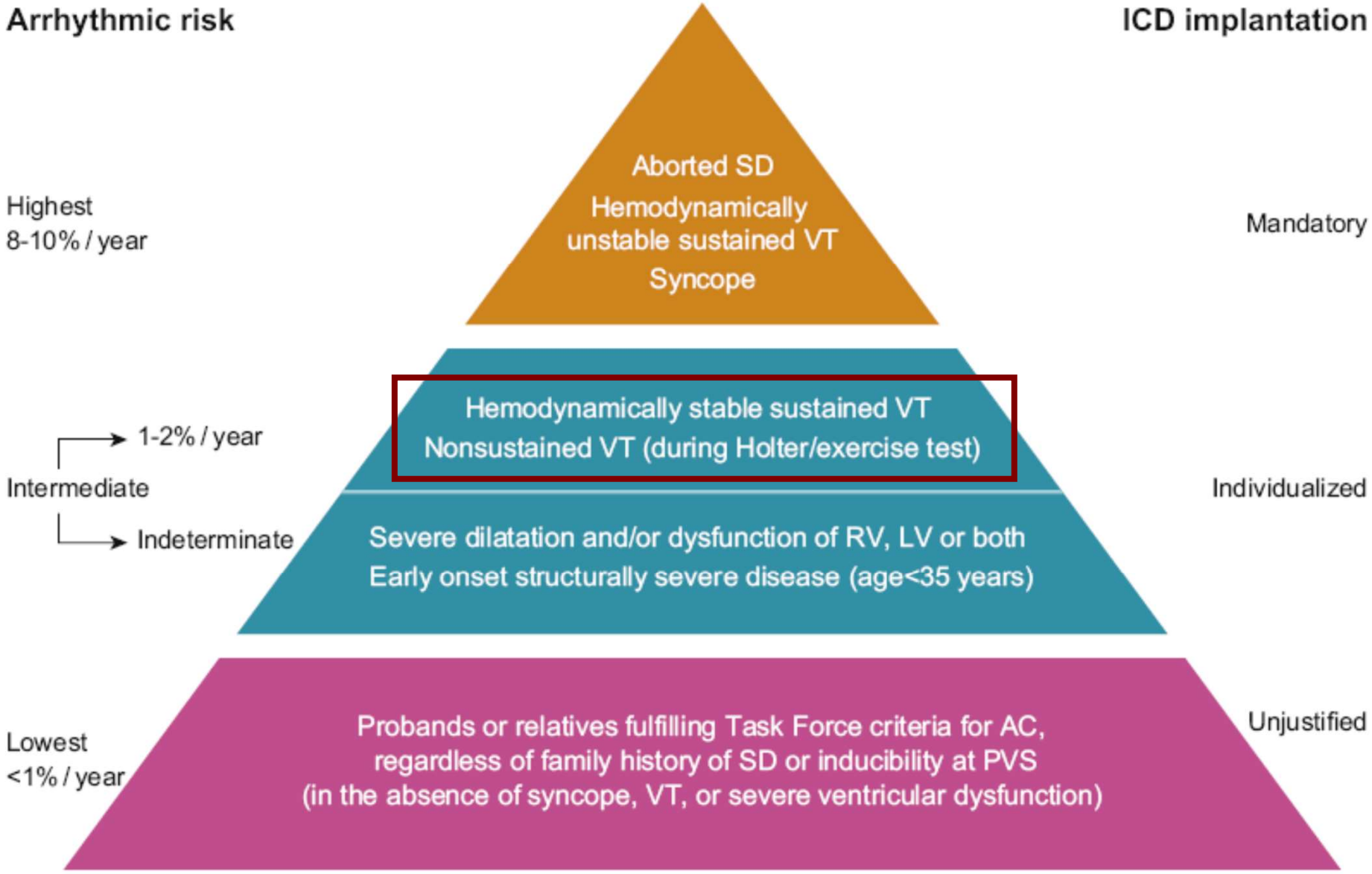
Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC)

Authors/Task Force Members: Silvia G. Priori*(Chairperson) (Italy) Carina Blomström-Lundqvist*(Co-chairperson) (Sweden) Andrea Mazzanti† (Italy), Nico Blom[a] (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



Corrado D et al. Card Electrophysiol Clin. 2011;3:311-321

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

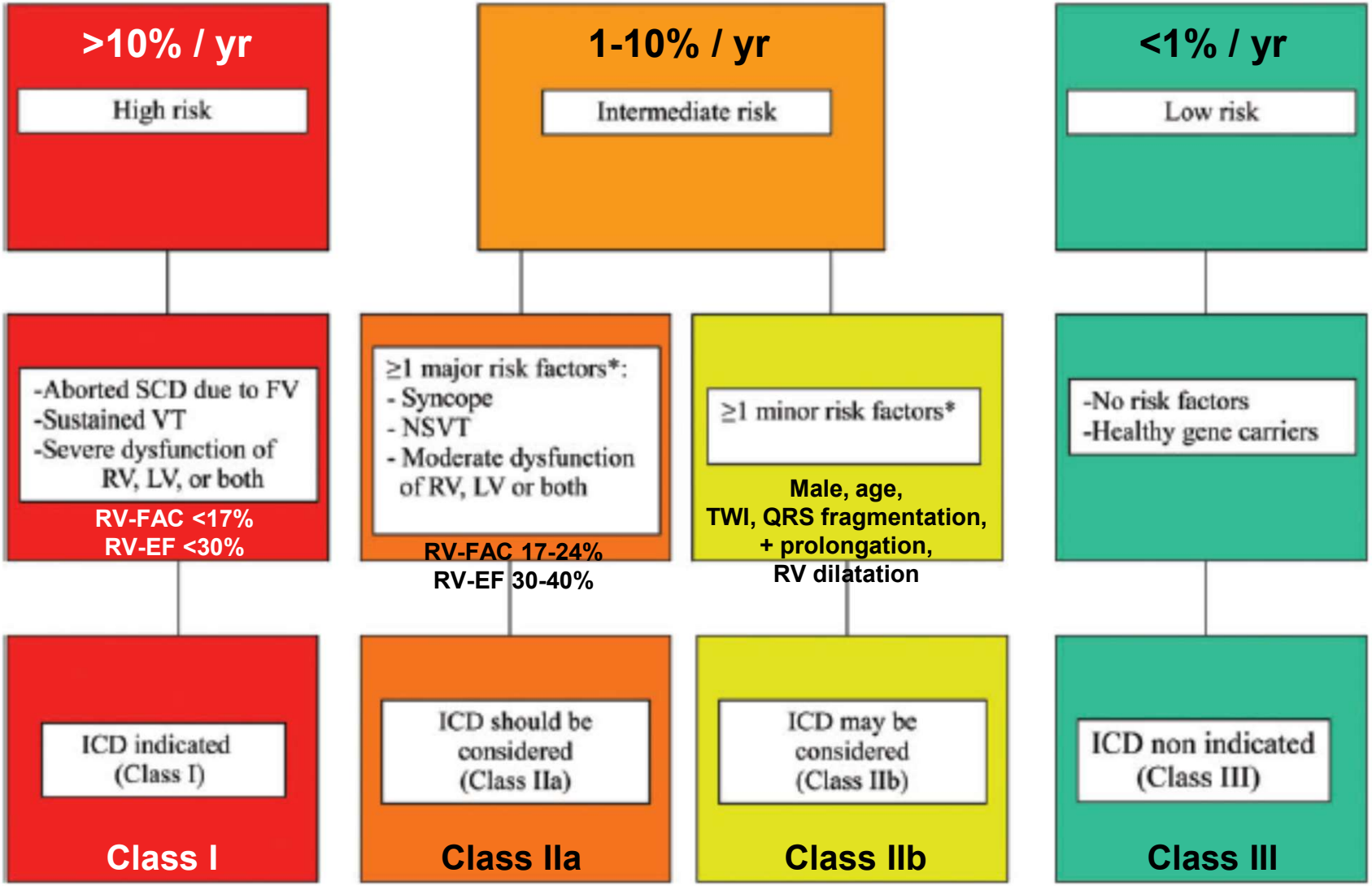
Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement

Domenico Corrado[1*], Thomas Wichter[2], Mark S. Link[3], Richard Hauer[4], Frank Marchlinski[5], Aris Anastasakis[6], Barbara Bauce[1], Cristina Basso[1], Corinna Brunckhorst[7], Adalena Tsatsopoulou[8], Harikrishna Tandri[9], Matthias Paul[10], Christian Schmied[7], Antonio Pelliccia[11], Firat Duru[7], Nikos Protonotarios[8], NA Mark Estes III[3], William J. McKenna[12], Gaetano Thiene[1], Frank I. Marcus[13], and Hugh Calkins[9]

Eur Heart J. 2015;36: online July 27

ICD Indication in ARVC

2015 Task Force Consensus on ARVC Treatment



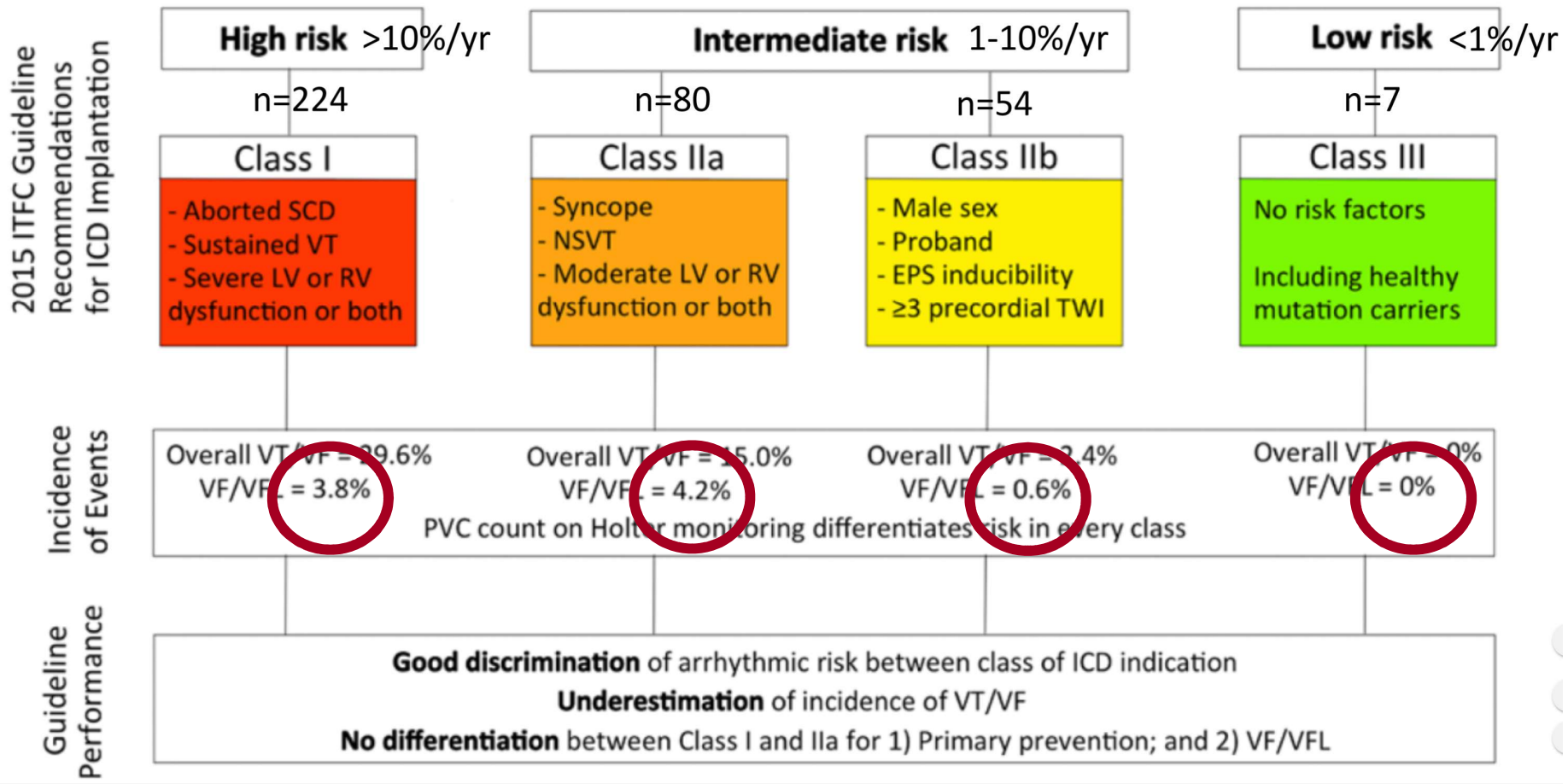
Corrado D, Wichter T, et al. Eur Heart J. 2015 and Circulation 2015

ARVC: Risk Stratification

Indications for ICD implantation

2015 ESC Guideline for Management of Ventricular Arrhythmias

Validation of 2015 Task Force



Orgeron et al. Circ Arrhythm Electrophysiol. 2018:11 online

ARVC: Risk Calculator (work in progress)

Niels-Stensen-Kliniken
Marienhospital Osnabrück

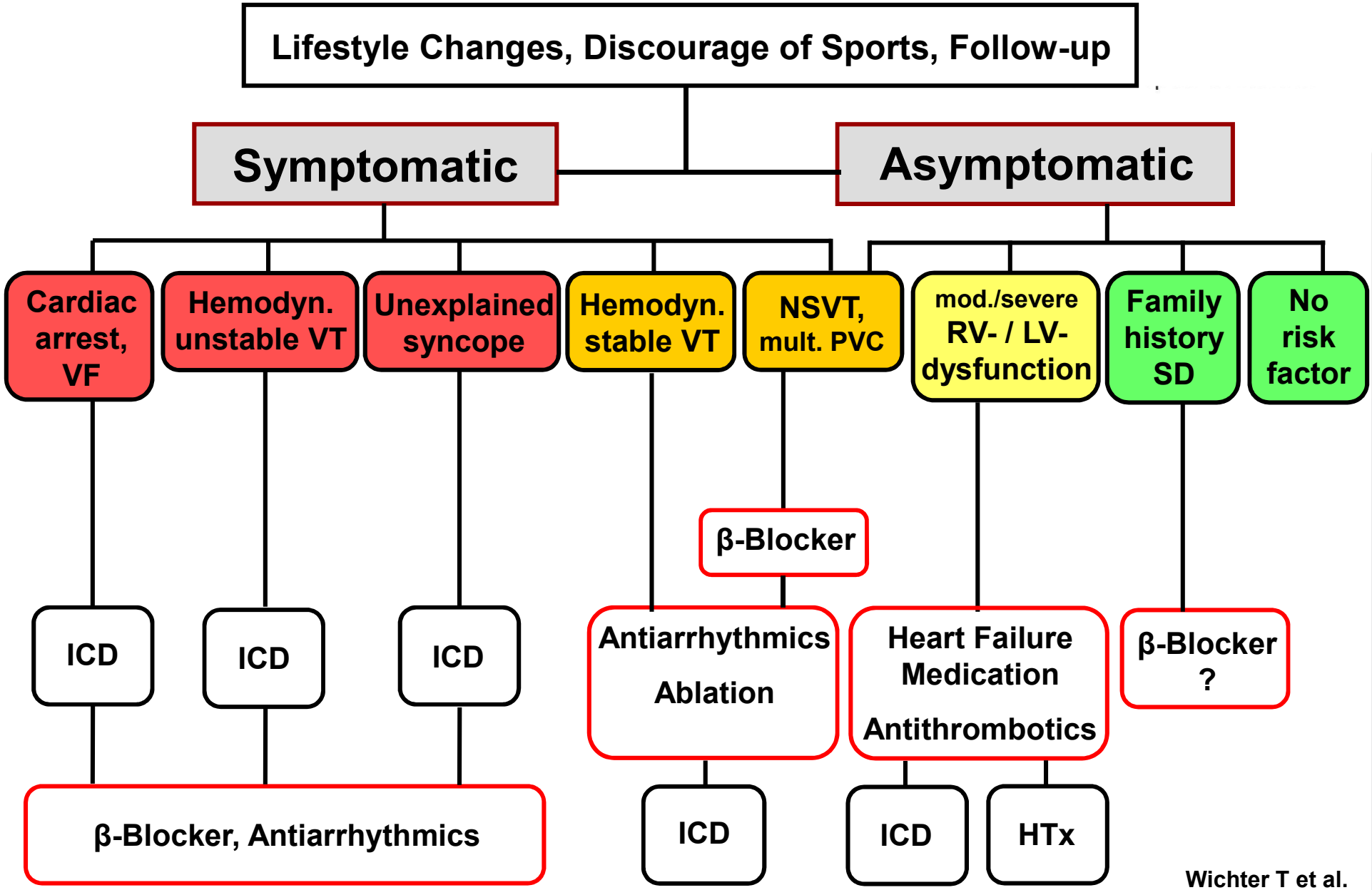
Collaboration of 14 centers

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			

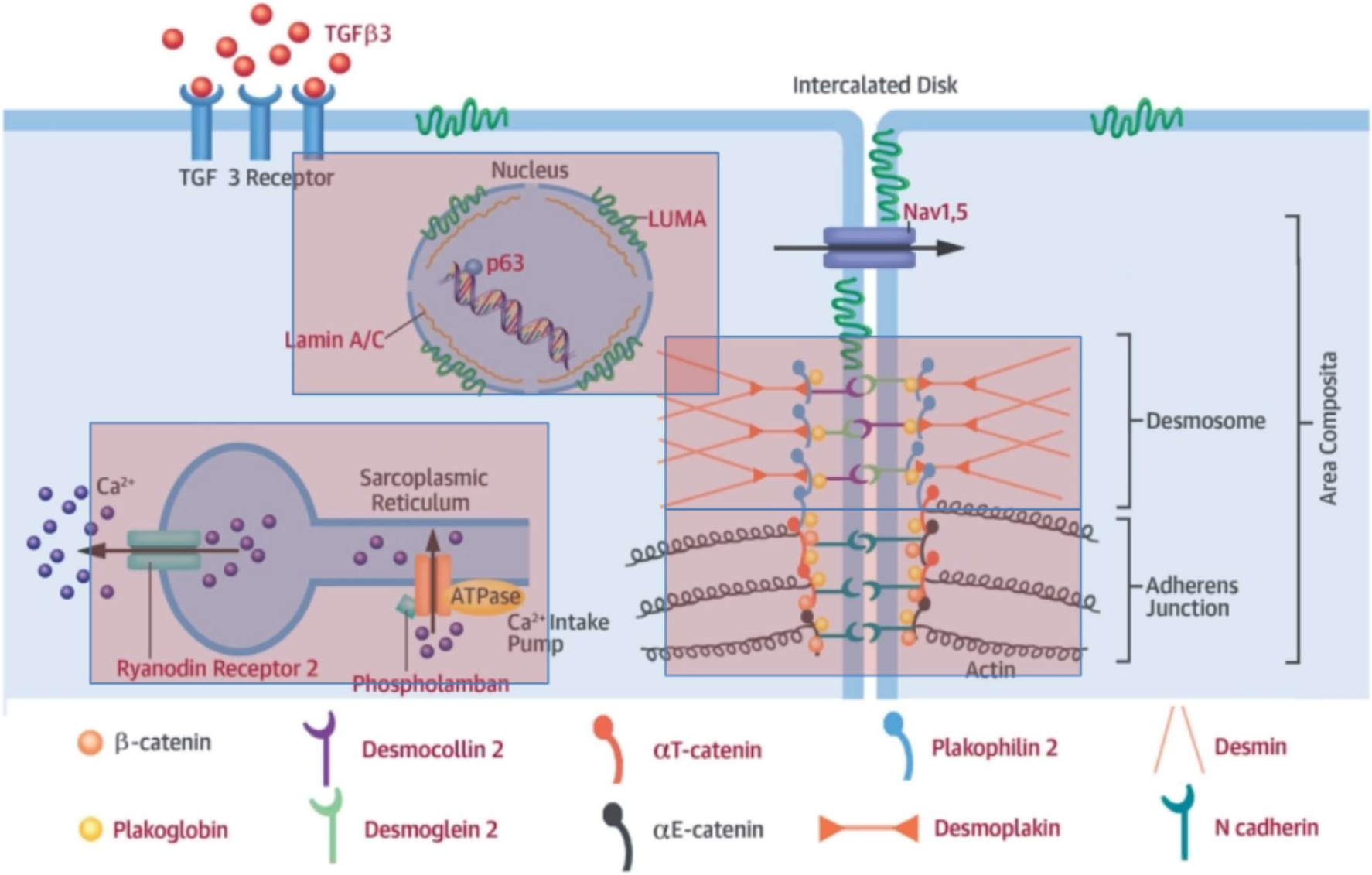
Cadrin-Tourigny J et al. HRS-Congress, Chicago 2018

Treatment of ARVC



Wichter T et al.
Kardiologe 2014

ARVC: Target-Directed Therapies ?



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

Treatment of ARVC:
Summary and Recommendations

Niels-Stensen-Kliniken
Marienhospital Osnabrück

- 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

Niels-Stensen-Kliniken
Marienhospital Osnabrück

Symposium: ARVC: from pathology to prognosis

Treatment of ARVC …

… Current Standards and Future Perspectives

Thomas Wichter, MD, FESC

Professor of Medicine (Cardiology)

Dept. of Internal Medicine / Cardiology
Heart Center Osnabrück / Bad Rothenfelde

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Osnabrück, Germany (DE)