CARDIOLOGY 2024

Left Ventricular Non-compaction

Genetics, Syndromes, and Pediatric Cardiovascular Disease

Jeffrey J. Kim, MD, FAAP, FACC, FHRS

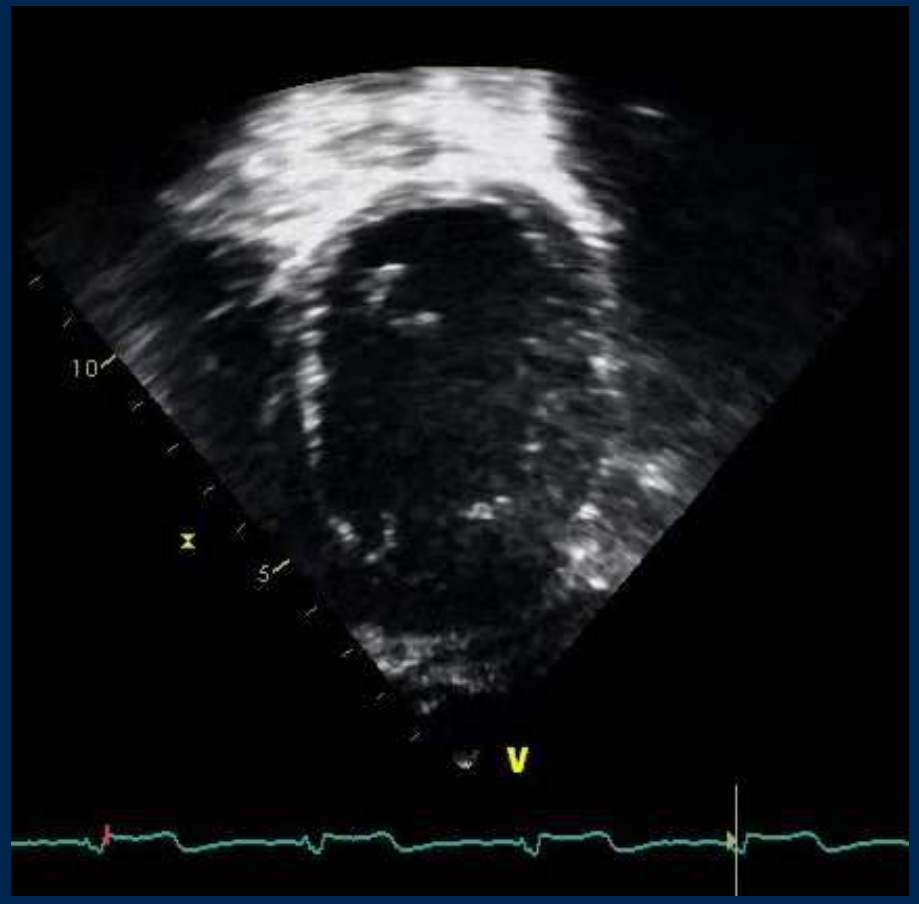
27th Annual Update on Pediatric & Congenital Cardiovascular Disease

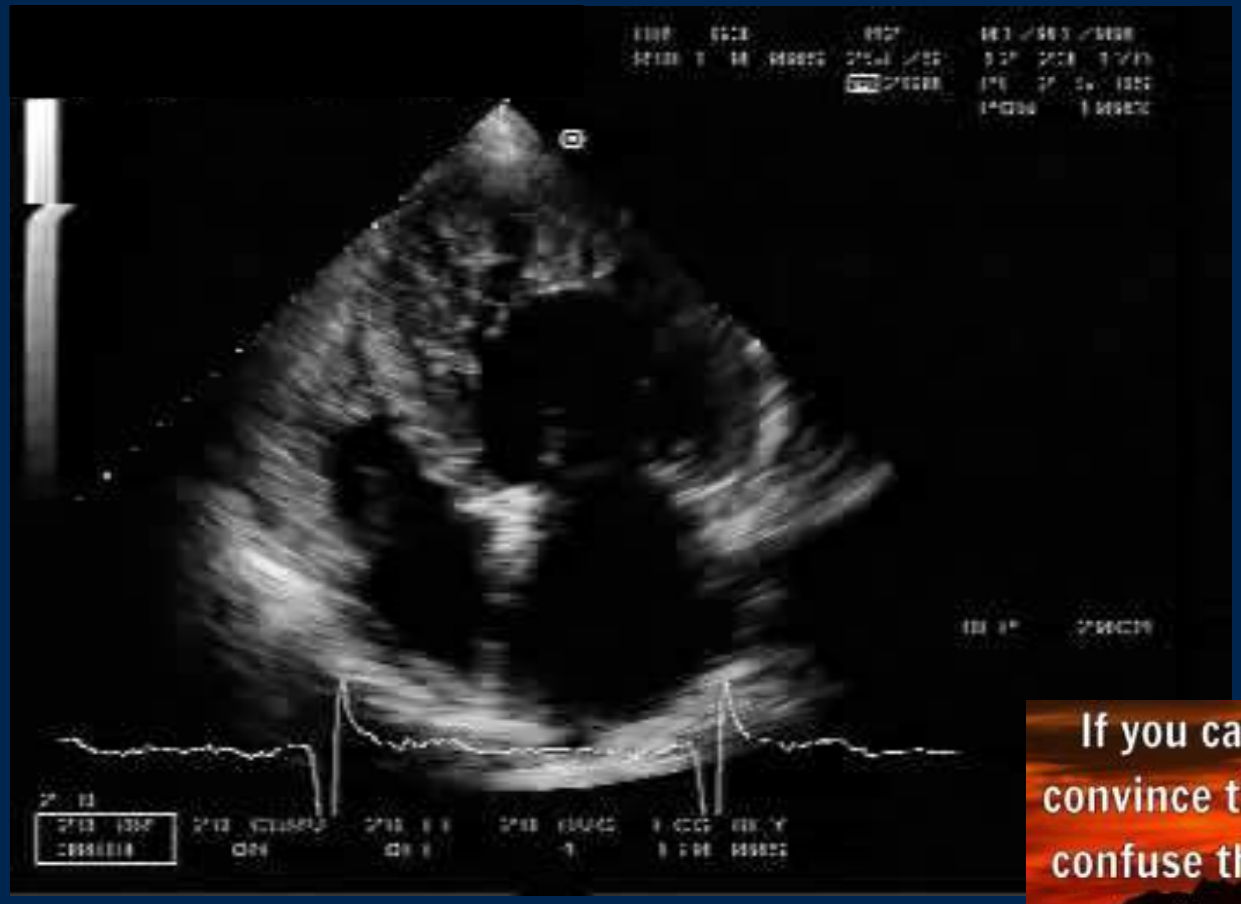
February 17, 2024

Disclosures

No relevant financial disclosures

Left Ventricular Non-compaction





1st described pathologically as spongy myocardium in 1975 (Dusek)

Clinically recognized with echocardiography in 1984 (Engberding)

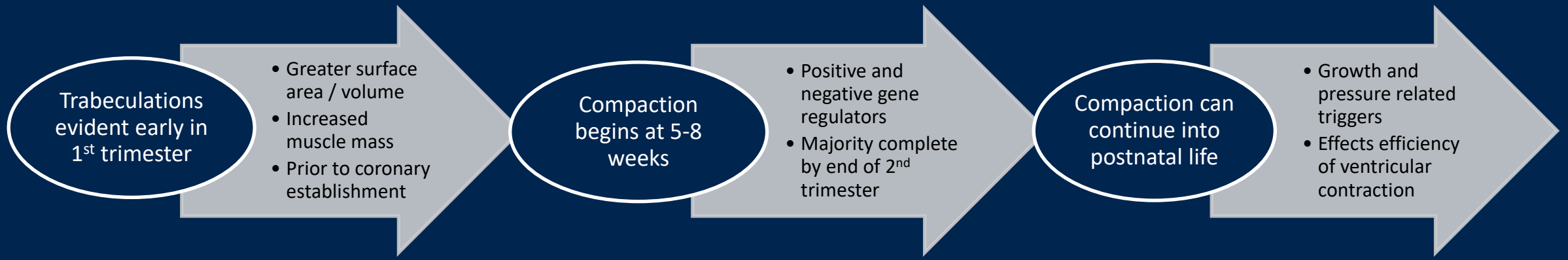
Classified as distinct form of cardiomyopathy in 2006 (AHA)

Still clinically debated as a distinct entity

Left Ventricular Non-compaction Embryology

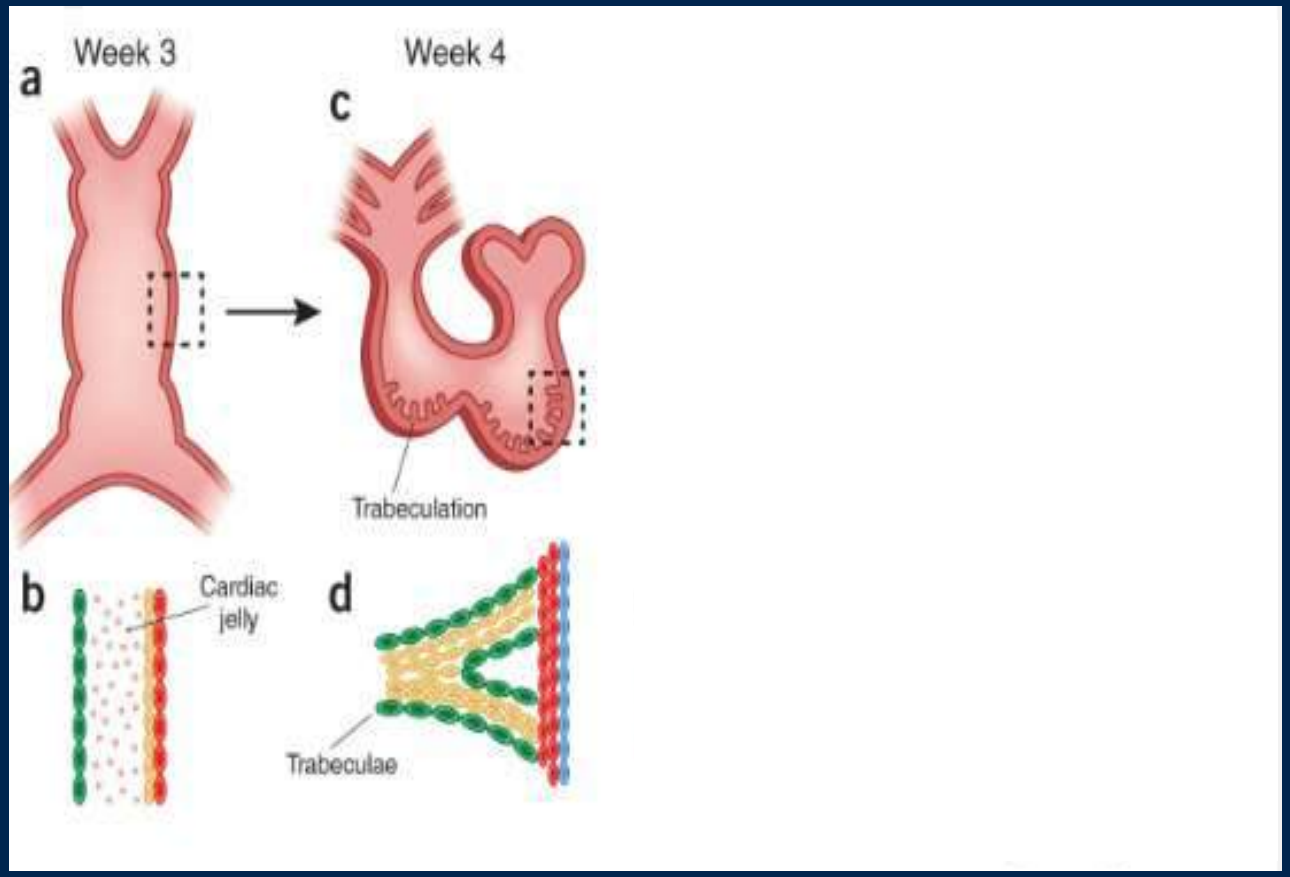
- Embryologically, the theory is that there is a “failure of the compaction process during fetal development”

- Normal development and compaction:

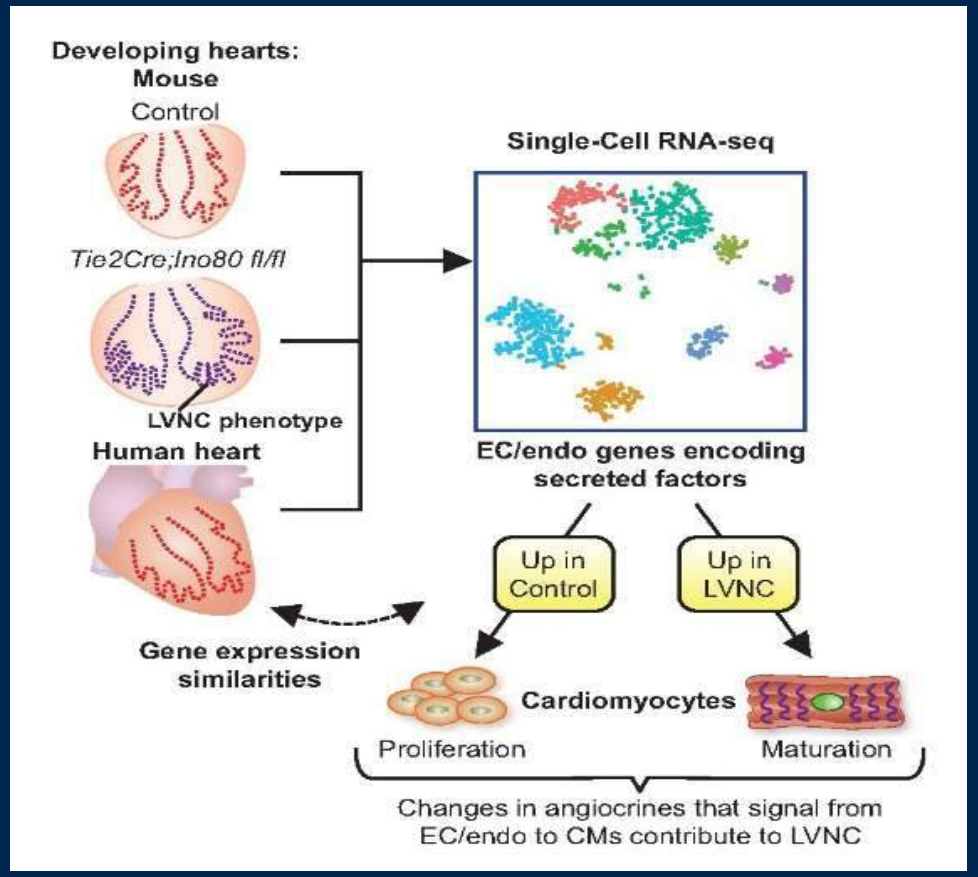


Sedmera D, et al. Heart Failure Clinics. 2008 Henderson D, et al, Pediatric Cardiology. 2009 Faber et al. iScience. 2022

Left Ventricular Non-compaction Embryology



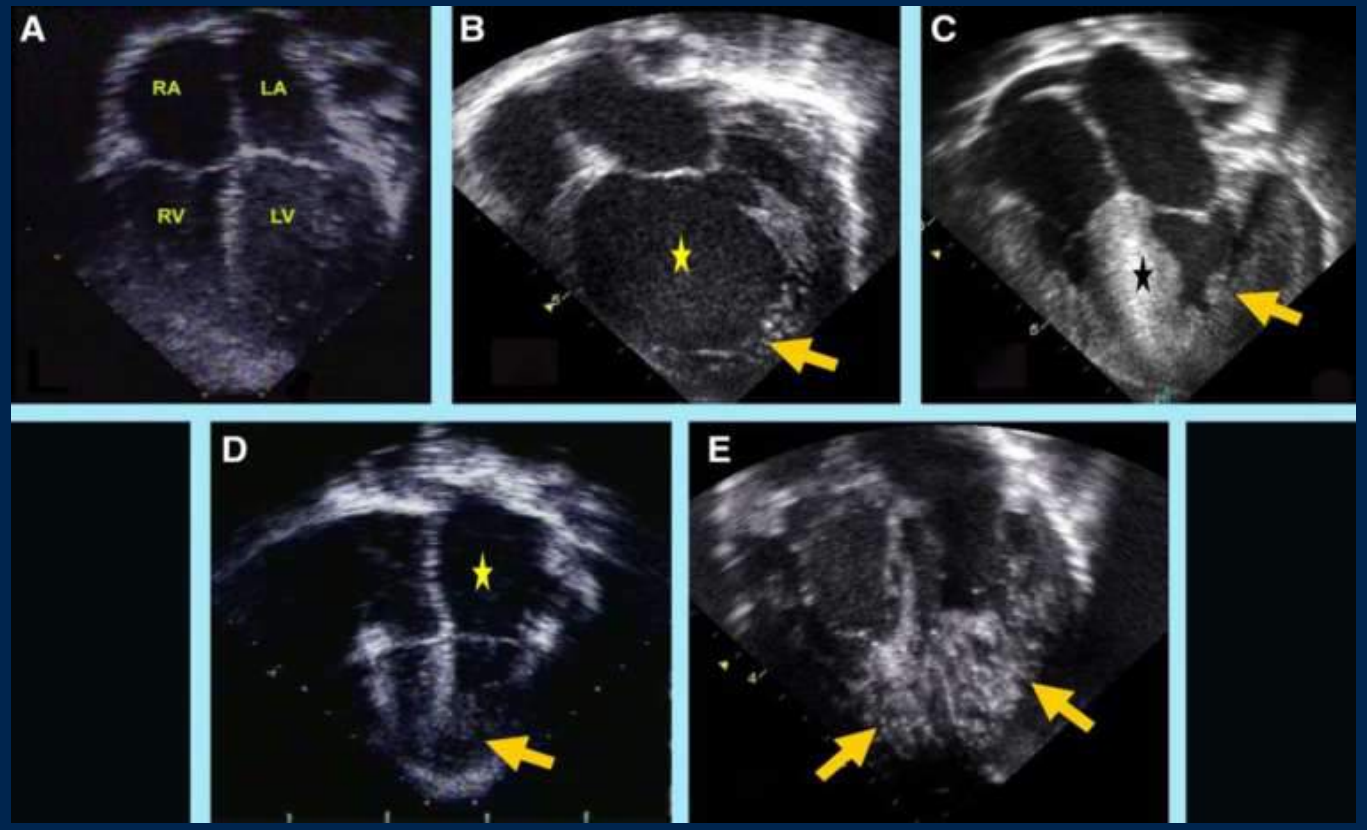
Misra C, et al. Nature. 2013

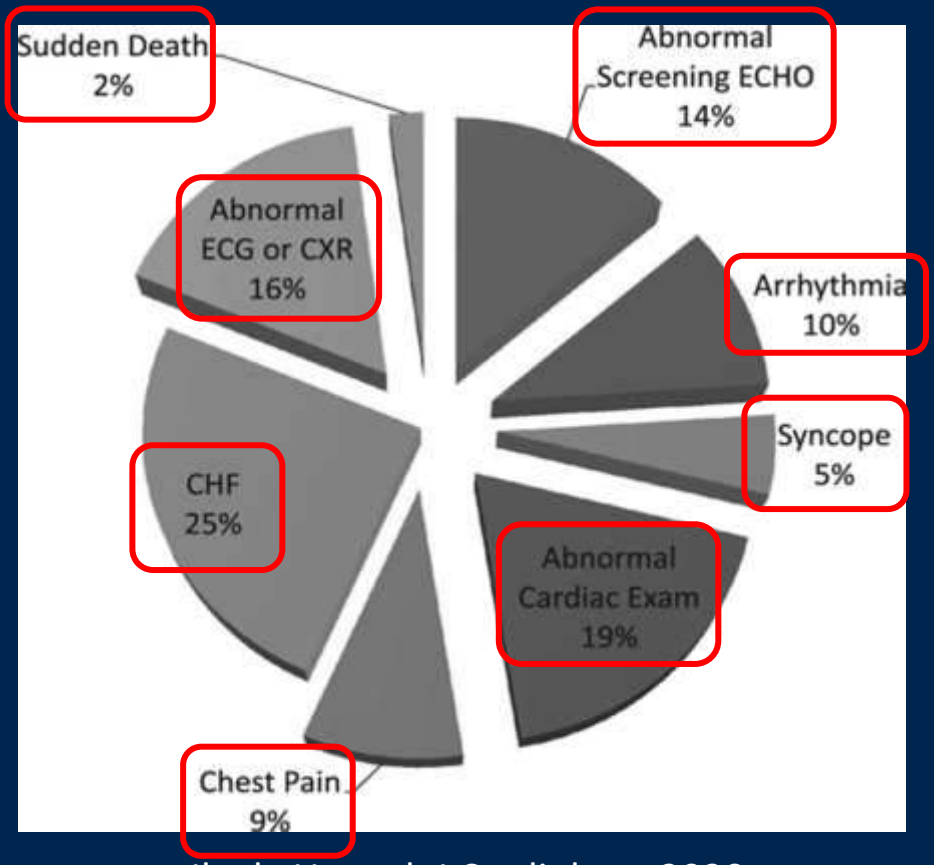


Rhee S, et al. Eur Heart Journal. 2021

Left Ventricular Non-compaction

- Currently makes up 3-10% of all pediatric cardiomyopathy





Brescia S, et al. Circulation. 2013

Towbin JA. Circulation Research. 2017

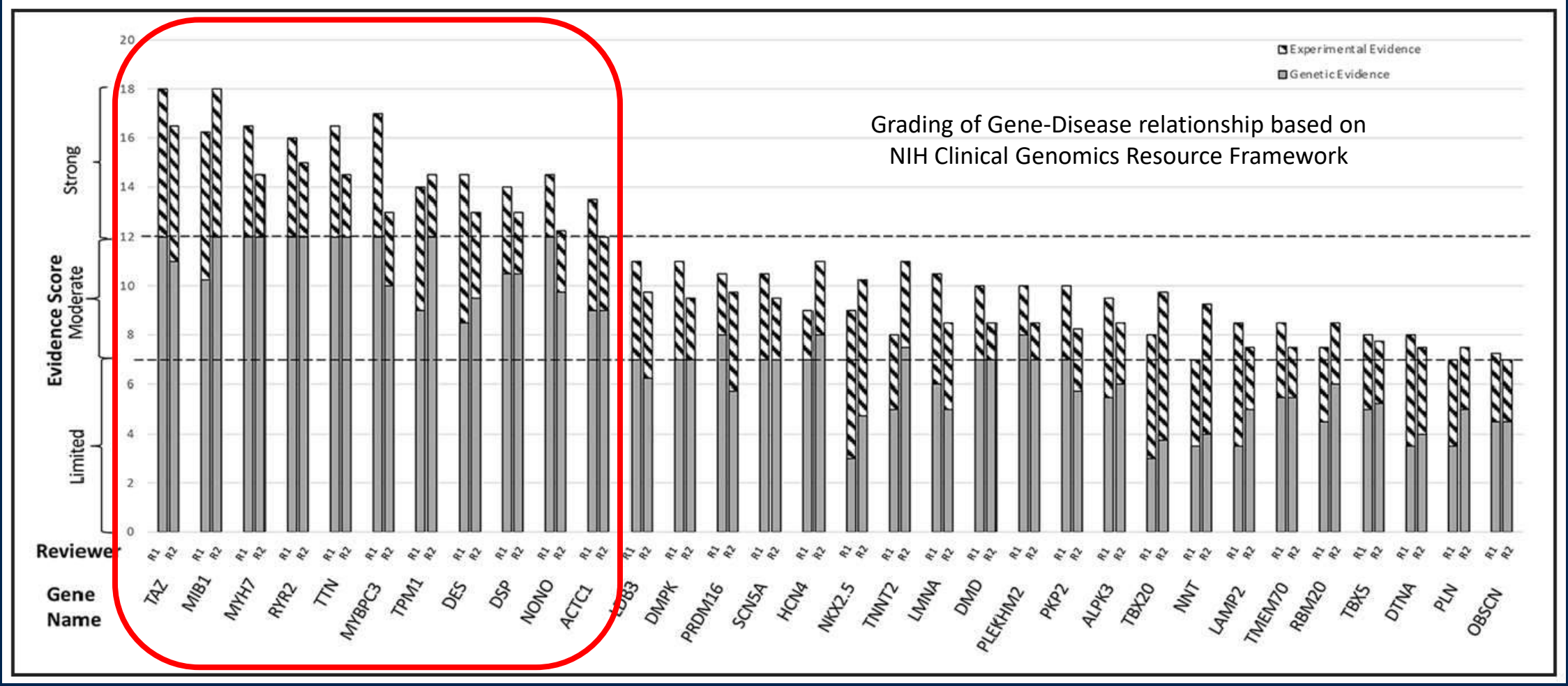
Ikeda U, et al. J Cardiology. 2020

Left Ventricular Non-compaction Genetics

- LVNC has a familial occurrence rate of ~30% in new presentations
- More heterogeneous and complex than other forms of cardiomyopathy
- Inheritance can be Autosomal Dominant, X-linked, AR, or mitochondrial

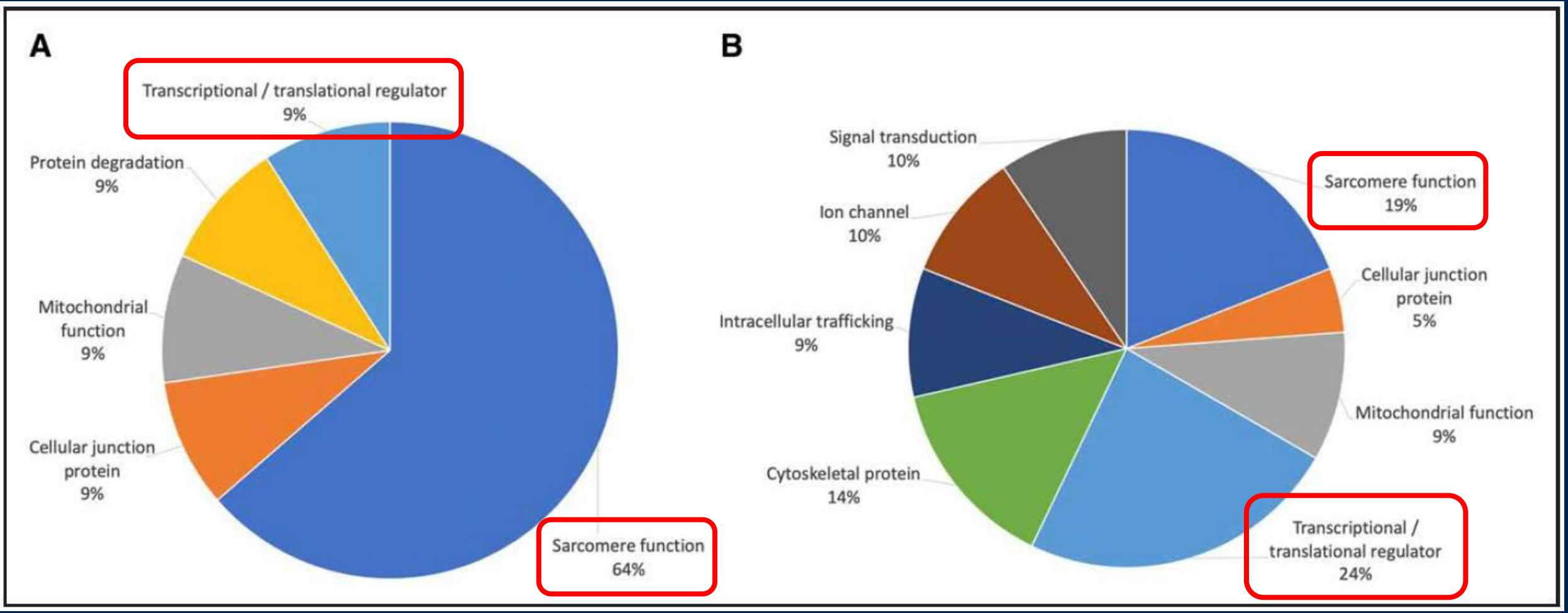
Bhatia, et al. J Car Fail. 2013 Van Waning J, et al. JACC. 2018 Rojanasopondist, et al. Circ Genom Precis Med. 2022

Left Ventricular Non-compaction Genetics



Rojanasopondist, et al. Circ Genom Precis Med. 2022

Left Ventricular Non-compaction Genetic Pathway



Rojanasopondist, et al. Circ Genom Precis Med. 2022

Left Ventricular Non-compaction Genetics Testing

Genetic Evaluation of Cardiomyopathy—A Heart Failure Society of America Practice Guideline

RAY E. HERSHBERGER, MD,[1,2] MICHAEL M. GIVERTZ, MD,[3] CAROLYN Y. HO, MD,[3] DANIEL P. JUDGE, MD,[4] PAUL F. KANTOR, MD,[5] KIM L. MCBRIDE, MD,[6] ANA MORALES, MS, CGC,[1] MATTHEW R.G. TAYLOR, MD,[7] MATTEO VATTA, PhD,[8,9,10] AND STEPHANIE M. WARE, MD, PhD[9,11]

Guideline 4

Genetic testing is recommended for patients with cardiomyopathy.

4a. Genetic testing is recommended for the most clearly affected family member.

4b. Cascade genetic testing of at-risk family members is recommended for pathogenic and likely pathogenic variants.

Genetic testing is *not recommended* in asymptomatic patients with incidental findings of prominent trabeculations or "suspicions" of disease

Cardiomyopathy Phenotype	Level of Evidence
[illegible]	A
[illegible]	A
[illegible]	A
Restrictive cardiomyopathy (RCM)	B
Cardiomyopathies associated with other extracardiac manifestations	A
Left ventricular noncompaction (LVNC)	See Background

Hershberger, et al. J Card Fail. 2018

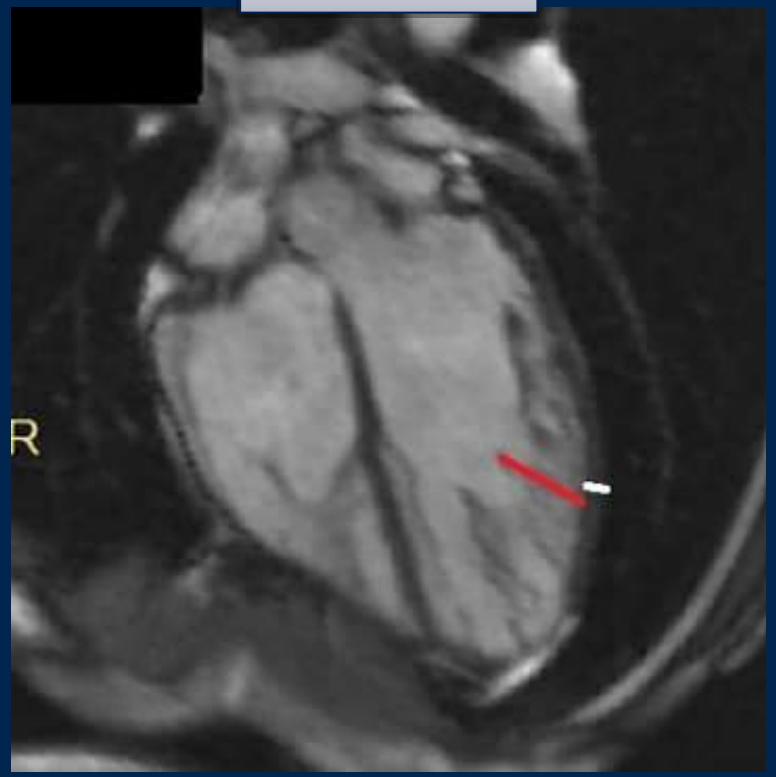
Left Ventricular Non-compaction Imaging

	Chin	Jenni	Stollberger
Measurement Example			
Diagnostic Criteria	• Decreasing X/Y ratio* from base to apex • No specific cut-off reported	• Two-layer myocardium with NC/C* ratio >2 • Non-compaction predominantly located in mid-lateral, apical, and mid-inferior regions • Perfusion of intertrabecular spaces demonstrated by color Doppler • Absence of coexisting cardiac abnormalities	• >3 prominent trabeculations • Trabeculations move synchronously with myocardium • Trabeculations part of noncompacted layer of the two-layered myocardium • Perfusion of intertrabecular spaces demonstrated by color Doppler
Cardiac Phase	• End-diastole	• Systole	• Trabeculations: End-diastole • Two-layered myocardium: End-systole
Echocardiographic View/Segment	• Parasternal long-axis at level of mitral valve and papillary muscle; • Subcostal long-axis or apical four-chamber view at level of apex	• Parasternal short-axis	• Trabeculations: Parasternal short axis, apical level • Two-layered myocardium: "Atypical apical 2-chamber view"

Taylor C, et al. Progress Ped Cardiol. 2021

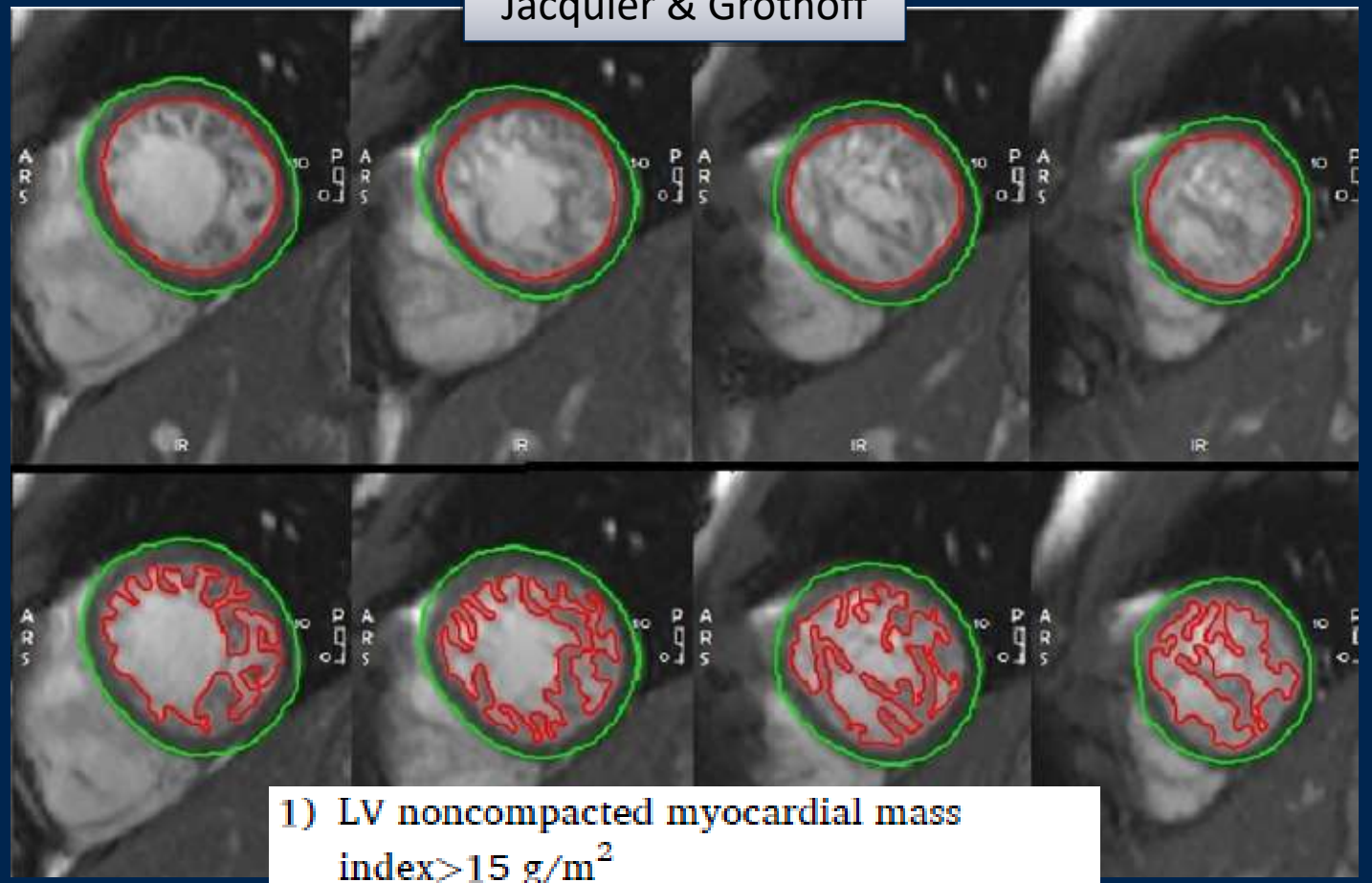
Left Ventricular Non-compaction Imaging

Petersen



NC:C myocardial ratio > 2.3 end-diastole

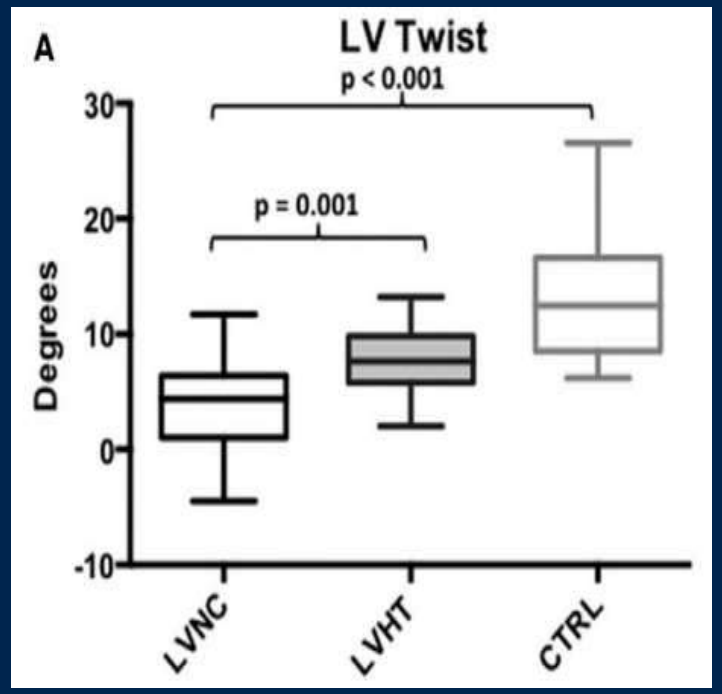
Jacquier & Grothoff

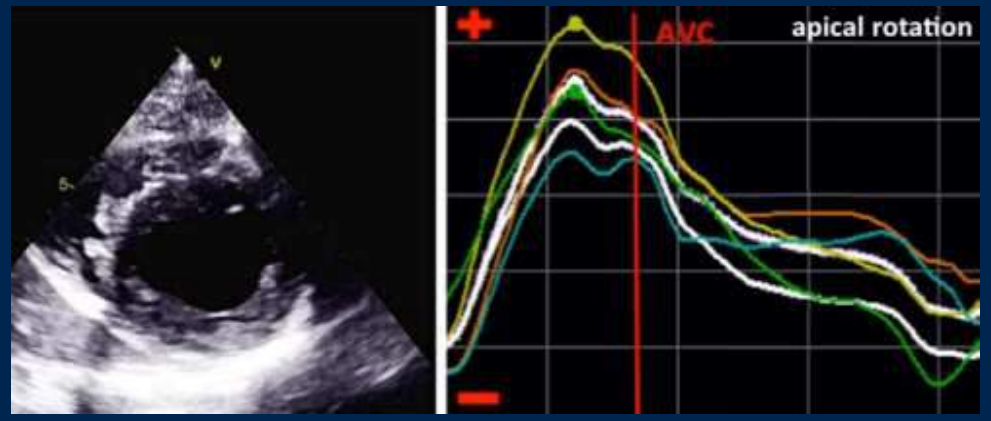


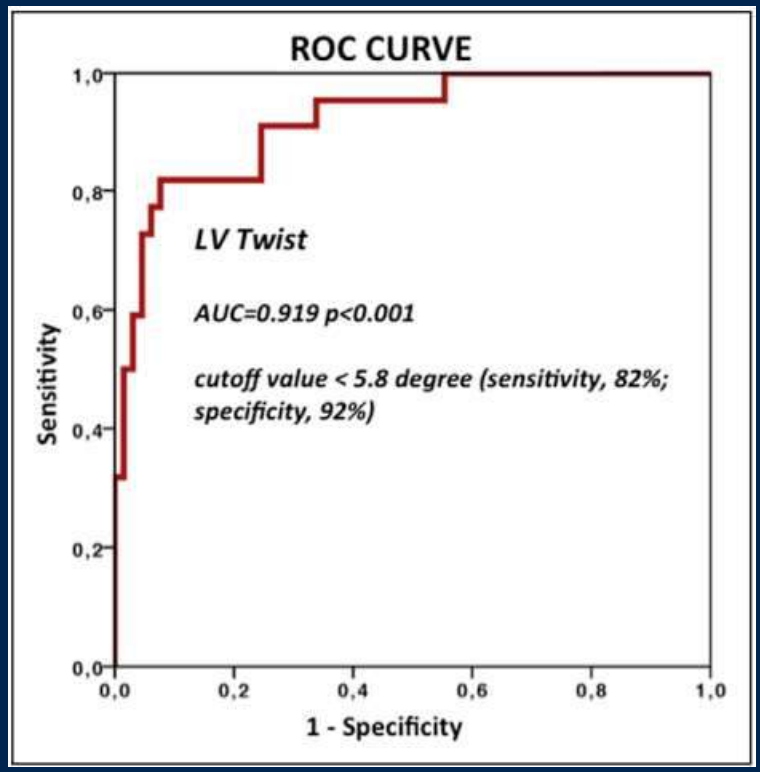
1) LV noncompacted myocardial mass index>15 g/m^2
2) Noncompacted LV mass > 25% of total LV mass

Taylor C, et al. Progress Ped Cardiol. 2021

Left Ventricular Non-compaction Imaging

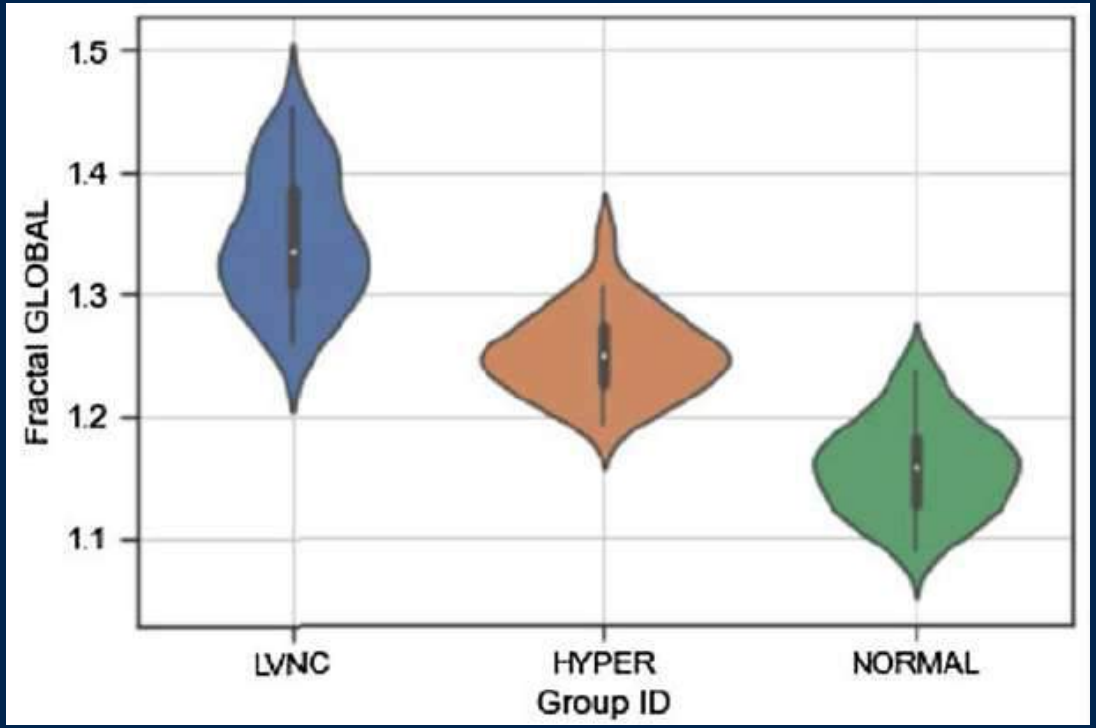


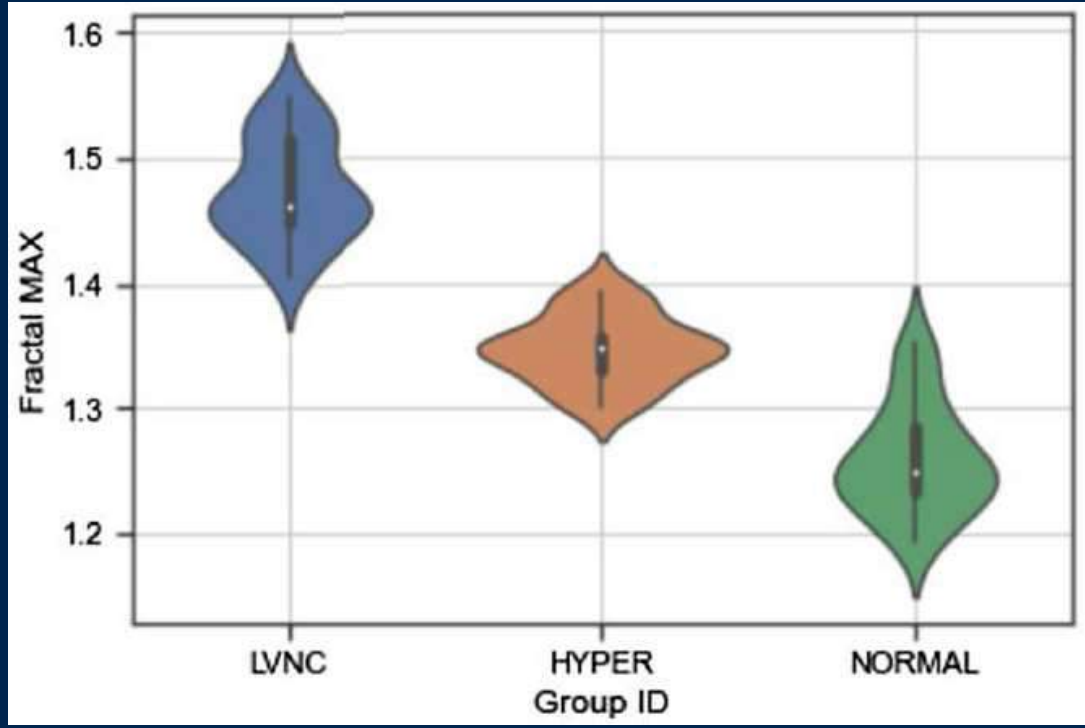




Sabatino J, et al. Circ Cardiovasc Imaging. 2019

Left Ventricular Non-compaction Imaging





	LVNC	Hypertrabeculation	Controls
Basal third	1.274 (0.078)	1.179 (0.082) p < 0.001*	1.140 (0.088) p = 0.078**
Mid third	1.394 (0.082)	**1.327 (0.025) p = 0.001***	**1.251 (0.042) p < 0.001****
Apical third	**1.467 (0.035)**	1.316 (0.058) p < 0.001*	1.195 (0.074) p < 0.001**

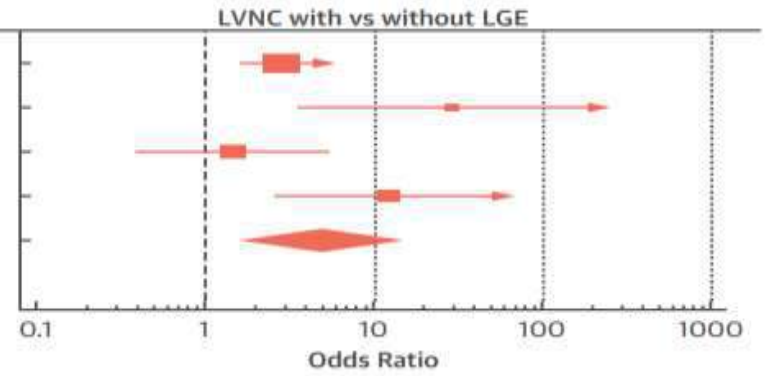
Krupickova S, et al. J Cardiovasc Magn Reson. 2021

Left Ventricular Non-compaction Imaging

Combined Endpoint

First Author	LGE Events/ Patients	No LGE Events/ Patients	Odds Ratio	95% CI	P value
Ivanov	30/84	31/192	2.9	1.6 - 5.2	< 0.0001
Andreini	10/11	26/102	29.2	3.5 - 239	< 0.0001
Amzulescu	5/22	6/36	1.47	0.39 - 5.54	0.73
Mazurkiewicz	11/46	2/81	12.4	2.6 - 58	< 0.0001
Pooled	**56/163**	**65/411**	**4.9**	**1.63 - 14.6**	**0.005**

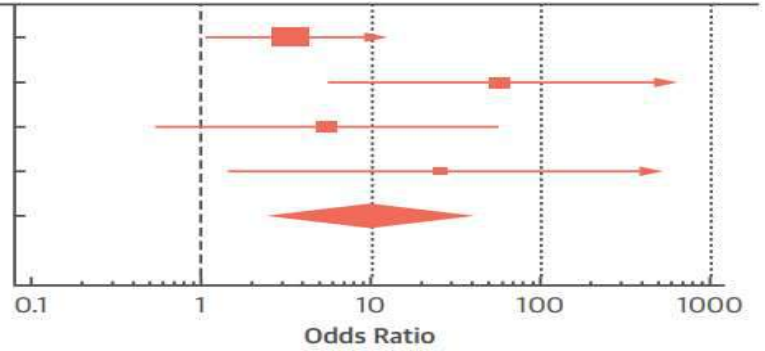
Cochran's Q = 8.7 p = 0.03; I^2 = 65% (95% CI 0-88)



Cardiac Death

First Author	LGE Events/ Patients	No LGE Events/ Patients	Odds Ratio	95% CI	P value
Ivanov	7/84	5/192	3.4	1.05 - 11	< 0.0001
Andreini	4/11	1/102	57.7	5.6 - 588	< 0.0001
Amzulescu	3/22	1/36	5.5	0.54 - 57	0.15
Mazurkiewicz	6/46	0/81	26.2	1.4 - 476	< 0.0001
Pooled	**20/163**	**7/411**	**9.8**	**2.44 - 39.5**	**0.001**

Cochran's Q = 5.4 p = 0.14; I^2 = 45% (95% CI 0-81)



Grigoratos, et al. JACC: Cardiovasc Imaging. 2019

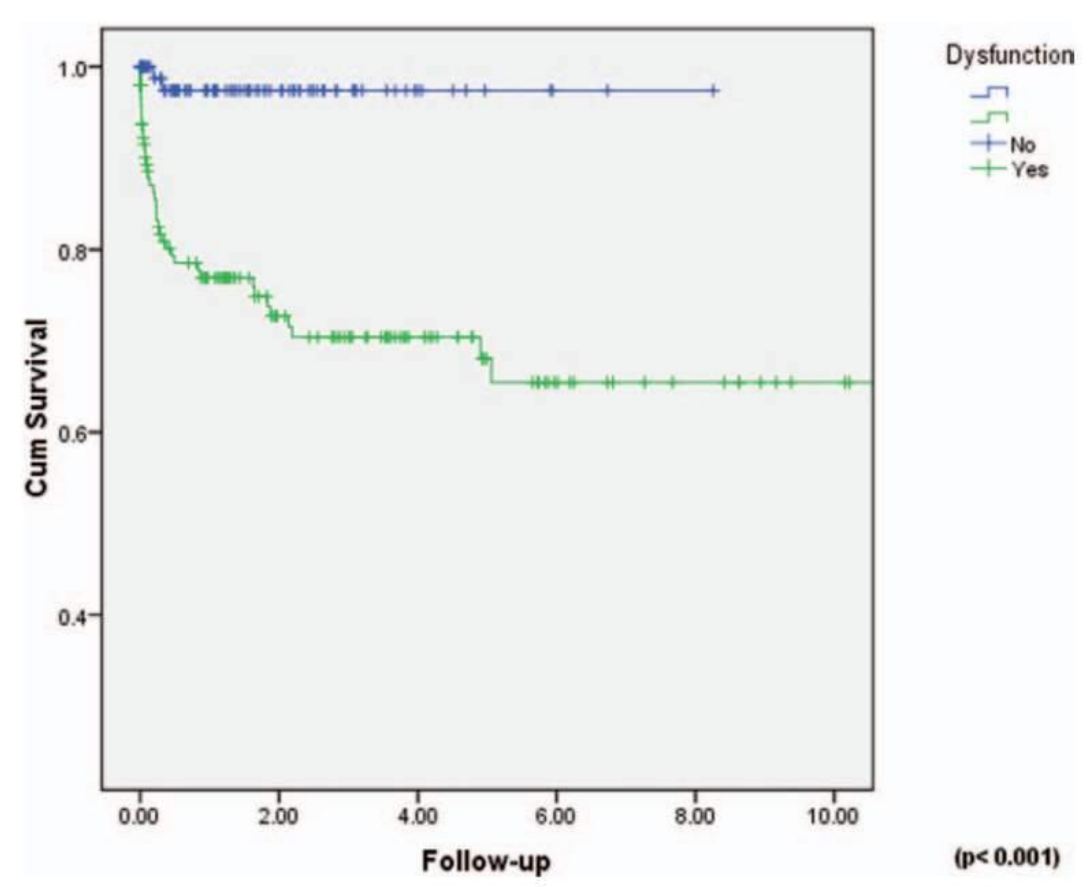
Left Ventricular Non-compaction Heart Failure

Pediatric patients	Ichida F et al. (7)	Wald R et al. (24)	Koh C et al. (8)	Brescia ST et al. (25)	Wang C et al. (21)		van Waning JI et al. (12)	Shi WY et al. (1)	Sabatino J et al. (9)
					Infanitile type	Juvenile type			
Number of patients	27	22	10	242	108	97	52	29	23
Male patients, *n* (%)	15 (56%)	40%	7 (70%)	145 (60%)	59 (55%)	51 (53%)	—	20 (69%)	12 (52%)
Age range, years	1–15	—	0.019–12	0.3–13.9	0–1	1–15	0–15	0.08–1.3	0–18
Length of follow-up (median)	17 years	16 years	8 years	4 years	3.5 years	5.9 years	4.2 years	6.8 years	5.4 years
Age at diagnosis (median)	—	3.9 years	—	7.2 ± 6.9 years	2.7 months	7.3 years	—	0–1 years	—
Family history of cardiomyopathy								9 (31%)	3 (13%)
Death in follow-up								14 (48%)	—
Clinical characteristic (at the time of diagnosis)									
Asymptomatic	—	—	1 (10%)	89 (37%)	21 (19%)	52 (54%)	9 (17%)	—	—
Heart failure	6 (22%)	54%	8 (80%)	60 (25%)	65 (60%)	22 (23%)	13 (27%)	24 (83%)	—
Arrhythmia	6 (22%)	—	3 (30%)	80 (33%)	9 (8%)	11 (11%)	9 (17%)	—	2 (9%)
Thromboembolism	2 (7%)	—	0(0%)	—	5(5%)	5(5%)	2(4%)	—	0(0%)

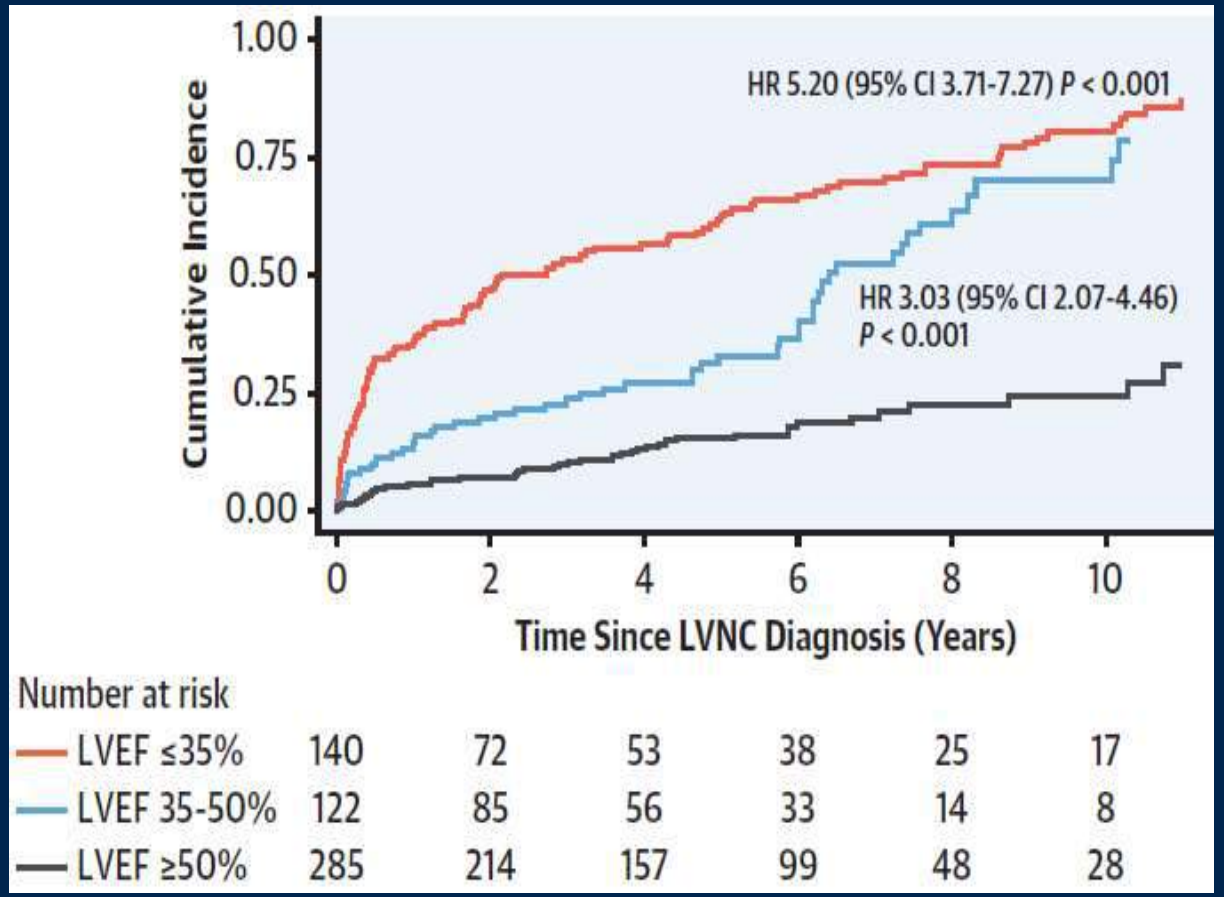
In general, ~2/3 of patients with LVNC develop Heart Failure over the course of their disease

Li, et al. Frontiers in Pediatrics. 2023

Left Ventricular Non-compaction Heart Failure

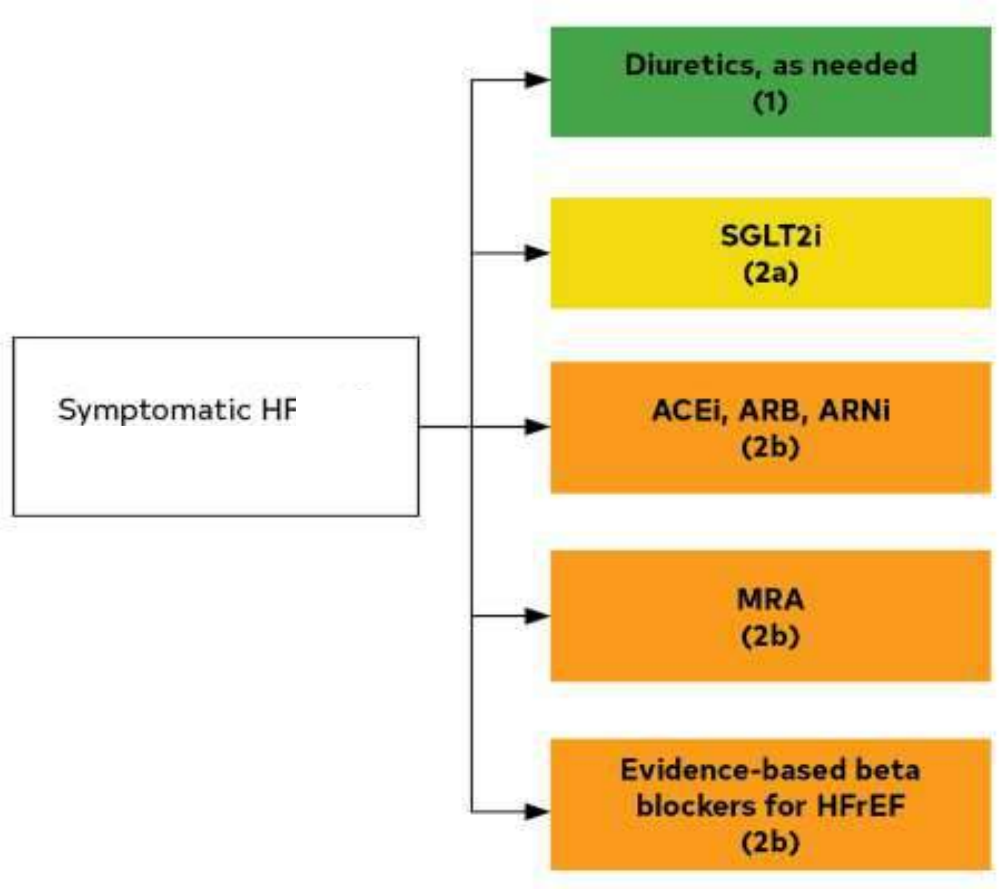


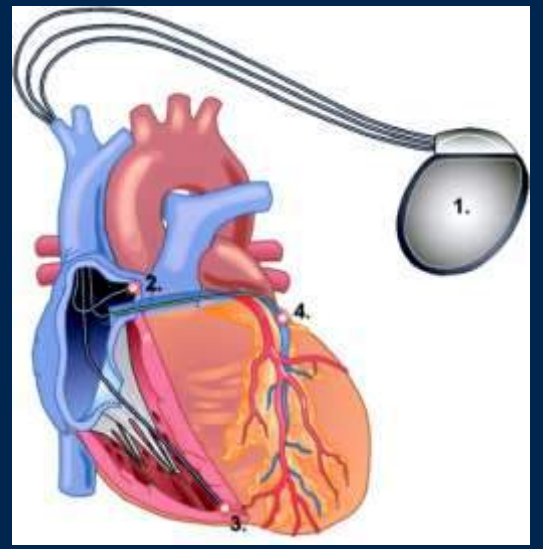
Brescia S, et al. Circulation. 2013



Casas G, et al. JACC. 2021

Left Ventricular Non-compaction Heart Failure

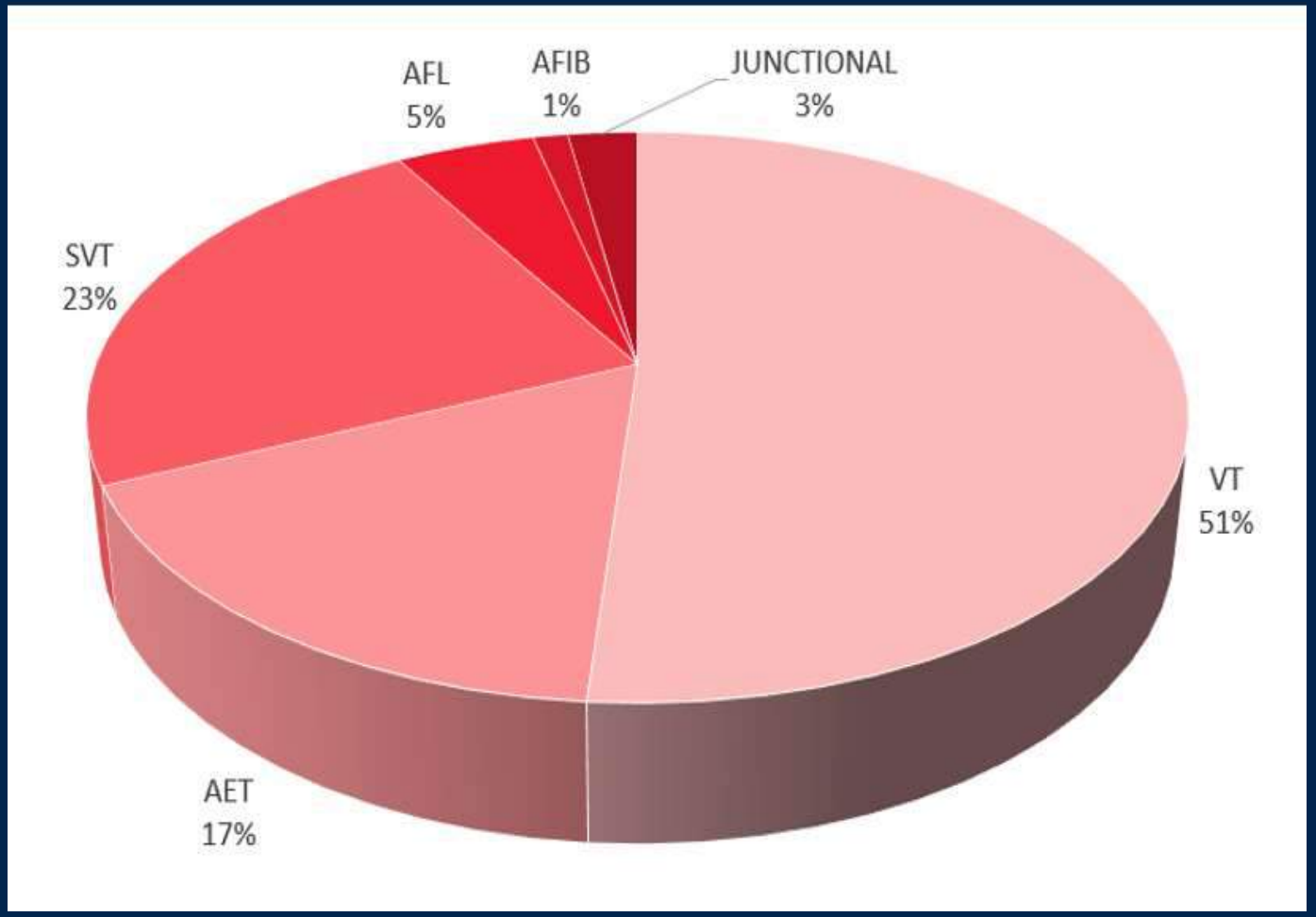




Heidenreich PA, et al. 2022 AHA/ACC/HFSA Guideline for Management of Heart Failure. Circulation. 2022

Left Ventricular Non-compaction Arrhythmias

- Overall prevalence of Arrhythmias in children with LVNC ~30%
- VT > SVT > Atrial Tachy (Afib rare in children)
- Arrhythmias associated with increased overall mortality (HR 3; *P*<0.01)



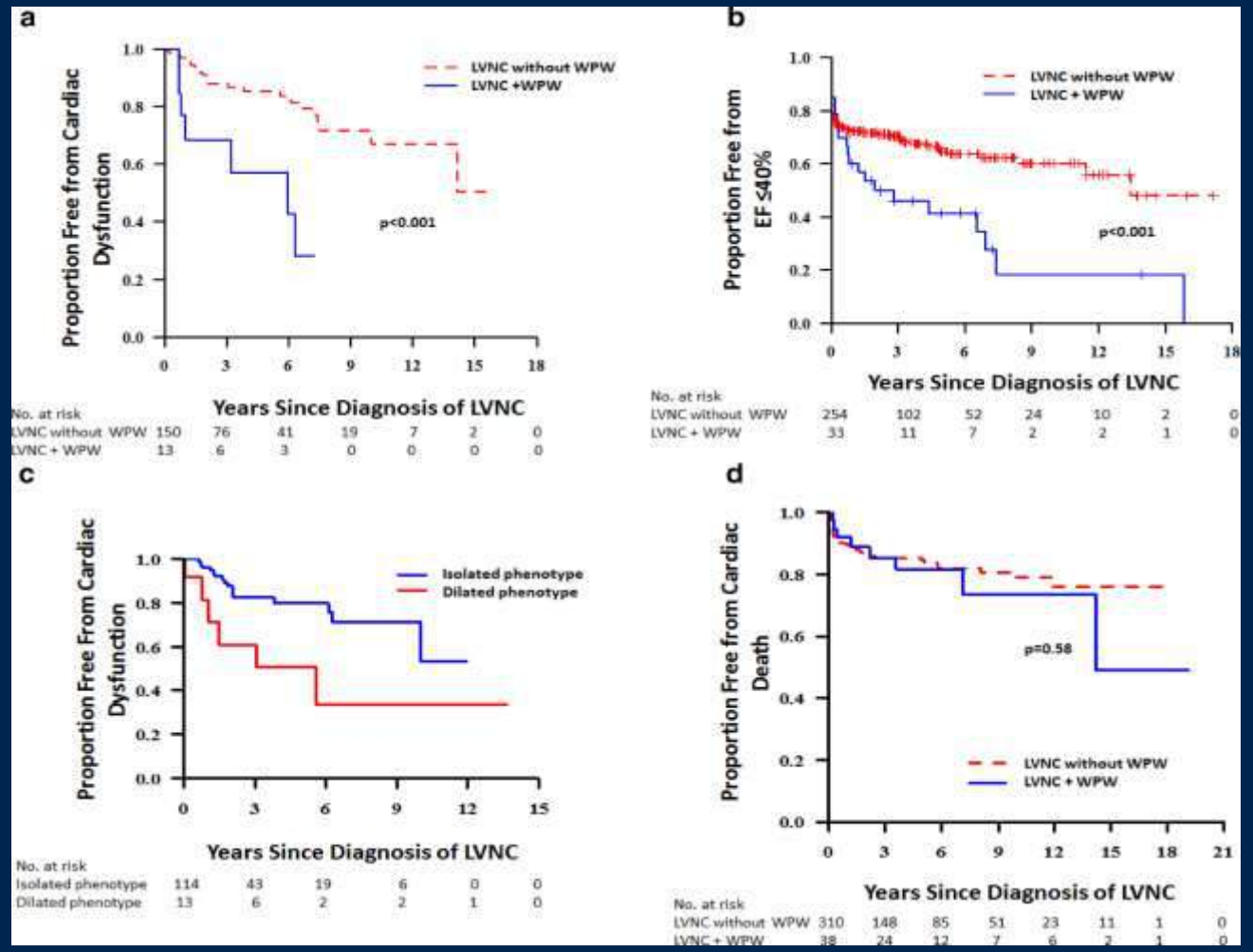
Brescia S, et al. Circulation. 2013

Jefferies JL,et al. Tex Heart Inst J. 2022

Left Ventricular Non-compaction Arrhythmias

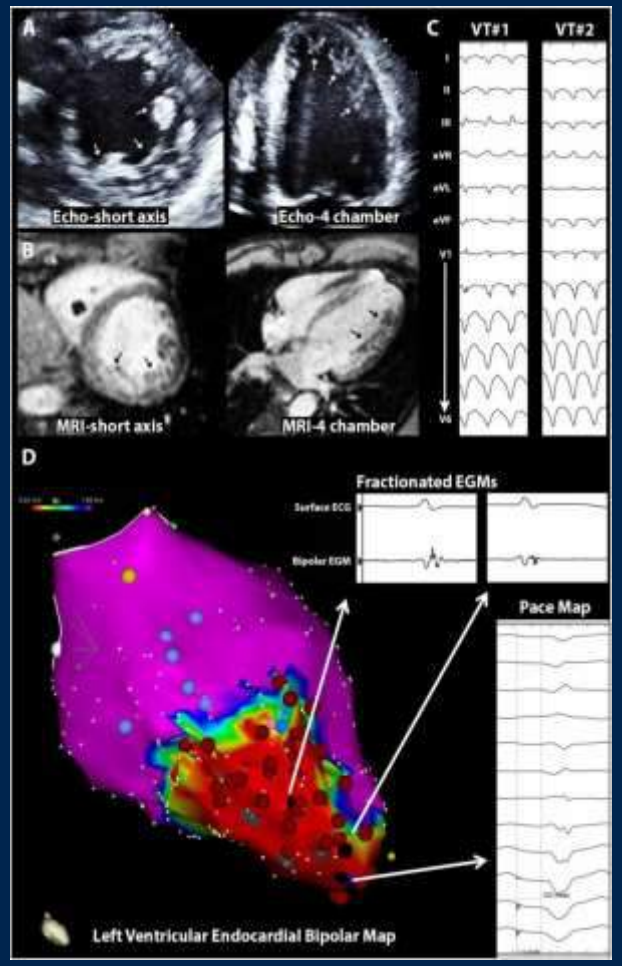
WPW in LVNC

- Prevalence of WPW in LVNC as high as 11%
- WPW associated with a higher risk of dysfunction related to dyssynchrony
- Ablations can result in improved (normalized) cardiac function

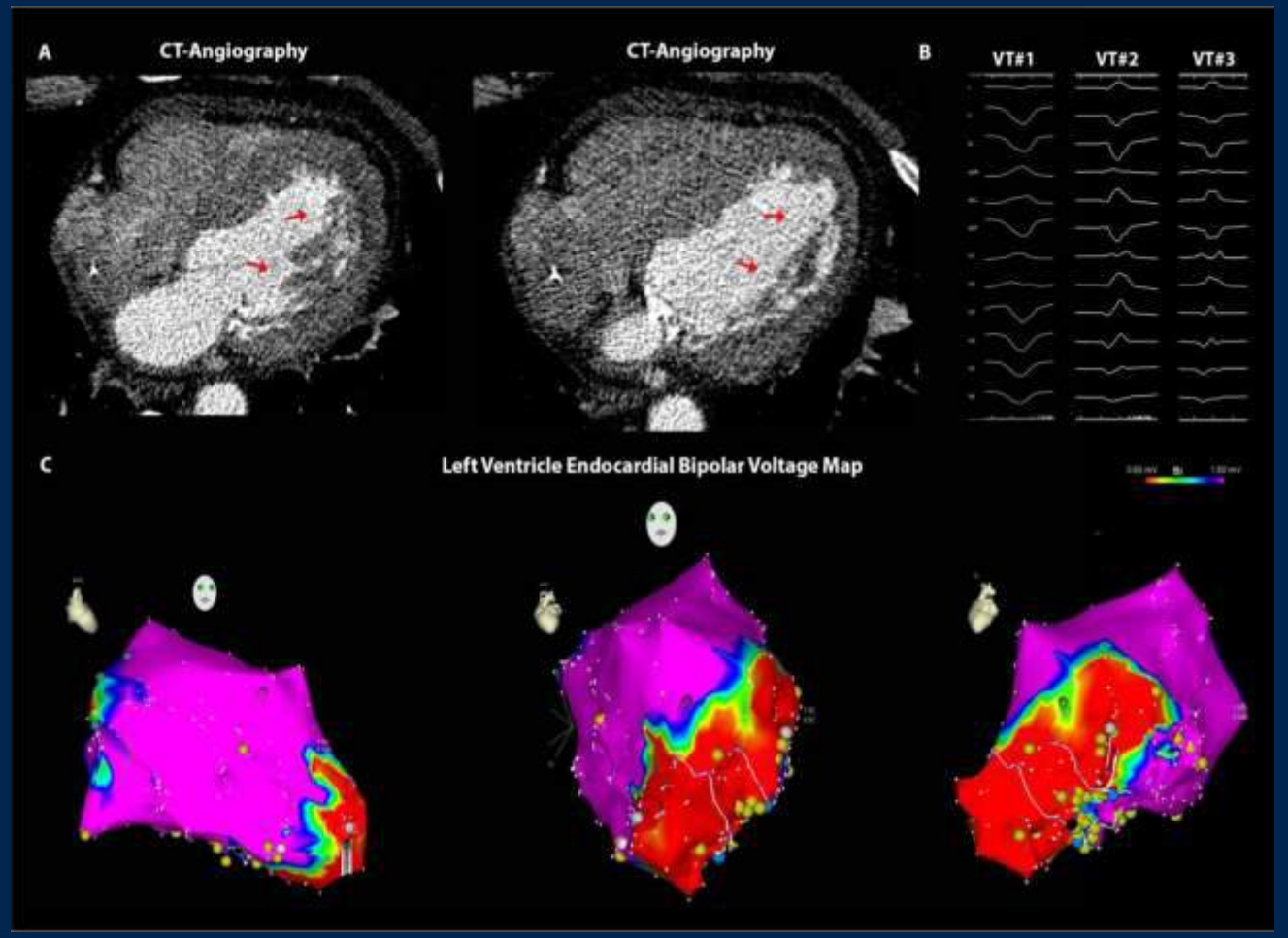


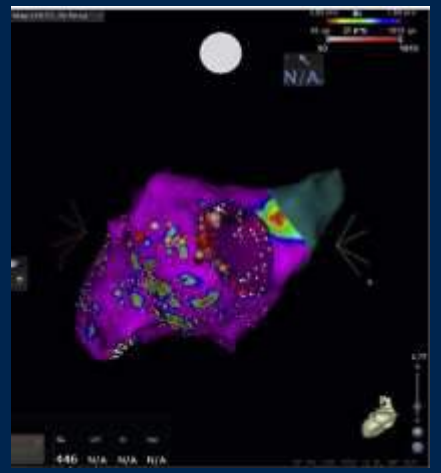
Howard TS, et al. J Card Failure. 2019

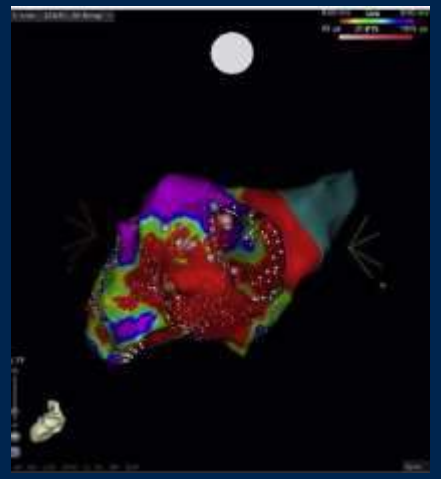
Left Ventricular Non-compaction Arrhythmias



Muser D. Heart Rhythm. 2017



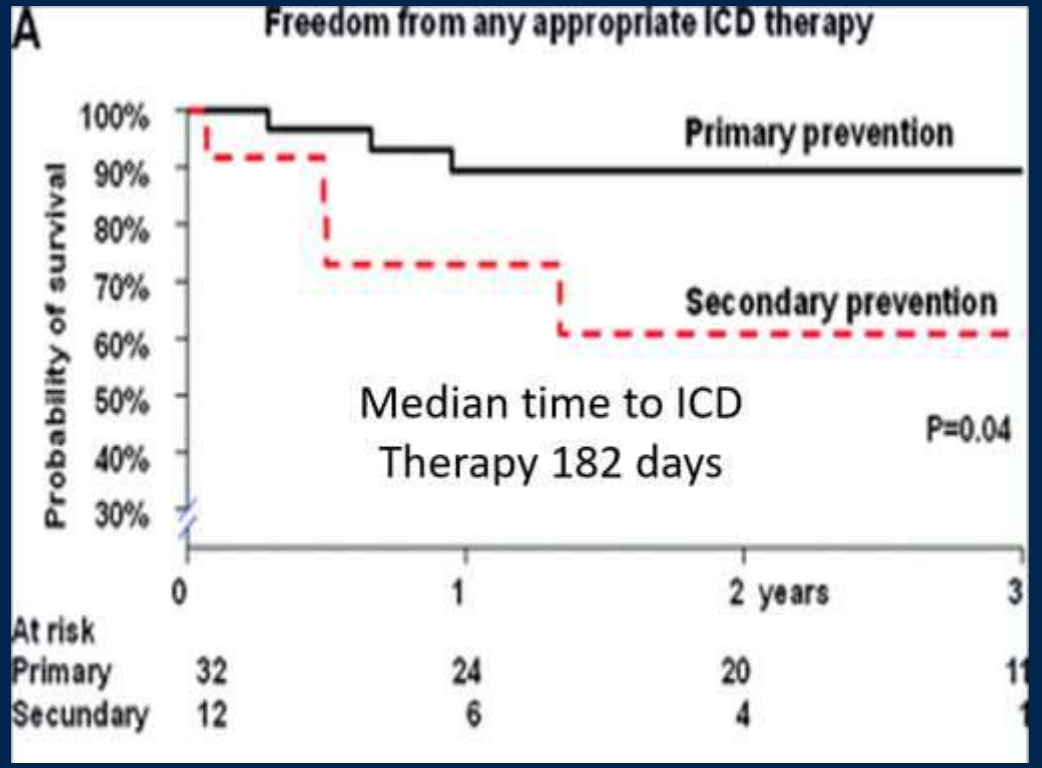




Sanchez Muňoz JJ. Heart Rhythm. 2021

Left Ventricular Non-compaction Arrhythmias

- Incidence of SCD in children with LVNC remains imprecisely defined (risk phenotype dependent)
  - Range 6-18% over variable follow-up
- Cardiac dysfunction and arrhythmias associated w/ SCD (HR 7.6; P=0.01)

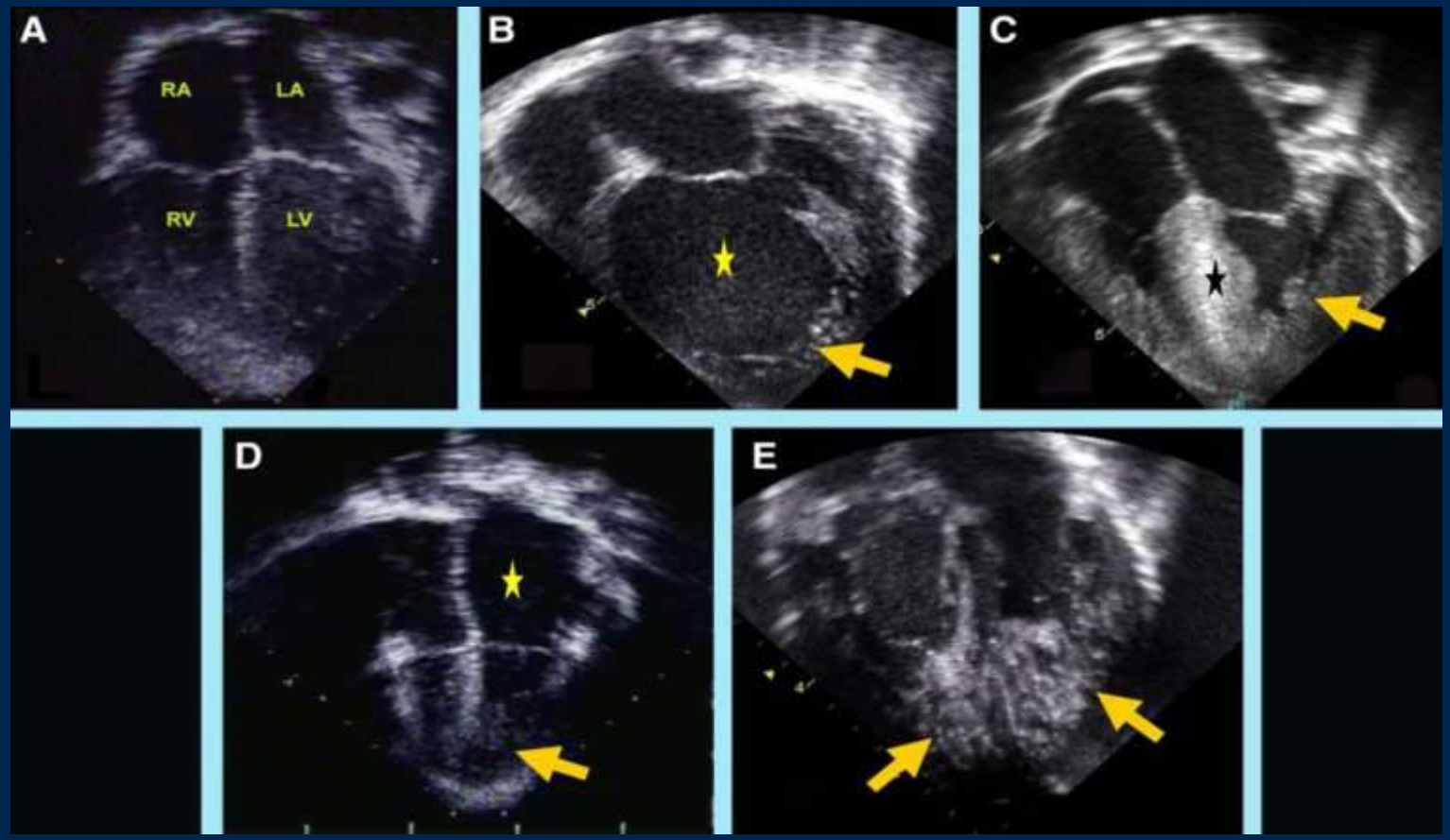


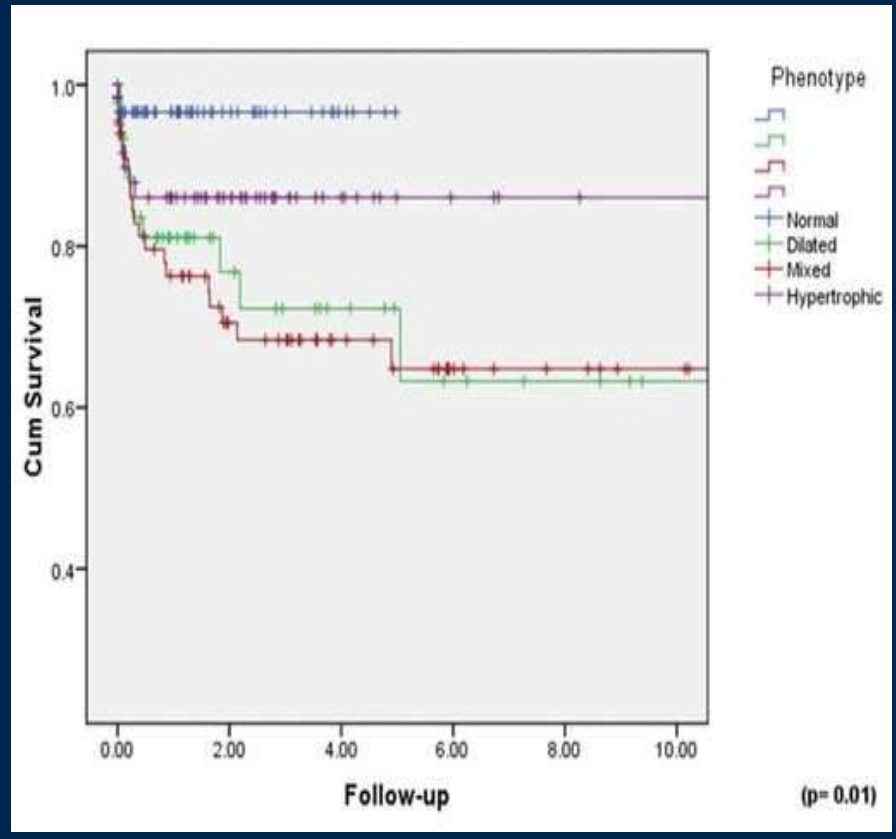
Brescia S, et al. Circulation. 2013

Miyake, et al. Cardiac EP Clinics. 2015

Kaya E. J Am Coll Cardiol EP. 2023

Left Ventricular Non-compaction Outcomes





Towbin JA. Circulation Research. 2017.

Brescia, et al. Circulation. 2013.

Left Ventricular Non-compaction Outcomes

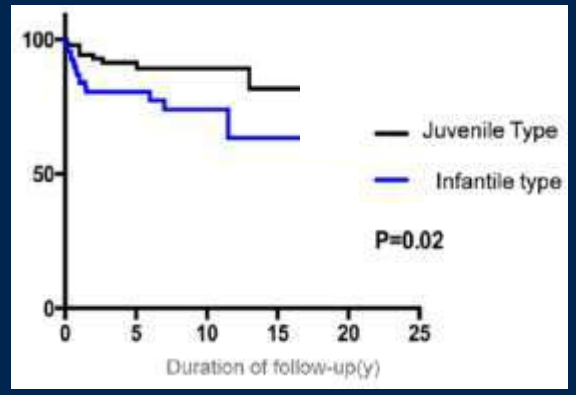


Table 2. Risk Factors for Death or Transplantation

Risk Factor	Hazard Ratio	95% Confidence Interval	*P* Value
Cardiac dysfunction	11.1	2.6–45	<0.001
T-wave inversion	2.1	1.1–4.2	0.02
ST-segment abnormalities or strain	4.0	1.0–19.9	0.05
Any arrhythmias	2.8	1.4–5.6	0.002
Ventricular arrhythmias	4.0	2.1–9.0	<0.001
Presentation <1 y	2.1	1.0–3.9	0.02
Presentation <1 y with ventricular arrhythmias	12.0	2.4–68.9	<0.001

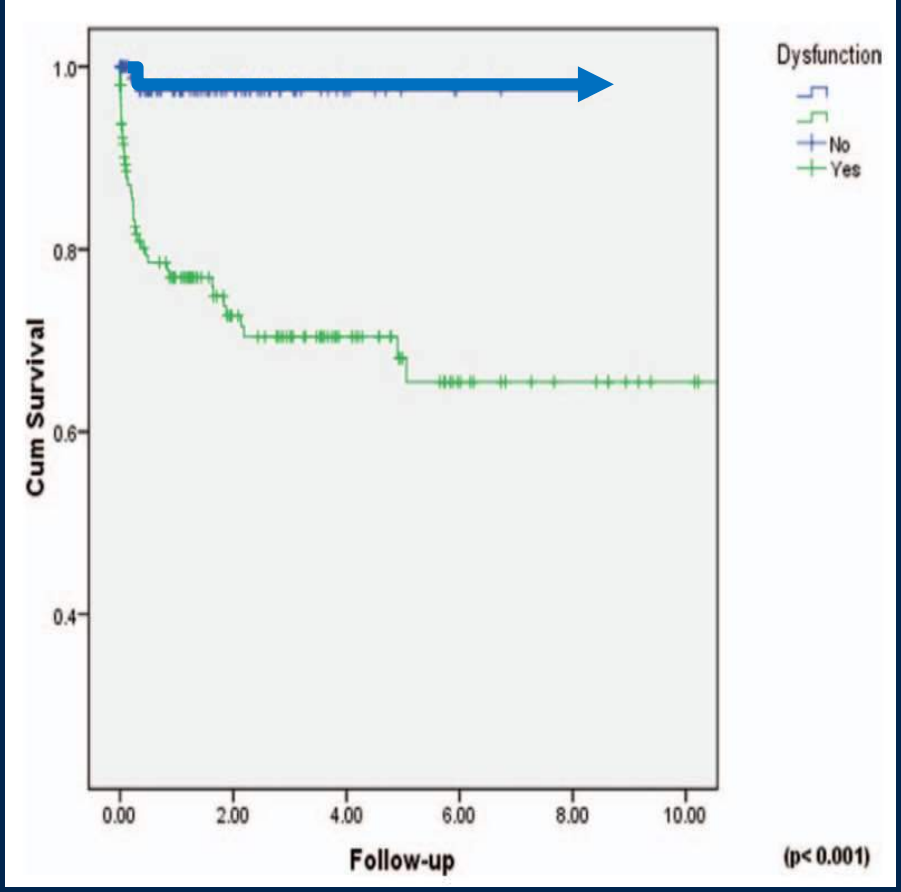
The table demonstrates the significant risk factors for death or cardiac transplantation during follow-up. Separate Cox proportional hazards models were used for demographic factors and other risk factors. $P<0.05$ was considered significant. Only factors found to be statistically significant are displayed.

Brescia S, et al. Circulation. 2013

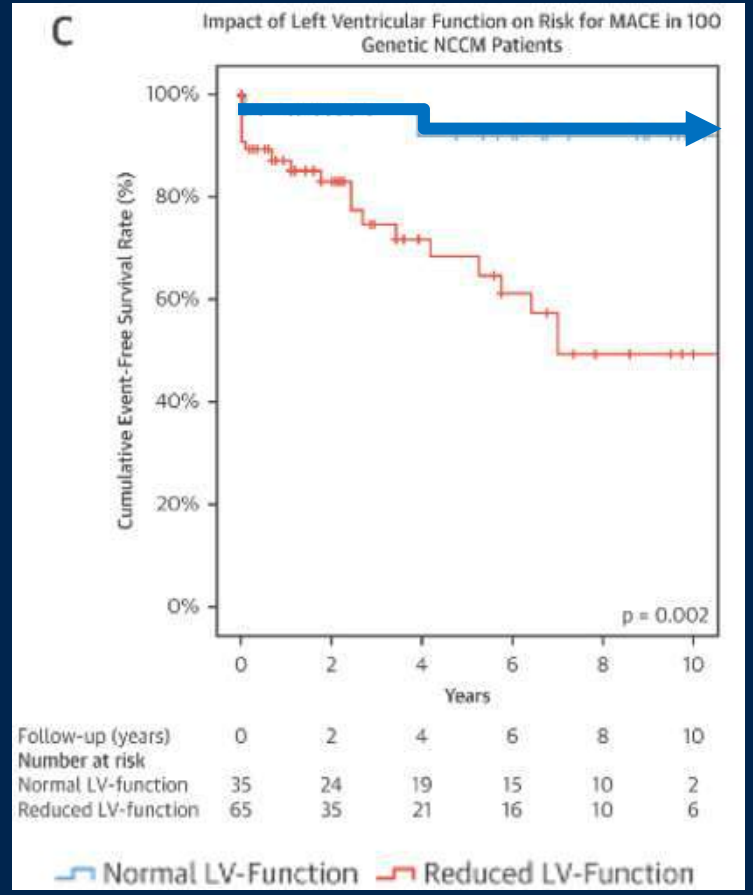
Shi, et al. Circulation. 2018

Ichida et al. J Cardiol. 2020

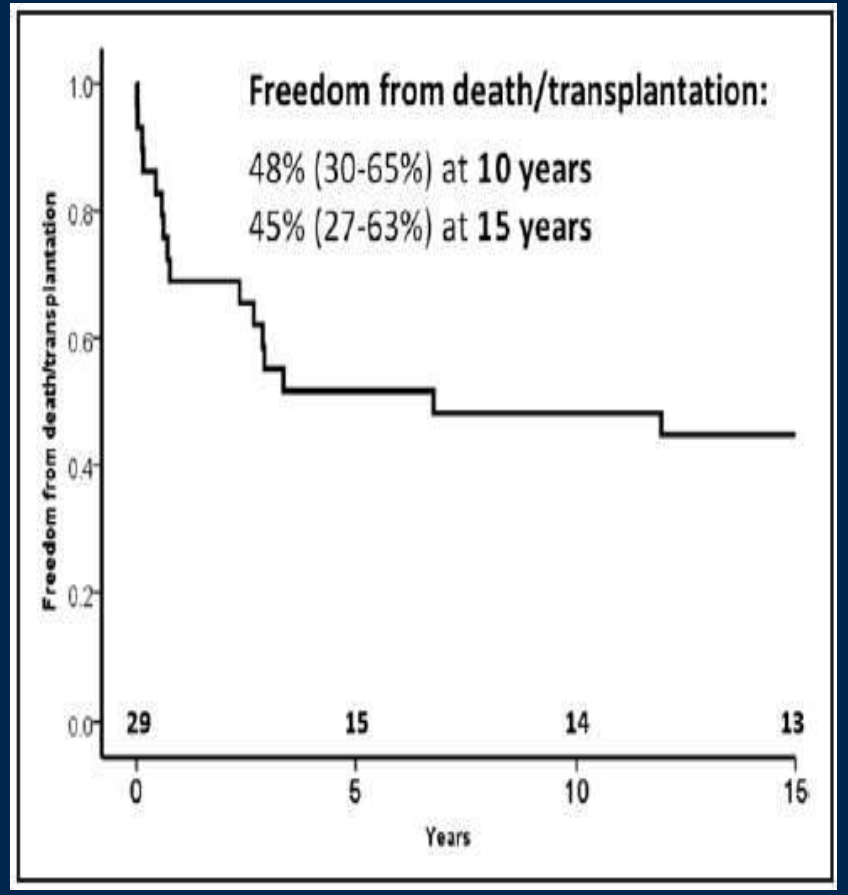
Left Ventricular Non-compaction Outcomes



Brescia S, et al. Circulation. 2013

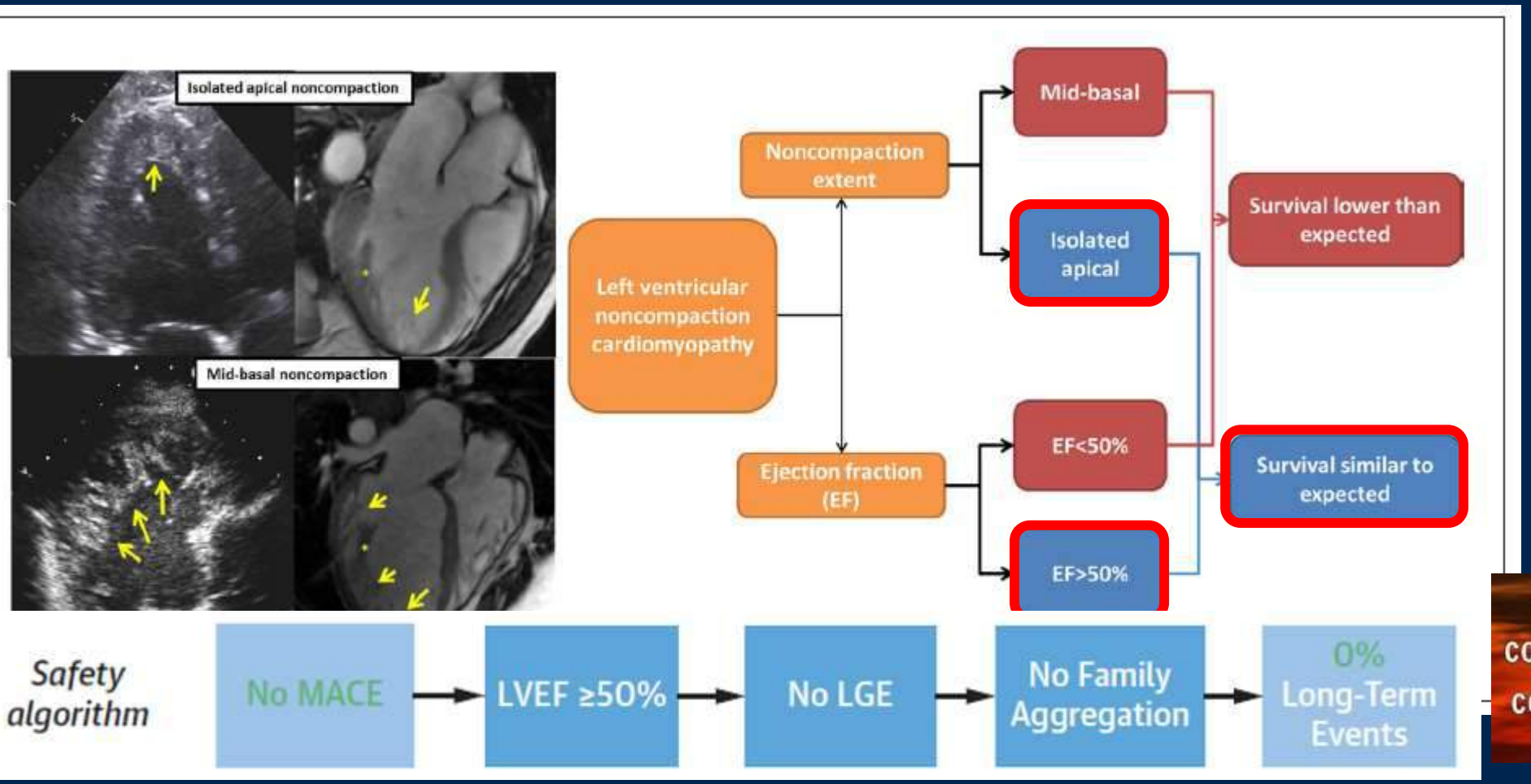


Van Waning JI. *JACC*. 2018



Shi, et al. Circulation. 2018

Left Ventricular Non-compaction Outcomes



Vaidya, et al. J Am Heart Assoc. 2021

Casas G, et al. JACC. 2021

Left Ventricular Non-compaction

Summary

- LVNC is a unique form of cardiomyopathy characterized by prominent trabeculations and deep intratrabecular recesses
- Genetically heterogeneous and complex
- Diagnosis remains a conundrum, but dependent on evolving imaging modalities and genetic evaluation
- Outcomes primarily associated with phenotype, presence of cardiac dysfunction, and arrhythmias
- Those with normal dimensions, normal function, no arrhythmias (i.e. prominent trabeculations) should be expected to do very well


Thank You