Arrhythmogenic cardiomyopathy

"What lies beneath"

Thomas Gossios, PhD

Cardiologist

Cardiomyopathies Lab,

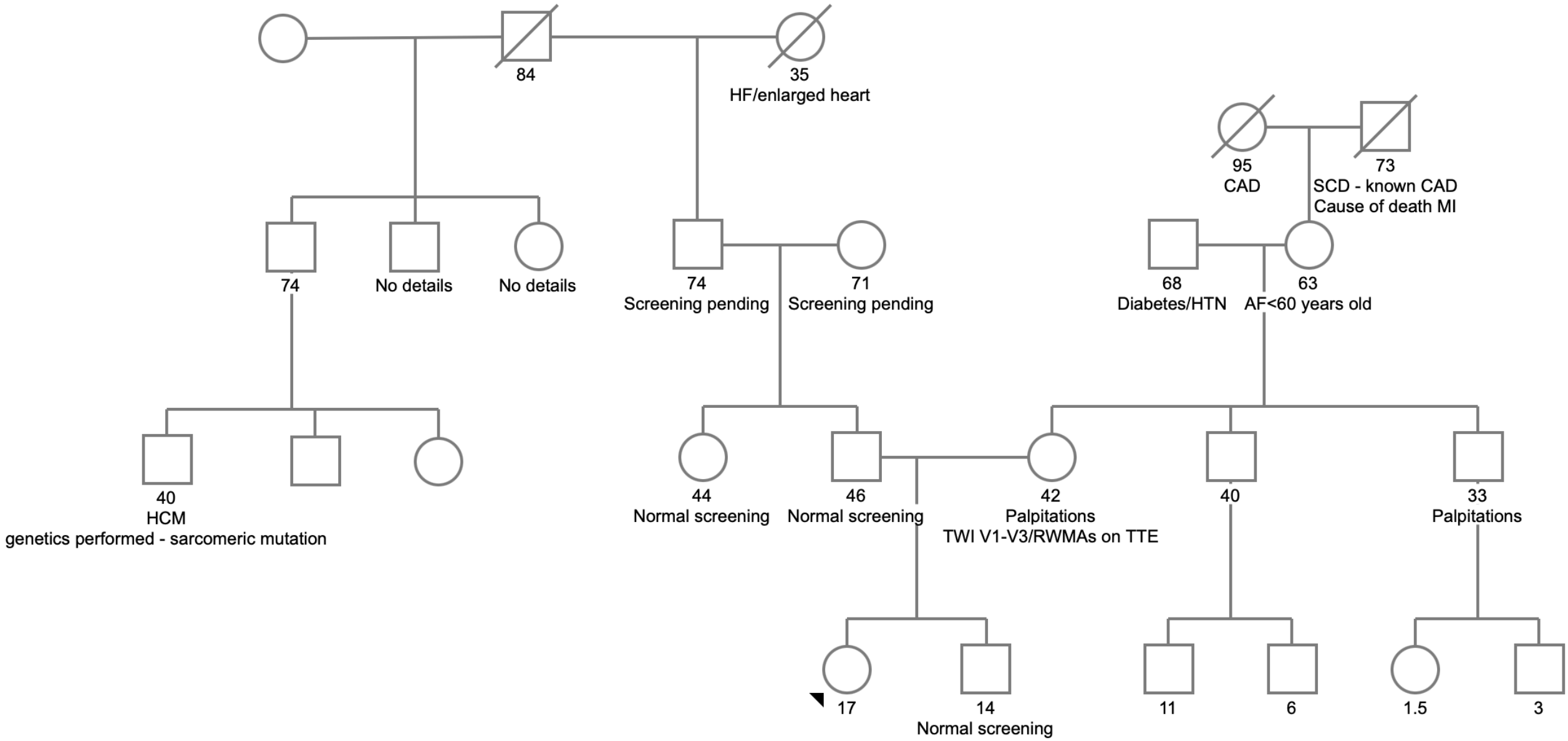
AUTH 1st Cardiology Department

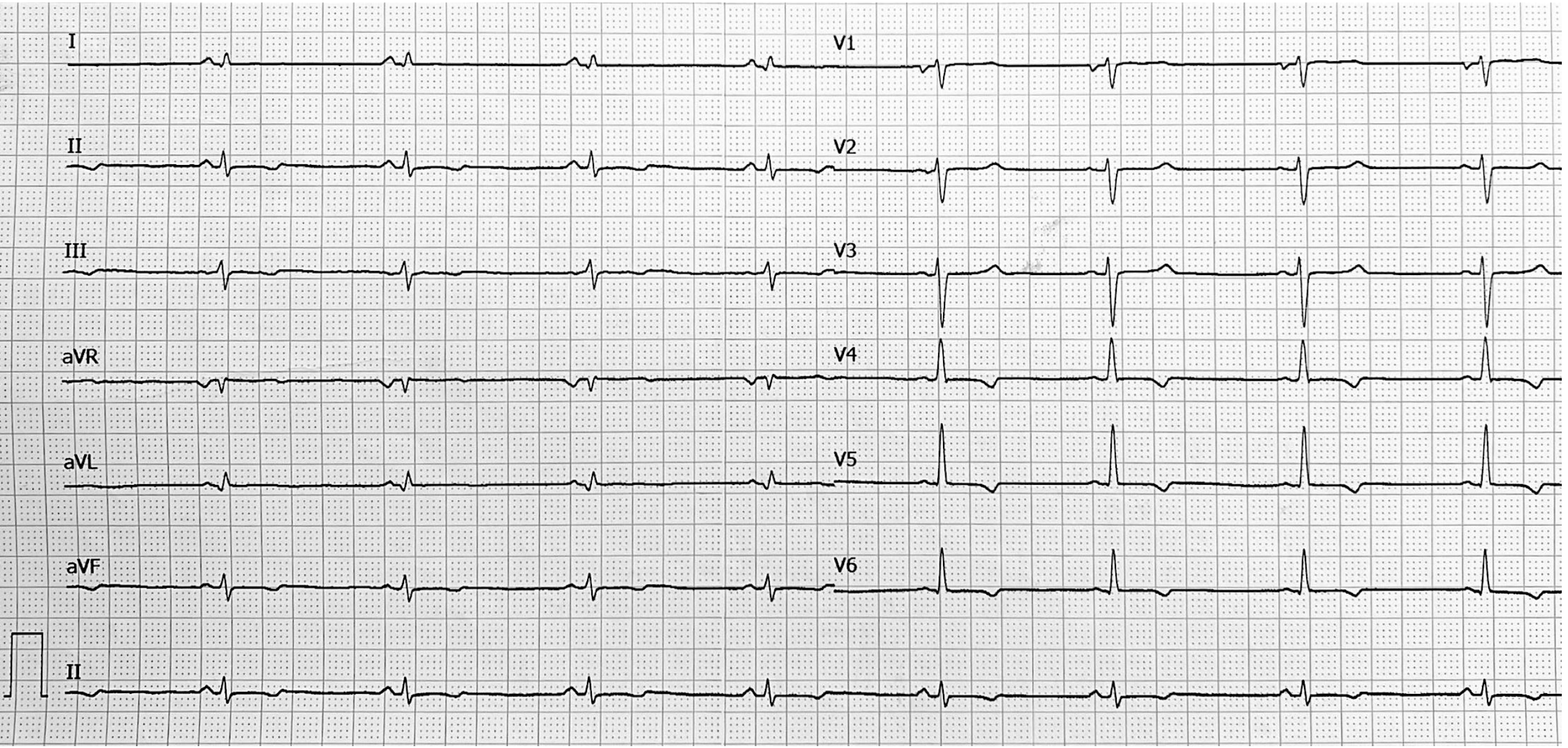
thomagossios@hotmail.com / t.gkosios@nhs.net

Proband

- 16-year-old female, ex-elite rower (5 years, 7 training sessions/wk).
- Episodes of Tn+ chest pain, progressively worsening SOB (NYHA II), reduced exercise capacity and palpitations.

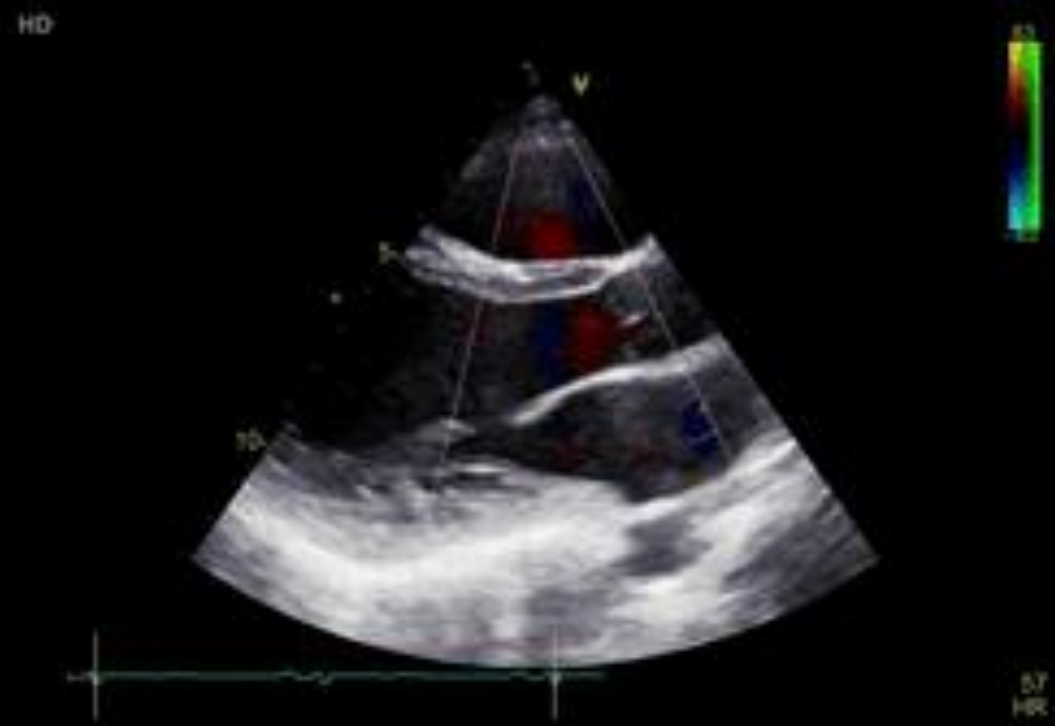
- Tn+ on random sampling max value – 1687 (ULN 19).
- CPEX – VO_2 max 69% of predicted.


84
35
HF/enlarged heart
74
No details
No details
74
Screening pending
71
Screening pending
95
CAD
73
SCD - known CAD
Cause of death MI
68
Diabetes/HTN
63
AF<60 years old
40
HCM
genetics performed - sarcomeric mutation
44
Normal screening
46
Normal screening
42
Palpitations
TWI V1-V3/RWMAs on TTE
40
33
Palpitations
17
14
Normal screening
11
6
1.5
3


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

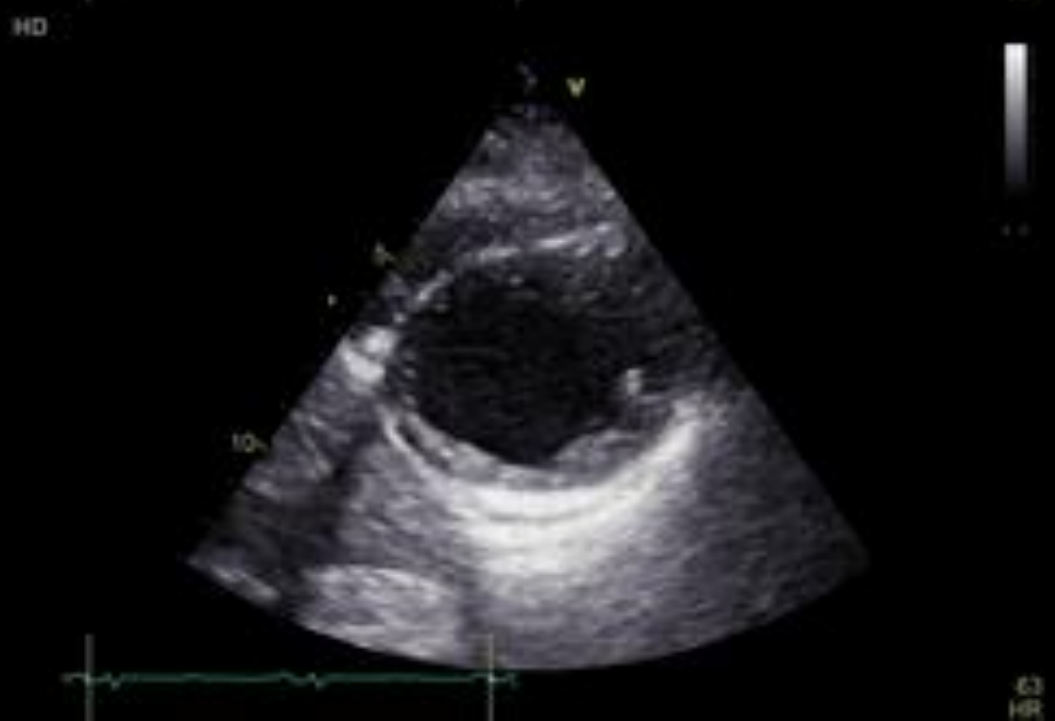
Further electrocardiographic testing

- Holter 1 – 6324 PVCS, sustained episode of idioventricular rhythm.
- Holter 2 – 6625 PVCs, no complex arrhythmias.
- Signal averaged ECG
  - QRSd 97 ms (<114 ms)
  - HFLAD 15 ms (<38 ms)
  - RMS40 67 μV

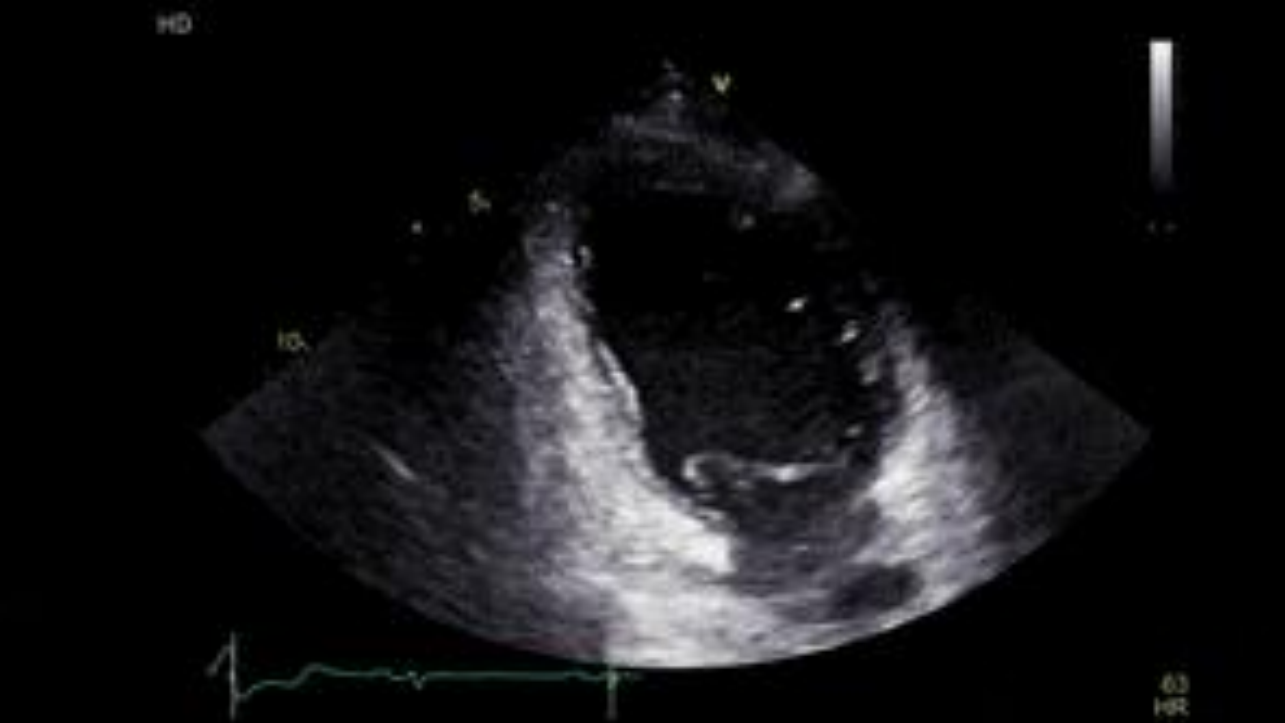

HD
57
HR


HD
57
HR


HD
59
HR

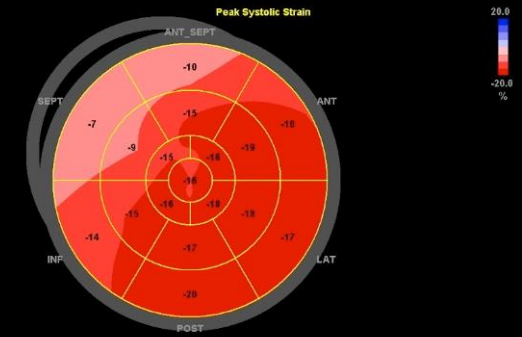

HD
63
HR


HD
58
HR


HD
63
HR


HD
61
HR


HD
65
HR



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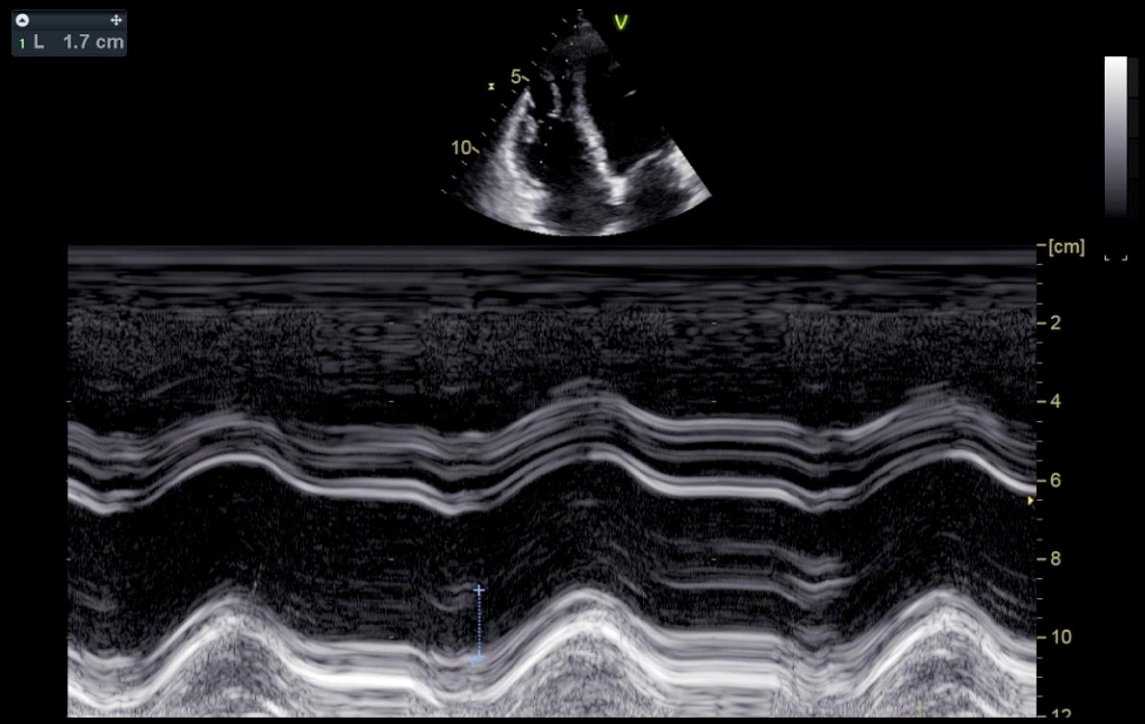
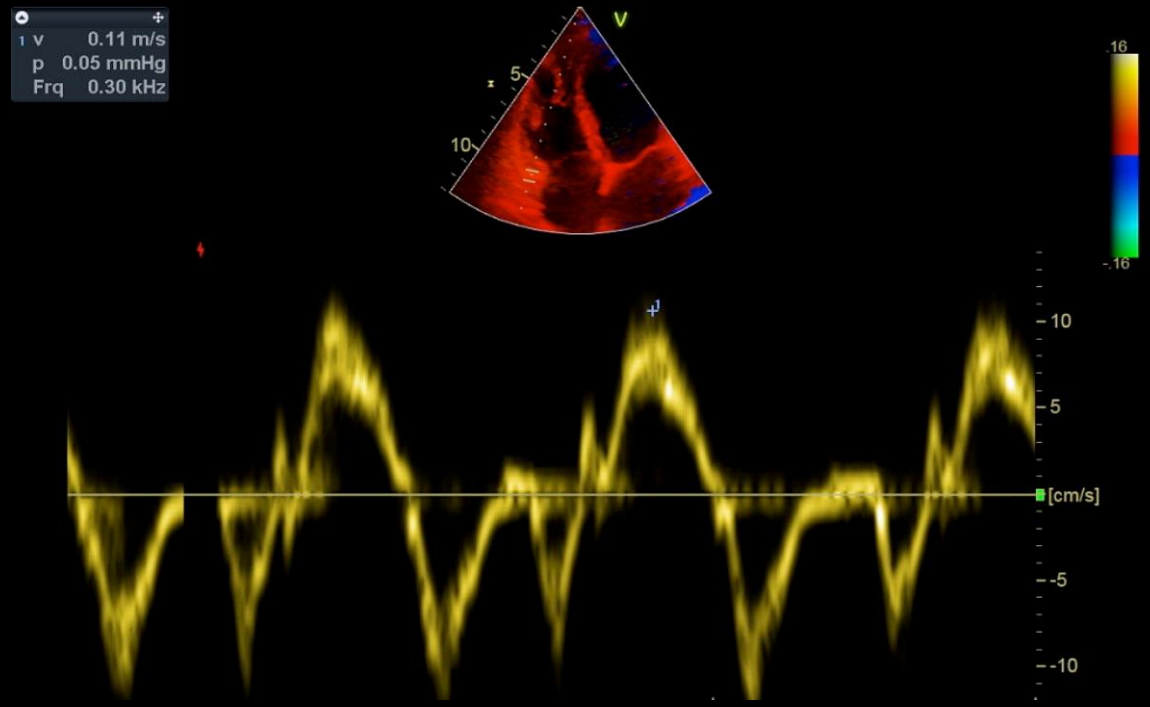
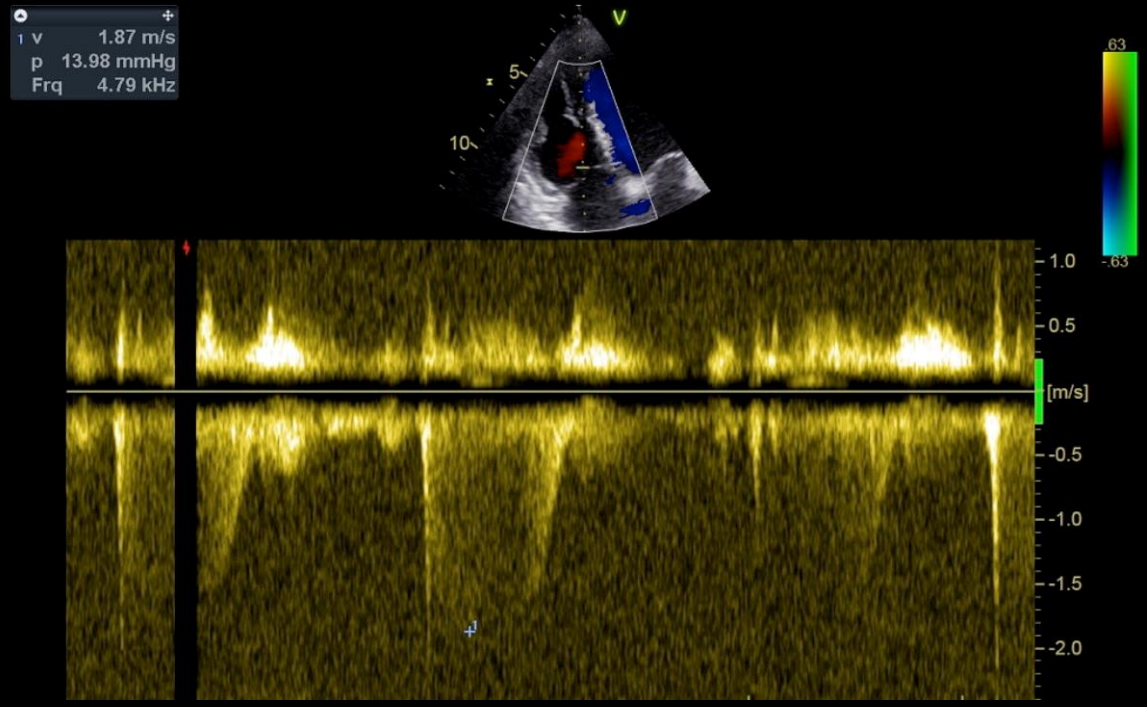
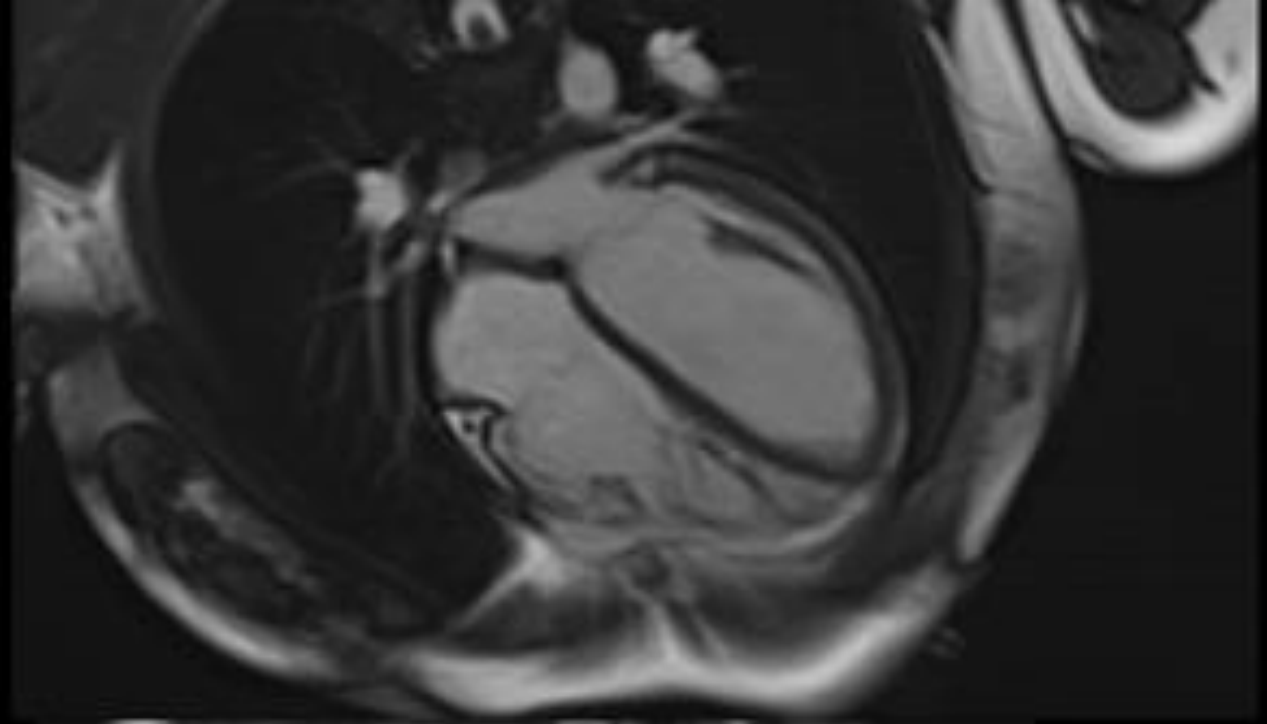
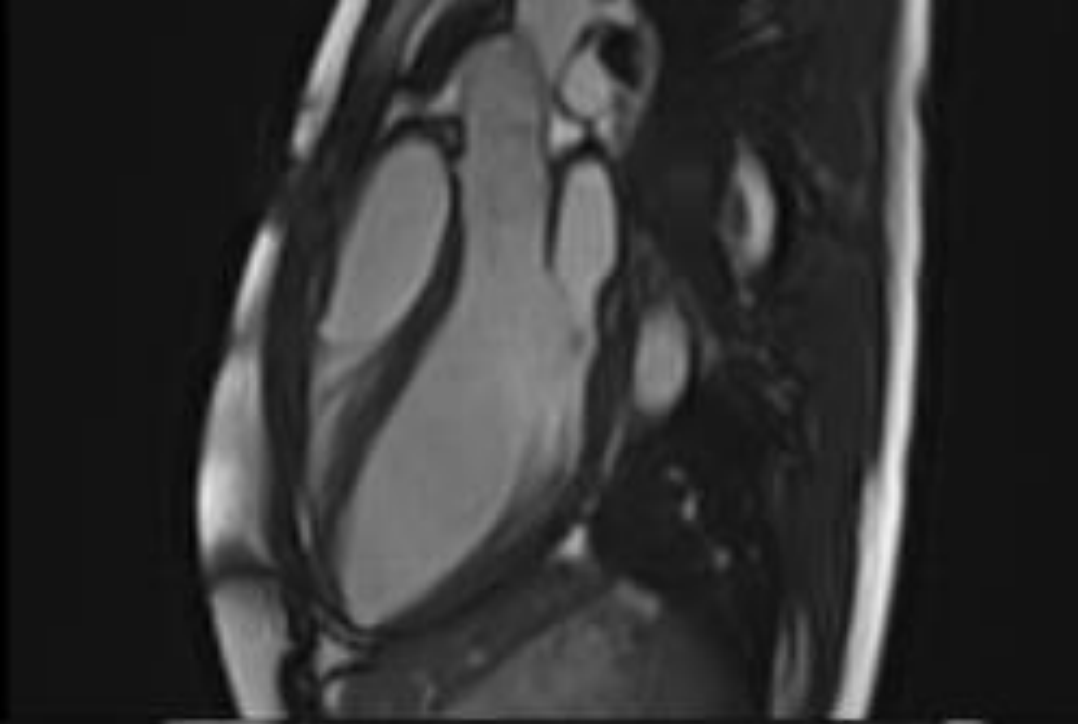
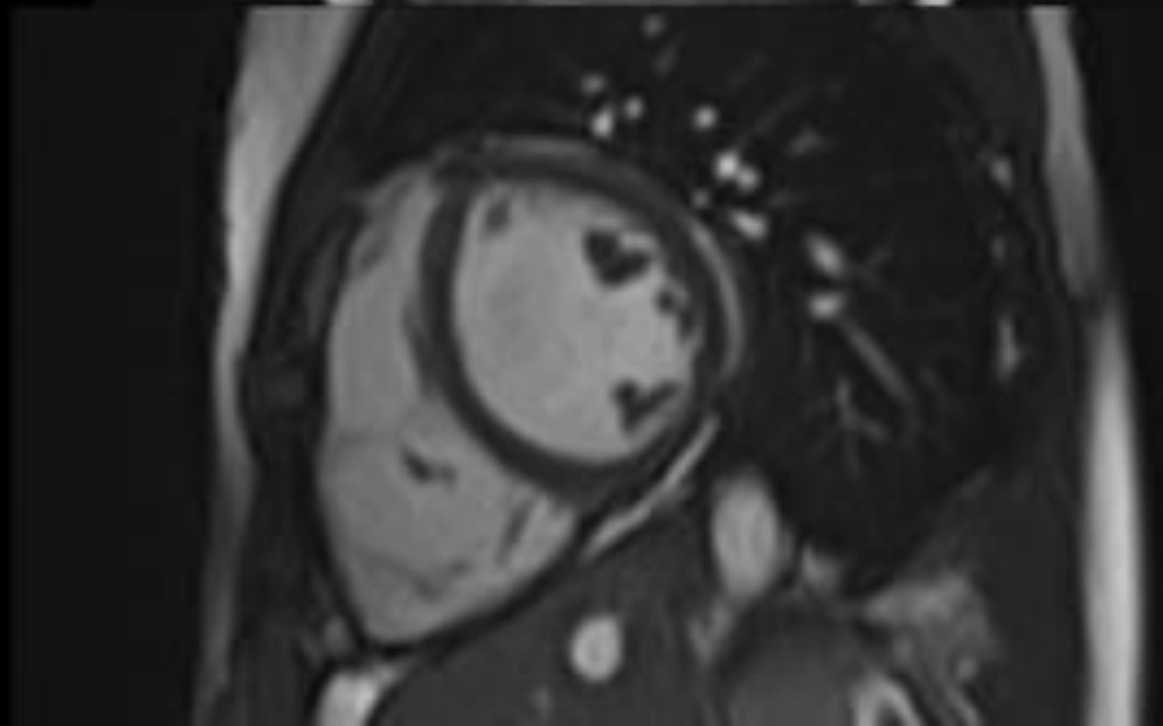
GLPS_LAX	-15.1 %	AVC_AUTO	381 msec
GLPS_A4C	-14.4 %	HR_ApLAX	64 bpm
GLPS_A2C	-16.2 %	FR_min	55 fps
GLPS_Avg	-15.2 %		

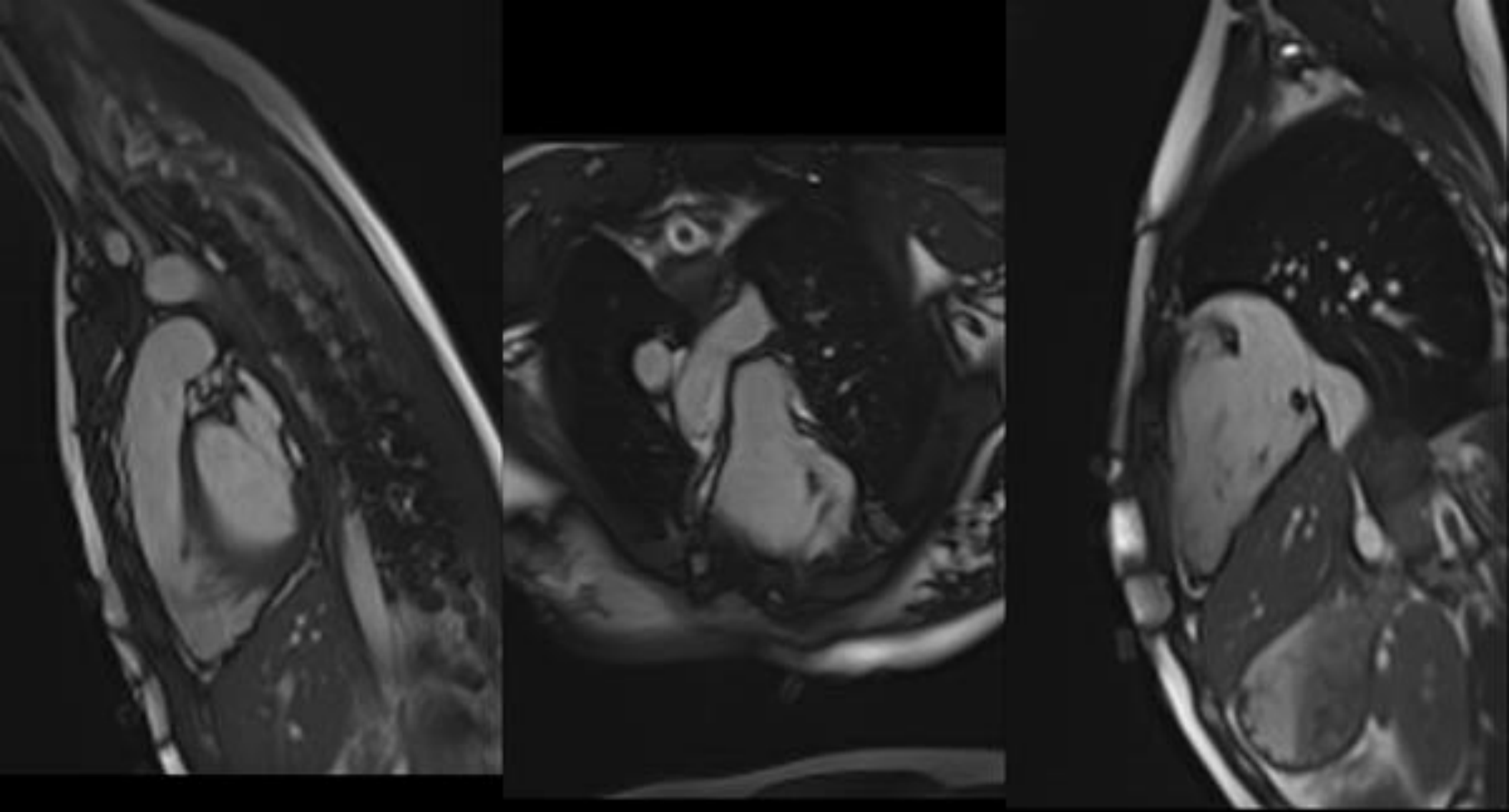


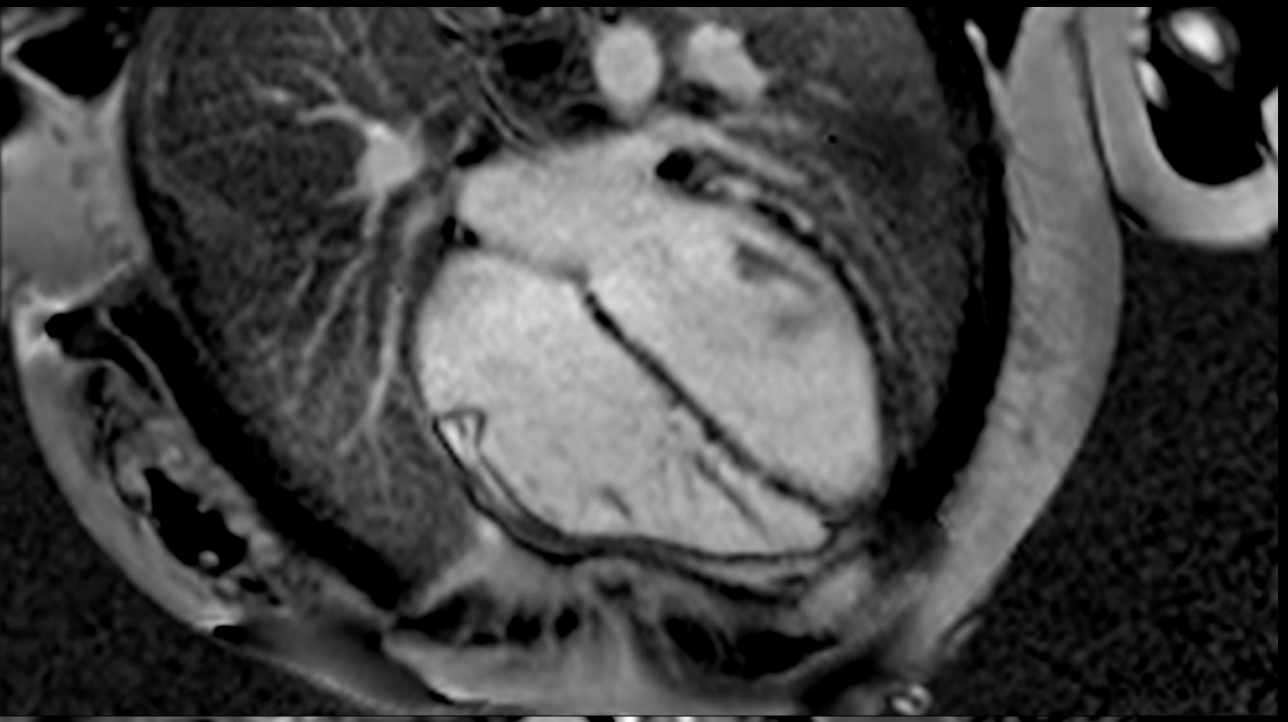
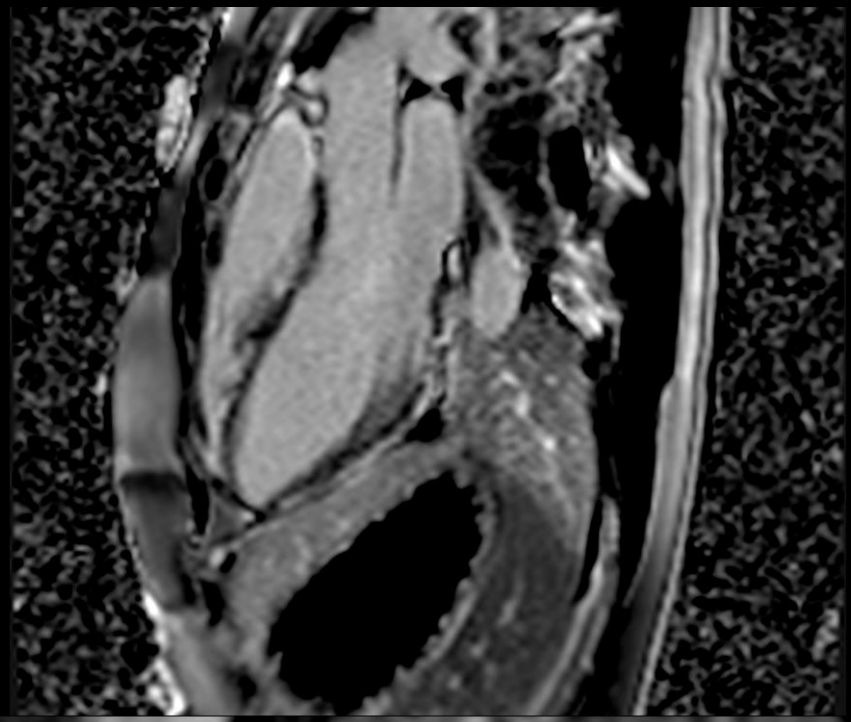
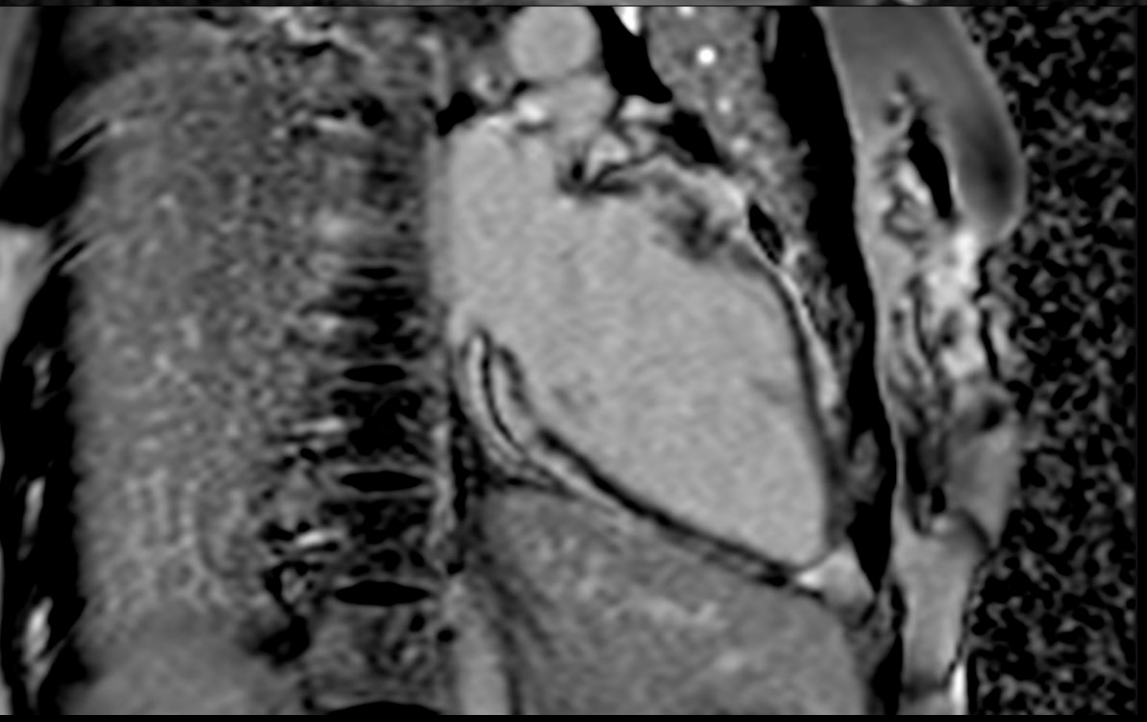
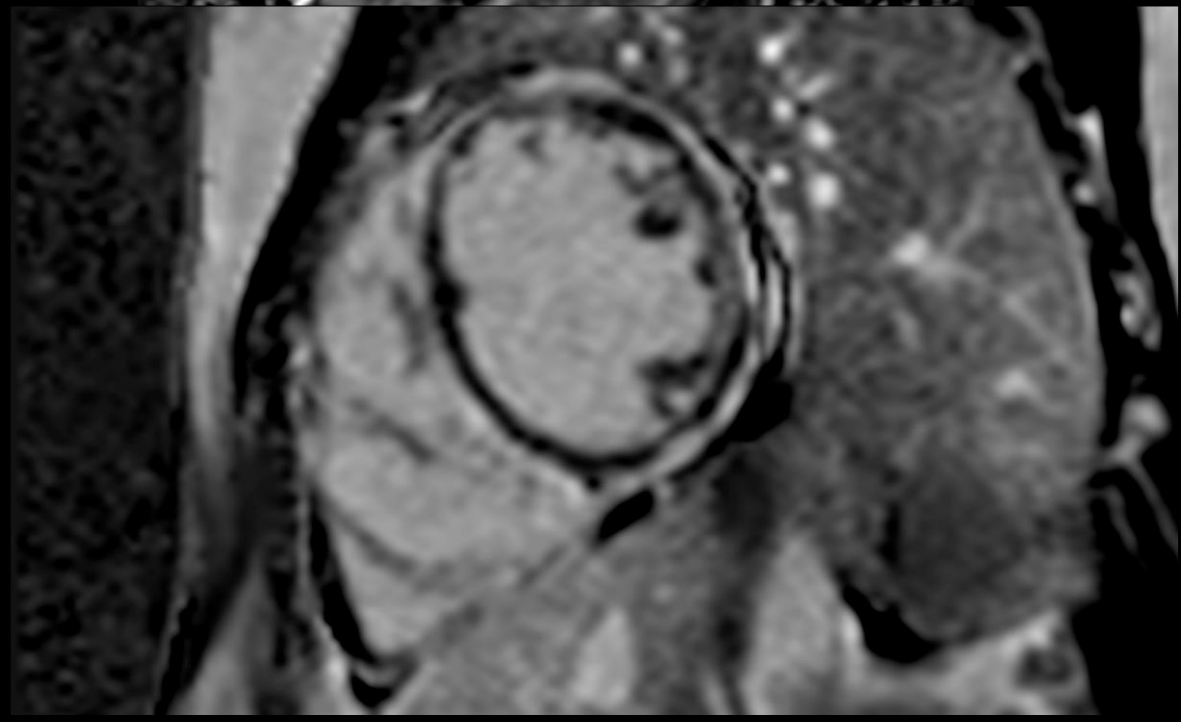




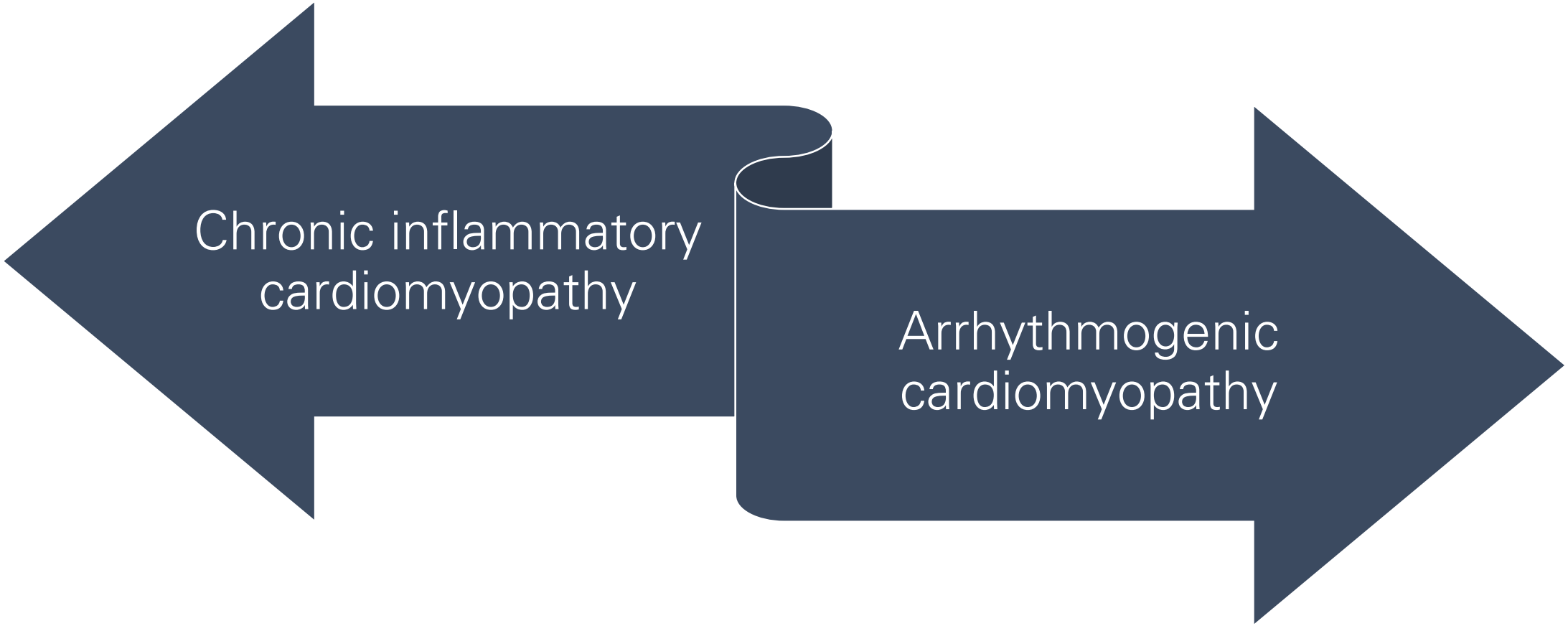







Differential diagnosis

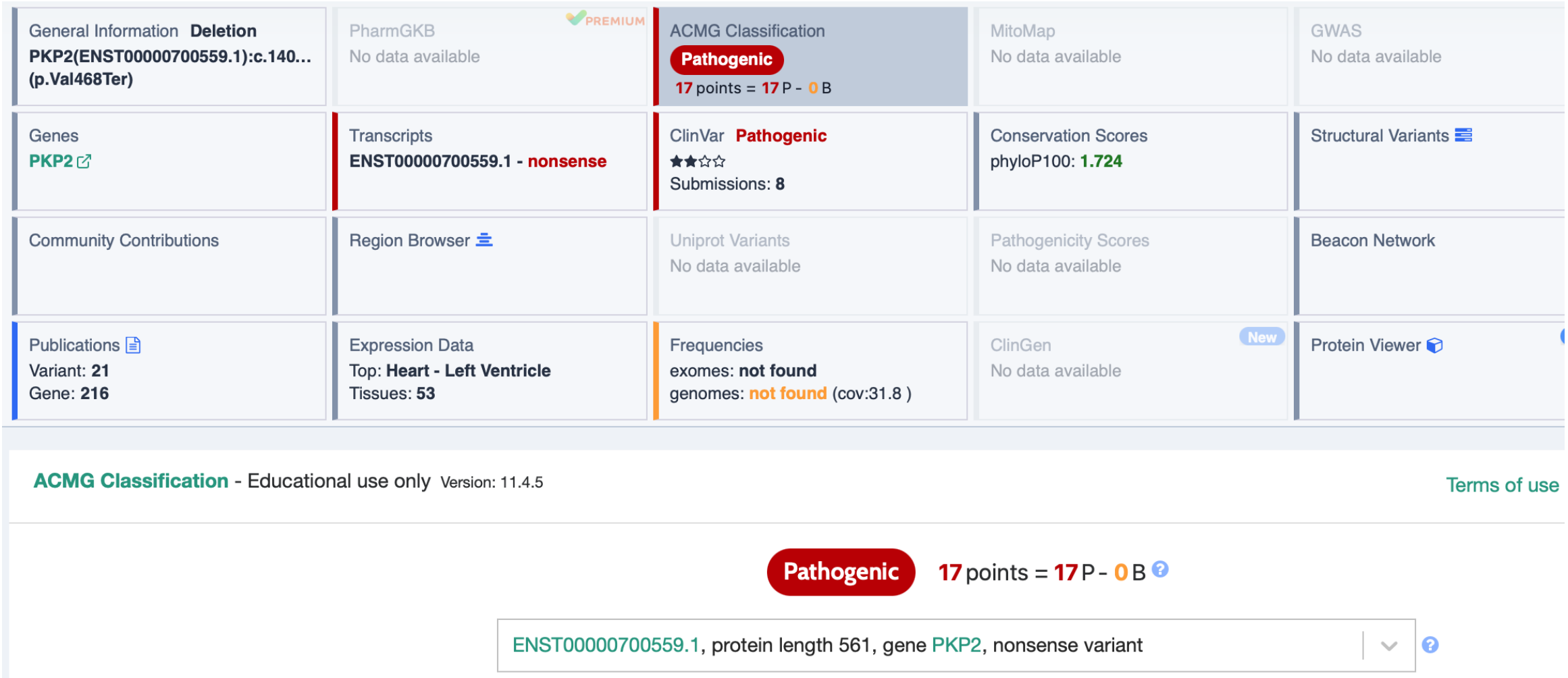


*Tertiary differential: cardiac sarcoidosis

Endomyocardial biopsy

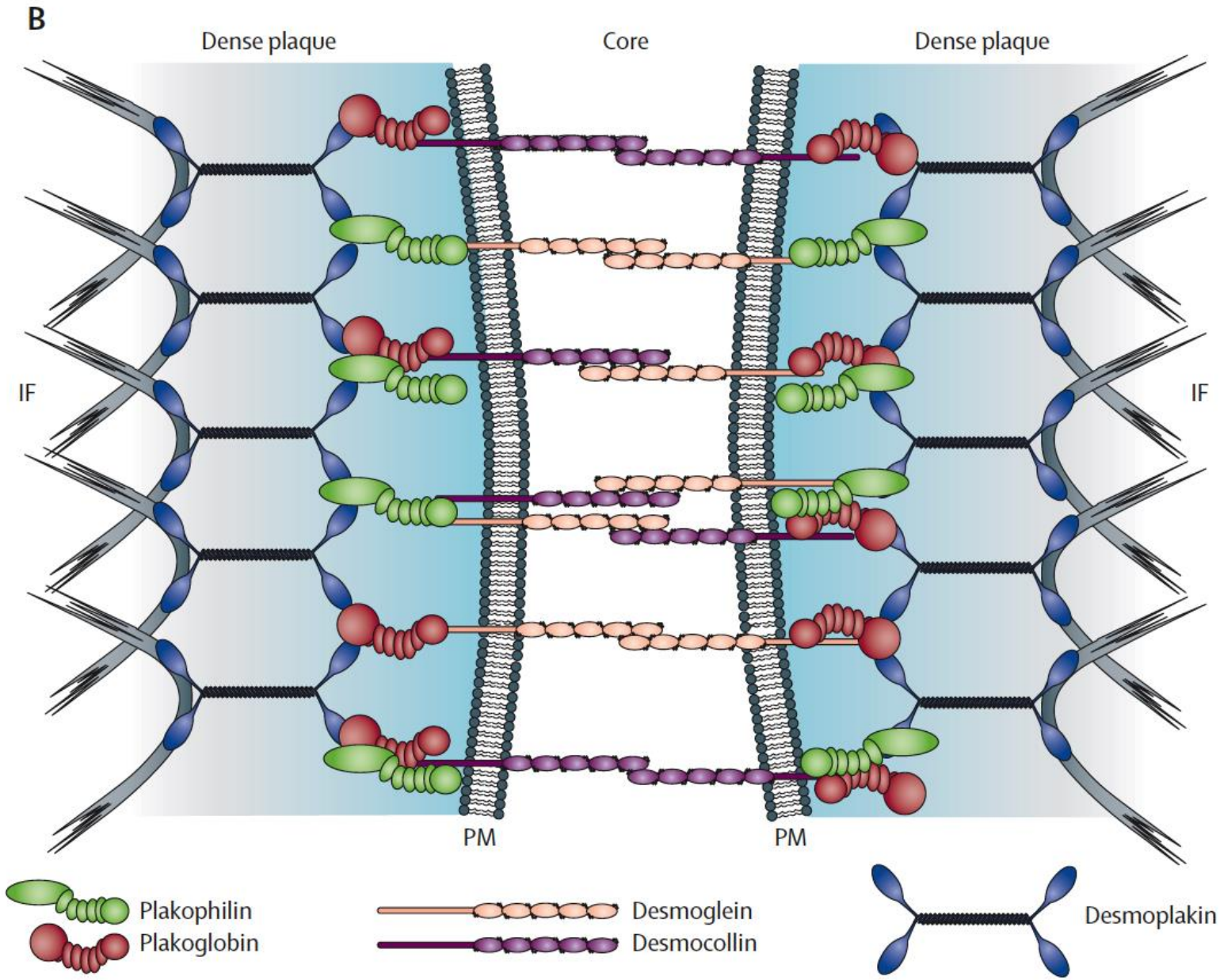
- Close temporal proximity to Tn+ episode.
- Diffuse fibrosis, non-specific muscle cell hypertrophy.
- Immunohostochemistry negative for inflammatory infiltrates.

Genetic testing - PKP2 c.2509delA p.(Ser837ValfsX94)



ARVC: A Disease of the Desmosome

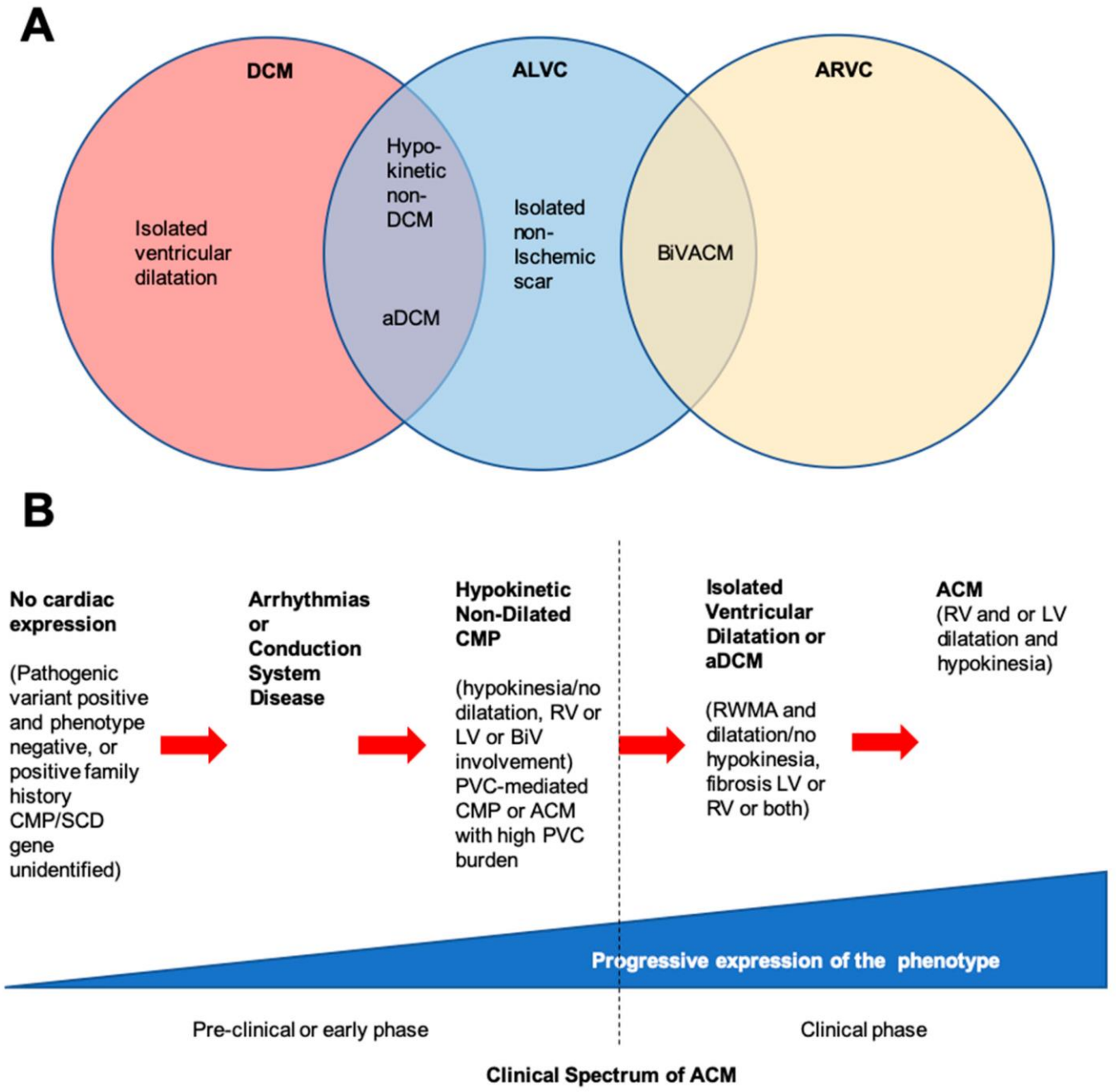
- Desmosomes: specialised intercellular junctions of cardiac & epithelial tissue
- Connect intermediate filaments to cytoplasmic membrane in adjacent cells



Basso C, et al. Lancet. 2009.

A shifting paradigm – ARVC to ALVC to ACM

- ACM includes all of the following:
  - Isolated RV involvement (ARVC)
  - Biventricular cardiomyopathy
  - Isolated LV involvement (with or without LV dysfunction) – (ALVC)



Patel V, et al. International Journal of Molecular Sciences. 2020

The Padua criteria for Arrhythmogenic Cardiomyopathy (ACM)

- ALVC ("dominant-left" variant)
- 1. Structural (with or without morpho- ALVC ("dominant-left" variant) functional) abnormalities of the LV

  2. ACM-causing gene-mutation, in the absence of RV involvement

Category	Right ventricle (upgraded 2010 ITF diagnostic criteria)	Left ventricle (new diagnostic criteria)
I. Morpho-functional ventricular abnormalities	*By echocardiography, CMR or angiography:* *Major* • Regional RV akinesia, dyskinesia, or bulging *plus* one of the following: - global RV dilatation (increase of RV EDV according to the imaging test specific nomograms) - global RV systolic dysfunction (reduction of RV EF according to the imaging test specific nomograms) *Minor* • Regional RV akinesia, dyskinesia or aneurysm of RV free wall	*By echocardiography, CMR or angiography:Minor* • Global LV systolic dysfunction (depression of LV EF or reduction of echo-cardiographic global longitudinal strain), with or without LV dilatation (increase of LV EDV according to the imaging test specific nomograms for age, sex, and BSA) *Minor* • Regional LV hypokinesia or akinesia of LV free wall, septum, or both
II. Structural myocardial abnormalities	*By CE-CMR:Major* • Transmural LGE (stria pattern) of ≥1 RV region(s) (inlet, outlet, and apex in 2 orthogonal views) *By EMB (limited indications):Major* • Fibrous replacement of the myocardium in ≥1 sample, with or without fatty tissue	*By CE-CMR:Major* • LV LGE (stria pattern) of ≥1 Bull's Eye segment(s) (in 2 orthogonal views) of the free wall (subepicardial or midmyocardial), septum, or both (excluding septal junctional LGE)
III. Repolarization abnormalities	*Major* • Inverted T waves in right precordial leads (V_1,V_2, and V_3) or beyond in individuals with complete pubertal development (in the absence of complete RBBB) *Minor* • Inverted T waves in leads V1 and V2 in individuals with completed pubertal development (in the absence of complete RBBB) • Inverted T waves in V1,V2,V3 and V4 in individuals with completed pubertal development in the presence of complete RBBB.	*Minor* • Inverted T waves in left precordial leads (V_4-V_6) (in the absence of complete LBBB)
IV. Depolarization abnormalities	*Minor* • Epsilon wave (reproducible low-amplitude signalsbetween end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3) • Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2, or V3 (in the absence of complete RBBB)	*Minor* • Low QRS voltages (<0.5 mV peak to peak) in limb leads (in the absence of obesity, emphysema, or pericardial effusion)
V. Ventricular arrhythmias	*Major* • Frequent ventricular extrasystoles (>500 per 24 h), non-sustained or sustained ventricular tachycardia of LBBB morphology *Minor* • Frequent ventricular extrasystoles (>500 per 24 h), non-sustained or sustained ventricular tachycardia of LBBB morphology with inferior axis ("RVOT pattern")	*Minor* • Frequent ventricular extrasystoles (>500 per 24 h), non-sustained or sustained ventricular tachycardia with a RBBB morphology (excluding the "fascicular pattern")
VI. Family history/genetics	*Major* • ACM confirmed in a first-degree relative who meets diagnostic criteria • ACM confirmed pathologically at autopsy or surgery in a first degree relative • Identification of a pathogenic or likely pathogenetic ACM mutation in the patient under evaluation *Minor* • History of ACM in a first-degree relative in whom it is not possible or practical to determine whether the family member meets diagnostic criteria • Premature sudden death (<35 years of age) due to suspected ACM in a first-degree relative • ACM confirmed pathologically or by diagnostic criteria in a second-degree relative	

Corrado D, et al. Int J Cardiol. 2020

Myocarditis and ARVC
An old paradigm resurfacing

Circulation
Volume 94, Issue 5, 1 September 1996; Pages 983-991
https://doi.org/10.1161/01.CIR.94.5.983

ARTICLE

Arrhythmogenic Right Ventricular Cardiomyopathy

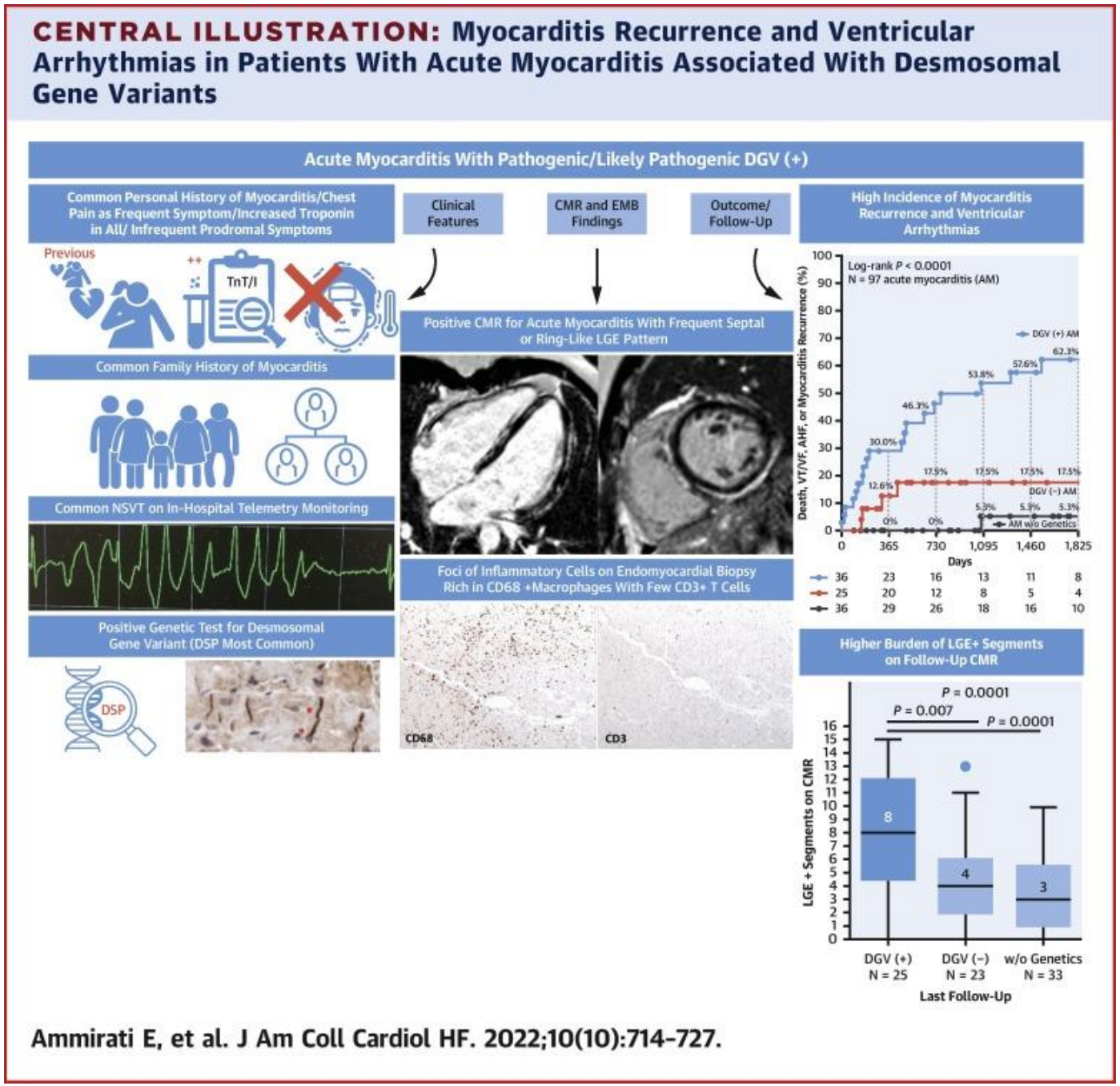
Dysplasia, Dystrophy, or Myocarditis?

Cristina Basso, Gaetano Thiene, Domenico Corrado, Annalisa Angelini, Andrea Nava, and Marialuisa Valente

Desmosomal ACM

vs

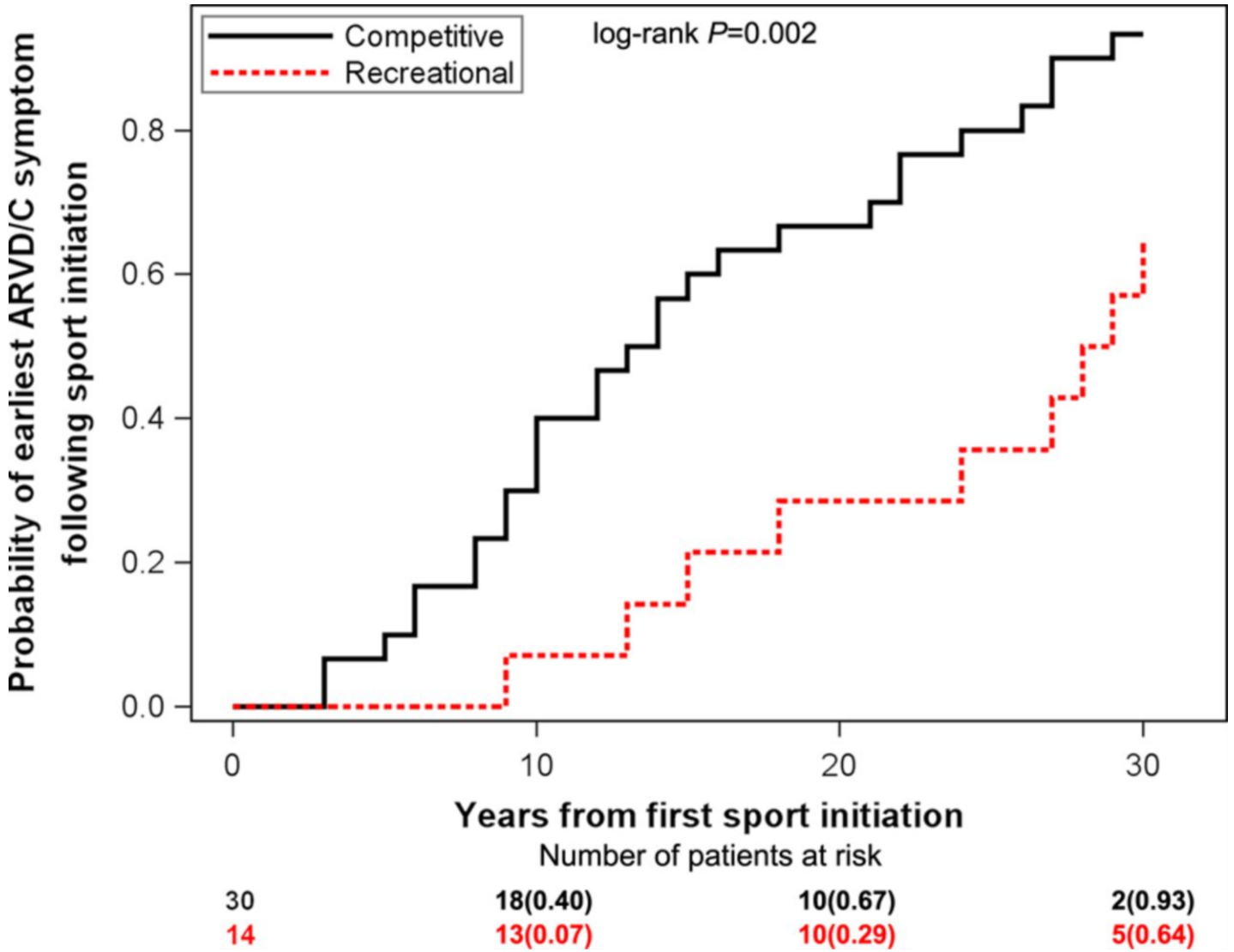
Myocarditis



Ammirati E, et al. J Am Coll Cardiol HF. 2022;10(10):714–727.

Clinical management based on genetic results

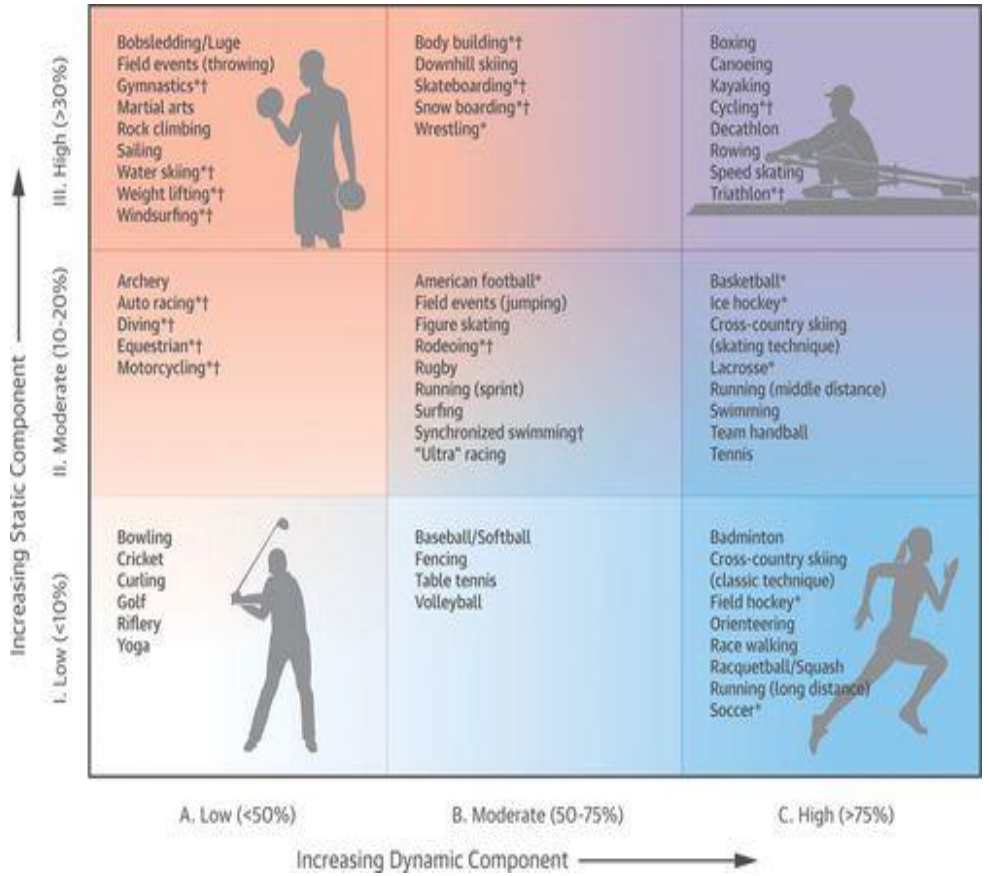
- Exercise promotes phenotype expression/symptoms regardless of age



Ruwald AC, Eur Heart J. 2015; 36(27):1735-43.

Current recommendations

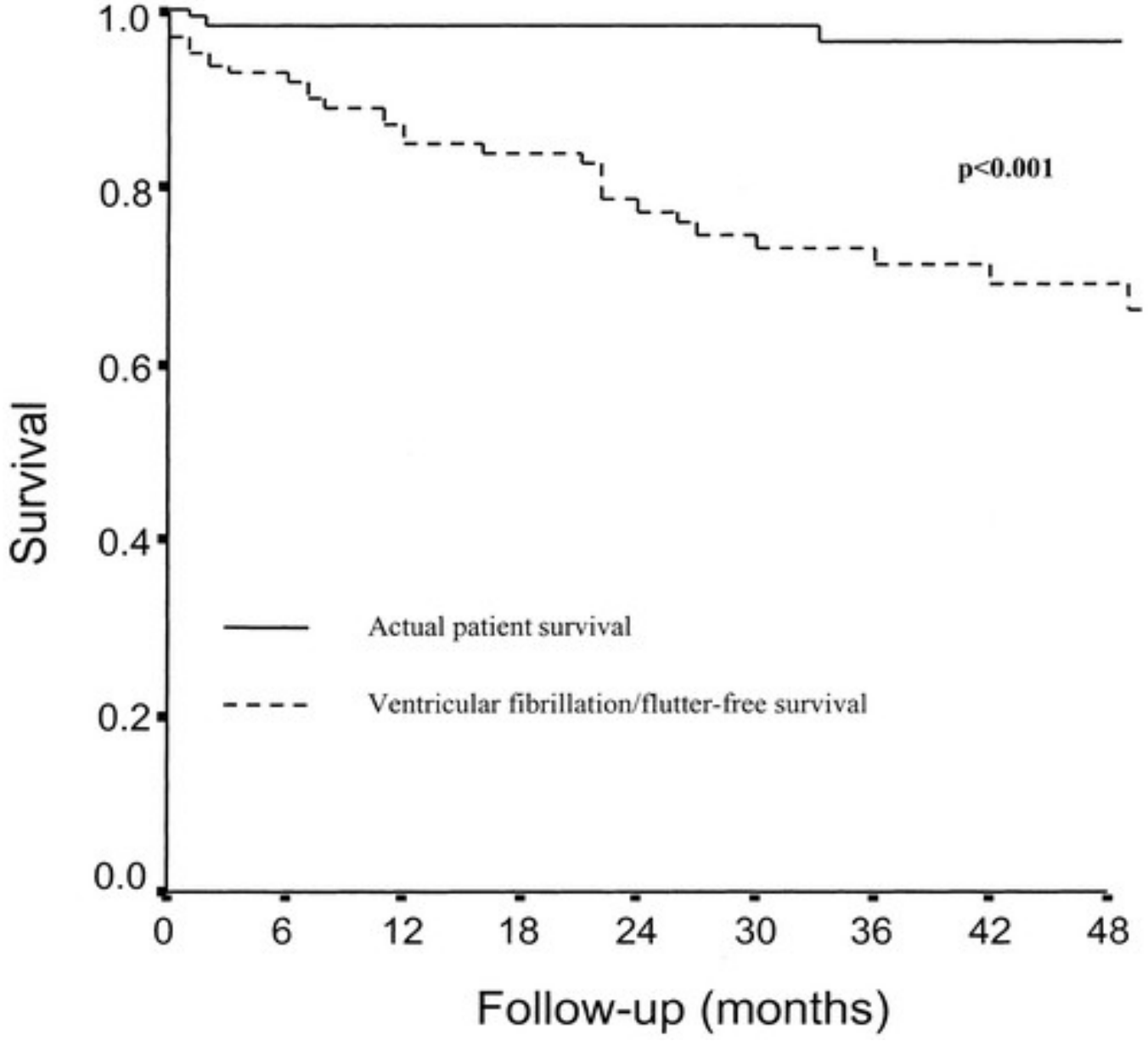
- AHA/ACC 2015: Athletes with a possible diagnosis of ARVC should not participate in most competitive sports, with the possible exception of low-intensity class 1A sports (Class III; Level of Evidence C).
- EAPC/ESC 2019: Athletes who are genetic carriers of pathogenic AC-associated desmosomal mutations (even in the absence of phenotypic expression of the disease) should not participate in competitive sports. These athletes should be advised to limit their exercise programmes to leisure-time activities and remain under clinical surveillance (Class IIa/Level of Evidence C).



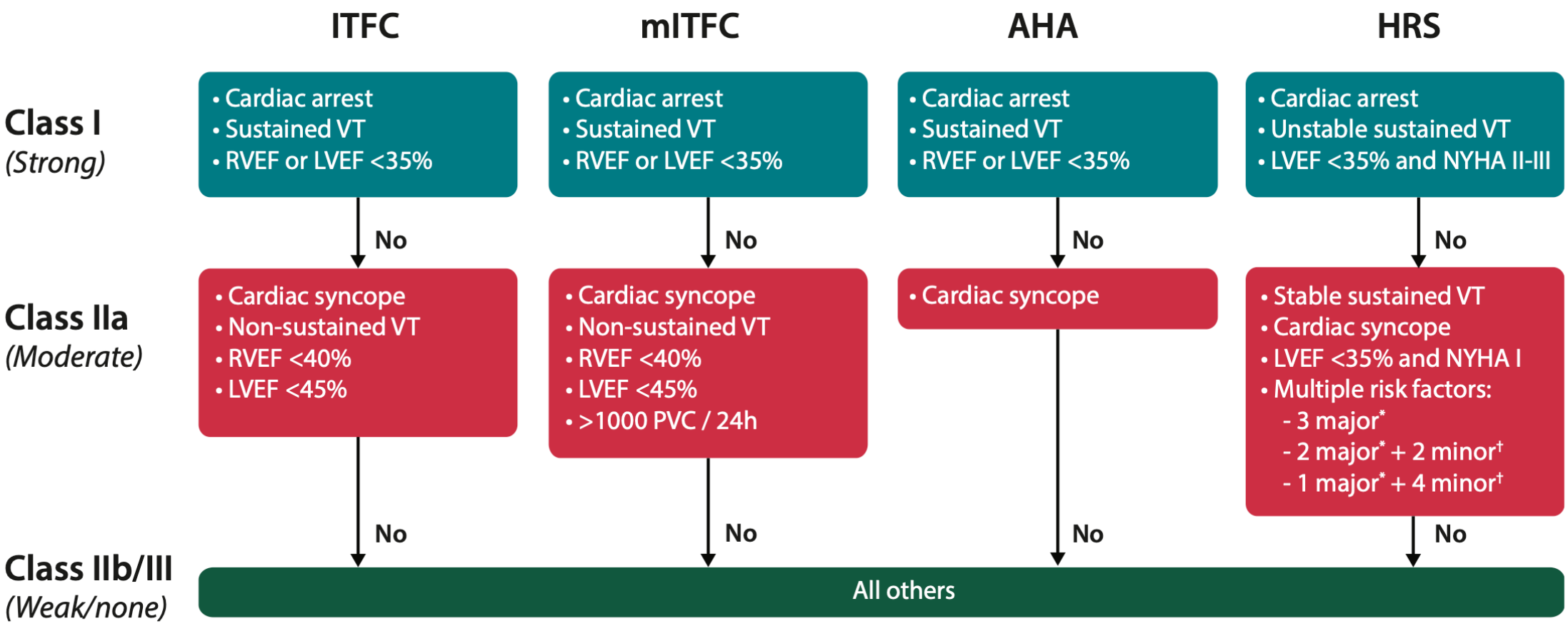
Maron BJ, et al. Circulation. 2015 Dec 1;132(22):e273-80.

Pelliccia A, et al. Eur Heart J. 2019 Jan 1;40(1):19-33.

Primary prevention ICD implantation improves survival in ARVC/ACM



Corrado D, et al. Circulation. 2003.



*Major: Non-sustained VT, inducibility to VT at EPS, LVEF ≤49%

†Minor: Male sex, >1000 PVCs/24h, RV dysfunction as per major 2010 TFC, proband status, multiple desmosomal variants.

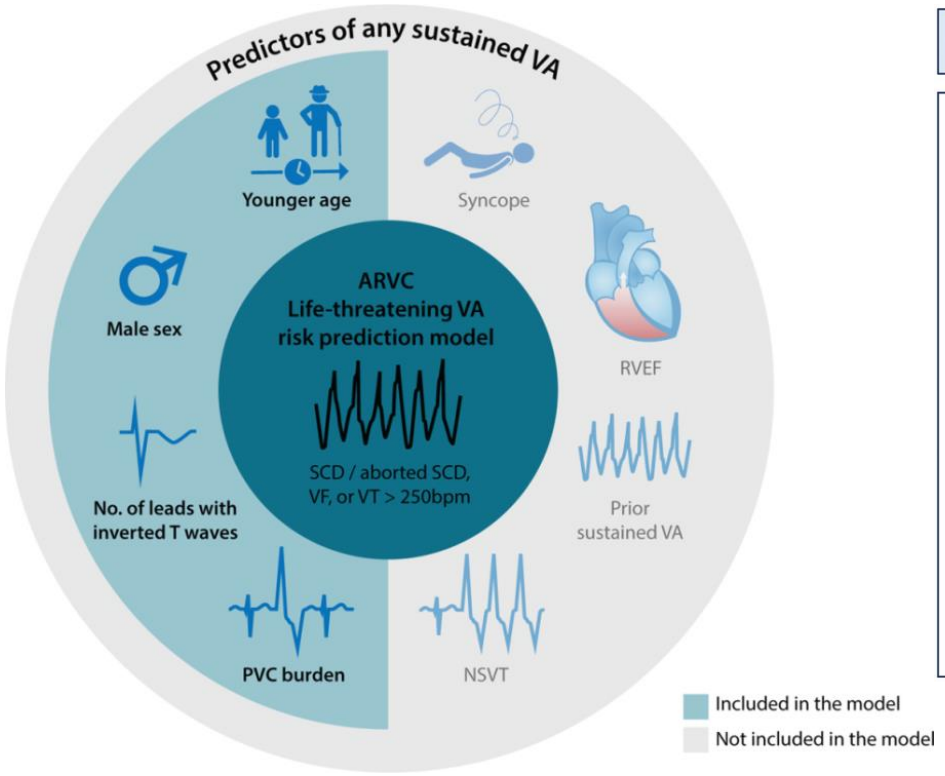
If both non-sustained VT and PVC criteria are present, only non-sustained VT can be used.

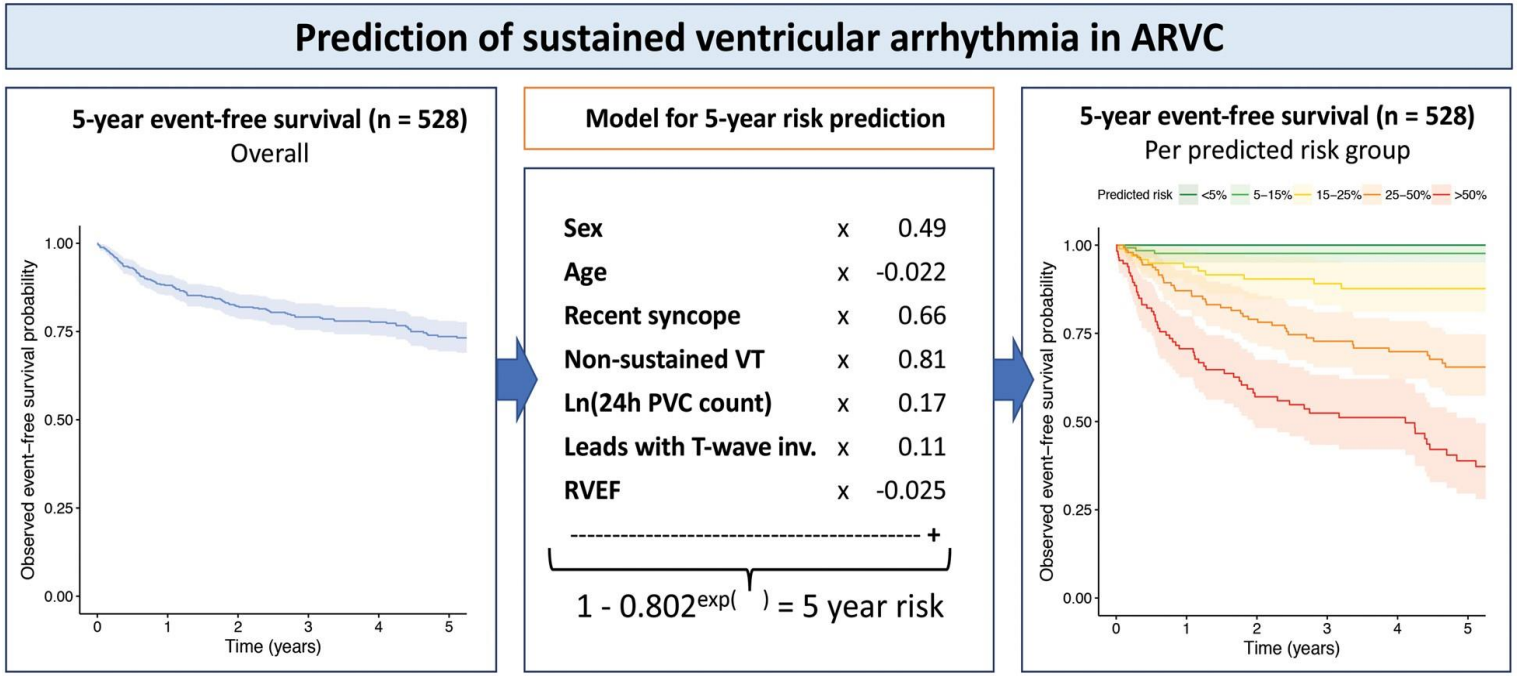
Bosman LP, et al. Europace. 2021

Electrophysiologic testing – VT stim

- Negative for sustained VT

Personalized risk estimation in ARVC





*applicable in 2011 TF criteria fulfilling patients

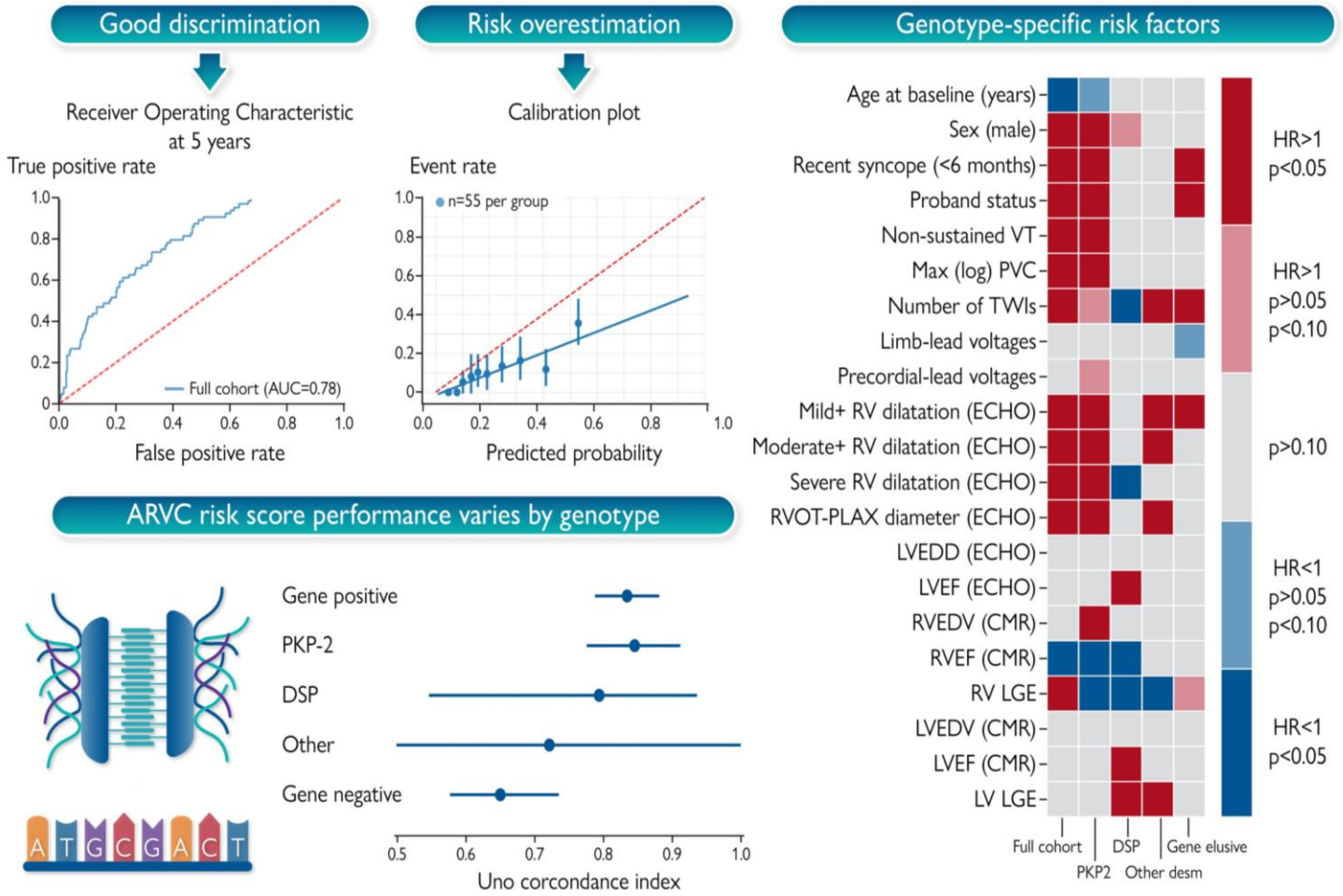
Cadrin-Tourigny J et al, Eur Heart J 2019

Cadrin-Tourigny J et al, J Am Coll Cardiol 2021

ARVC risk score performs better in PKP2 mutation carriers

Calculated ARVC Risk score 27.8%/5 years

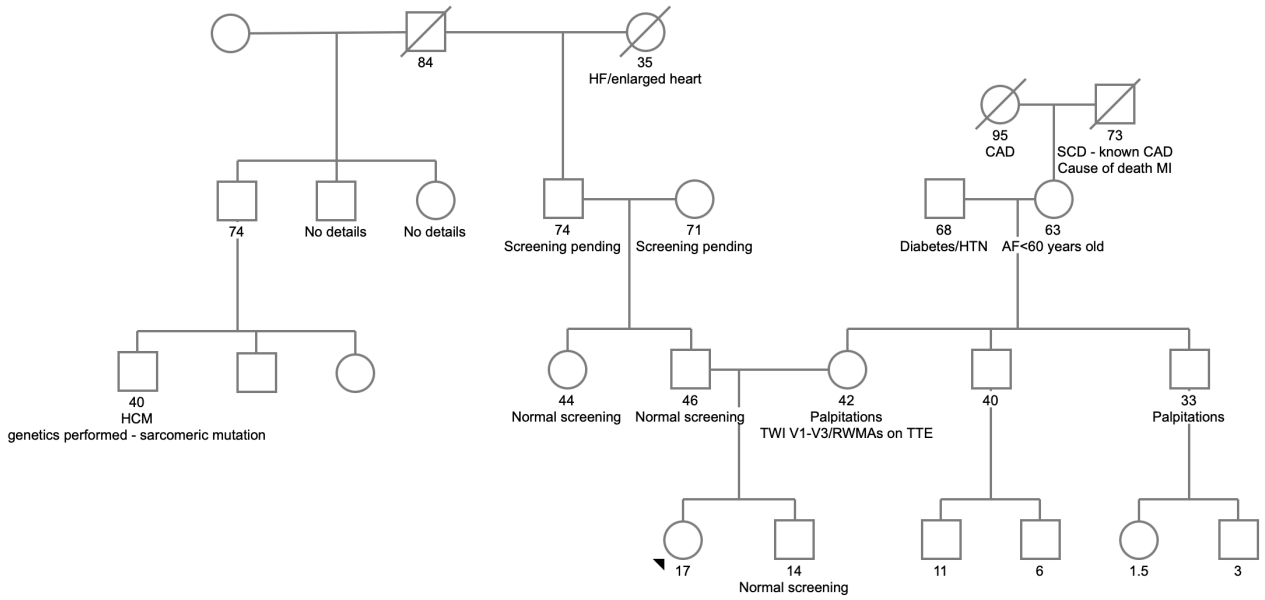
PVS adjusted risk 13.8%/5 years.



Protonotarios A, et al. Eur Heart J. 2022

Case resolution

- Primary prevention ICD implanted
- Appropriate shock for fast VT delivered 1 year after implantation, during exercise.
- Further EF reduction following VT episode.
- Mother tested positive for PKP2 mutation, cascade screening ongoing.



Conclusions

- Arrhythmogenic cardiomyopathy may frequently exhibit as myocarditis-like episodes.
- Desmosomal mutations are the primary genetic background for such presentations, even in the absence of a clearly malignant family history.
- Phenotype may be exaggerated or concealed by exercise or lack thereof respectively.
- Genetic testing:
  - Establishes an accurate diagnosis and guides treatment
  - Guides gene specific risk stratification for SCD
  - Allows for early lifestyle interventions (on proband and gene+ family members)