KLASIFIKACE A PATOFYZIOLOGIE KARDIOMYOPATIÍ

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ESC European Society of Cardiology

European Heart Journal (2023) **00**, 1–124
https://doi.org/10.1093/eurheartj/ehad194

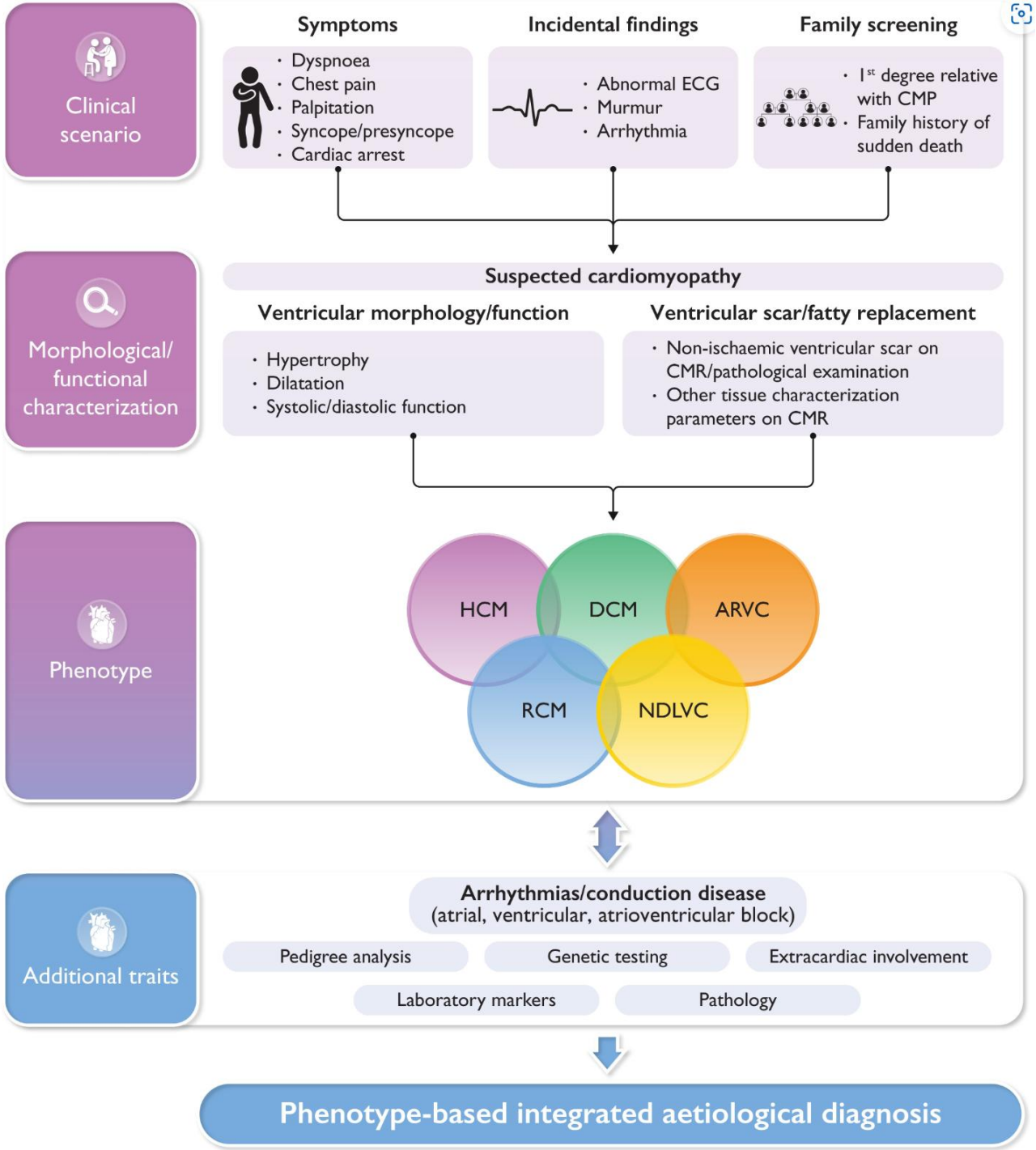
ESC GUIDELINES

2023 ESC Guidelines for the management of cardiomyopathies

Developed by the task force on the management of cardiomyopathies of the European Society of Cardiology (ESC)

Authors/Task Force Members: Elena Arbelo *†, (Chairperson) (Spain), Alexandros Protonotarios ‡, (Task Force Co-ordinator) (United Kingdom), Juan R. Gimeno ‡, (Task Force Co-ordinator) (Spain), Eloisa Arbustini (Italy), Roberto Barriales-Villa (Spain), Cristina Basso (Italy), Connie R. Bezzina (Netherlands), Elena Biagini (Italy), Nico A. Blom[1] (Netherlands), Rudolf A. de Boer (Netherlands), Tim De Winter (Belgium), Perry M. Elliott (United Kingdom), Marcus Flather (United Kingdom), Pablo Garcia-Pavia (Spain), Kristina H. Haugaa (Sweden), Jodie Ingles (Australia), Ruxandra Oana Jurcut (Romania), Sabine Klaassen (Germany), Giuseppe Limongelli (Italy), Bart Loeys [2] (Belgium), Jens Mogensen (Denmark), Iacopo Olivotto (Italy), Antonis Pantazis (United Kingdom), Sanjay Sharma (United Kingdom), J. Peter Van Tintelen (Netherlands), James S. Ware (United Kingdom), Juan Pablo Kaski *†, (Chairperson) (United Kingdom), and ESC Scientific Document Group

Clinical diagnostic workflow of cardiomyopathy



Arbelo et al. Eur Heart J. 2023 Aug 25;ehad194. doi:10.1093/eurheartj/ehad194.

Morphological and functional traits used to describe cardiomyopathy phenotypes

Morphological traits

Ventricular **hypertrophy**: left and/or right

Ventricular **dilatation**: left and/or right

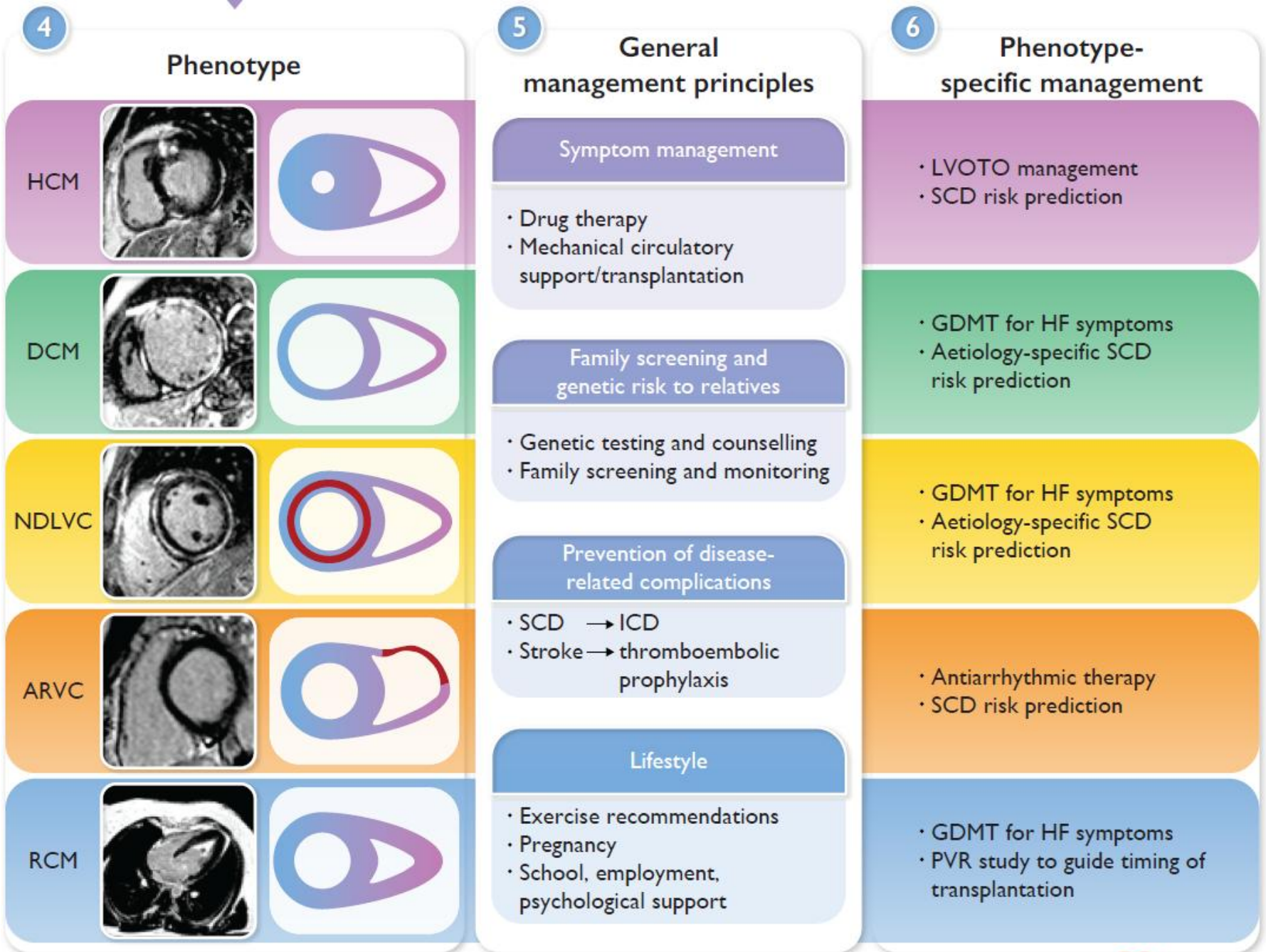
Non-ischaemic ventricular **scar and other myocardial tissue characterization** features on **cardiac magnetic resonance**

Functional traits

Ventricular **systolic dysfunction** (global, regional)

Ventricular **diastolic dysfunction** (restrictive physiology)

Arbelo et al. Eur Heart J. 2023 Aug 25;ehad194. doi:10.1093/eurheartj/ehad194.



Arbelo et al. Eur Heart J. 2023 Aug 25;ehad194. doi:10.1093/eurheartj/ehad194.

DILATED CARDIOMYOPATHY

Definitions – dilated cardiomyopathy

- **Dilated cardiomyopathy (DCM)** is defined as the presence of LV **dilatation and global or regional systolic dysfunction unexplained solely by abnormal loading conditions** (e.g. hypertension, valve disease, CHD) or CAD.

- Very rarely, LV dilatation can occur with normal ejection fraction (EF) in the absence of athletic remodelling or other environmental factors; this is not in itself a cardiomyopathy, but may represent an early manifestation of DCM.

Arbelo et al. Eur Heart J. 2023 Aug 25;ehad194. doi:10.1093/eurheartj/ehad194.

DCM definitions

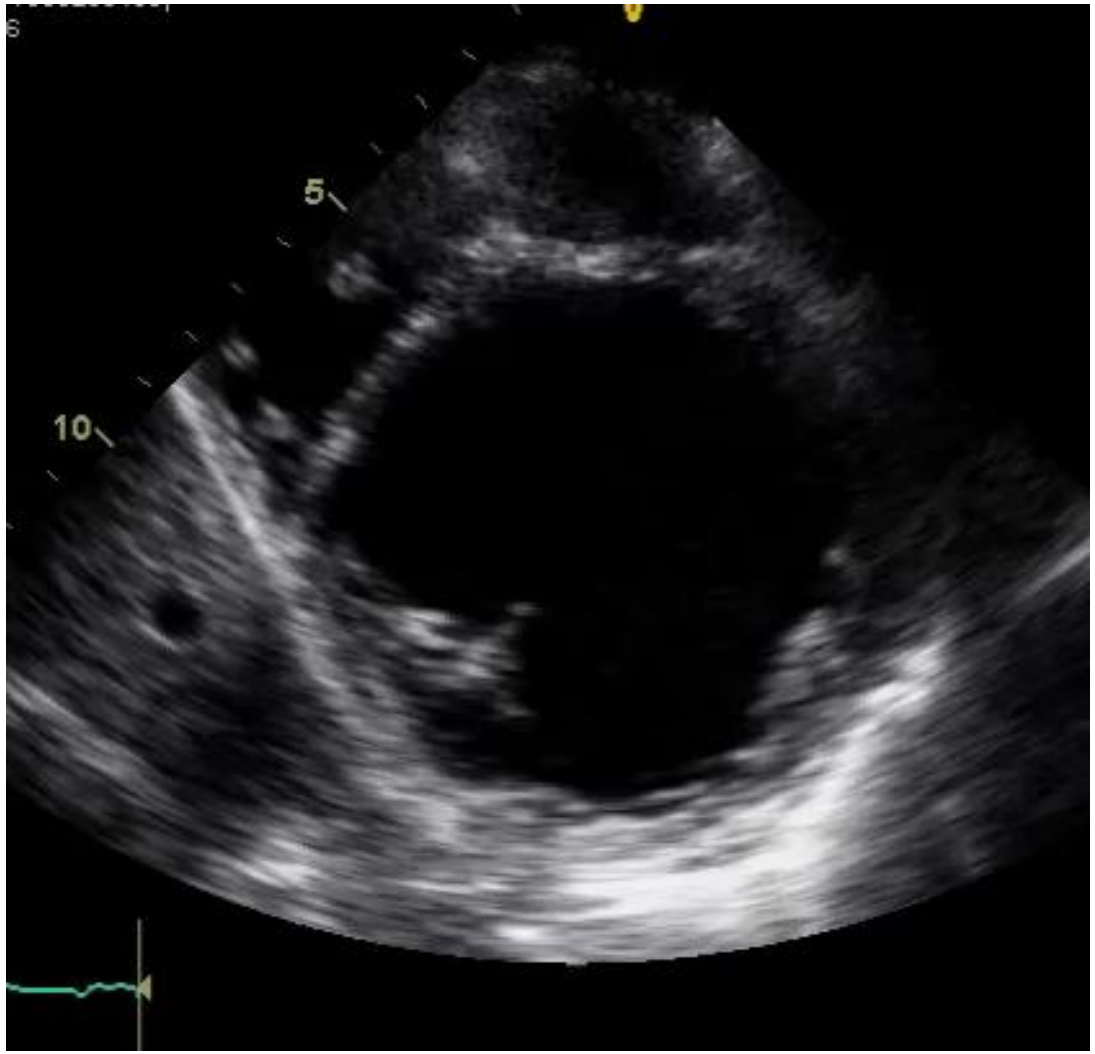
- Left ventricular dilatation is defined by LV end-diastolic dimensions or volumes **>2 z-scores above population mean** values corrected for body size, sex, and/or age.

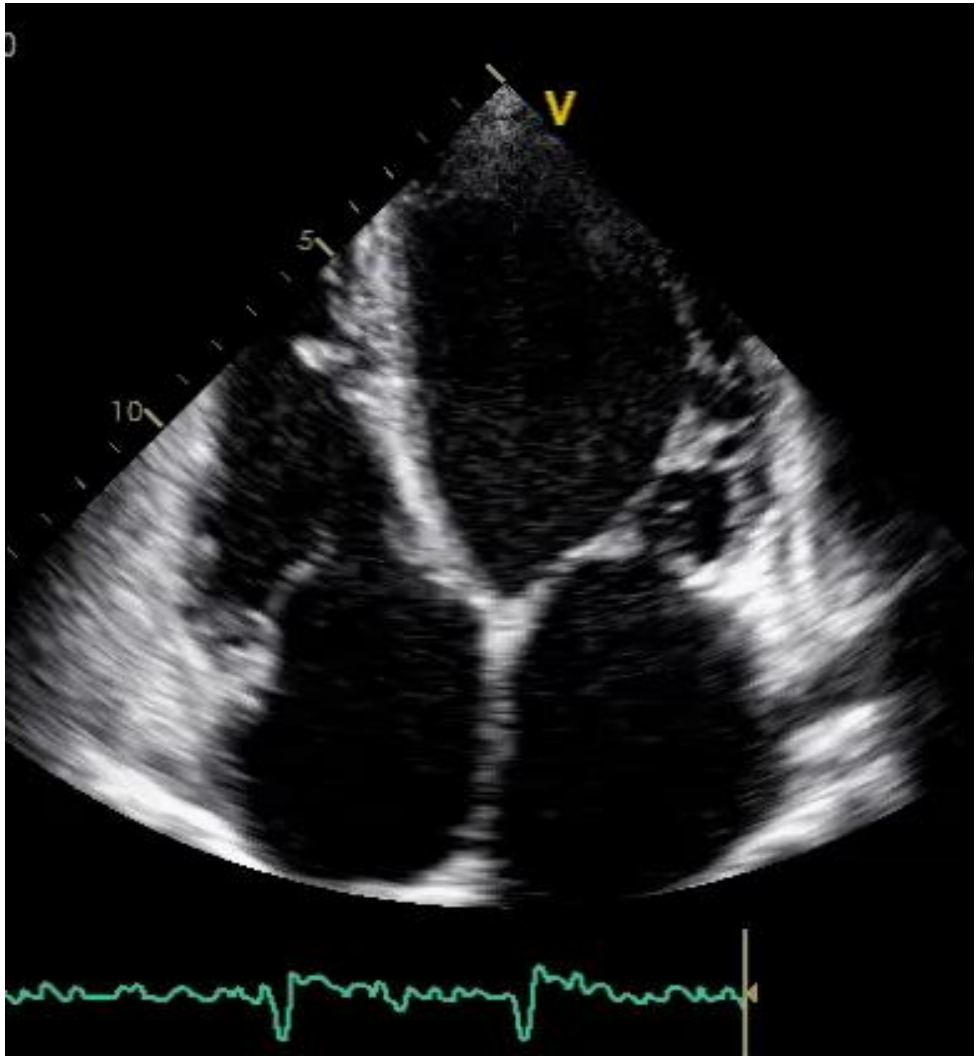
- For adults (ECHO)
  - LV enddiastolic diameter >58 mm in males and >52 in females
  - LVEDV index of ≥75 mL/m^2 in males and ≥62 mL/m^2 in females

- LV global systolic dysfunction is defined by LVEF <50%

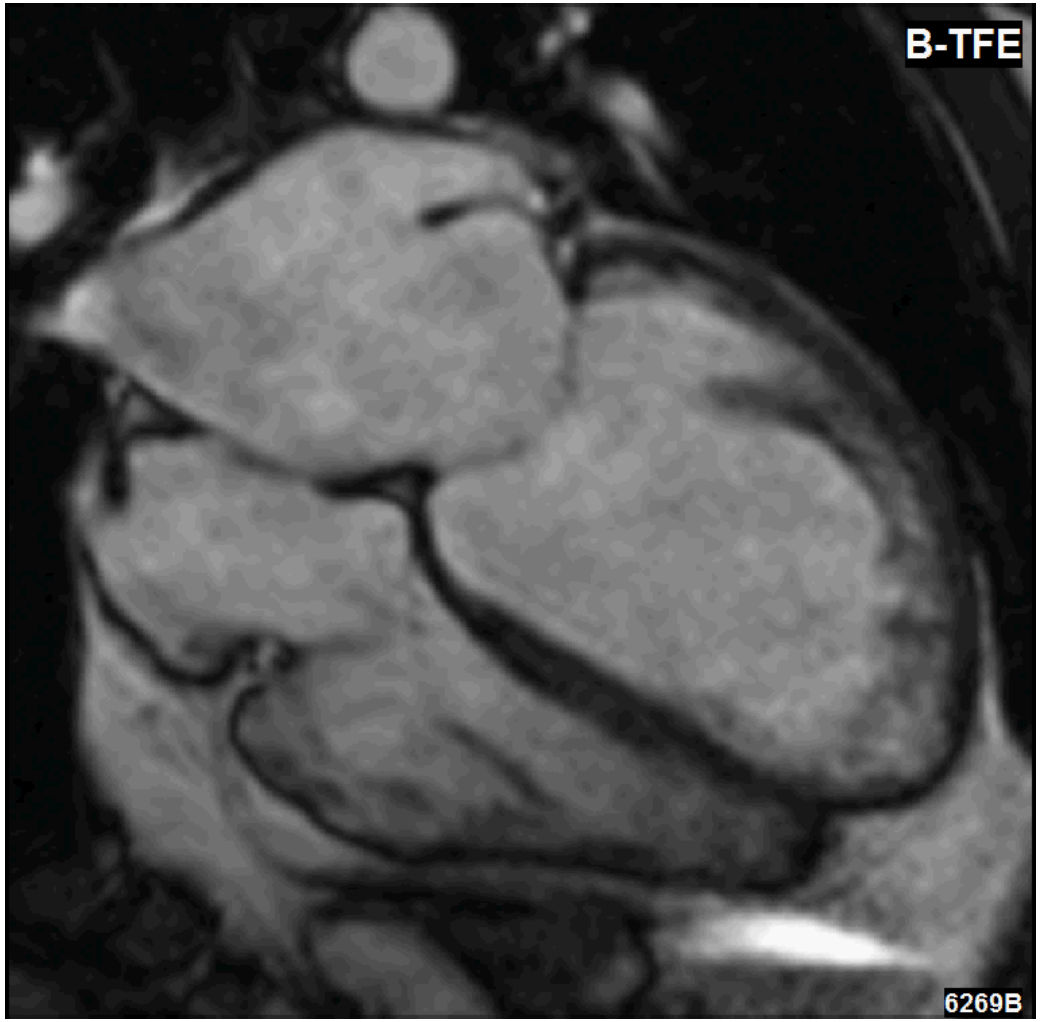
Arbelo et al. Eur Heart J. 2023 Aug 25;ehad194. doi:10.1093/eurheartj/ehad194.

Echocardiography

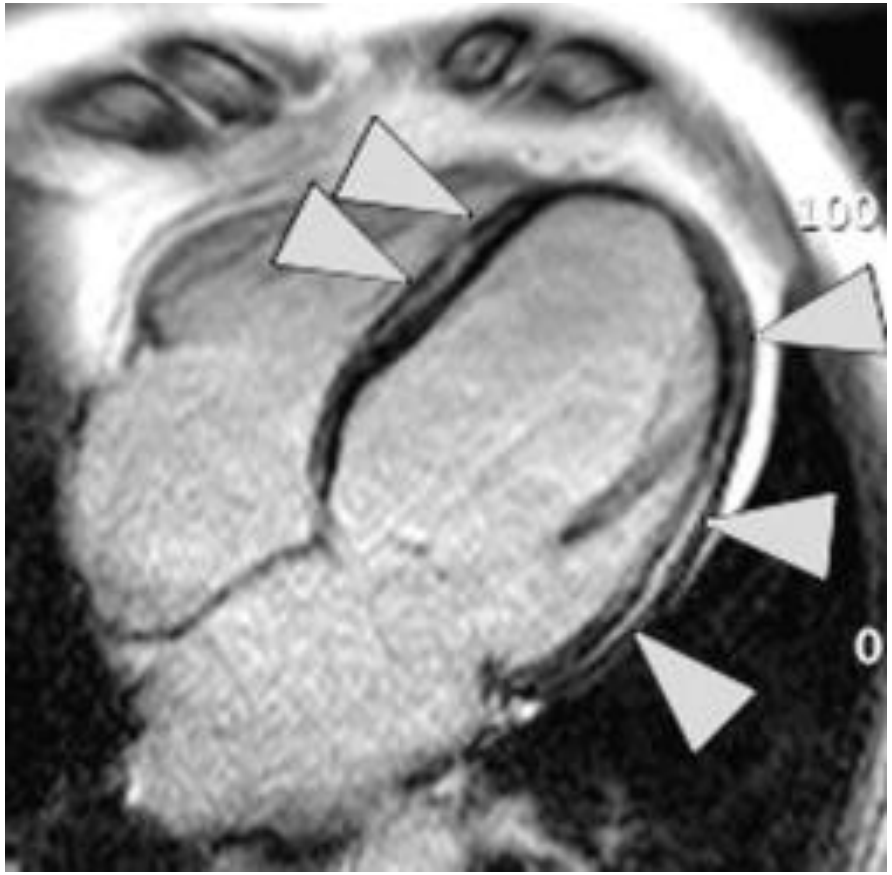




Typical DCM CMRI appearance



Midwall LGE (present in 30% patients)



White JA, Patel MR. Cardiol Clin. (2007)

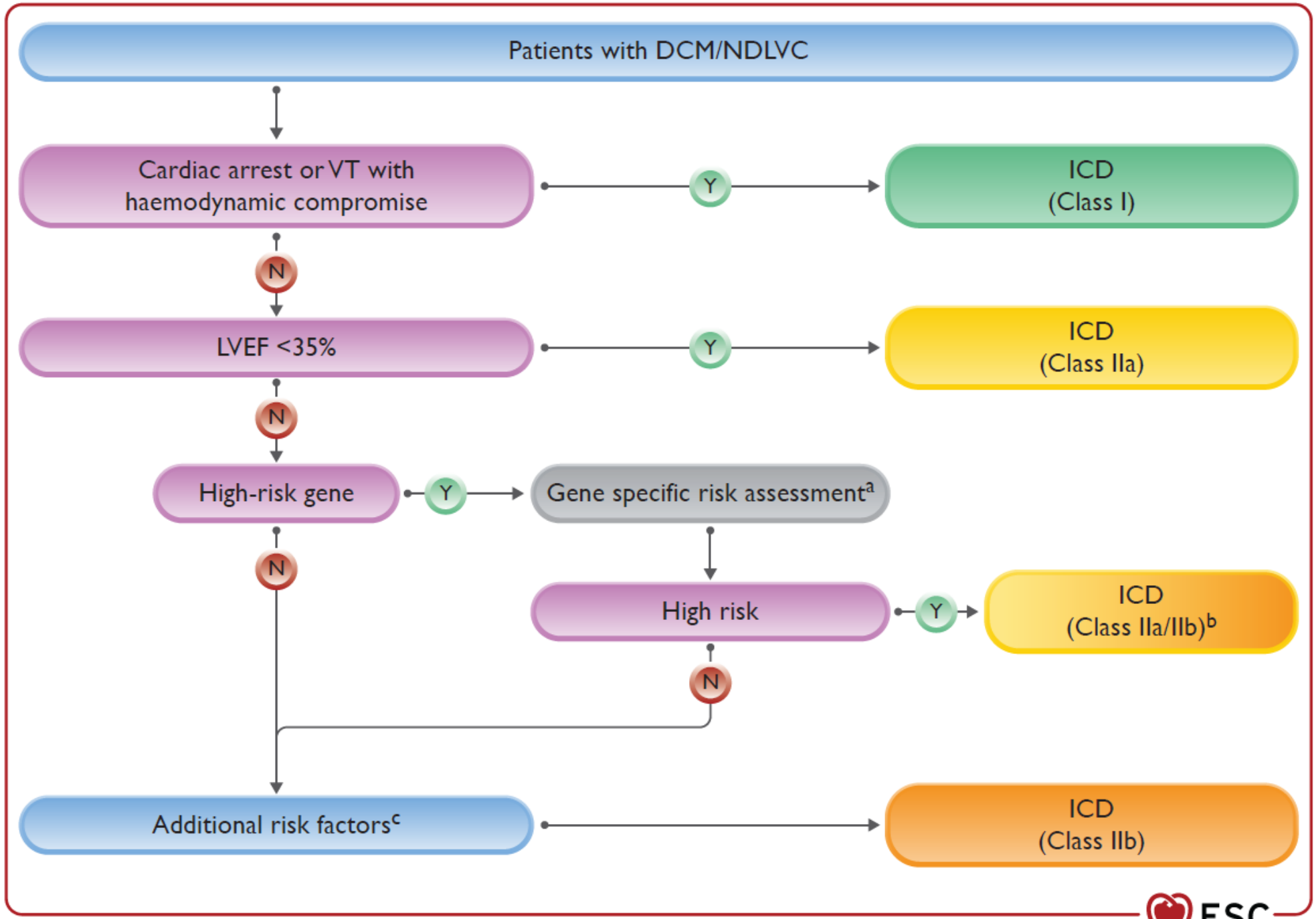
Imaging source: General University Hospital, Prague, CZ

Genes associated with isolated cardiac involvement and DCM

Titin (TTN)	~20-25% of familial DCM - AD mode
Lamin A/C (LMNA)	~6% ; AD mode; associated with AVB and VA; can also cause Limb-Girdle myopathy
Myosin heavy chain (MYH7)	~4% ; AD mode
Troponin T (TNNT2)	~2% ; AD mode
Myosin binding protein C (MYBPC3)	~2% ; AD mode
RNA Binding Motif-20 (RBM20)	~2% ; AD mode
Myopalladin (MYPN)	~2% ; AD mode
Sodium channel alpha unit (SCN5A)	~2% ; AD mode
BaCl2 associated athanogene 3 (BAG3)	~2%; AD mode
Phospholamban (PLN)	~1% ; AD mode; low QRS voltage on ECG

High-risk genotypes and associated predictors of sudden cardiac death

Gene	Annual SCD rate	Predictors of SCD
LMNA (Lamin A/C)	5-10%	Estimated 5-year risk of life-threatening arrhythmia using *LMNA* risk score (https://lmna-risk-vta.fr)
FLNC (filamin C) – truncating variants	5-10%	LGE on CMR; LVEF < 45%
TMEM43 (Transmembrane protein 43)	5-10%	Male Female and any of the following: LVEF <45%; NSVT; LGE on CMR; >200 VE on 24h Holter ECG
PLN (phospholamban)	3-5%	Estimated 5-year risk of life-threatening arrhythmia using *PLN* risk score (https://plnriskcalculator.shinyapps.io/final_shiny) LVEF < 45%; LGE on CMR; NSVT
DSP (desmoplakin)	3-5%	LGE on CMR; LVEF < 45%
RBM (RNA binding motif protein)	3-5%	LGE on CMR; LVEF < 45%


Patients with DCM/NDLVC
Cardiac arrest or VT with haemodynamic compromise
Y
ICD (Class I)
N
LVEF <35%
Y
ICD (Class IIa)
N
High-risk gene
Y
Gene specific risk assessment[a]
N
High risk
Y
ICD (Class IIa/IIb)[b]
N
Additional risk factors[c]
ICD (Class IIb)
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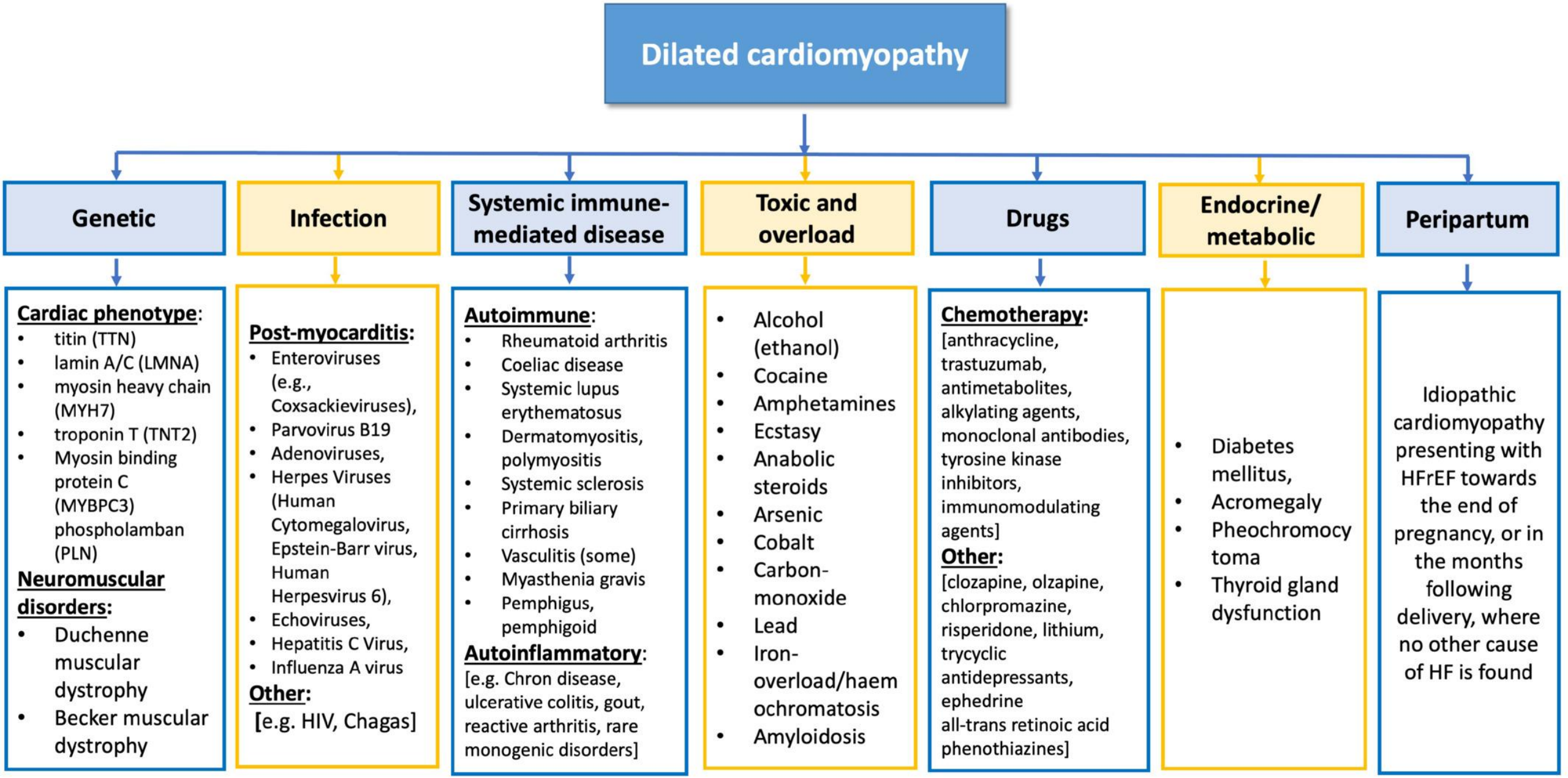
ESC European Society of Cardiology

European Journal of Heart Failure (2019) 21, 553–576
doi:10.1002/ejhf.1461

POSITION PAPER

Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology

Petar M. Seferović[1,2]*, Marija Polovina[1,3], Johann Bauersachs[4], Michael Arad[5], Tuvia Ben Gal[6], Lars H. Lund[7], Stephan B. Felix[8], Eloisa Arbustini[9], Alida L.P. Caforio[10], Dimitrios Farmakis[11], Gerasimos S. Filippatos[11], Elias Gialafos[12], Vladimir Kanjuh[2], Gordana Krljanac[1,3], Giuseppe Limongelli[13], Aleš Linhart[14], Alexander R. Lyon[15], Ružica Maksimović[1,16], Davor Miličić[17], Ivan Milinković[3], Michel Noutsias[18], Ali Oto[19], Öztekin Oto[20], Siniša U. Pavlović[1,21], Massimo F. Piepoli[22], Arsen D. Ristić[1,3], Giuseppe M.C. Rosano[23], Hubert Seggewiss[24], Milika Ašanin[1,3], Jelena P. Seferović[25,26], Frank Ruschitzka[27], Jelena Čelutkiene[28,29], Tiny Jaarsma[30], Christian Mueller[31], Brenda Moura[32], Loreena Hill[33], Maurizio Volterrani[34], Yuri Lopatin[35], Marco Metra[36], Johannes Backs[37,38], Wilfried Mullens[39,40], Ovidiu Chioncel[41,42], Rudolf A. de Boer[43], Stefan Anker[44,45,46], Claudio Rapezzi[47], Andrew J.S. Coats[48,49], and Carsten Tschöpe[50]



Seferović et al. European Journal of Heart Failure (2019)21, 553–576

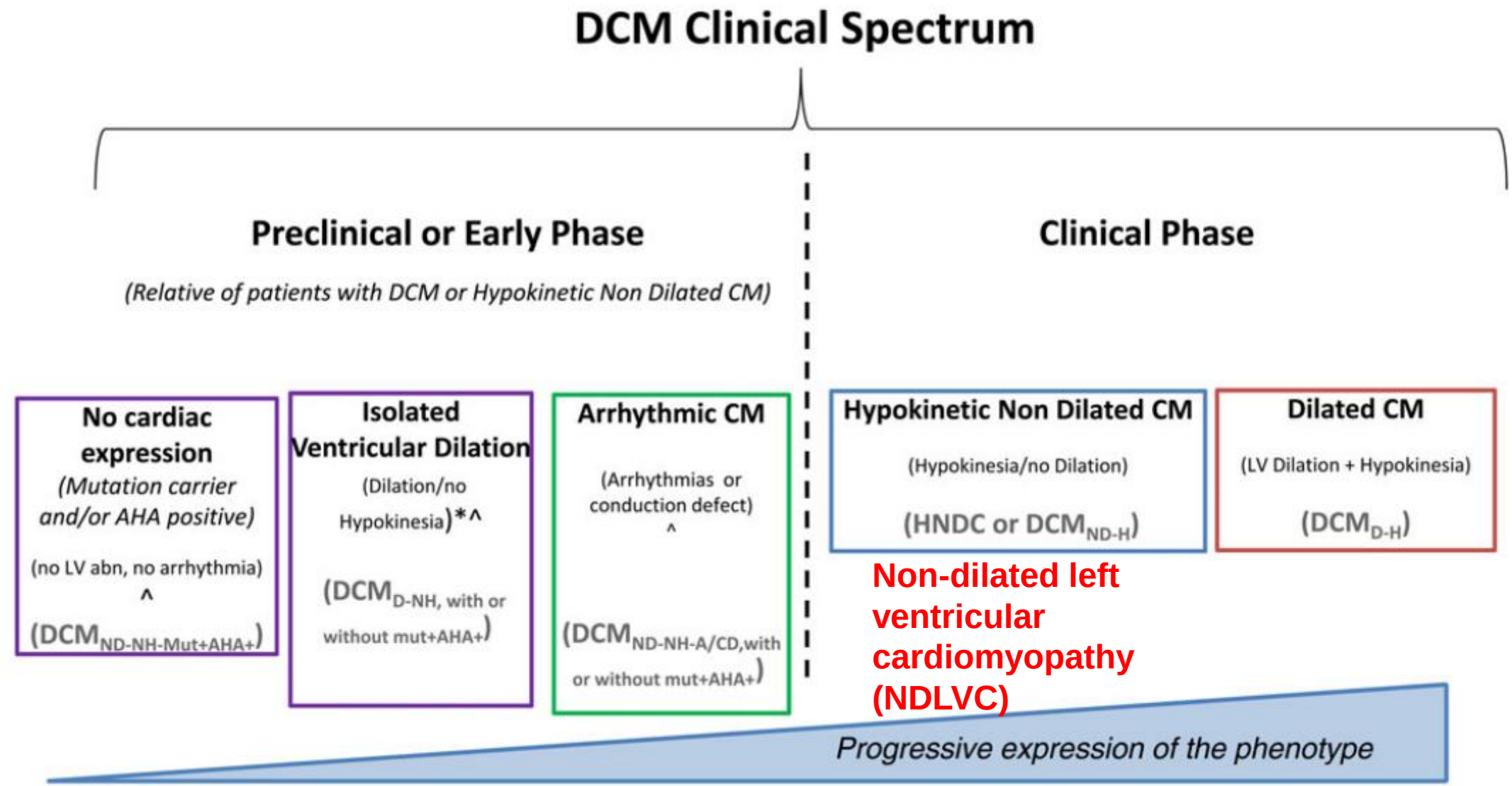
NON-DILATED LEFT VENTRICULAR CARDIOMYOPATHY (NDLVC)

European Heart Journal (2016) **37**, 1850–1858
doi:10.1093/eurheartj/ehv727

ESC REPORT

Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases

Yigal M. Pinto[1]*, Perry M. Elliott[2], Eloisa Arbustini[3], Yehuda Adler[4], Aris Anastasakis[5], Michael Böhm[6], Denis Duboc[7], Juan Gimeno[8], Pascal de Groote[9,10], Massimo Imazio[11], Stephane Heymans[12,13], Karin Klingel[14], Michel Komajda[15], Giuseppe Limongelli[16], Ales Linhart[17], Jens Mogensen[18], James Moon[19], Petronella G. Pieper[20], Petar M. Seferovic[21], Stephan Schueler[22], Jose L. Zamorano[23], Alida L.P. Caforio[24], and Philippe Charron[25,26]



*Shown by two independent imaging modalities, ^mutation carrier or not; anti-heart autoantibody (AHA) positive or negative

Definitions - Non-dilated left ventricular cardiomyopathy (NDLVC)

- NDLVC phenotype is defined by the **presence of non-ischaemic LV scarring or fatty replacement in the absence of LV dilatation**, with or without global or regional wall motion abnormalities, **or isolated global LV hypokinesia without scarring** (as assessed by the presence of LGE on CMR) that is unexplained solely by abnormal loading conditions (hypertension, valve disease) or CAD.
- Global LV systolic dysfunction is defined by abnormal LVEF (i.e. <50%).

- The NDLVC phenotype will include individuals that up until now may have variably been described as **having DCM (but without LV dilatation), arrhythmogenic left ventricular cardiomyopathy (ALVC), left dominant ARVC, or arrhythmogenic DCM (but often without fulfilling diagnostic criteria for ARVC)**

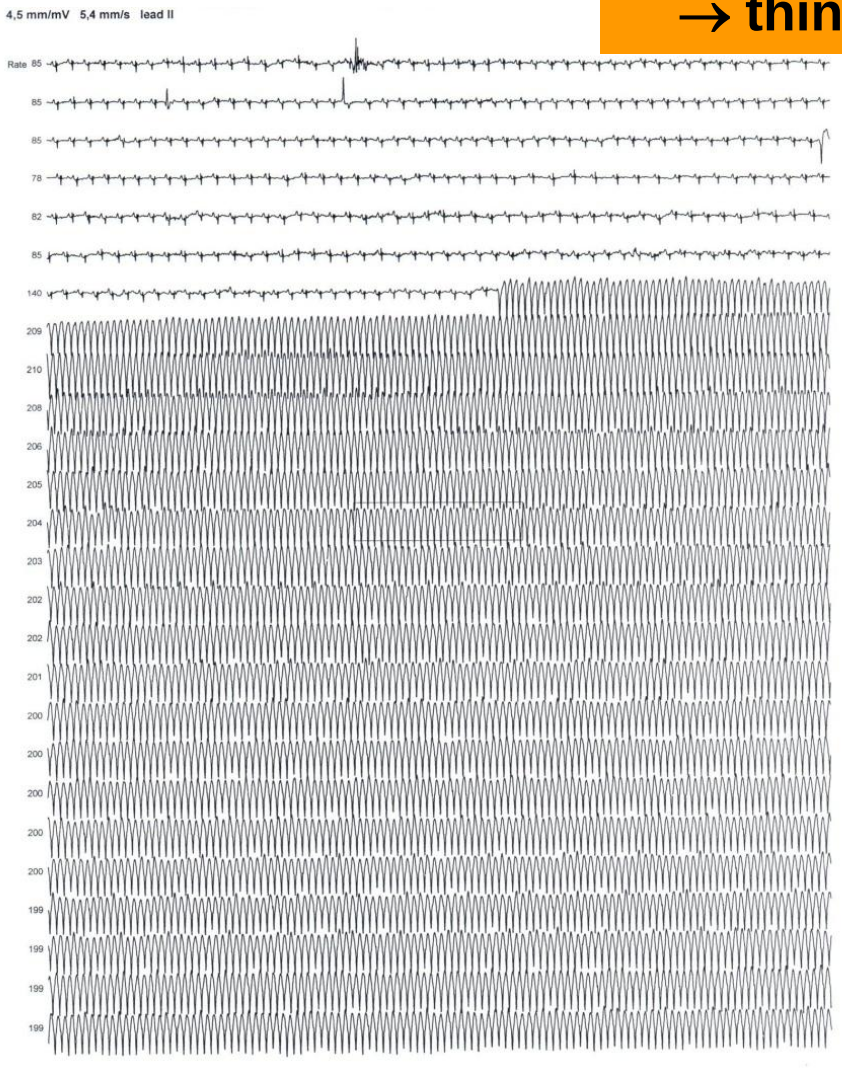
Arbelo et al. Eur Heart J. 2023 Aug 25;ehad194. doi:10.1093/eurheartj/ehad194.

Arrhythmogenic LV cardiomyopathy

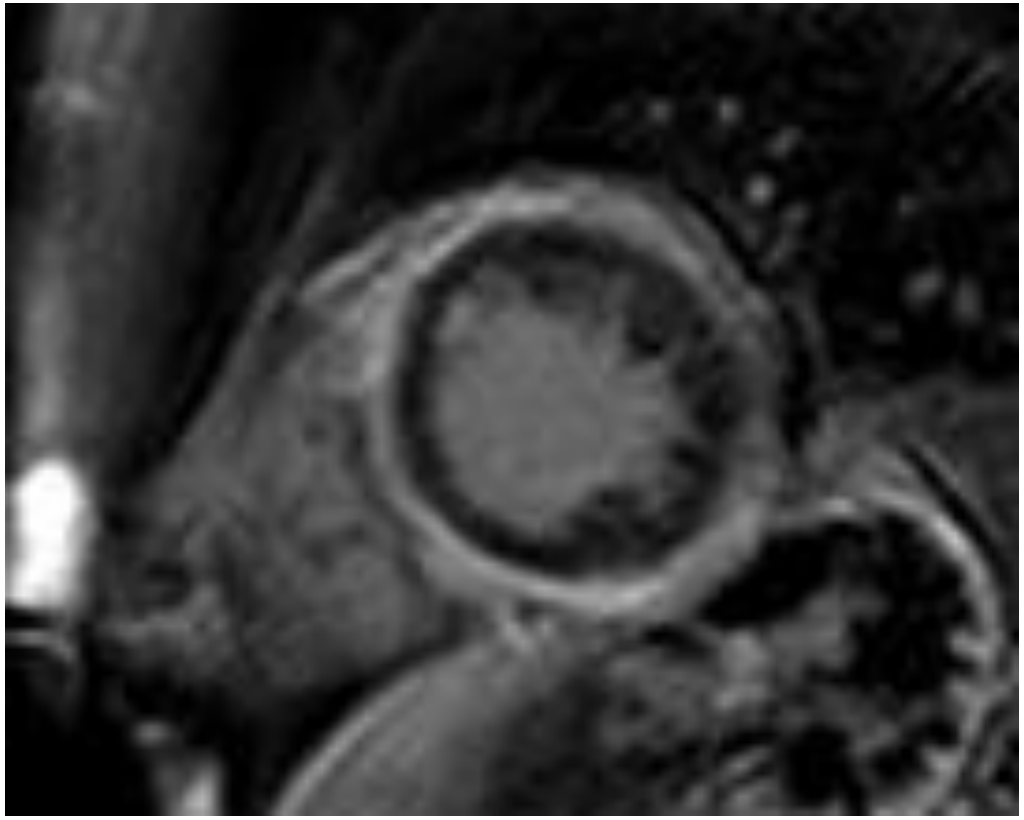
38-year old man with symptoms of palpitations, LVEF 40-45%; Myocarditis ?

Mild LV systolic dysfuncion + VT

→ **think about ALVC** (and sarcoidosis) **!**

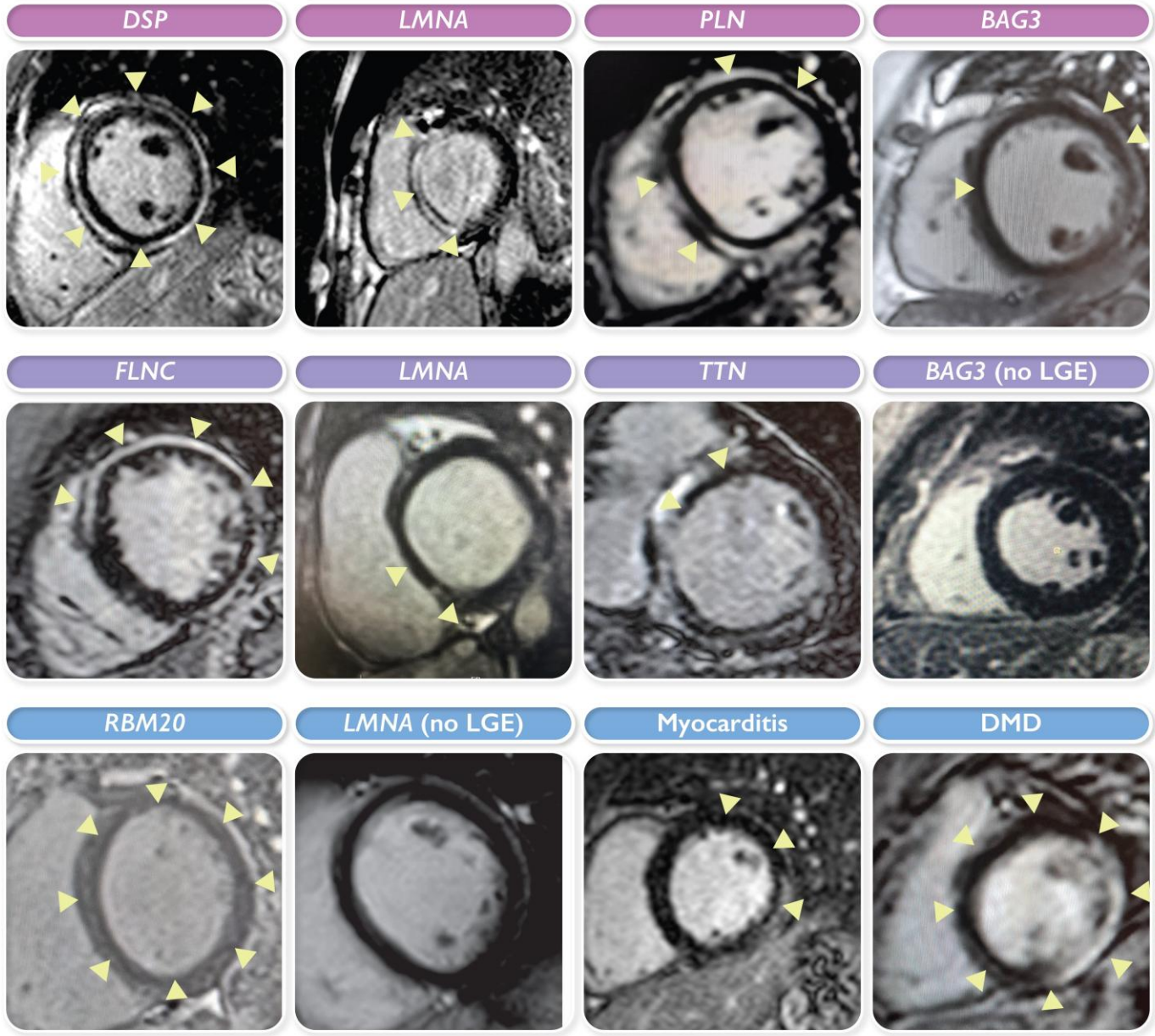


Circumferential subepicardial LGE



Imaging source: General University Hospital, Prague, CZ

Examples of non-dilated left ventricular cardiomyopathy phenotypes and their aetiological correlates.



Arbelo et al. Eur Heart J. 2023 Aug 25;ehad194. doi:10.1093/eurheartj/ehad194.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy?

Presence of increased left ventricular (LV) wall thickness (with or without RV hypertrophy) or mass that is not solely explained by abnormal loading conditions.

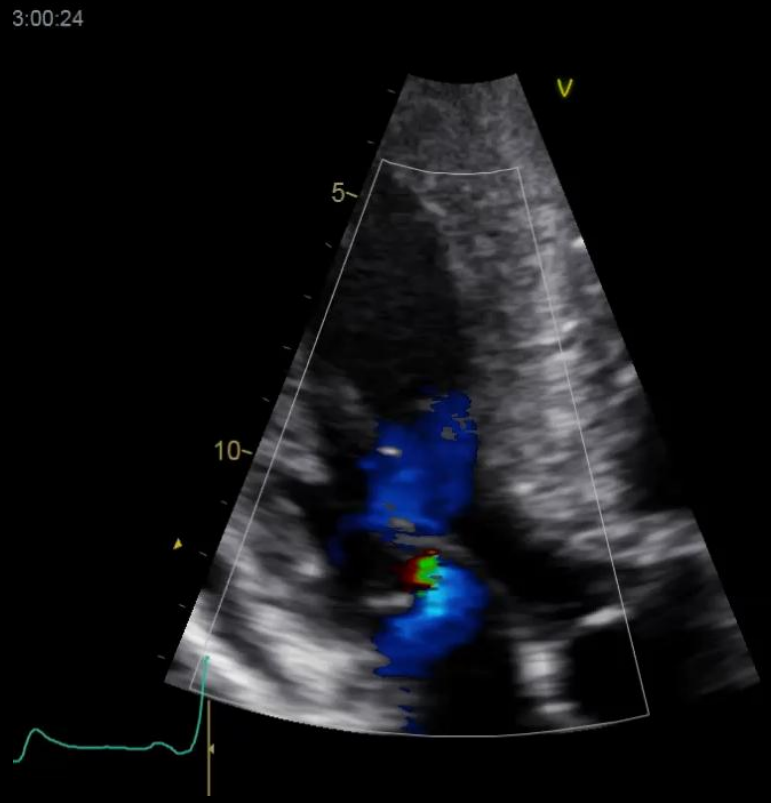
In an adult ≥15 mm in one or more LV myocardial segments—by any imaging technique

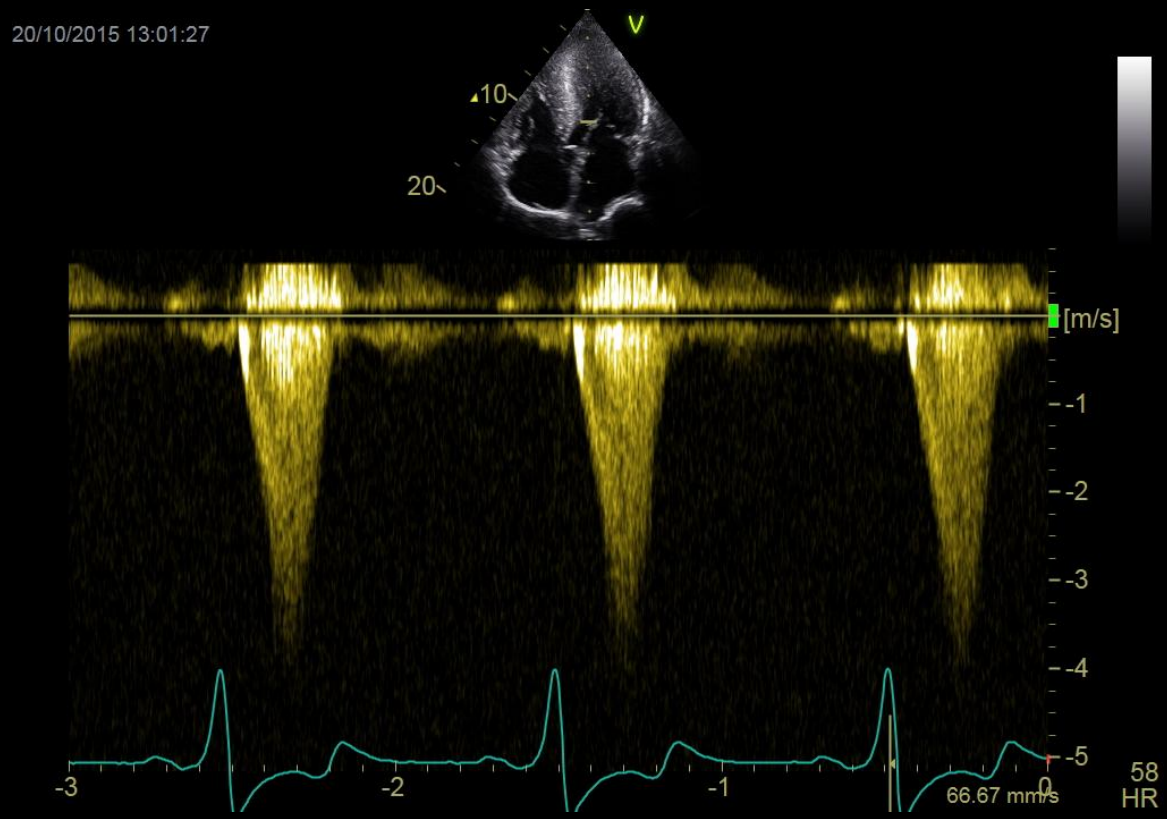
- ~ **In relatives ≥13 mm**
- ~ **Genetic & nongenetic disorders 13–14 mm**

In children > 2 SD of the predicted mean **(z-score >2)**

Elliott et al. Eur Heart J. 2014 Oct 14;35(39):2733-79.
Arbelo et al. Eur Heart J. 2023 Aug 25;ehad194. doi:10.1093/eurheartj/ehad194

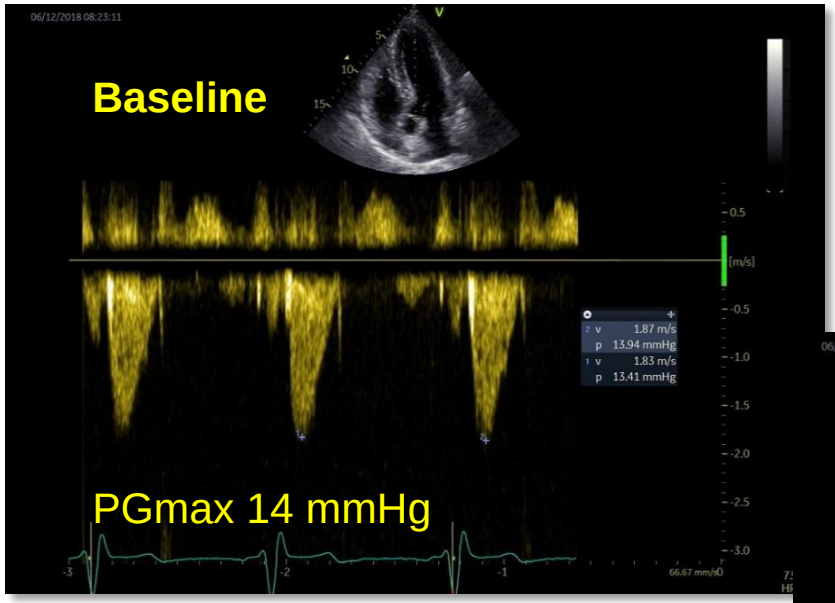
Classical Cause of LVOTO

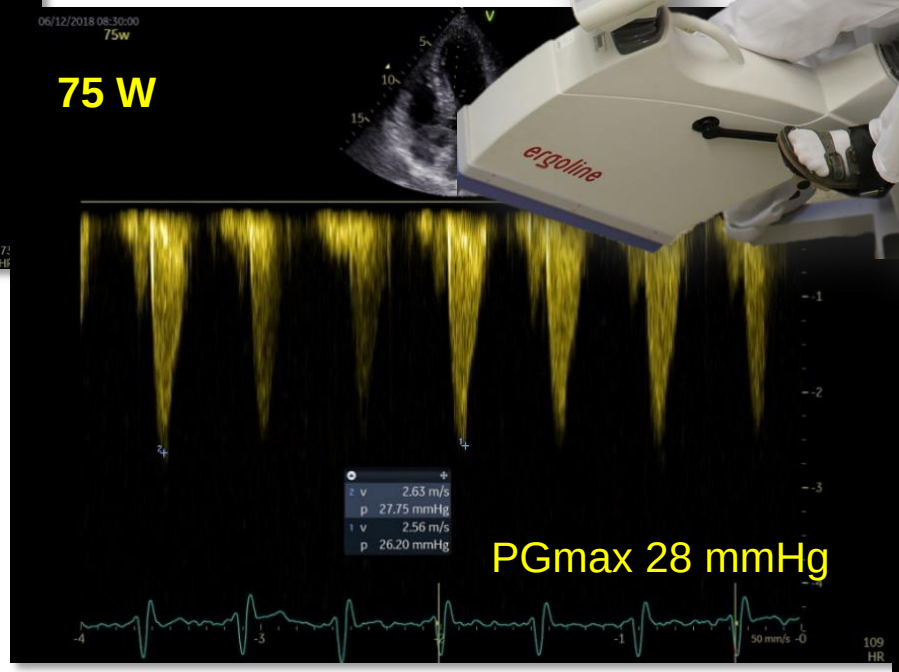


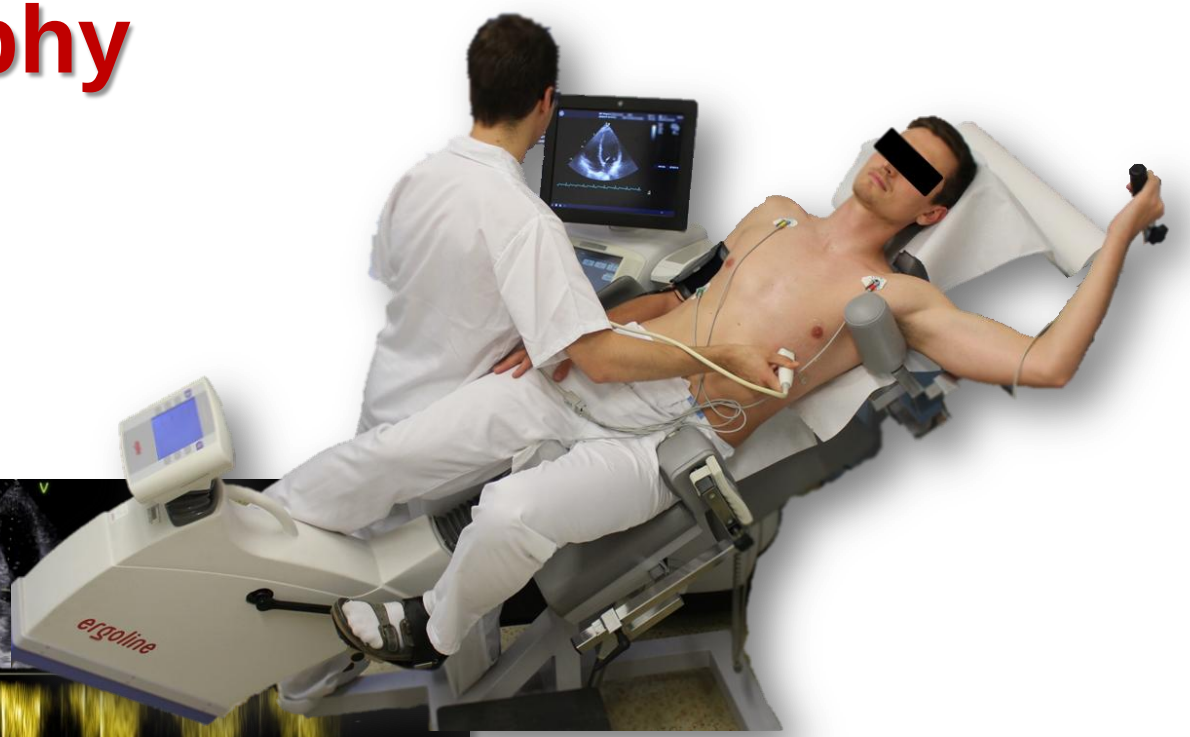


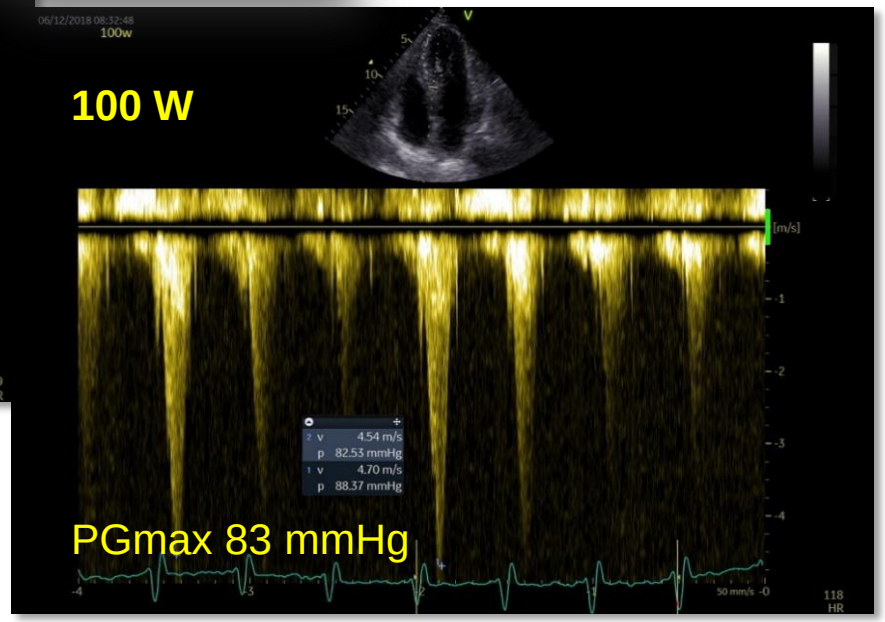
Imaging: General University Hospital, Prague, Czech Republic

Exercise echocardiography







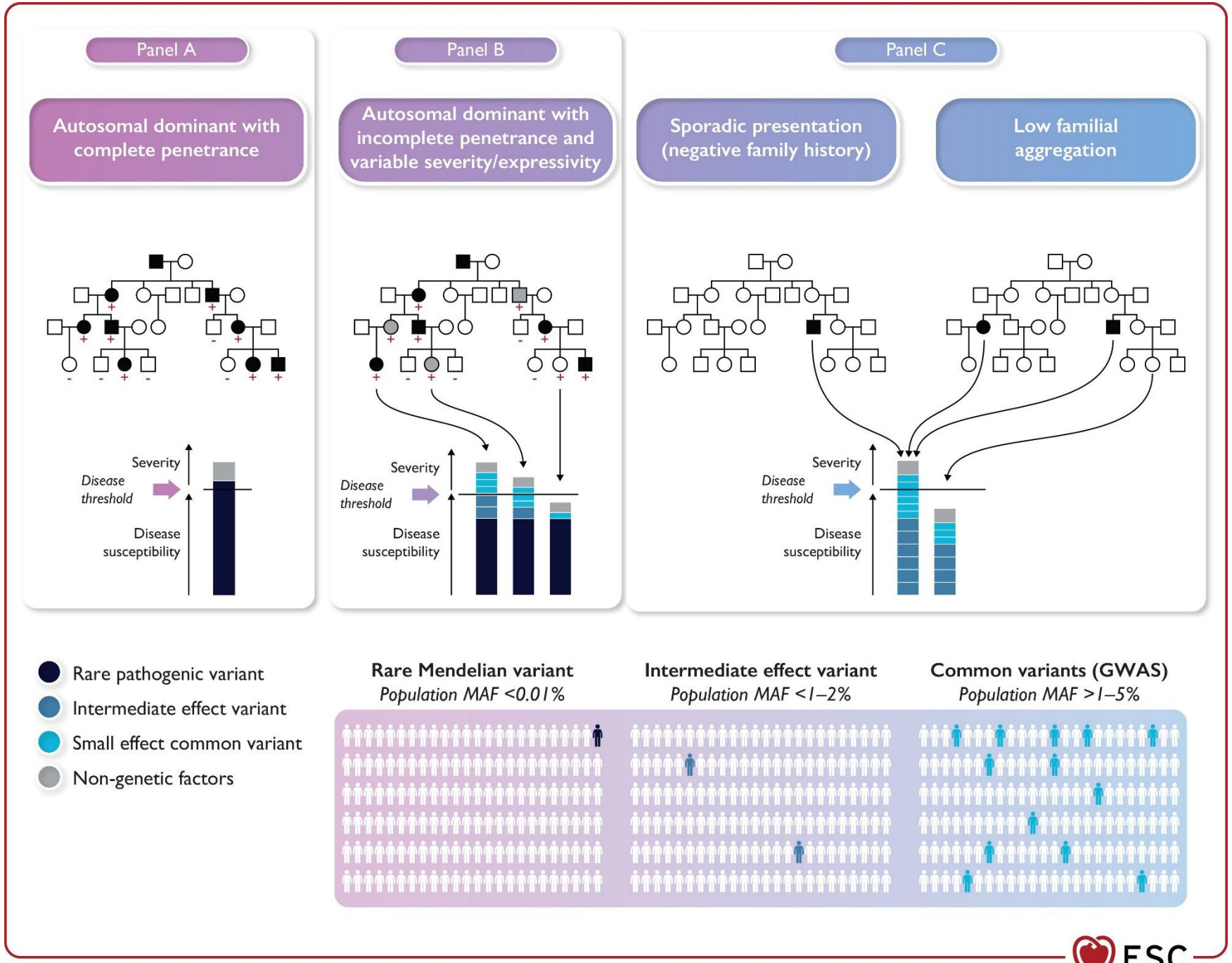


37% - obstruction at rest
33% - provoked obstruction

1. Maron MS, et al. *Circulation.* 2006;114:2232-2239.2. Maron MS, et al. *J Am Coll Cardiol.* 2016;67:1399-1409.
3. Rowin EJ, et al. *JACC Cardiovasc Imaging.* 2017;10:1374-1386. 4. Elliott PM, et al. *Eur Heart J.* 2006;27:1933-41.

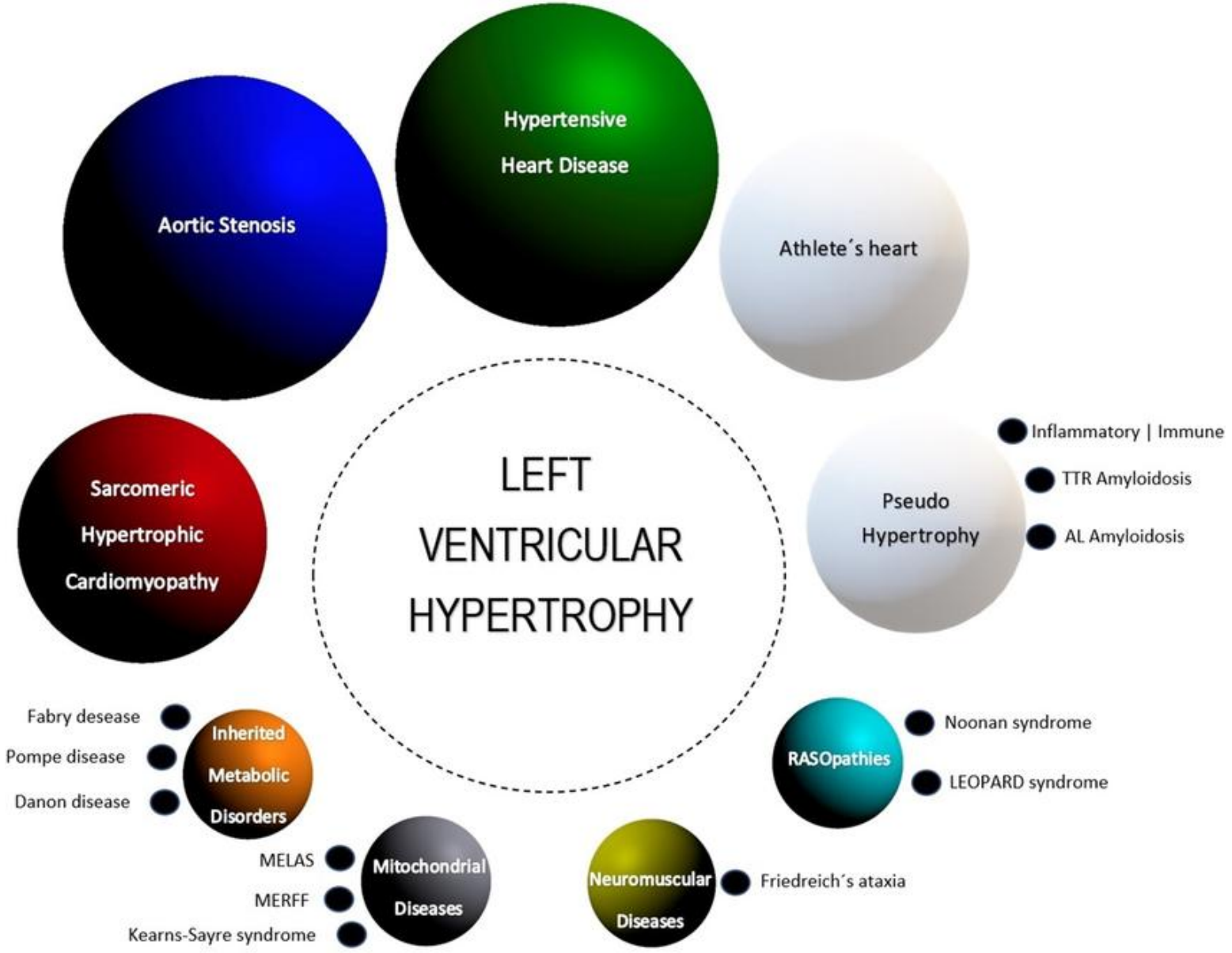
Imaging: General University Hospital, Prague, Czech Republic

Genetic causes of cardiomyopathies



Arbelo et al. Eur Heart J. 2023 Aug 25;ehad194. doi:10.1093/eurheartj/ehad194

Differential diagnosis of cardiac hypertrophy



Aguiar Rosa….Olivotto, The International Journal of Cardiovascular Imaging (2023) 39:793–809

RESTRICTIVE CARDIOMYOPATHY

ESC European Society of Cardiology

European Heart Journal (2022) **43**, 4679–4693
https://doi.org/10.1093/eurheartj/ehac543

STATE OF THE ART REVIEW
Heart failure and cardiomyopathies

Restrictive cardiomyopathy: definition and diagnosis

Claudio Rapezzi[1,2]*, Alberto Aimo [3,4], Andrea Barison [3,4], Michele Emdin[3,4], Aldostefano Porcari[5], Ales Linhart [6], Andre Keren [7,8], Marco Merlo [5], and Gianfranco Sinagra[5]

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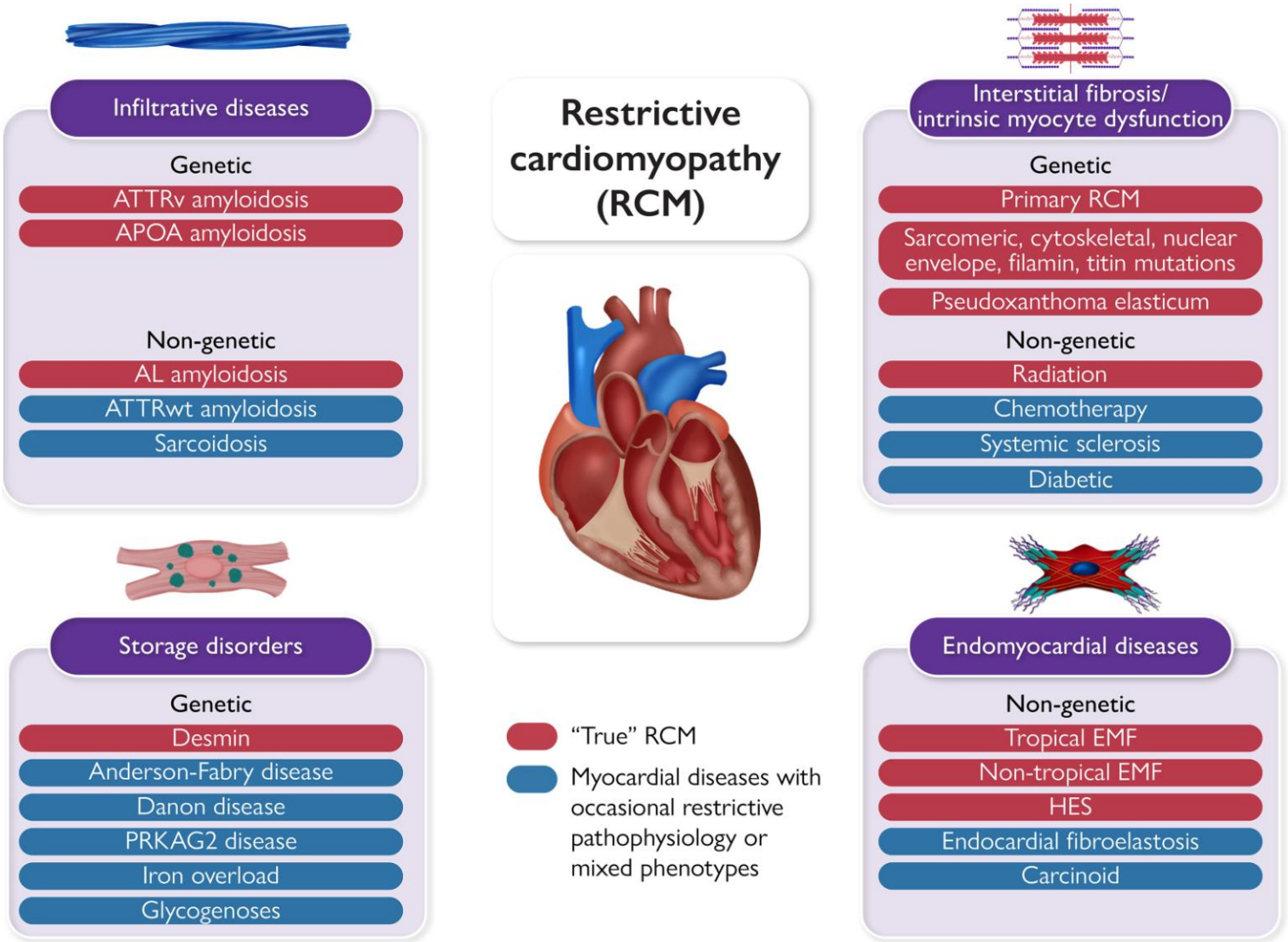
RCM definition

- Restrictive cardiomyopathy (RCM) is a heterogeneous group of diseases characterized by restrictive left ventricular pathophysiology, i.e. a rapid rise in ventricular pressure with only small increases in filling volume due to increased myocardial stiffness.
- More precisely, the defining feature of RCM is the coexistence of **persistent restrictive pathophysiology, diastolic dysfunction, non-dilated ventricles, and atrial dilatation, regardless of ventricular wall thickness and systolic function.**

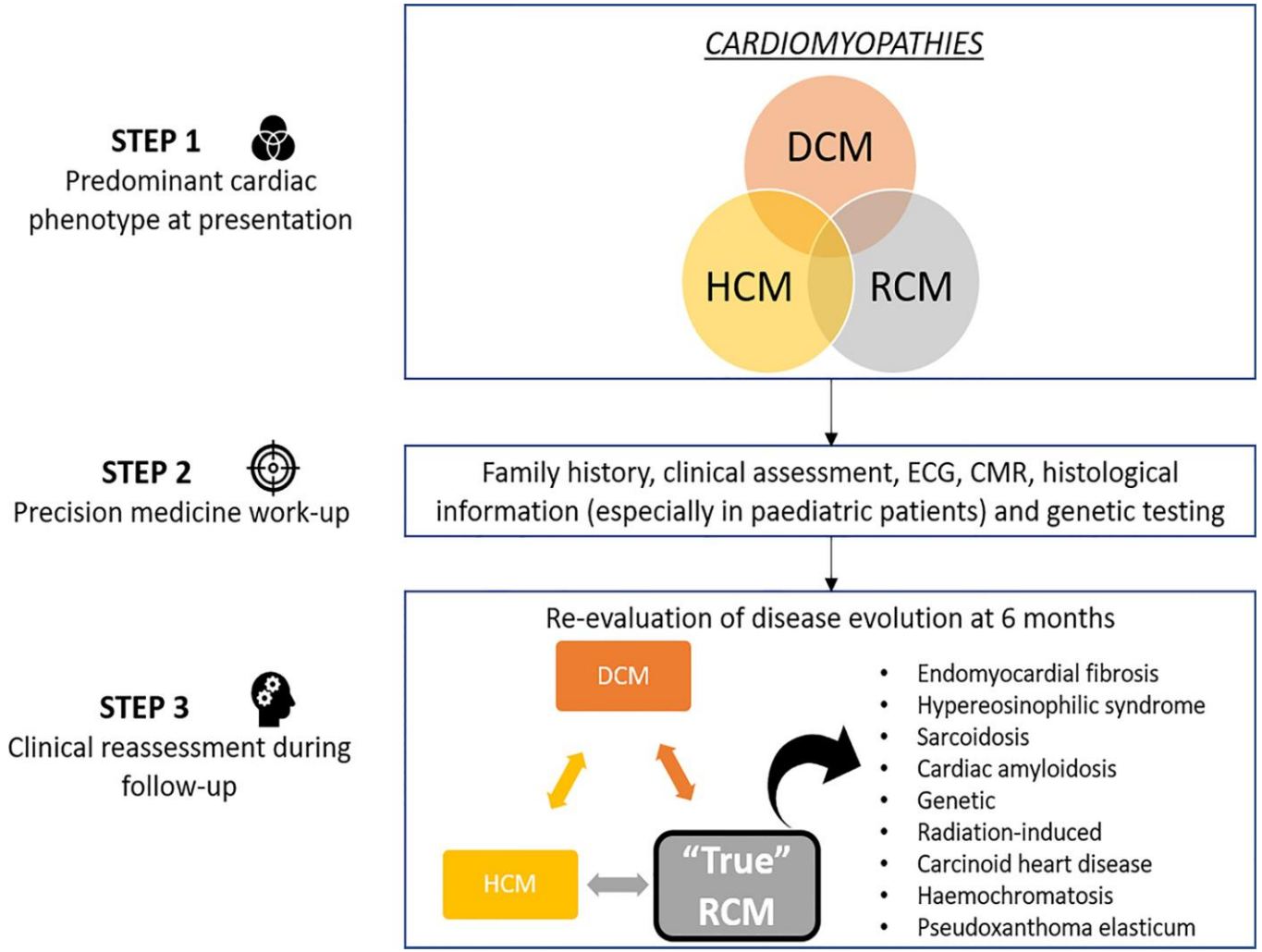
Rapezzi et al. Eur Heart J, Volume 43, Issue 45, 1 December 2022, Pages 4679–4693,

Proposed classification of restrictive cardiomyopathy



Rapezzi et al. Eur Heart J, Volume 43, Issue 45, 1 December 2022, Pages 4679–4693,

Proposed flowchart for contemporary diagnostic work-up of restrictive cardiomyopathy.



Rapezzi et al. Eur Heart J, Volume 43, Issue 45, 1 December 2022, Pages 4679–4693,

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

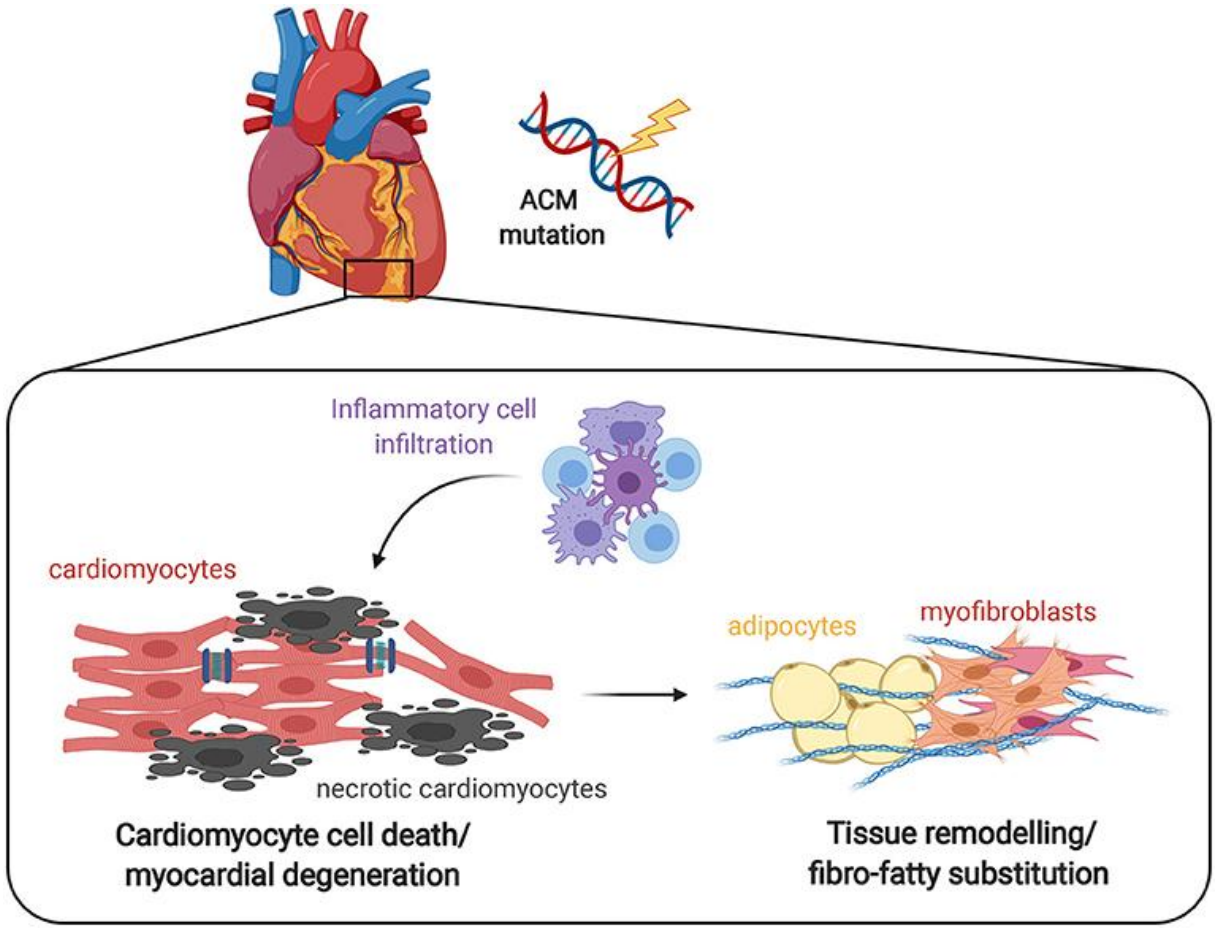
Arrhythmogenic right ventricular cardiomyopathy

- Presence of predominantly RV dilatation and/or dysfunction in the presence of histological involvement and/or electrocardiographic abnormalities

- The term ARVC can be used to describe the original variant in which ventricular dilatation or wall motion abnormalities are predominantly confined to the right ventricle, with or without LV involvement, and the 2010 modified Task Force criteria for the diagnosis of ARVC can be applied.

Arbelo et al. Eur Heart J. 2023 Aug 25;ehad194.
doi:10.1093/eurheartj/ehad194

Classical concepts behind ARVC



Gene symbol	Protein name
Desmosomes	Plakoglobin
JUP	
PKP2	Plakophilin-2
DSP	Desmoplakin
DSG2	Desmoglein-2
DSC2	Desmocollin-2
***Area Composita* and connexome structure**	
CTNNA3	αT-catenin
CDH2	Cadherin-2
SCN5A	Sodium Voltage-Gated Channel Alpha Subunit-5
ANK2	Ankyrin-B
TJP1	Tight junction protein 1
TMEM43	Transmembrane protein 43
Cytoskeleton	
DES	Desmin
LMNA	Lamin A/C
TTN	Titin
FLNC	Filamin C
ILK	Integrin-linked kinase
Calcium handling machinery	
RYR2	Ryanodine receptor 2
PLN	Phospholamban
Cell signaling pathways	
TGFB3	Transforming growth factor-β3
TP63	Tumor pro tein P63
PPP1R13L	Protein phosphatase 1 regulatory subunit 13
PNPLA2	Patatin-like phospholipase domain containing 2

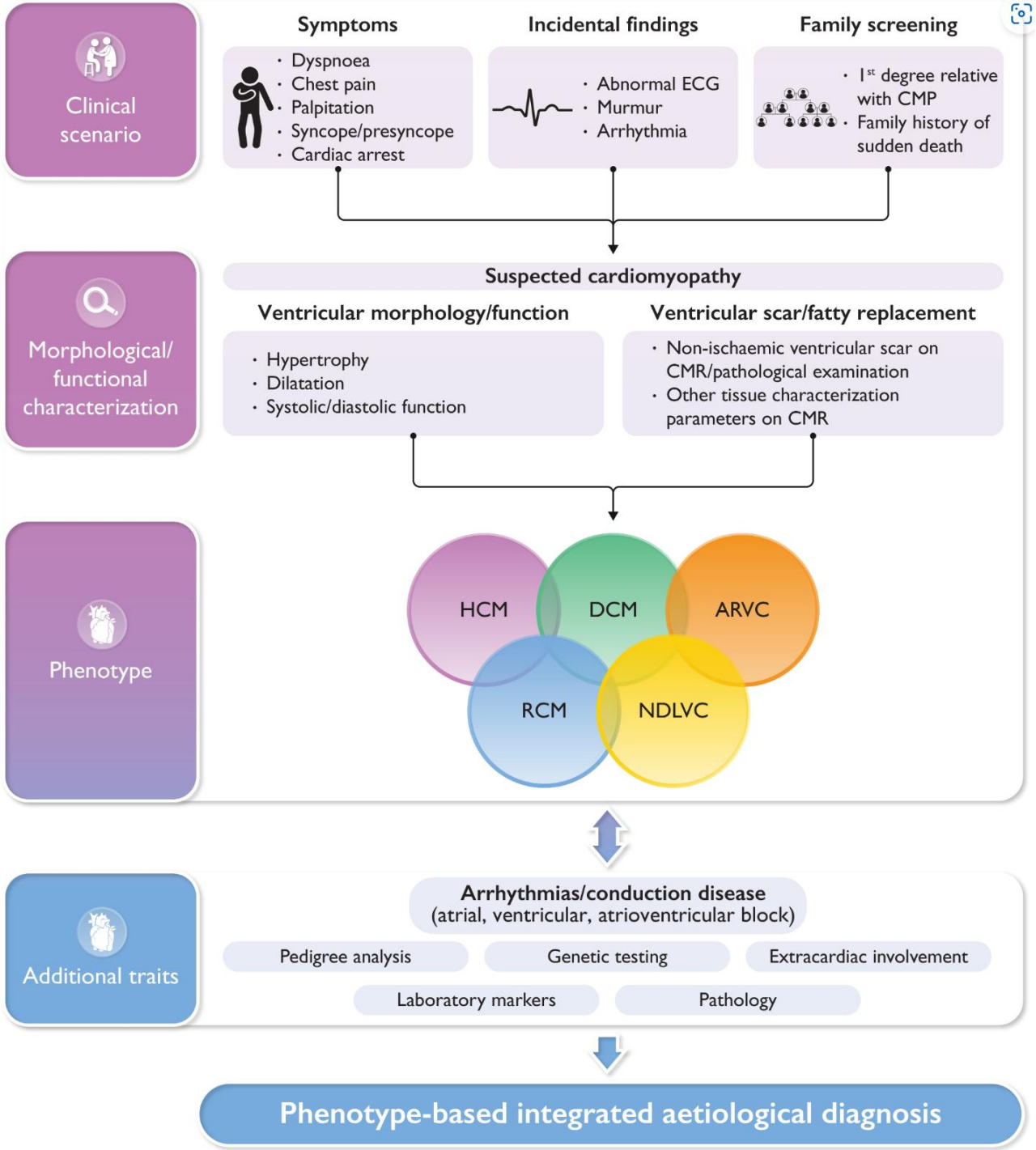
Meraviglia et al. Front. Cardiovasc. Med., 20 December 2021
Sec. Cardiovascular Metabolism

LEFT VENTRICULAR HYPERTRABECULATION (LEFT VENTRICULAR NON-COMPACTION)

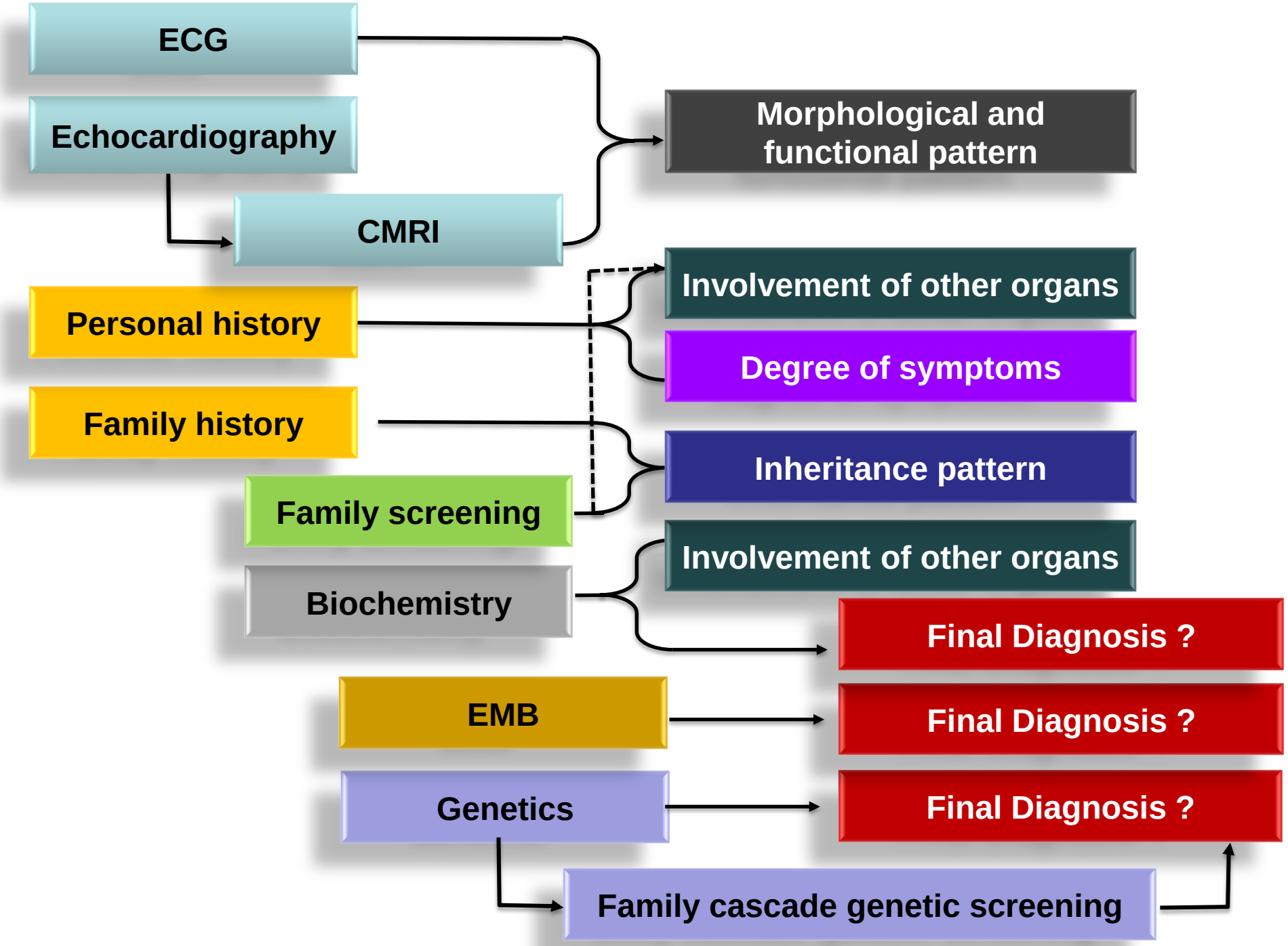
LVNC is no longer a cardiomyopathy per se

- The Task Force **does not consider LVNC to be a cardiomyopathy in the general sense.**
- Instead, it is seen as a phenotypic trait that can occur either in isolation or in association with other developmental abnormalities, ventricular hypertrophy, dilatation, and/or systolic dysfunction.
- Given the lack of morphometric evidence for ventricular compaction in humans **the term ‘hypertrabeculation’, rather than LVNC, is recommended**, particularly when the phenomenon is transient or clearly of adult onset.

Clinical diagnostic workflow of cardiomyopathy



Arbelo et al. Eur Heart J. 2023 Aug 25;ehad194. doi:10.1093/eurheartj/ehad194.


ECG
Echocardiography
CMRI
Morphological and functional pattern
Personal history
Involvement of other organs
Degree of symptoms
Family history
Inheritance pattern
Family screening
Involvement of other organs
Biochemistry
Final Diagnosis ?
EMB
Final Diagnosis ?
Genetics
Final Diagnosis ?
Family cascade genetic screening