CME Series on Lysosomal Disorders

Cardiac Structural Abnormalities & Arrhythmias in Lysosomal Disorders

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This program was supported by educational grants from Takeda and Ultragenyx

THANK YOU

Disclosures

Dr. Goker-Alpan is on the Advisory Board/Consultant/ receives grants/research support : Chiesi, Takeda, Sanofi, Prevail/Lilly, Spur Therapeutics, Uniqure, Team Sanfilippo. She is on the speaker bureau for Sanofi, Takeda, Amicus, Chiesi

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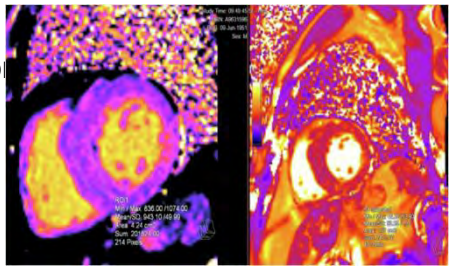
Lysosomal Disorders with Prominent Cardiac Involvement

Sphingolipidoses

- Fabry Disease (GLA): Hypertrophic cardiomyopathy, valvular disease, arrhythmia, conductio
- Gaucher Disease (GBA): Pulmonary hypertension, cardiac calcifications
- Niemann-Pick Type A/B (SMPD1): Lipid infiltration of myocardium; coronary artery disease
- Niemann-Pick Type C (NPC1/2): Progressive cardiomyopathy, arrhythmias
- GM1 Gangliosidosis (GLB1): Dilated or hypertrophic cardiomyopathy
- Danon Disease (LAMP2): Severe HCM, Wolff-Parkinson-White syndrome



From Doughterty et al, 2025, npJ Cardiovascular Health
A, B In the T1 map on the Left, the low T1 (mean 943 ms) in the septum at 1.5 T CMR establishes the diagnosis of Fabry disease in its storage phase, indicative of sphingolipid accumulation in the septum. The T2 map on the right shows normal T2 values at the septum.

GAG Metabolism Disorders -- MPS and Mucolipidoses

- MPS I (Hurler/Scheie): Valvular disease, coronary stenosis, cardiomyopathy
- MPS II (Hunter): Valvular thickening, conduction abnormalities, restrictive cardiomyopathy
- MPS IV (Morquio) and VI (Maroteaux-Lamy): Aortic regurgitation, valvular stenosis
- Mucolipidosis II and III: Valvular disease is PRIMARY -- severe aortic/mitral involvement from infancy

Structural Cardiac Abnormalities: Sphingolipidoses

Myocardial Disease

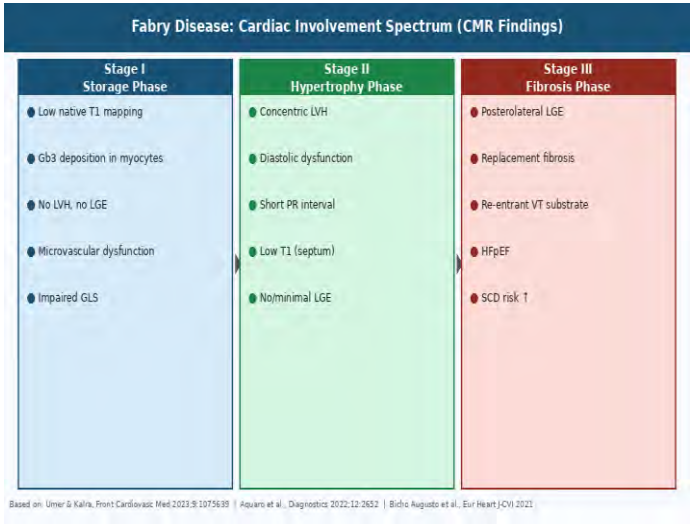
- Concentric LVH: hallmark of Fabry disease (GLA);
- also prominent in Pompe (GAA) and Danon (LAMP2)
- Myocardial fibrosis n Fabry disease
- Dilated cardiomyopathy: predominates advanced GM1 gangliosidosis

Vascular and Valvular Disease

- Coronary microvascular disease: Gb3 deposition in endothelia

impairs microvasculatures Fabry)

- Mitral valve and aortic involvement Fabry; disease progresses to mixed stenosis-regurgitation
- Lipid infiltration of valve interstitial cells: thickening and reduced leaflet mobility in NPC and Gaucher
- Pulmonary arterial hypertension: prominent in Gaucher disease type 1
- Aortic root dilation/calcifications: reported in Gaucher disease and selected sphingolipidoses



Schematic based on: ***Umer & Kalra, Front Cardiovasc Med 2023 (doi:10.3389/fcvm.2022.1075639); Aquaro et al., Diagnostics 2022;12:2652 (CC BY 4.0)***

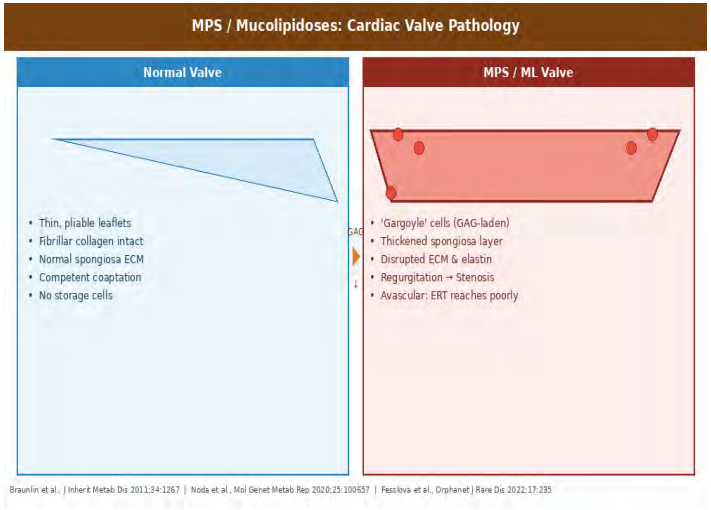
Structural Cardiac Abnormalities: MPS and Mucolipidoses

Valvular Disease -- Primary in Mucolipidosis II and III

- ML II and III: valvular disease is the PREDOMINANT cardiac feature -- aortic and mitral valve thickening present in nearly all patients from infancy
- MPS I, II, VI: mitral regurgitation most common; mixed stenosis/regurgitation as GAG deposition progresses
- Valve cusps and chordae infiltrated by storage macrophages causing immobility
- MPS IV and VI: aortic regurgitation predominates; annular dilation contributes

Myocardial, Coronary and Conduction Involvement

- Cardiomyopathy: restrictive physiology from myocardial GAG deposition in MPS I, II, VI
- Coronary artery disease: intimal GAG deposition narrows coronary ostia (MPS I, II) -- ischemia without atherosclerosis
- Pulmonary hypertension: obstructive airway disease and glycosaminoglycan deposits in pulmonary vasculature
- Conduction disease: GAG in AV node and bundle branches causes heart block and bundle branch block
- Pericardial effusion: reported in MPS I and mucolipidosis II



Schematic based on: ***Braunlin et al., J Inherit Metab Dis 2011;34:1267; Noda et al., Mol Genet Metab Rep 2020;25:100657; Fesslova et al., Orphanet J Rare Dis 2022;17:235***

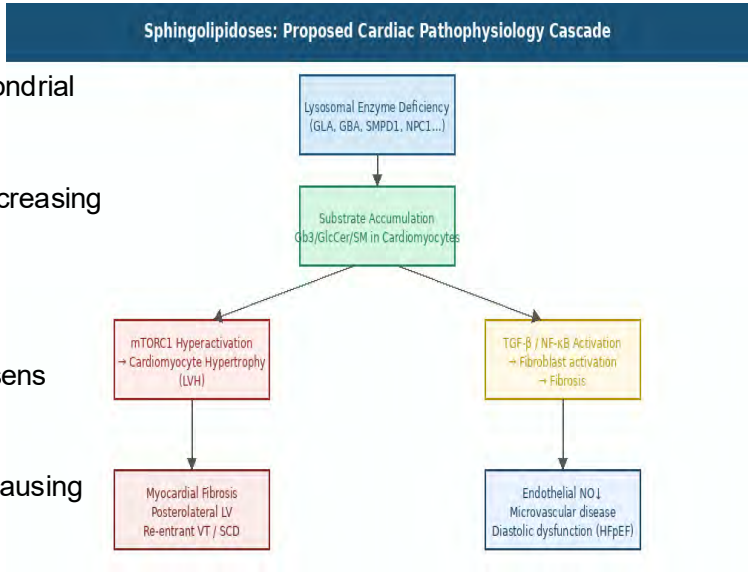
Pathophysiology of Cardiac Disease: Sphingolipidoses

Primary Storage and Lysosomal Dysfunction

- Substrate accumulation (Gb3, glucocerebroside, sphingomyelin, GM1/2) directly disrupts cardiomyocyte sarcomeric architecture
- Lysosomal membrane permeabilization releases cathepsins, triggering mitochondrial apoptosis
- Impaired autophagy/mitophagy flux: dysfunctional mitochondria accumulate, increasing reactive oxygen species

Secondary Signalling Cascades

- mTORC1 hyperactivation drives anabolic hypertrophy; TFEB suppression worsens lysosomal biogenesis
- TGF-beta upregulation by storage macrophages activates cardiac fibroblasts causing collagen deposition and fibrosis
- NF-kB-mediated release of IL-6 and TNF-alpha sustains chronic myocardial inflammation and remodelling
- Ceramide/S1P imbalance: ceramide is proapoptotic; excess S1P dysregulates cardiomyocyte Ca2+ handling
- Reduced endothelial NO bioavailability promotes microvascular disease and diastolic dysfunction



Schematic based on: ***Wanner et al., Lancet 2018;392:409; Nordbeck et al., Eur Heart J 2021;42:1122; Liebau et al., J Am Soc Nephrol 2019;30:2051***

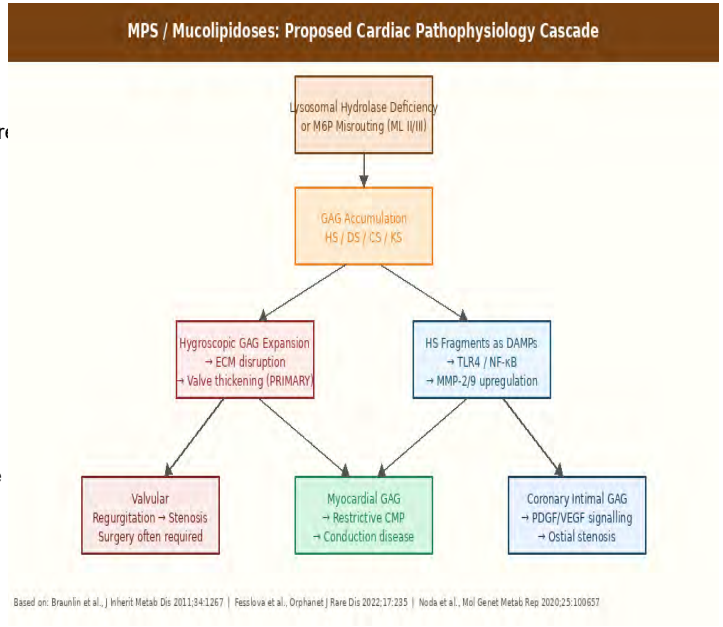
Pathophysiology of Cardiac Disease: MPS and Mucolipidoses

Primary GAG Accumulation Effects

- Heparan, dermatan, chondroitin, keratan sulfates accumulate in cardiomyocytes, valve interstitial cells, and coronary intima
- GAGs are hygroscopic: tissue expansion compresses adjacent structures and disrupts ECM architectur
- Direct inhibition of elastin cross-linking by heparan sulfate reduces valve and vessel compliance
- Chondroitin sulfate in valve spongiosa expands and weakens leaflet coaptation zone

Inflammatory and Secondary Mechanisms

- Heparan sulfate fragments act as DAMPs, activating TLR4 and NF-kB-driven inflammation
- GAG-activated macrophages infiltrate valve leaflets, myocardium and coronary intima
- MMP-2 and MMP-9 upregulated by activated macrophages degrade fibrillar collagen, weakening valve structure
- ML II/III: misrouting of lysosomal enzymes (absent M6P targeting) amplifies extracellular GAG accumulation -- valves particularly vulnerable due to avascular, enzyme-poor microenvironment
- Coronary intimal GAG deposition activates PDGF and VEGF signalling, promoting smooth muscle proliferation and luminal stenosis



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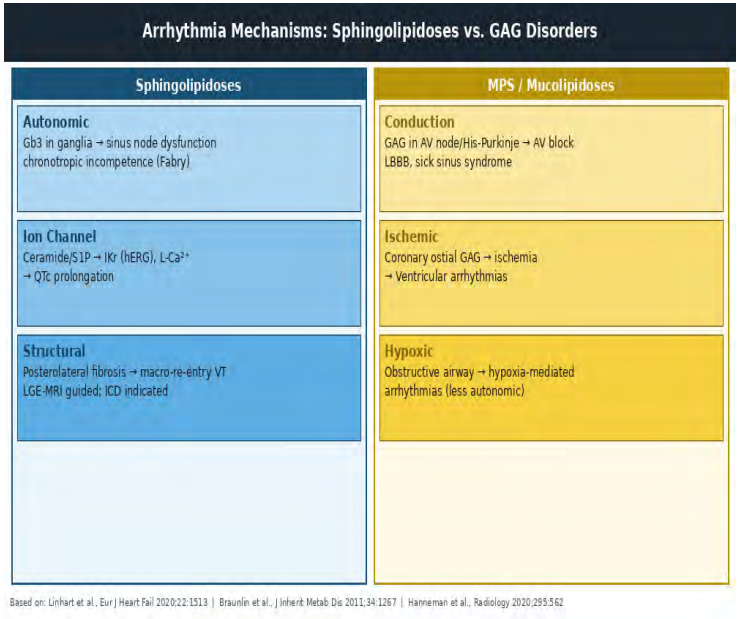
Arrhythmia Mechanisms:

Ion Channel and Autonomic Basis

- Gb3 in autonomic ganglia impairs sympathovagal balance causing sinus node dysfunction and chronotropic incompetence (Fabry)
- Ceramide/S1P imbalance modulates cardiac IKr (hERG) and L-type Ca2+ channels, prolonging QTc interval
- Lysophospholipid accumulation blocks Nav1.5 (SCN5A) trafficking, reducing peak INa and slowing conduction
- Mitochondrial ROS oxidises connexin-43 gap junctions, fragmenting electrical coupling between cardiomyocytes
- Posterolateral scar in Fabry: macro-re-entrant VT substrate; short PR in early disease (Gb3 in AV nodal fat pad)

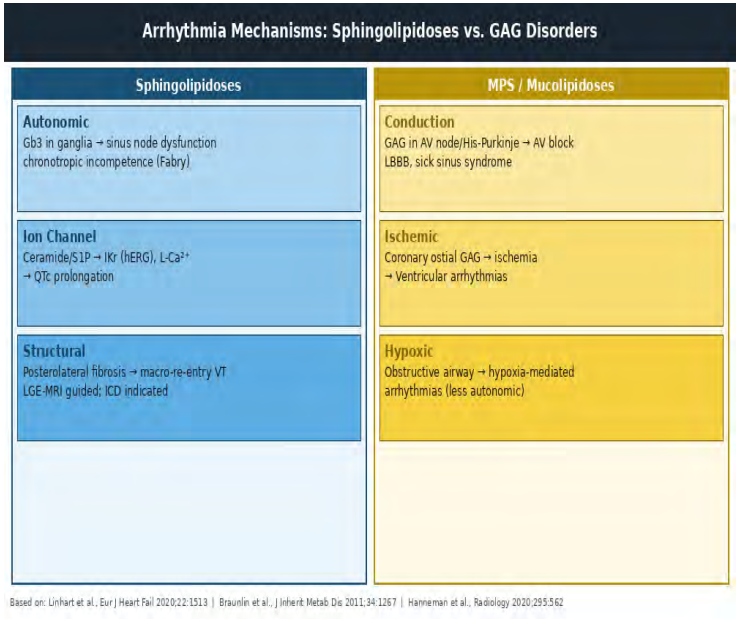


Schematic based on: ***Linhart et al., Eur J Heart Fail 2020;22:1513; Braunlin et al., J Inherit Metab Dis 2011;34:1267; Hanneman et al., Radiology 2020;295:562***

Arrhythmia Mechanisms:

Structural Conduction Basis

- GAG deposition in AV node, His bundle and bundle branches causes progressive AV block and LBBB
- Structural remodelling of the sinus node region by GAG-laden connective tissue causes sick sinus syndrome
- Conduction disease in MPS correlates with GAG type: dermatan sulfate (MPS I, II, VI) most arrhythmogenic
- Ventricular arrhythmias driven by myocardial fibrosis from GAG-induced inflammation and ischemia
- Hypoxia-mediated arrhythmias from progressive obstructive airway disease more prominent than in sphingolipidoses



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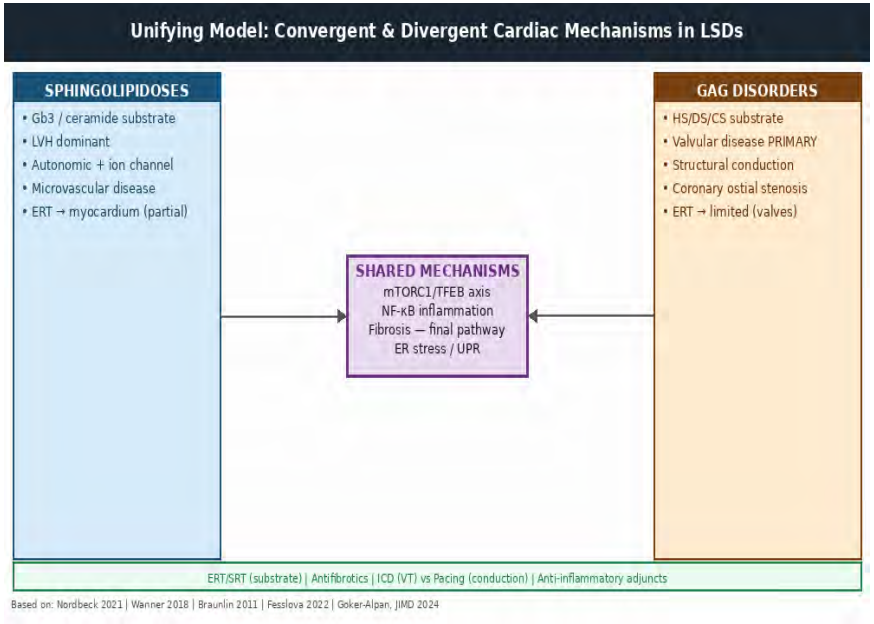
Unifying Pathophysiological Model and Therapeutic Implications

Shared Convergent Mechanisms Across LDs

- Both groups: lysosomal dysfunction activates mTORC1 (hypertrophy) and suppresses TFEB (impaired lysosomal biogenesis)
- Both groups: NF-kB-driven chronic inflammation -- from ceramide (sphingolipidoses) or heparan sulfate DAMPs (MPS/ML)
- Both groups: progressive myocardial fibrosis as a final common pathway for arrhythmia and heart failure
- Both groups: ER stress and UPR activation from substrate excess promotes cardiomyocyte apoptosis



Based on: ***Nordbeck 2021; Wanner 2018; Braunlin 2011; Fesslova 2022; Goker-Alpan, JIMD 2024***

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THANK YOU

Lysosomal Disorders and the Heart

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Disclosures

- Dr. Jefferies serves on the advisory boards of Sanofi Genzyme, Chiesi, Rocket, Amicus, Bristol Myers Squibb, 9+1Al, CuesHub, PATH, HEARTio, LifeScience Bio, and Medtronic. He is also on the speaker bureau of Sanofi Genzyme.

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Outline

- Introduction to lysosomal disorders and the heart, and the need for better guidance
- Role of the cardiologist in the multidisciplinary team
- Case studies involving cardiomyopathy to diagnose a lysosomal disorder (e.g., Fabry disease) and as a chronic condition in a lysosomal disorder (e.g., early onset Pompe disease)
- Best practices and resources to manage cardiomyopathies in various lysosomal disorders (e.g., treating the disease vs treating the cardiomyopathy)
- Research trends involving cardiomyopathy and lysosomal disorders
- Q&A

Learning Objectives

- *Describe the role of the cardiologist in the team approach to care*
- *List best practices to diagnosing cardiovascular disease in lysosomal disorders*
- *Identify best practices to treat cardiovascular disease in lysosomal disorders*

Lysosomal Disorders

- Heterogeneous group of conditions
- Historically, LDs were grouped according to the composition of the storage or tissue deposits
  - E.g., sphingolipids
- More recently, classification focuses more on the nature of the protein defect
- These protein defects inevitably impact the cardiovascular system

Lysosomal Disorders

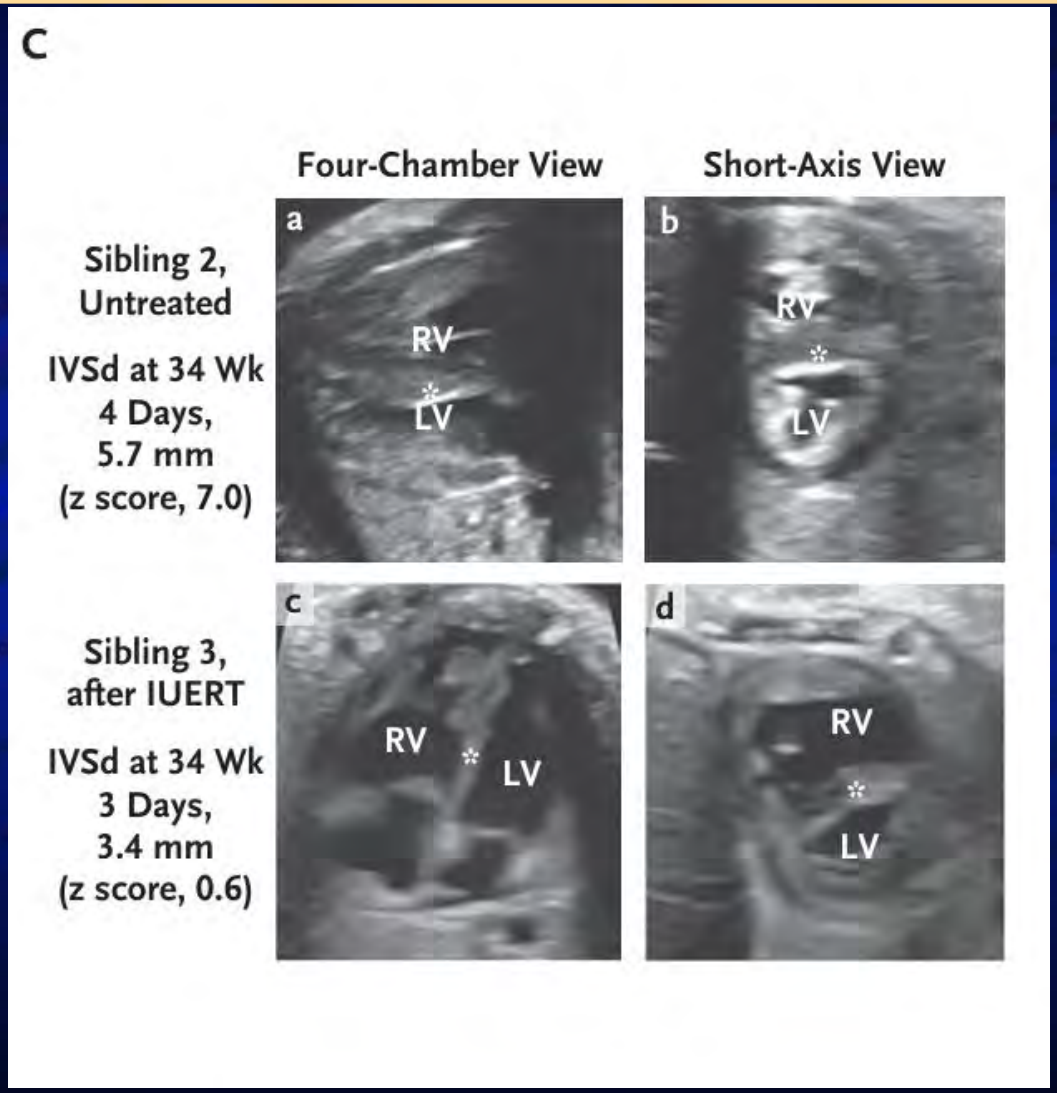
- Cardiovascular implications are significant
- Major driver of morbidity and mortality
- Discussion of cardiologist involvement, testing, and surveillance strategies are translatable across different LDs
- A proactive and durable approach is needed in patients with LDs

Pompe Disease

Infantile Pompe Disease Cardiovascular Findings

- Classic infantile findings include:
  - Left (Bi) ventricular hypertrophy with or without left ventricular outflow tract obstruction
  - ECG Findings: Large QRS complexes, short PR interval, pre-excitation patterns, repolarization abnormalities, bundle branch blocks, and atrioventricular blocks
  - Arrhythmias: Supraventricular or ventricular

Echocardiographic Findings in Infantile Pompe Disease



Cohen et al. *N Engl J Med* 2022:387:2150-8.

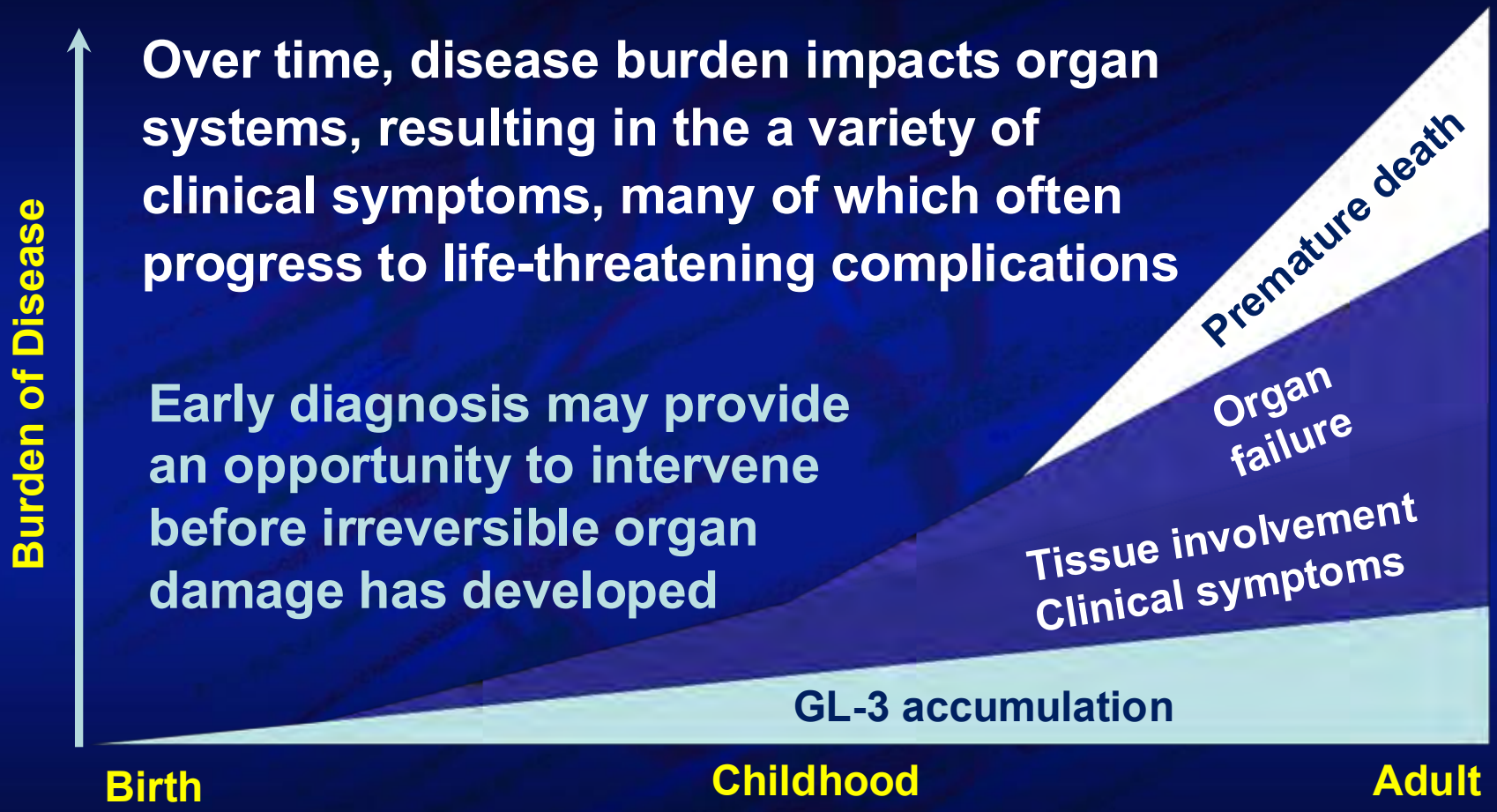
Late-Onset Pompe Disease

Cardiovascular Findings in Late-Onset Pompe Disease

- Typically, less severe cardiovascular phenotype than infantile
  - Left ventricular hypertrophy
  - LGE burden in <20% by cardiac MRI
  - ECG Findings: Large QRS complexes and short PR interval
  - Arterial aneurysms

Fabry Disease

Clinical manifestations and disease progression over time



Eng et al. Genet Med 2006;8:539-48
Germain. Orphanet J Rare Dis 2010;5:30.

Signs and Symptoms

Symptoms	Childhood	Adolescence	Adulthood
Episodic pain crises	●	●	●
Neuropathic pain	●	●	●
Hypohidrosis/anhidrosis	●	●	●
Corneal and lenticular opacities	●	●	●
Recurrent fever	●	●	●
Heat and cold intolerance	●	●	●
Psychosocial manifestations	●	●	●
Gastrointestinal distress	●	●	●
Proteinuria		●	●
Angiokeratomas		●	●
Fatigue		●	●
Renal insufficiency			●
Neurological complications			●
Cerebrovascular disease			●
Cardiac dysfunction			●
Hearing loss and tinnitus			●

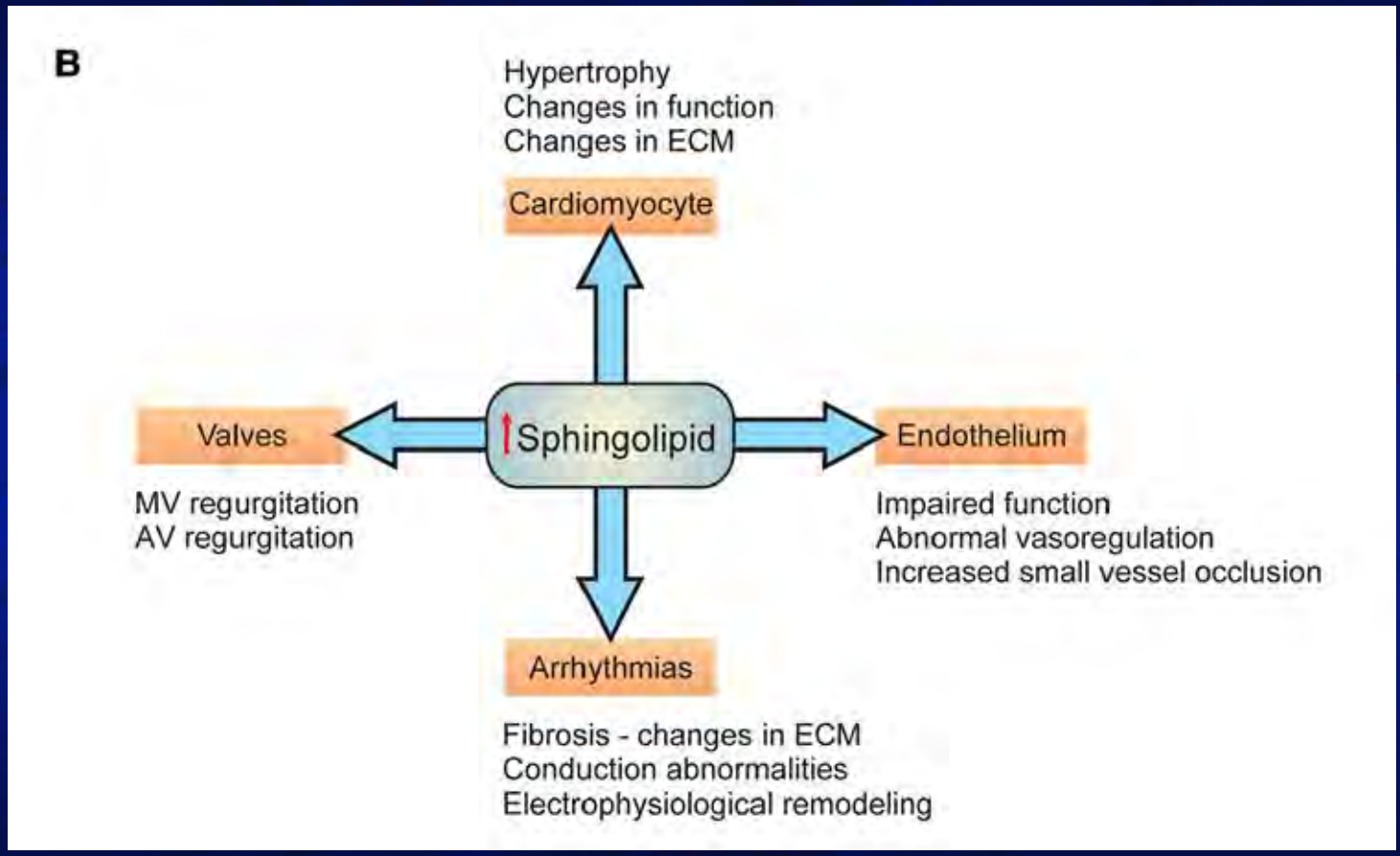
Cardiovascular Findings in Fabry Disease

- Cardiovascular manifestations in Fabry are broad and numerous
  - Systemic hypertension
  - Left ventricular hypertrophy
  - Heart rhythm and conduction system disease
  - Valvular heart disease
  - Vasculopathy
  - Ischemic heart disease
  - Sudden cardiac death
  - Aortic dilation

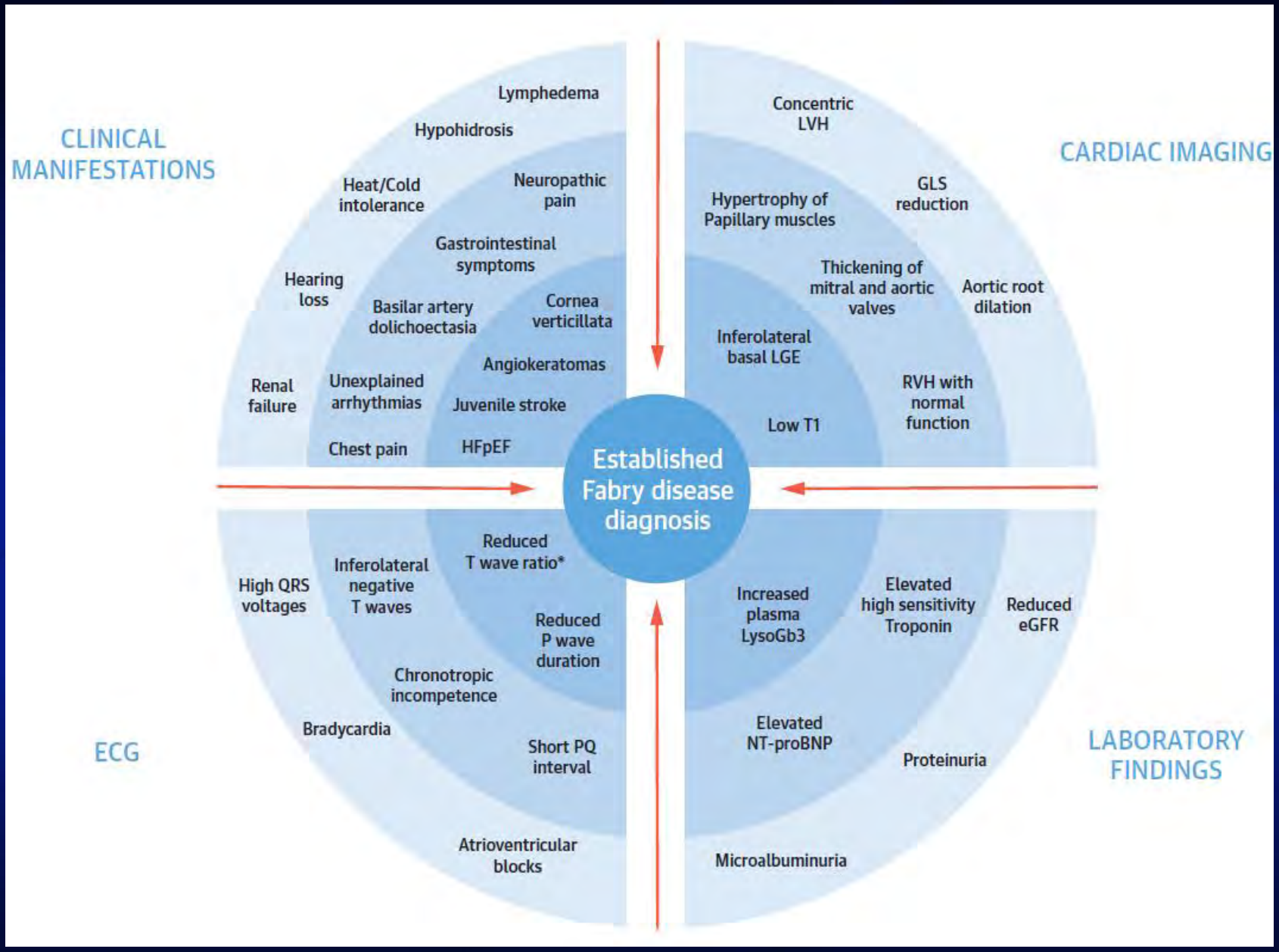
Role of the Cardiologist

- Member of the multidisciplinary team
- Ideally, the cardiologist is familiar with cardiomyopathy, heart failure, and genetics (adult and pediatric)
- Complex role as multiple phenotypic manifestations
- Beneficial to have other cardiologists with expertise in imaging, electrophysiology, catheterization, intensive care available

Cardiovascular Findings in Fabry Disease

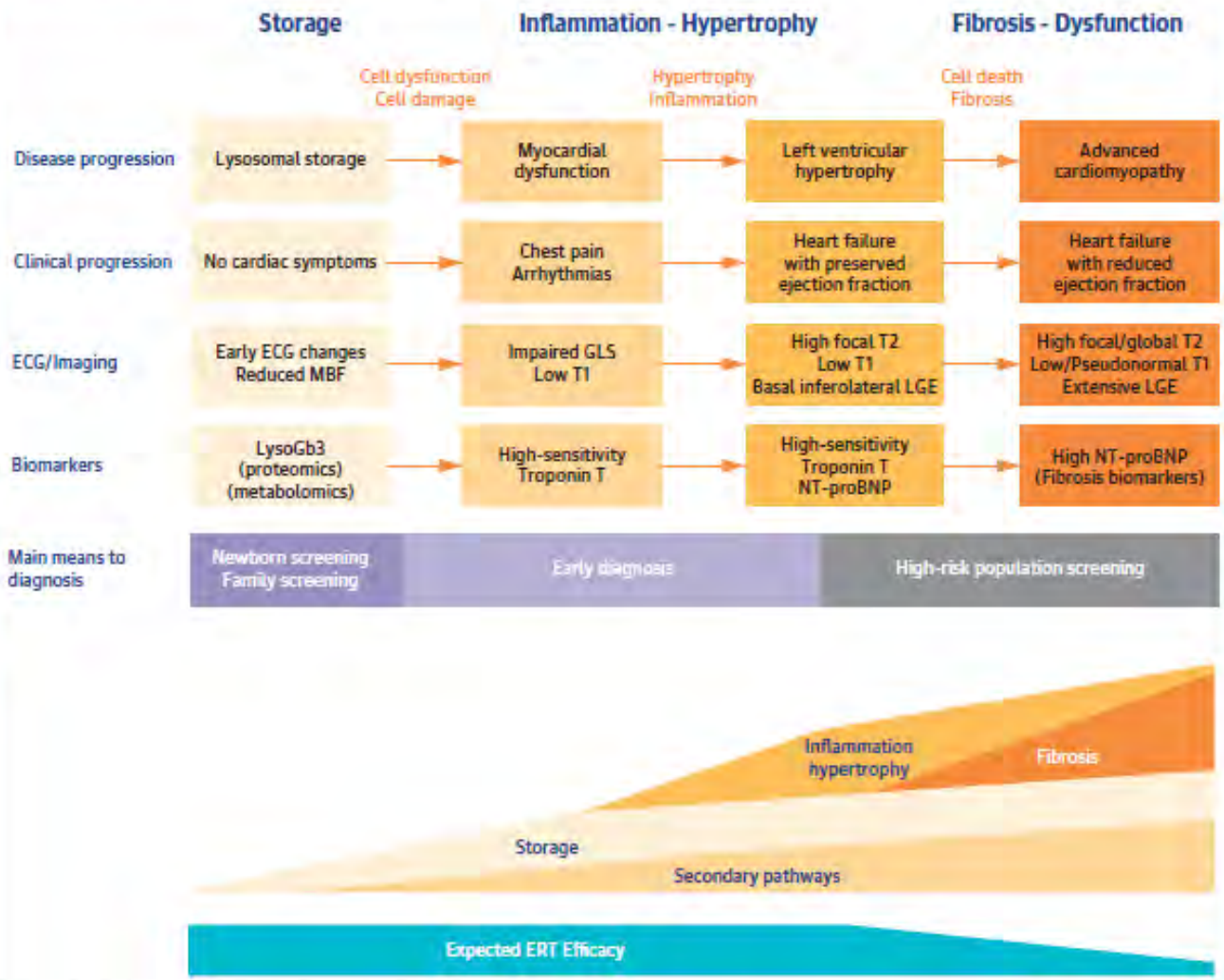


Putko et al. *Heart Fail Rev* 2014; July 17;epub ahead of print.



Pieroni et al. *J Am Coll Cardiol* 2021;77:922-36.

CENTRAL ILLUSTRATION Proposed Evolution of Cardiac Involvement in Fabry Disease



Pieroni, M. et al. J Am Coll Cardiol 2021;77(7):922-36.

Proposed stages of Fabry disease (FD) cardiac involvement evolution along with clinical progression, imaging, biomarkers, main means to diagnosis, and in relation to expected treatment efficacy. ECG = electrocardiography; ERT = enzyme replacement therapy; GLS = global longitudinal strain; LGE = late gadolinium enhancement; lyso-Gb3 = globotriaosylsphingosine; MBF = myocardial blood flow; NT-proBNP = NT-pro–brain natriuretic peptide.

Pieroni et al. *J Am Coll Cardiol* 2021;77:922-36.

Cardiovascular Findings in Fabry Disease

- These findings can progress to more significant disease over time
  - Life-threatening arrhythmias and sudden cardiac death
  - Heart failure
  - Myocardial ischemia
  - Stroke
- All these conditions can be difficult to treat and have significant associated morbidity and mortality

Cardiovascular Findings in Fabry Disease

- Goal of cardiovascular care should be directed at preventing these conditions
- Limited data regarding predictors of onset of disease
  - Majority of data are limited to middle-aged adult males
- Prognosis is negatively impacted once evidence of ischemic heart disease or heart failure are diagnosed

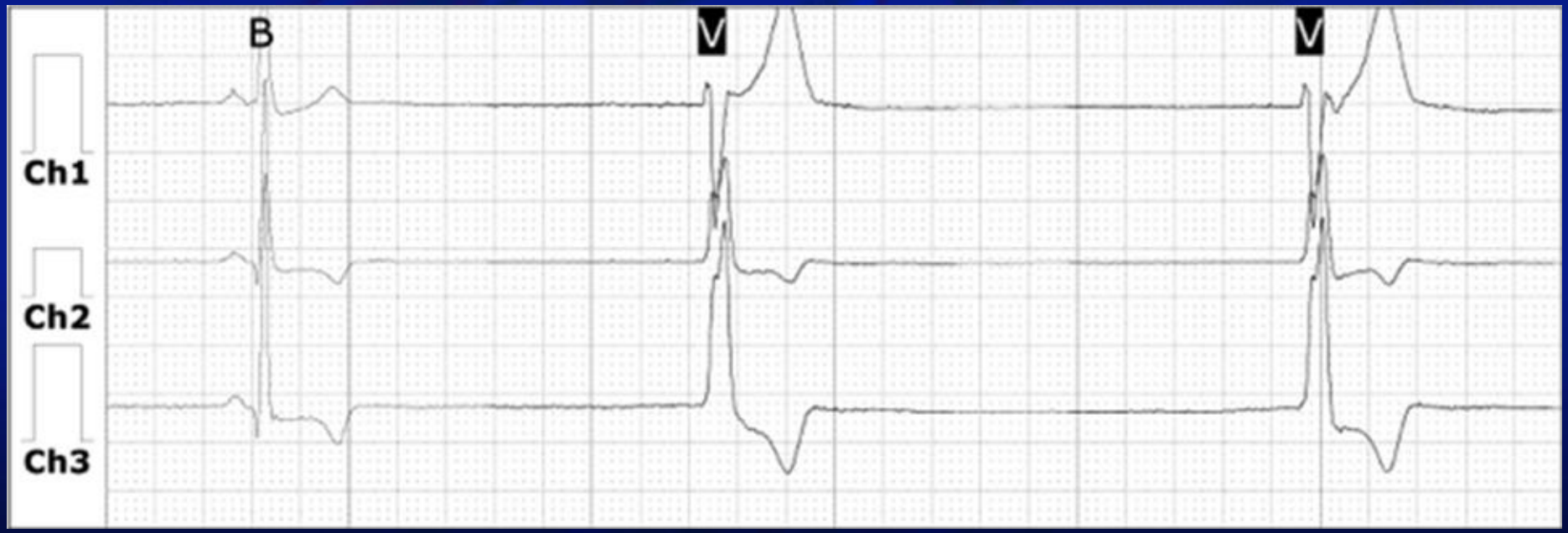
Patel V, et al. Heart 2015;101:961–966

Arrhythmias in Fabry Disease

- Arrhythmias can be a major cause of morbidity and mortality in Fabry disease
- Wide range of pathology can be diagnosed on electrocardiographic testing
- Bradyarrhythmias and tachyarrhythmias may be detected and require additional therapy
- Electrophysiologic testing may be used in some cases

Heart Rhythm Abnormalities

- Known associated ventricular and atrial arrhythmias and conduction system disease



Acharya et al. Card Electrophysiol Clin 2015;7:283-291

Heart Rhythm Abnormalities

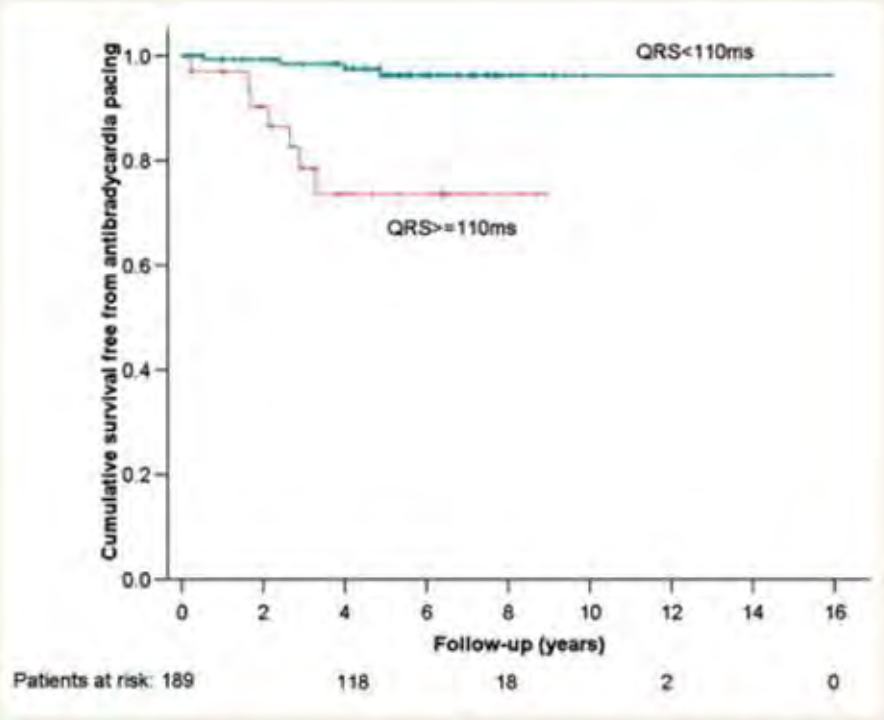
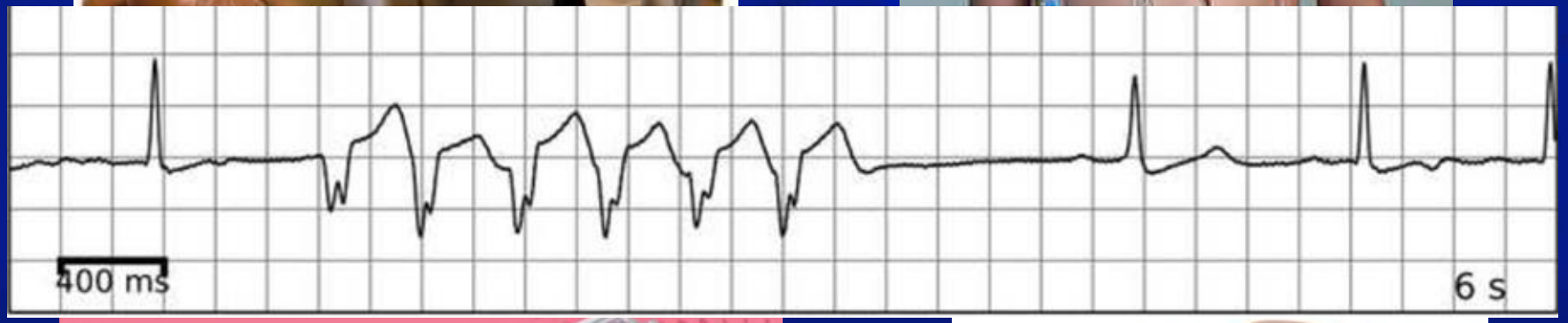


Figure 4 Kaplan–Meier curve for survival free from anti-bradycardia pacing.

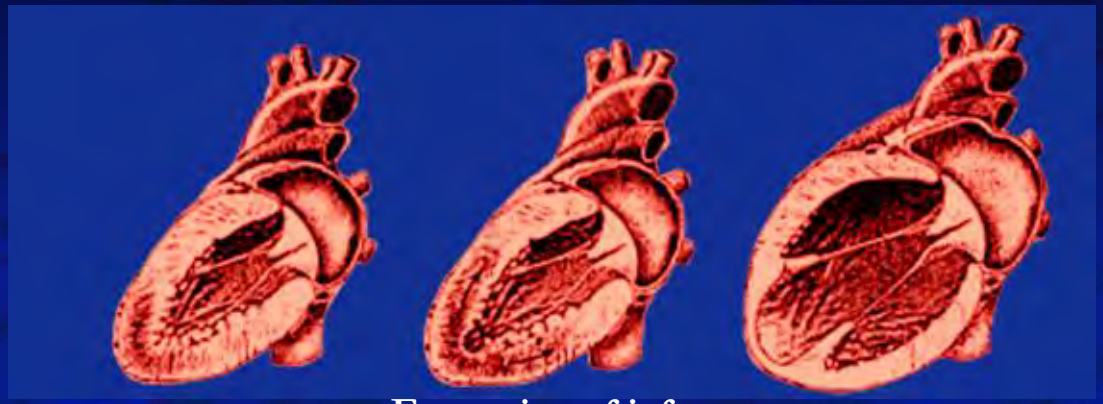
O'Mahony et al. Europace. 2011 Dec;13(12):1781-8.

Arrhythmias and Conduction System Disease



Pathologic Ventricular Remodeling

Ventricular Remodeling

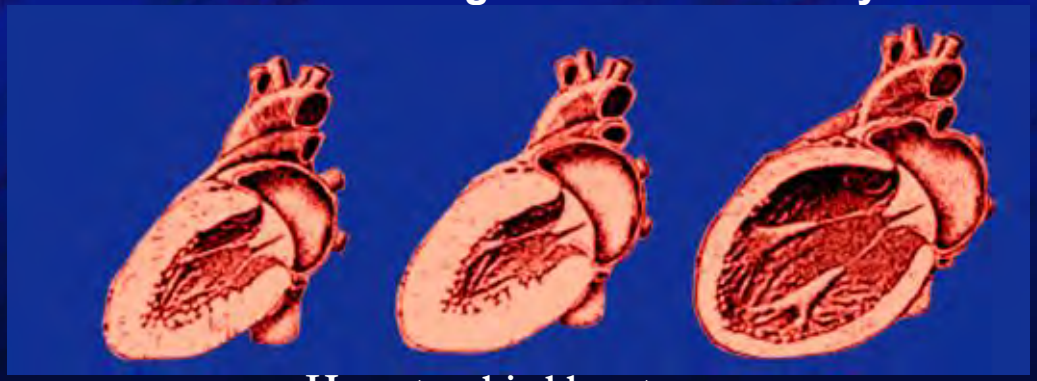


Trigger

Expansion of infarct
(hours to days)

Global remodeling
(days to months)

Ventricular Remodeling in Diastolic and Systolic



Normal heart

Hypertrophied heart
(diastolic HF)

Dilated heart
(systolic HF)

Jessup M et al. *N Engl J Med.* 2003;348:2007

Best Practiced in Managing LD Related Cardiomyopathies

- First step is accurate diagnosis
- Informed by imaging approach
- Phenotype guides treatment pathway
  - Dilated, hypertrophic, restrictive, noncompaction
- Different drug and device options available depending on cardiomyopathy phenotype
  - Can be isolated phenotype or mixed

Cardiovascular Findings in Fabry Disease

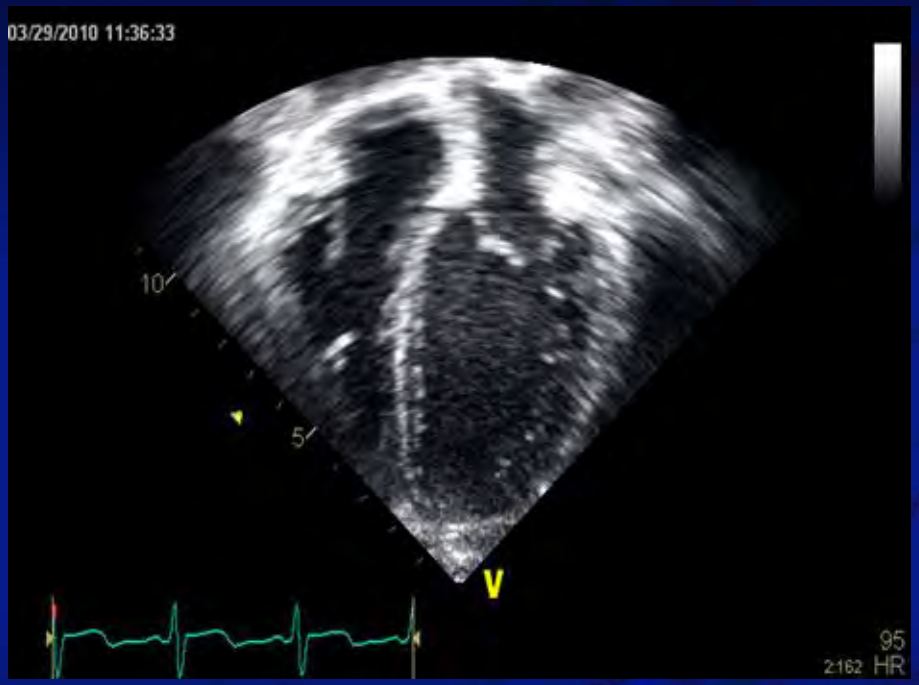
- Cardiovascular complications are now the leading cause of death in Fabry patients
  - Previously was kidney disease
- ~60% of patients have prior signs and symptoms
- Hypertension and edema most common
- History of a murmur, chest pain, or shortness of breath

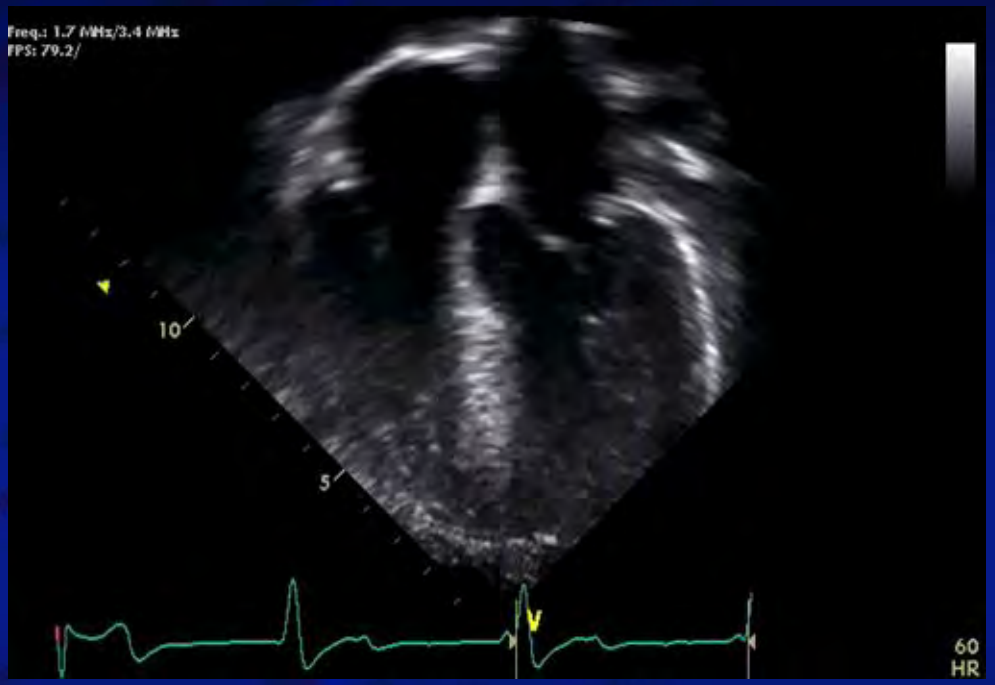
Putko et al. *Heart Fail Rev* 2014; July 17;epub ahead of print.

Noninvasive Imaging Echocardiography

- Traditional approach to screening utilizes transthoracic echocardiography
- Echocardiography is widely available and relatively easy to perform
- Advanced imaging techniques allow for additional information to be acquired from standard imaging protocols

Myocardial Assessment Echocardiography





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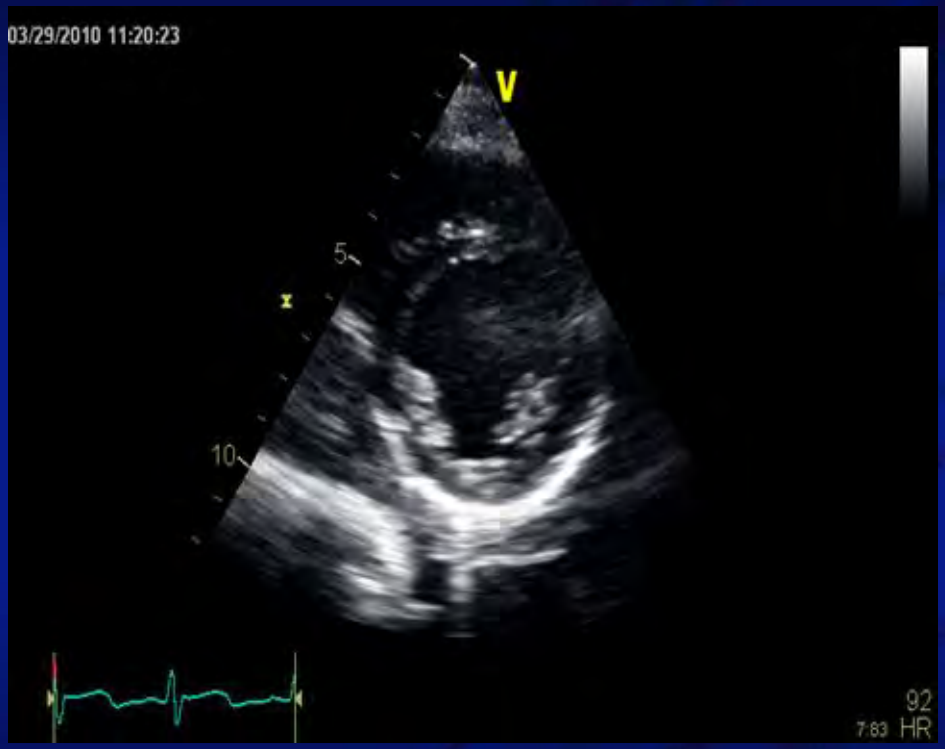
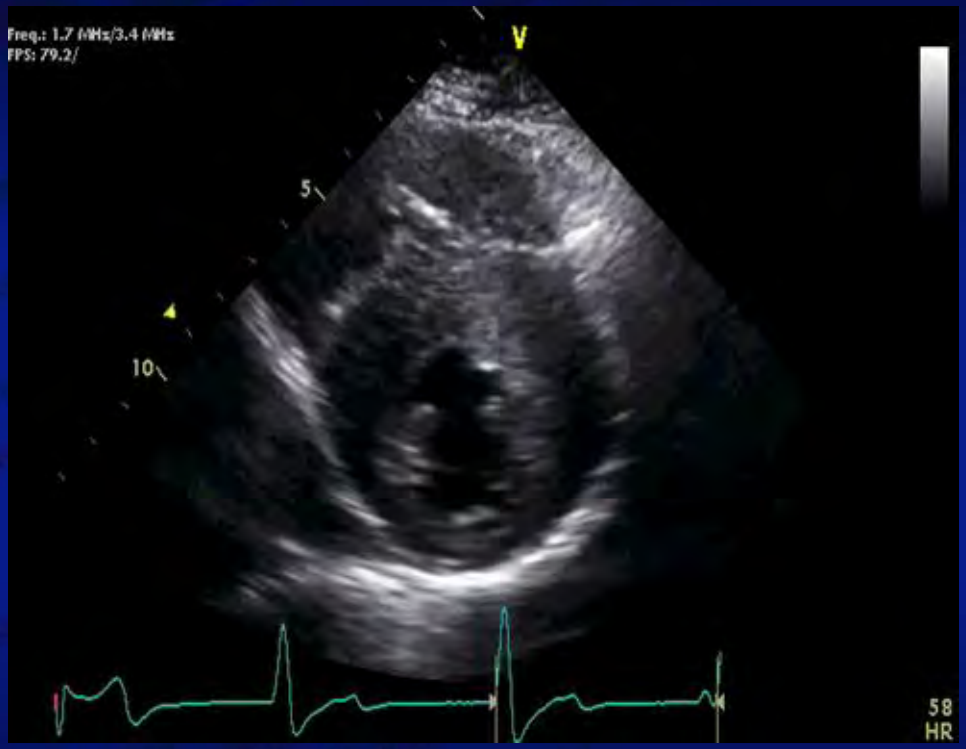
Myocardial Assessment Echocardiography





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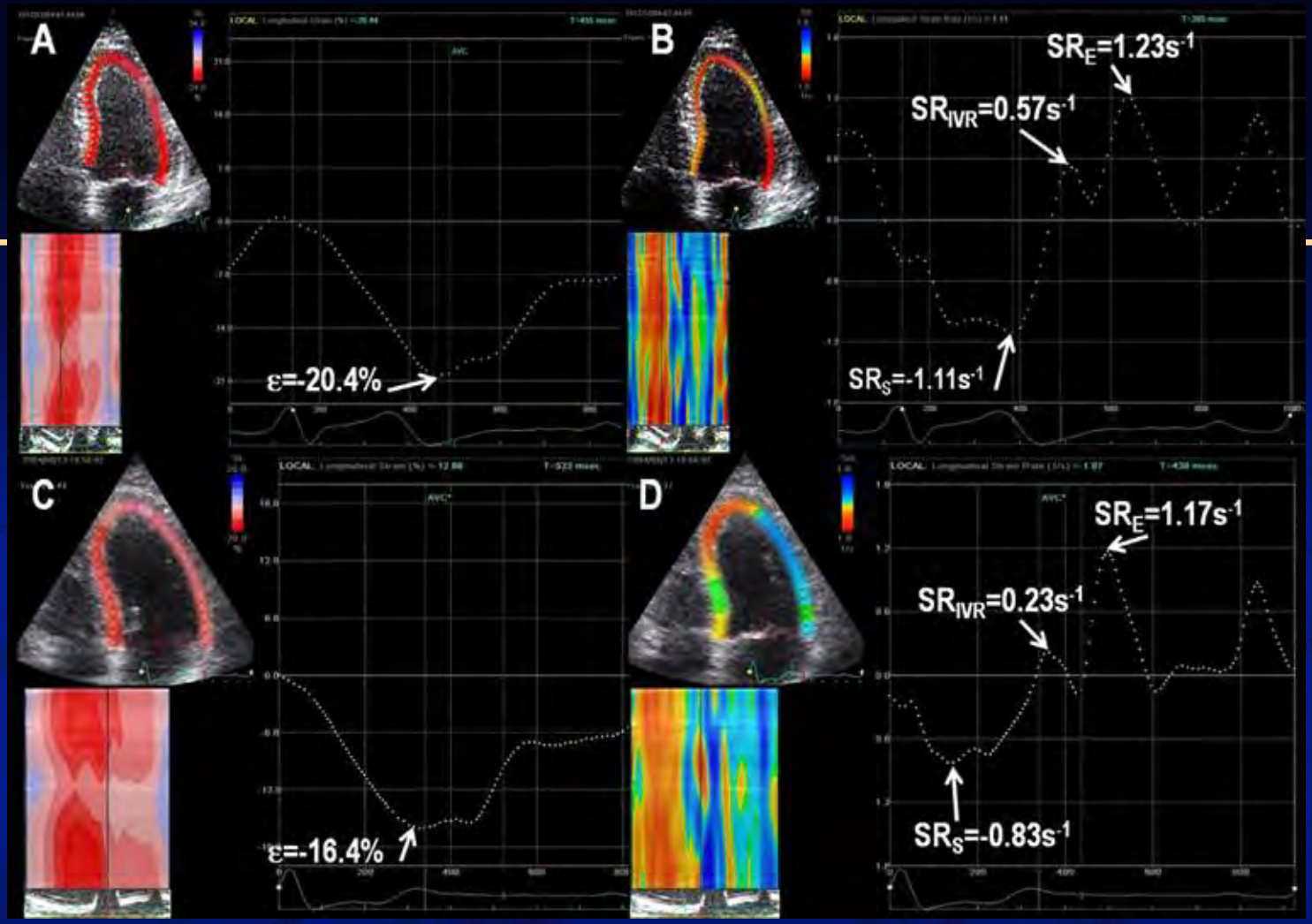
Advanced Imaging Techniques

- Additional information can be gathered from echocardiography
- Allows for early subclinical systolic and diastolic function
  - Strain and strain rate (SR) imaging
- 3D imaging can also be performed that allows for volume quantification



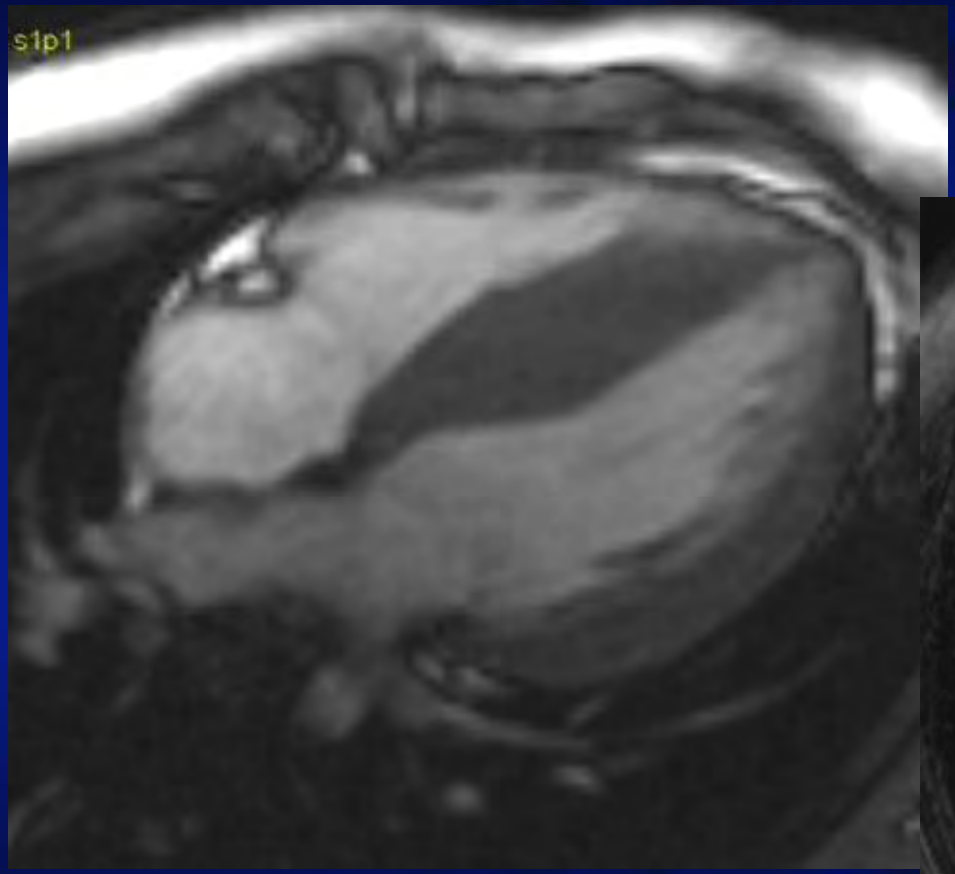
Conclusions: Strain and SR analysis is useful in identifying patients with FD with reduced myocardial function, with longitudinal systolic strain and diastolic isovolumic SR being superior to the other echocardiographic measurements of myocardial contraction and relaxation and independent of LVH. (J Am Soc Echocardiogr 2013;26:1407-14.)

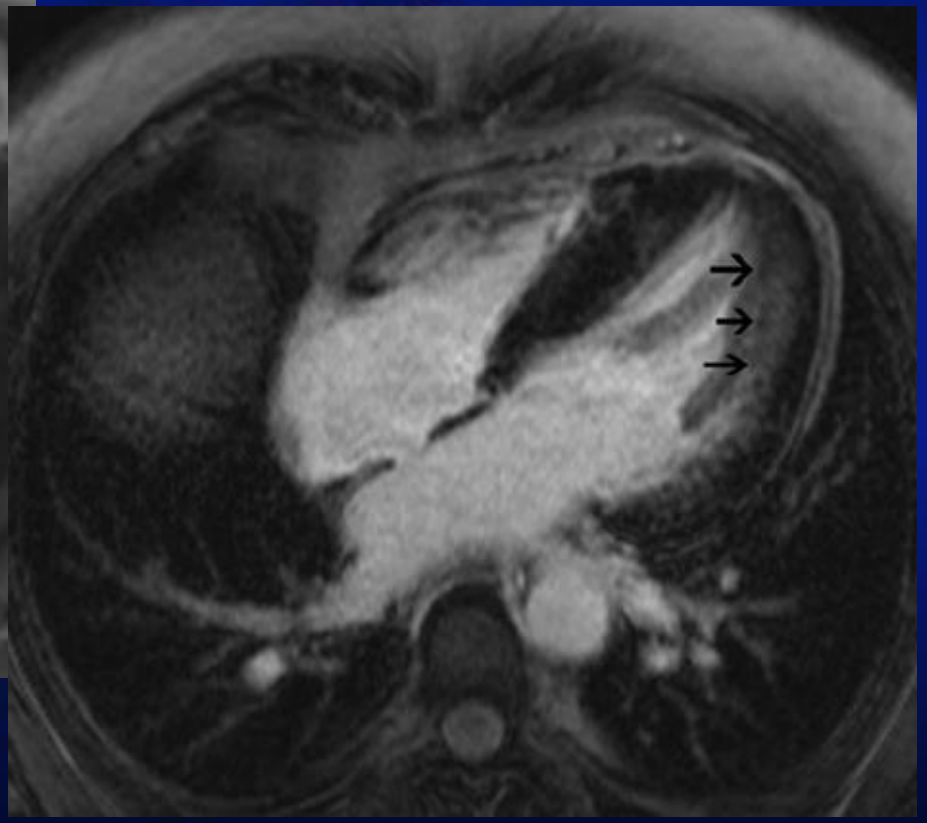
Shanks et al. *J Am Soc Echocardiogr* 2013;26:1407-14.

Cardiac Magnetic Resonance (CMR) Imaging

- Highly reproducible
- Precise calculation of volumes
- Assessment of arterial and venous vasculature
- Assessment of ventricular function
- Myocardial characterization
- No radiation exposure

Myocardial Characterization





T1 Mapping by Cardiac MRI

- T1 mapping can be performed to assess for pathologic changes in the myocardium
- Native T1 imaging can be performed without contrast exposure
- Identifies changes in the intracellular or extracellular space such as edema or deposition

T1 Mapping in Fabry Disease

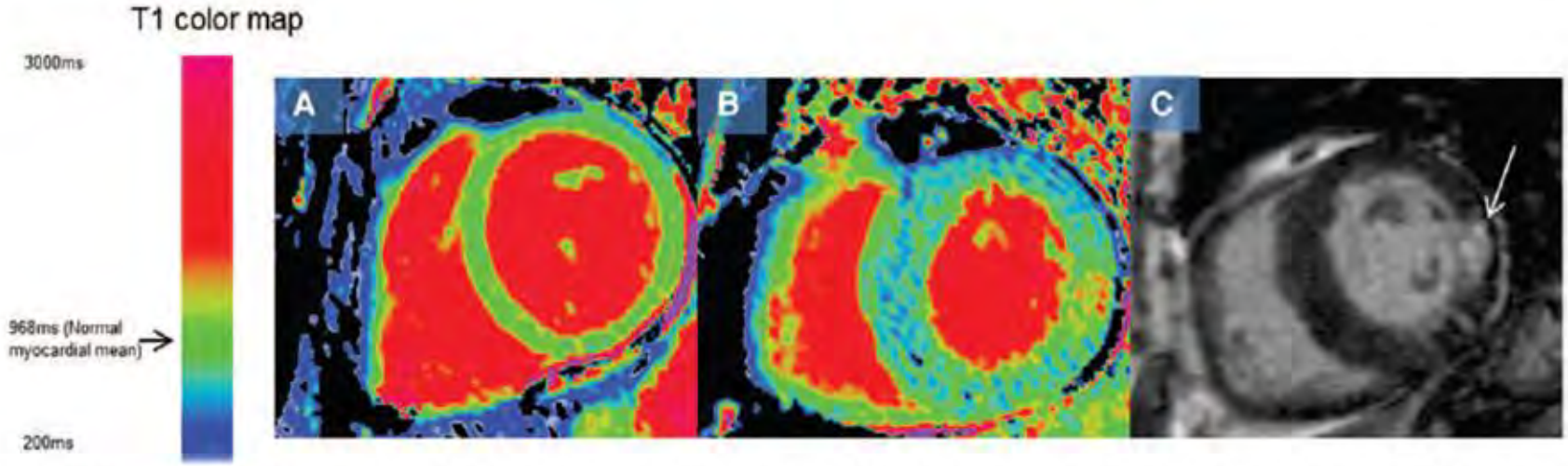
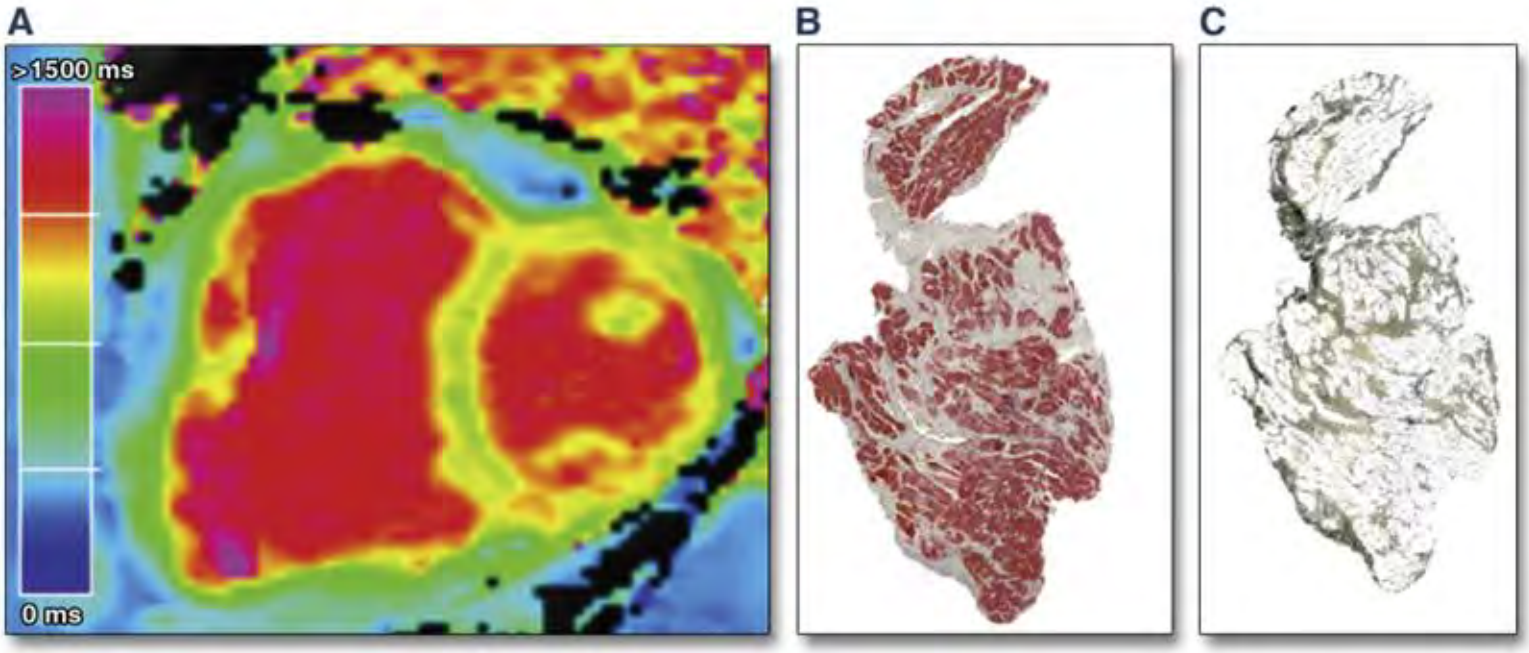


Figure 1. A noncontrast basal short-axis T_1 map from a healthy volunteer (**A**) and a patient with Anderson-Fabry disease (AFD; **B**). Blue areas (T_1 lowering) are seen in the AFD septum and red (T_1 increasing) in the inferolateral wall, correlating with the area of late gadolinium enhancement in the same patient (**C**, arrow).

Sado et al. *Circ Cardiovasc Imaging* 2013;6:392-398.

Extracellular Volume Using T1

FIGURE 1 Cardiac Magnetic Resonance T1 Map and Left Ventricular Histological Specimen



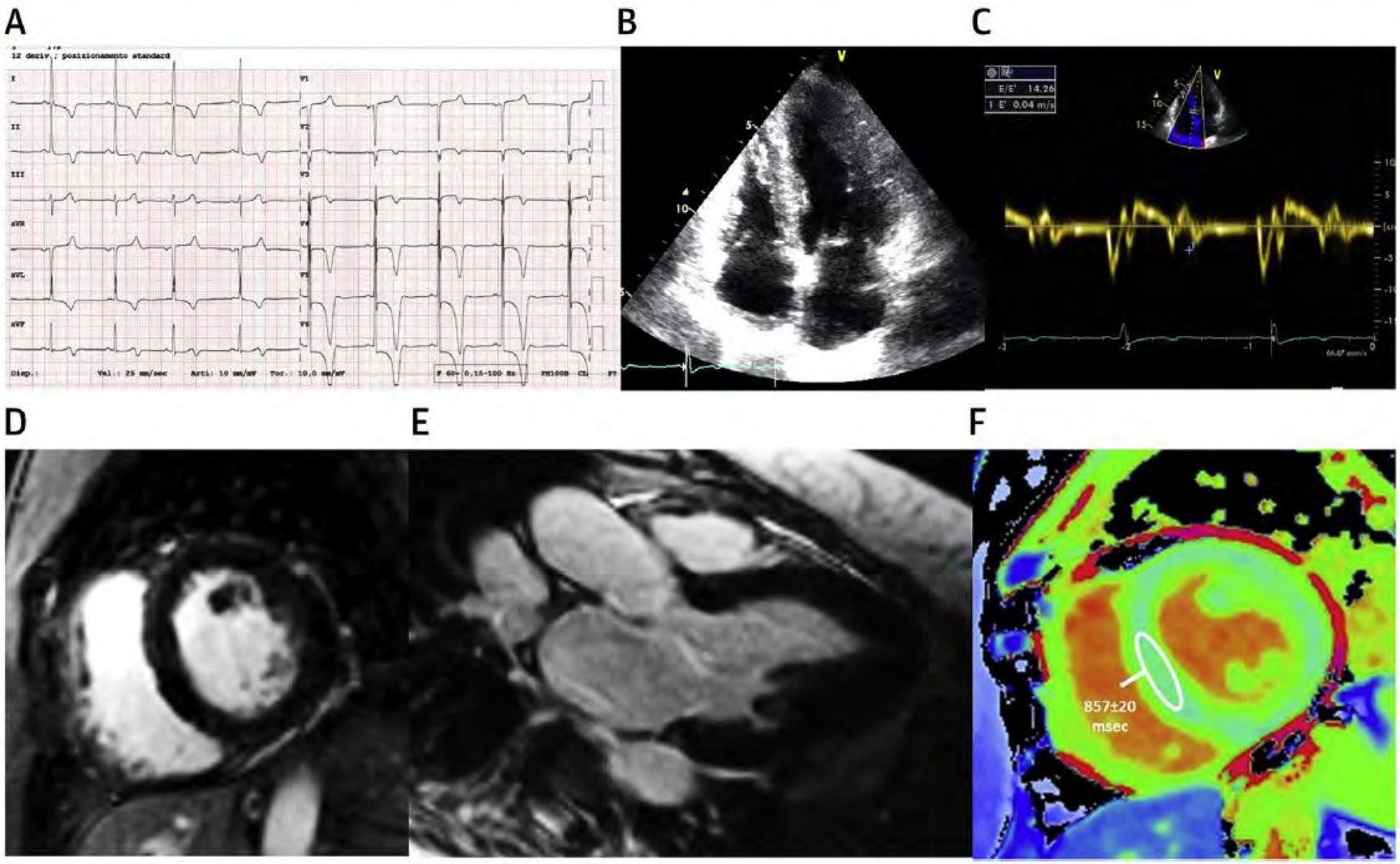
(A) Native T1 map in a patient with heart failure and preserved ejection fraction. Extracellular volume by cardiac magnetic resonance T1 mapping was 26.5%. **(B)** Left ventricular histological specimen of the same patient scanned with TissueFAXS software. **(C)** Same specimen after a color-threshold approach was used to visualize and quantify extracellular matrix (30.7%).

CMR-ECV was calculated with the formula (15)

$$\text{CMR} - \text{ECV} = (1 - \text{hematocrit}) \times \frac{\left(\frac{1}{\text{T1 myo post}}\right) - \left(\frac{1}{\text{T1 myo pre}}\right)}{\left(\frac{1}{\text{T1 blood post}}\right) - \left(\frac{1}{\text{T1 blood pre}}\right)}$$

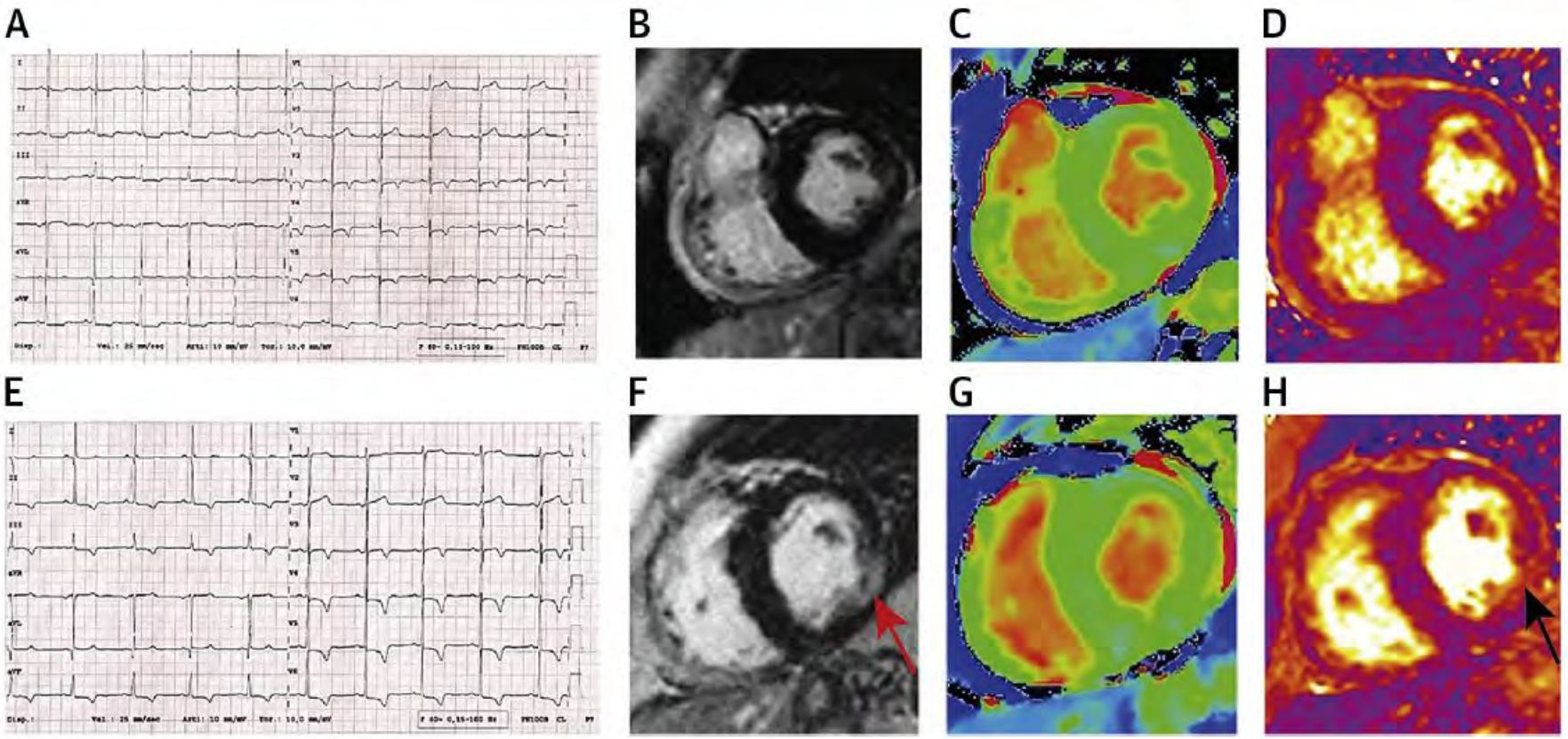
Kammerlander et al. *J Am Coll Cardiol Img* 2016;9:14-23.

FIGURE 5 A Representative Case of p.N215S Cardiac Variant With Apical LVH



Pieroni et al. *J Am Coll Cardiol* 2021;77:922-36.

FIGURE 6 A Representative Case of a 59-Year-Old Woman With Classic FD (c.124-125delAT) Showing Progression of Myocardial Damage and Inflammation



Pieroni et al. *J Am Coll Cardiol* 2021;77:922-36.

Potential Causes of Nonischemic Cardiomyopathy

Table 5. Other Potential Nonischemic Causes of HF

Cause	Reference
Chemotherapy and other cardiotoxic medications	23–25
Rheumatologic or autoimmune	26
Endocrine or metabolic (thyroid, acromegaly, pheochromocytoma, diabetes, obesity)	27–31
Familial cardiomyopathy or inherited and genetic heart disease	32
Heart rhythm–related (eg, tachycardia-mediated, PVCs, RV pacing)	33
Hypertension	34
Infiltrative cardiac disease (eg, amyloid, sarcoid, hemochromatosis)	21,35,36
Myocarditis (infectious, toxin or medication, immunological, hypersensitivity)	37,38
Peripartum cardiomyopathy	39
Stress cardiomyopathy (Takotsubo)	40,41
Substance abuse (eg, alcohol, cocaine, methamphetamine)	42–44

HF indicates heart failure; PVC, premature ventricular contraction; and RV, right ventricular.

Heidenreich et al. *Circulation*. 2022;145:e895-e1032.

Lymphedema in Fabry Disease

Prevalence of lymphedema among Anderson-Fabry disease patients: A report from the Fabry registry

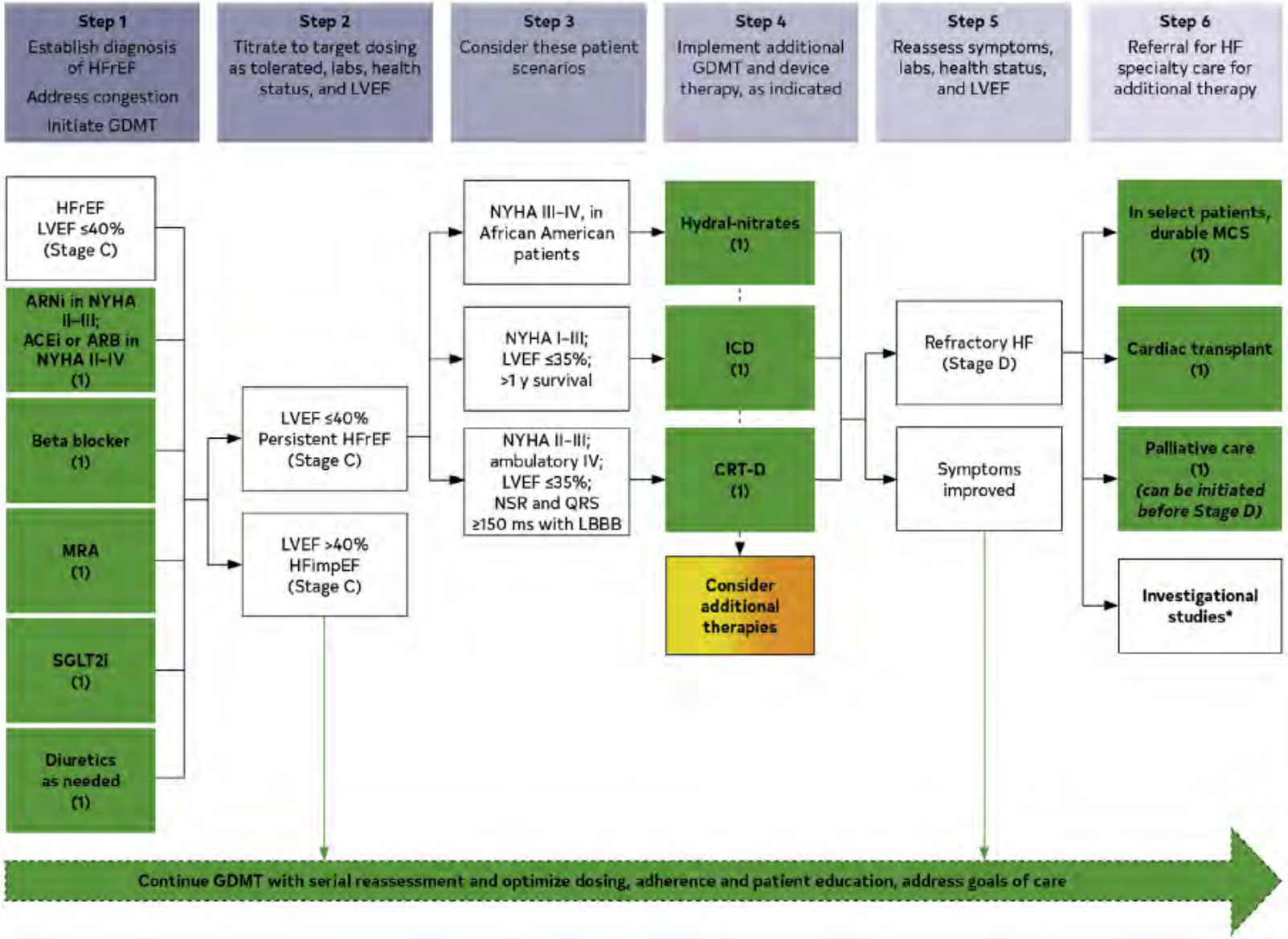
Deya Alkhatib [a,1,*], Jesus Avila Vega [b], Issa Pour-Ghaz [a], Omar Al-Taweel [c], Sania Khan [a], Kimberly DeCarr [d], Anandbir Bath [a], Aranyak Rawal [a], David Wilbanks [b], Joel Raja [a], Asra Butt [a], Neeraja Yedlapati [a], Robert J. Hopkin [e,f], John L. Jefferies [a]

Results: Our study showed that lymphedema occurred in 16.5% of the Fabry Registry patients who were ever assessed for lymphedema ($n = 5487$). Male patients when compared to female patient have higher prevalence (21.7% vs 12.7%) and experienced lymphedema at a younger age (median age at first reported lymphedema of 43.7 vs 51.7 years). When compared to other phenotypes, classic phenotype has the highest prevalence of lymphedema with the earliest reported lymphedema. Among those who reported lymphedema, 84.5% received AFD-specific treatment during their clinical course.

Conclusions: Lymphedema is a common manifestation of AFD in both genders, with a tendency to present later in female patients. Recognition of lymphedema can offer an important opportunity for intervention and potential impact on associated morbidity. Additional future studies are needed to characterize the clinical implications of lymphedema in AFD patients and identify additional treatment options for this growing population.

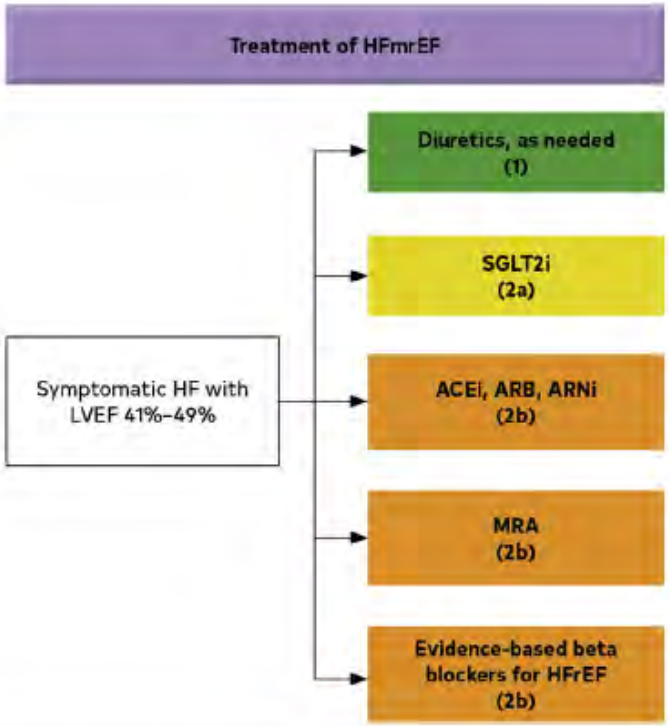
ACC/AHA Guideline Recommendations

FIGURE 6 Treatment of HFrEF Stages C and D

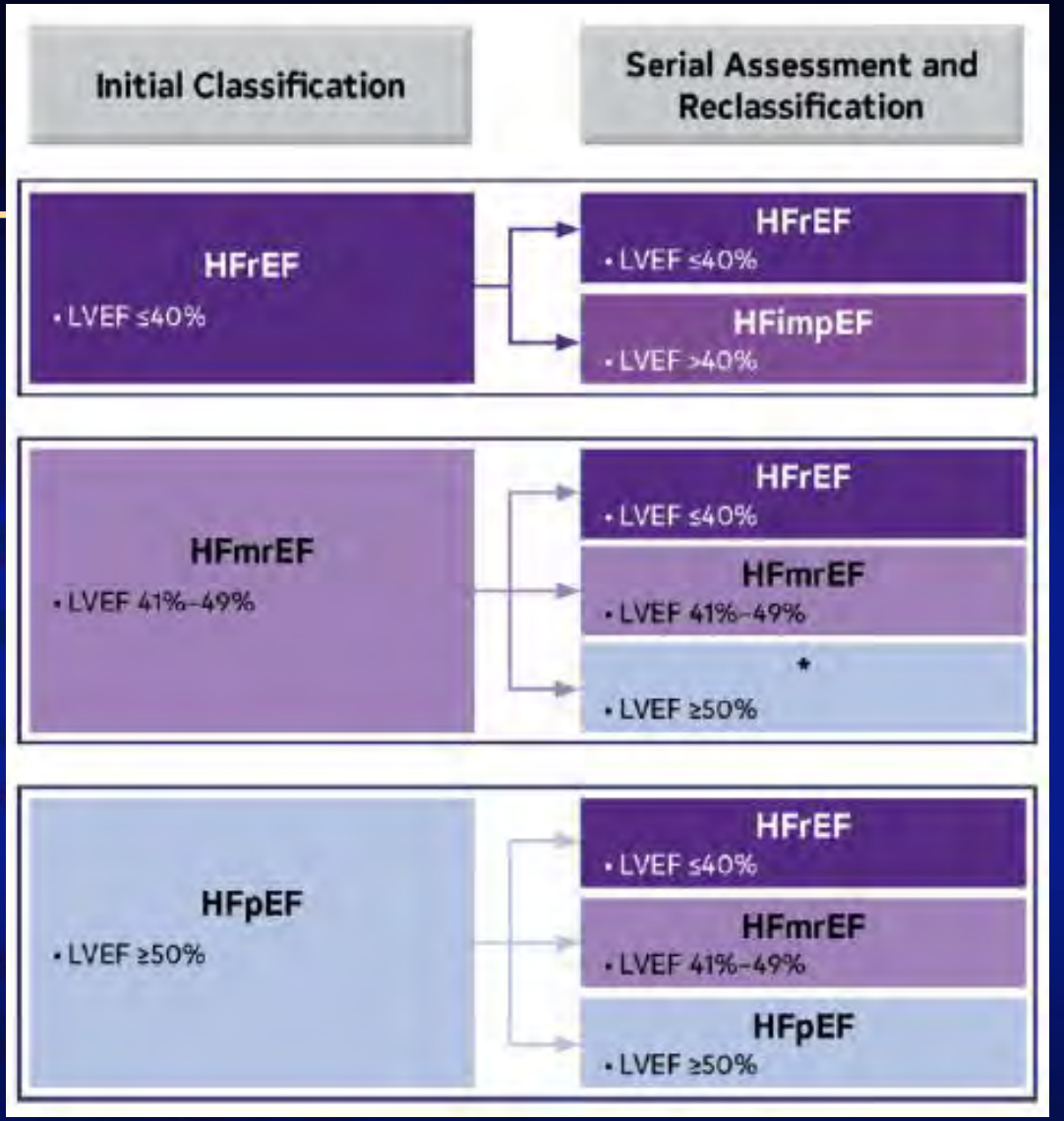


Heidenreich et al. *J Am Coll Cardiol*. 2022 May 3;79(17):e263-e421.

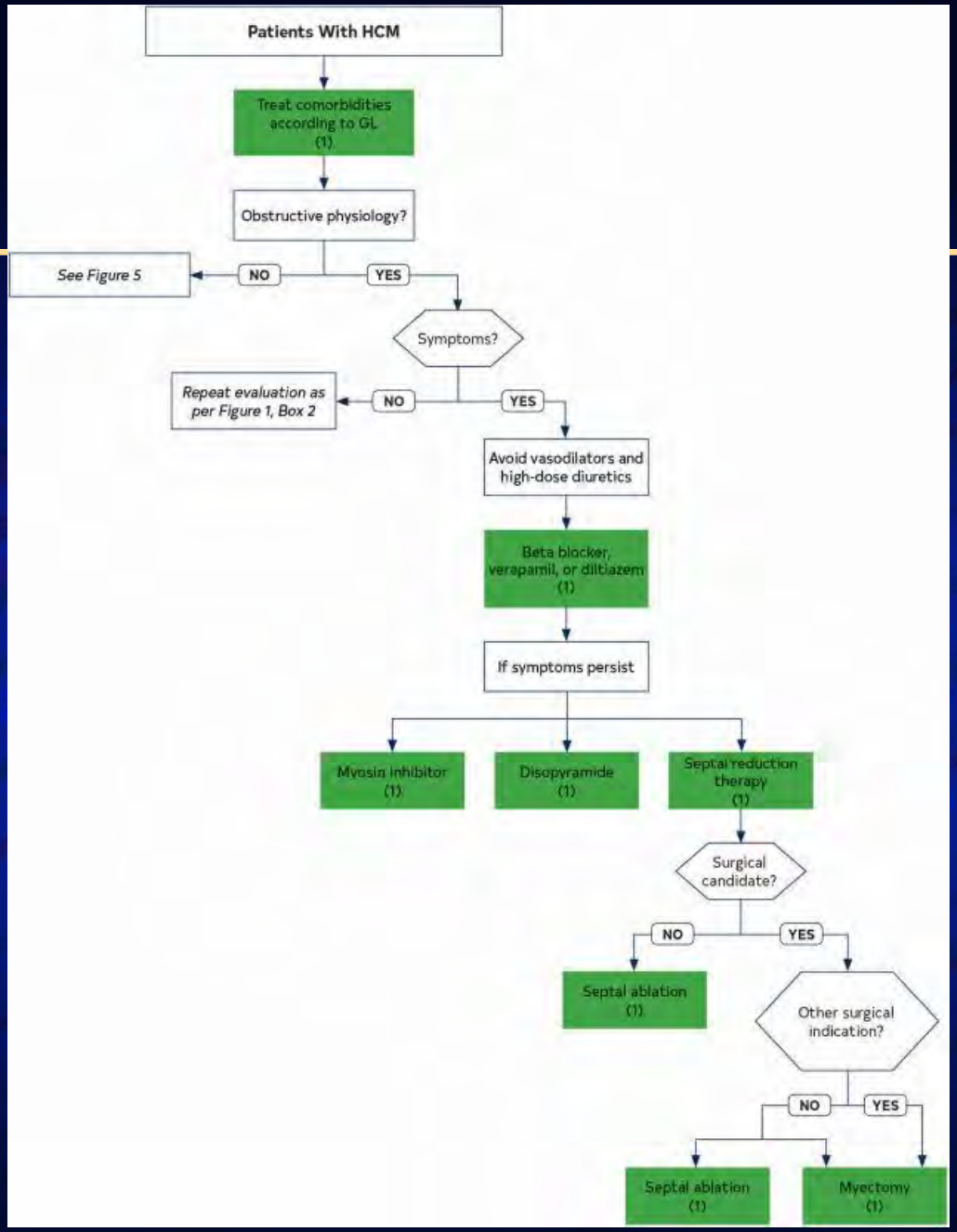
FIGURE 11 Recommendations for Patients With Mildly Reduced LVEF (41%–49%)



Colors correspond to COR in Table 2. Medication recommendations for HFmrEF are displayed. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; and SGLT2i, sodium- glucose cotransporter 2 inhibitor.

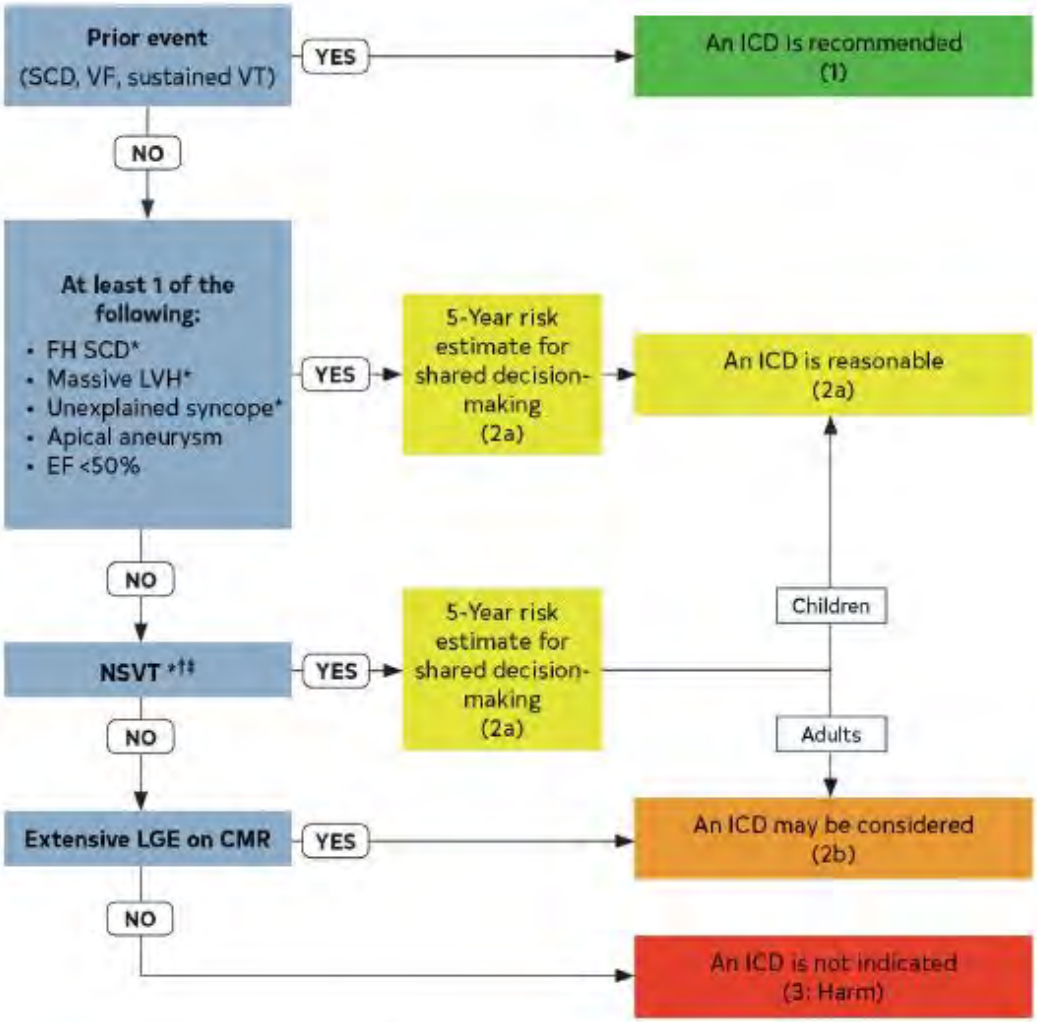


Heidenreich et al. *J Am Coll Cardiol*. 2022 May 3;79(17):e263-e421.



Ommen et al. *J Am Coll Cardiol* 2024 Jun 11;83(23): 2324-2405.

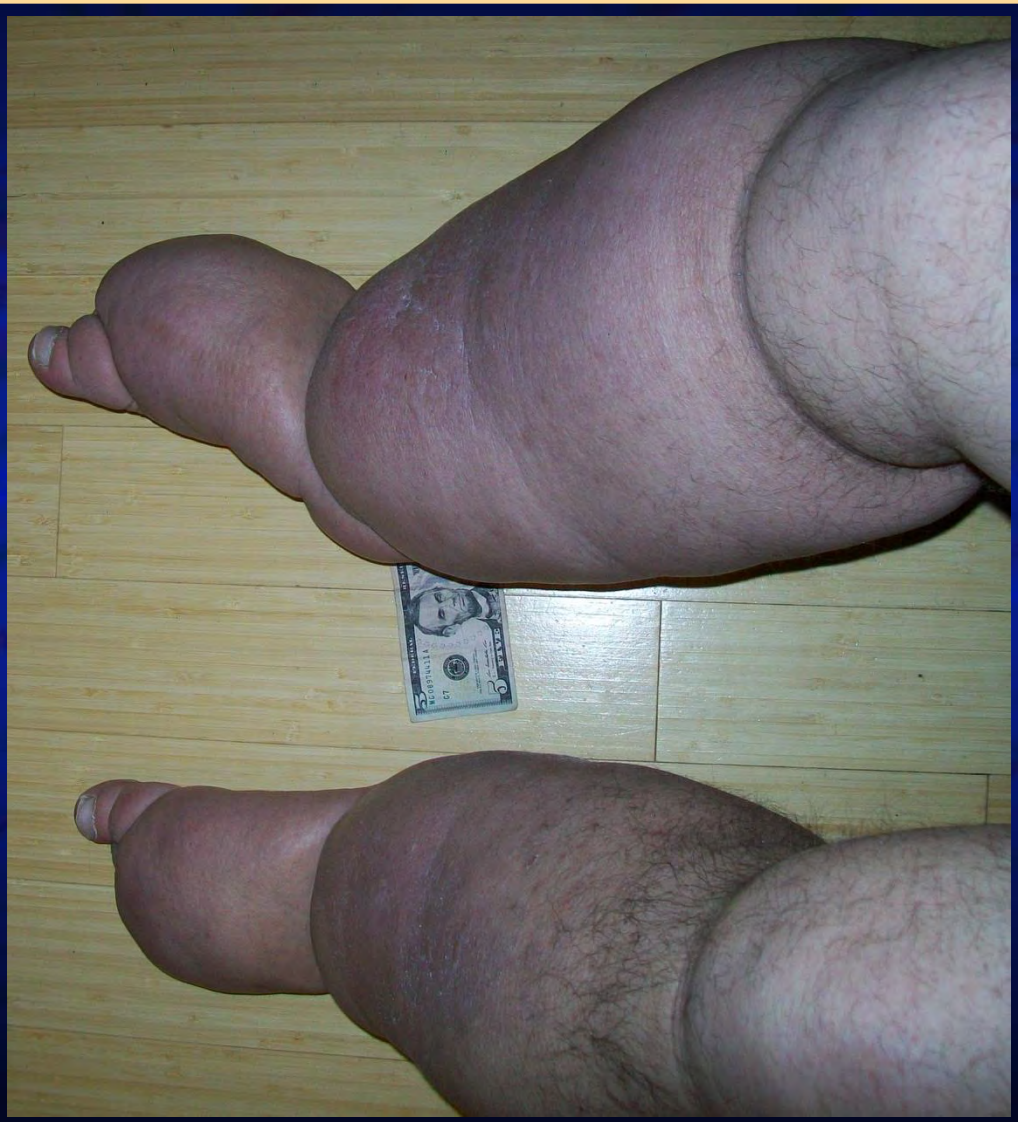
FIGURE 3 Patient Selection for ICD Use



Colors correspond to Table 3. *ICD decisions in pediatric patients with HCM are based on ≥1 of these major risk factors: family history of HCM SCD, NSVT on ambulatory monitor, massive LVH, and unexplained syncope. †5-year risk estimates can be considered to fully inform patients during shared decision-making discussions. ‡It would seem most appropriate to place greater weight on frequent, longer, and faster runs of NSVT. CMR indicates cardiovascular magnetic resonance; EF, ejection fraction; FH, family history; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Ommen et al. *J Am Coll Cardiol* 2024 Jun 11;83(23): 2324-2405.

Lymphedema in Fabry Disease



Screening for Cardiovascular Disease in Fabry Disease

- Established therapies for patients that have evidence of cardiovascular disease
- May be symptomatic at presentation
- More aggressive approach that identifies preclinical disease
- Allows for earlier intervention and more rigorous longitudinal follow-up

Identification of Fabry Disease Using Artificial Intelligence

- Model was developed using a large cloud-based curated dataset
- Data derived from deterministically linked, de-identified, patient-level healthcare claims, EMR, and other data
  - Includes medication history, prescription history, laboratory results, symptoms and signs, procedures, and diagnoses
- Study time period from January 2013-present day

Jefferies et al. *Orphanet J Rare Dis*. 2021 Dec 20;16(1): 518.

Identification of Fabry Disease Using Artificial Intelligence

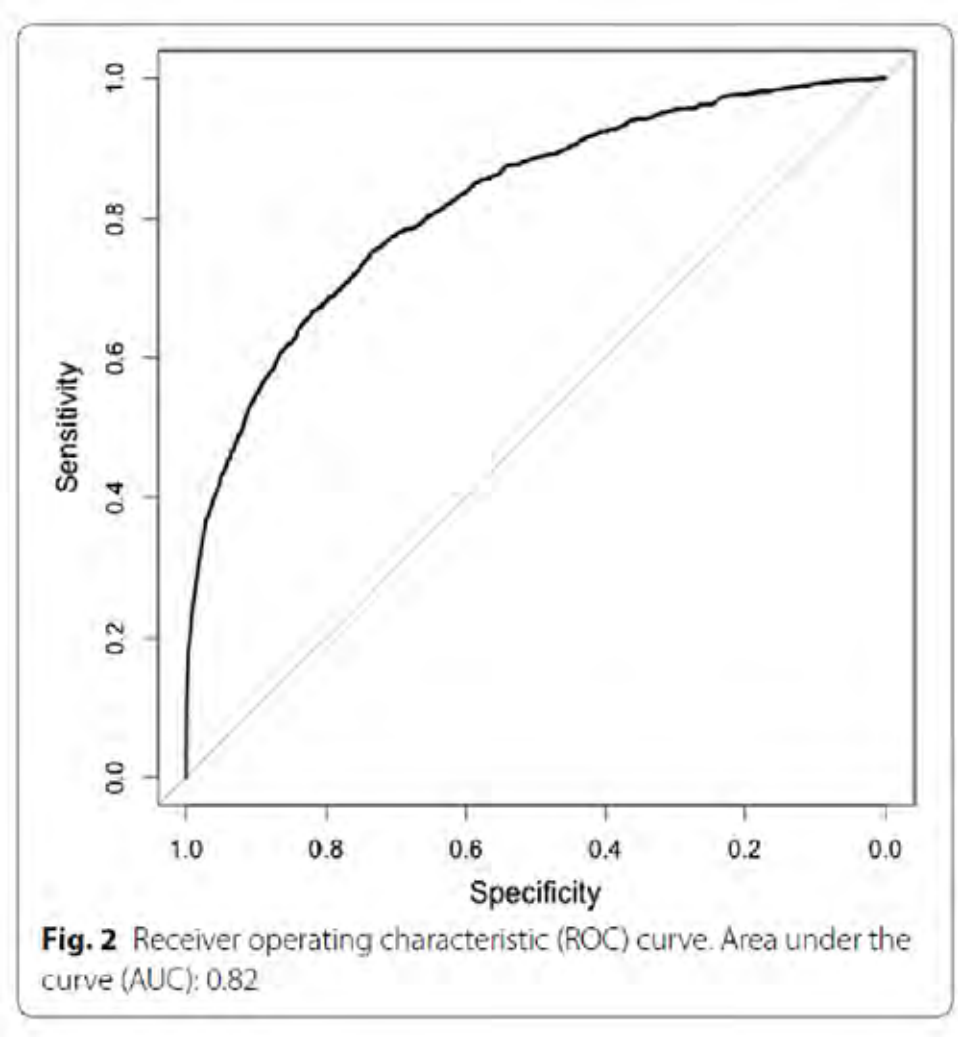


Fig. 2 Receiver operating characteristic (ROC) curve. Area under the curve (AUC): 0.82

Jefferies et al. *Orphanet J Rare Dis*. 2021 Dec 20;16(1): 518.

Red Flags

Extra-Cardiac Red Flags			Cardiac Red Flags		
Presenting Decades of Age	Any time	Family history of renal failure and/or stroke	Family history of LVH, particularly if no evidence of male-to-male transmission	History	Diagnostic Tool
	1–2	Neuropathic pain			
	1–2	Gastrointestinal symptoms	Short PQ interval†	Electrocardiography	
	1–2	Angiokeratomas	Bradycardia		
	1–2	Cornea verticillata*	Chronotropic incompetence		
	1–2	Hypohidrosis, heat/cold, and exercise intolerance	Atrioventricular blocks†		
	1–2	Albuminuria	LVH with normal systolic function	2D-echocardiography	
	3–4	Juvenile and/or cryptogenic TIA/stroke	Reduced global longitudinal strain		
	3–4	Hearing loss (either progressive or sudden)	Mild-to-moderate aortic root dilation		
	3–4	Dolichoectrasia of the basilar artery, chronic white matter hyperintensities at brain MRI	Mitral and aortic valve thickening with mild-to-moderate regurgitation		
	3–4	Proteinuria	Hypertrophy of papillary muscles	Cardiac Magnetic Resonance	
	3–4	Renal failure	Mid-layer posterolateral late gadolinium enhancement		
	3–4	Lymphedema	Low native T1		

Pieroni et al. *J Am Coll Cardiol* 2021;77:922-36.

ACC/AHA Heart Failure Guidelines

Type of HF According to LVEF	Criteria
HFrEF (HF with reduced EF)	LVEF ≤40%
HFimpEF (HF with improved EF)	Previous LVEF ≤40% and a follow-up measurement of LVEF >40%
HFmrEF (HF with mildly reduced EF)	LVEF 41%–49% Evidence of spontaneous or provokable increased LV filling pressures (eg, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)
HFpEF (HF with preserved EF)	LVEF ≥50% Evidence of spontaneous or provokable increased LV filling pressures (eg, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)

Heidenreich et al. *Circulation*. 2022;145:e895-e1032.

Research Trends

- Largest opportunity currently in diagnosis of underlying LSD
  - For example, HCM receives significant focus because of disease specific drugs now being available
  - 2-3% of HCM may be Fabry disease
- Repurposing existing drugs used in traditional heart failure for LSD population

Conclusions

- Broad spectrum of cardiovascular disease in Fabry disease
- Increasingly important cause of morbidity and mortality
- Historical approach to detection may result in late diagnosis of cardiovascular involvement
- This may result in delaying beneficial therapeutic strategies

John Jefferies
Email: johnljefferiesmd@gmail.com

Comprehensive Cardiovascular Care In Fabry Disease

- Evaluation of patients of all ages
- Detailed approach to pediatric patients
- Evaluation of female carriers
- Serial follow-up to assess for changes in findings and institute appropriate medical and device therapies
- Promote use of existing technologies

Comprehensive Cardiovascular Care In Fabry Disease

- By taking a more thoughtful and comprehensive approach:
  - Identify cardiovascular disease earlier
  - Utilize appropriate therapies
  - Potentially reduce morbidity and mortality
  - Monitor response to therapies
  - Collect data targeting new diagnostic and treatment strategies

Comprehensive Cardiovascular Care In Fabry Disease

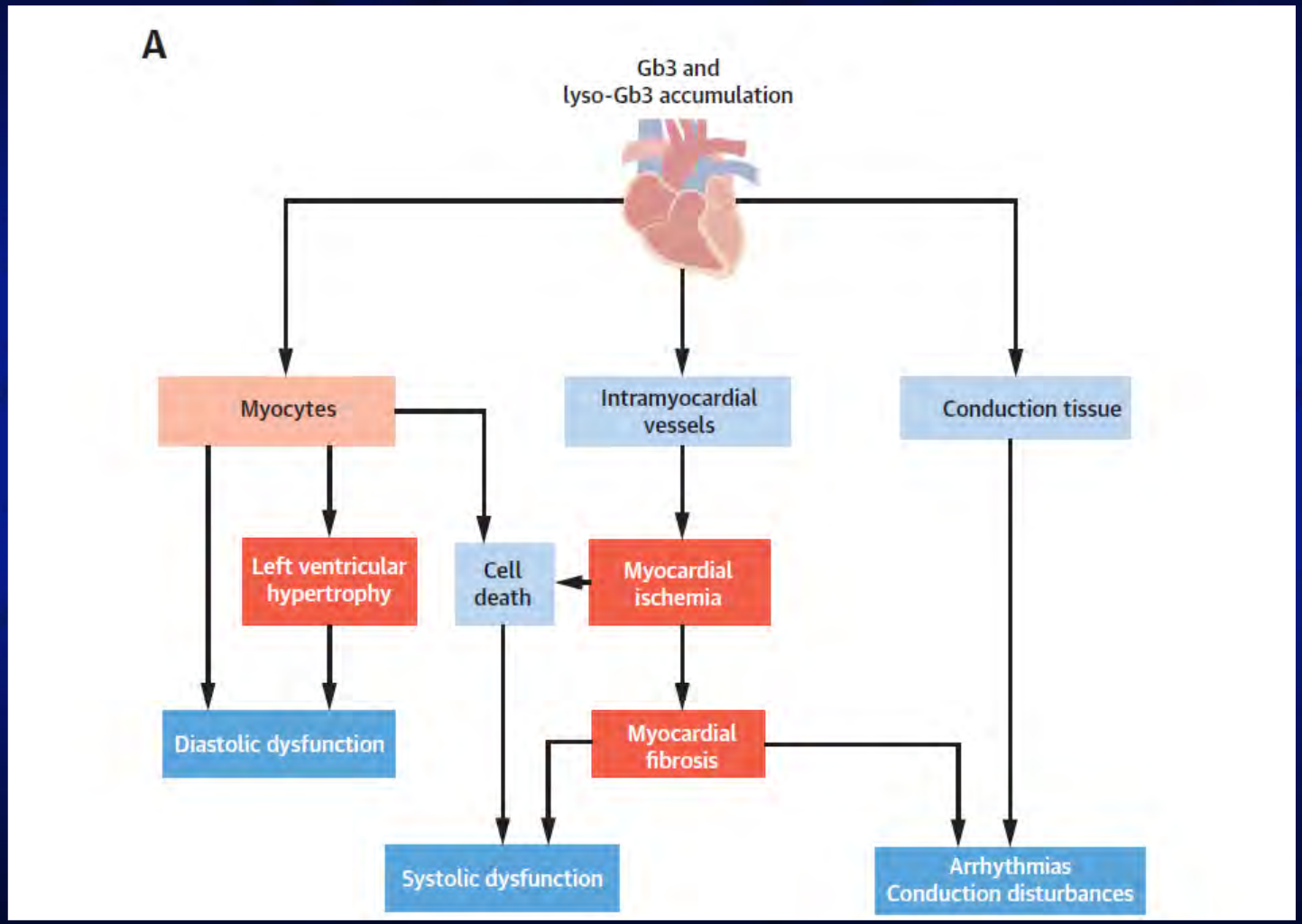
- Noninvasive and serologic testing
  - Imaging
    - Echocardiography
    - Cardiac MRI
  - EKG and Holter monitoring
  - Stress testing
  - Blood and urinary biomarker testing
- Offers additional opportunities to develop prognostic variables and assess response to therapies
- ***Artificial intelligence may help us identify undiagnosed patients with Fabry***

Fabry Disease

- A progressive, life-threatening X-linked genetic disorder
- Characterized by deficiency of the lysosomal enzyme α-galactosidase A (α-GAL)
- α-GAL enzyme deficiency leads to progressive cellular accumulation of glycosphingolipids, particularly globotriaosylceramide (GL-3), in many body tissues
- Clinical manifestations include life-threatening renal, cardiac and /or cerebrovascular complications
- GL-3 accumulation starts early in life and continues over decades

Germaine, D. OJRD 2010, 5:30

Pathophysiology



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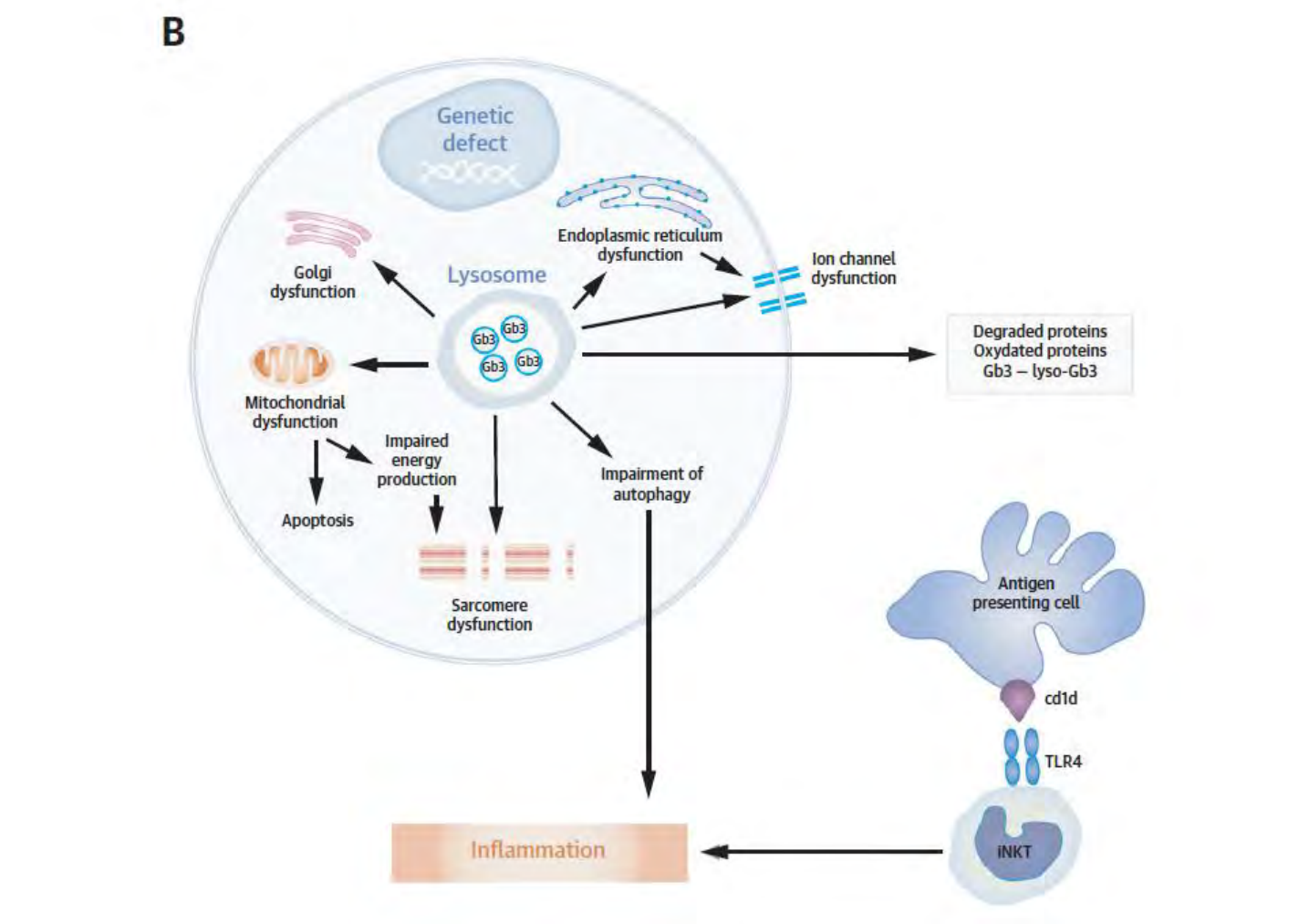
Pathophysiology



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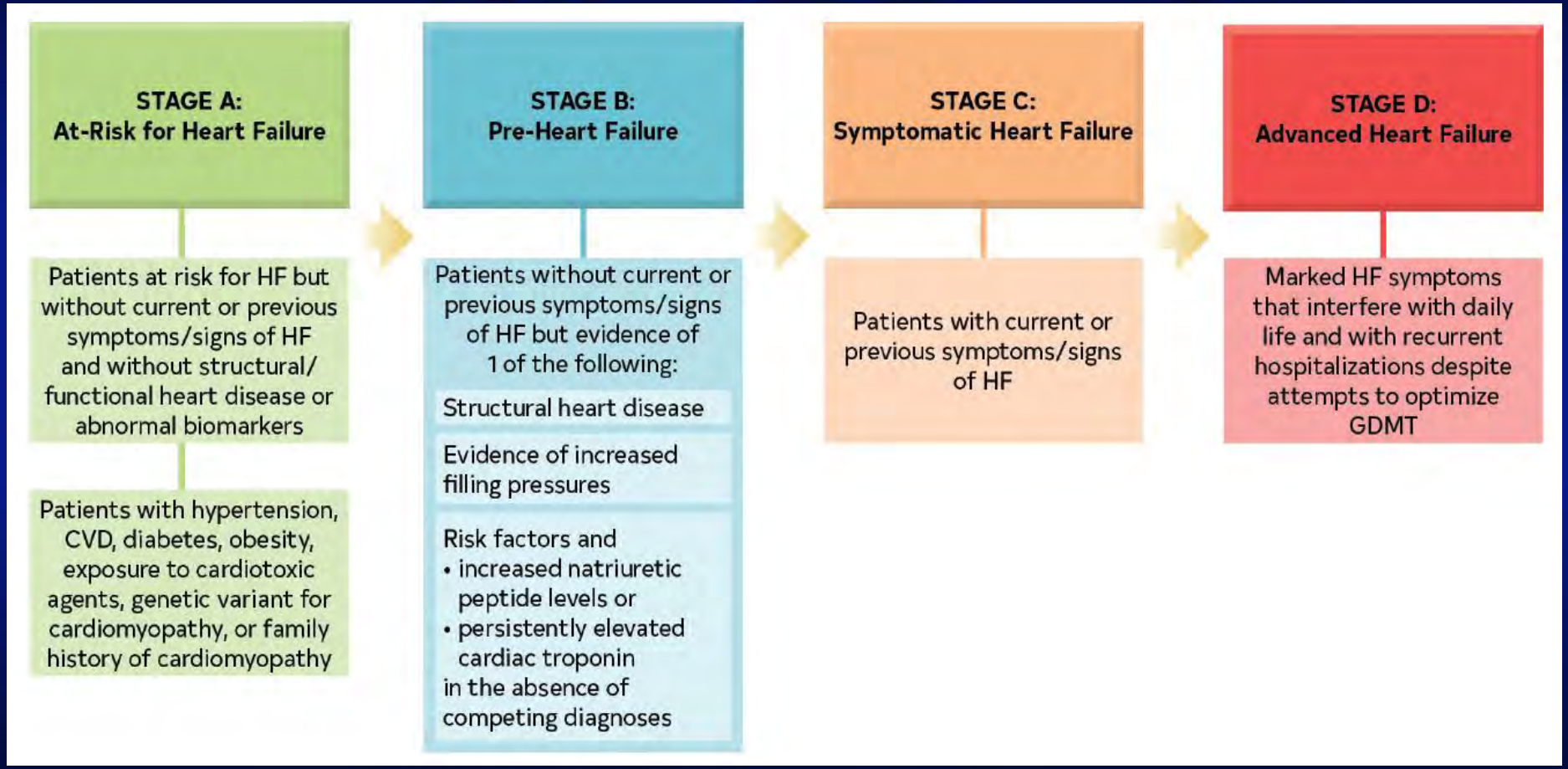
ACC/AHA Heart Failure Guidelines



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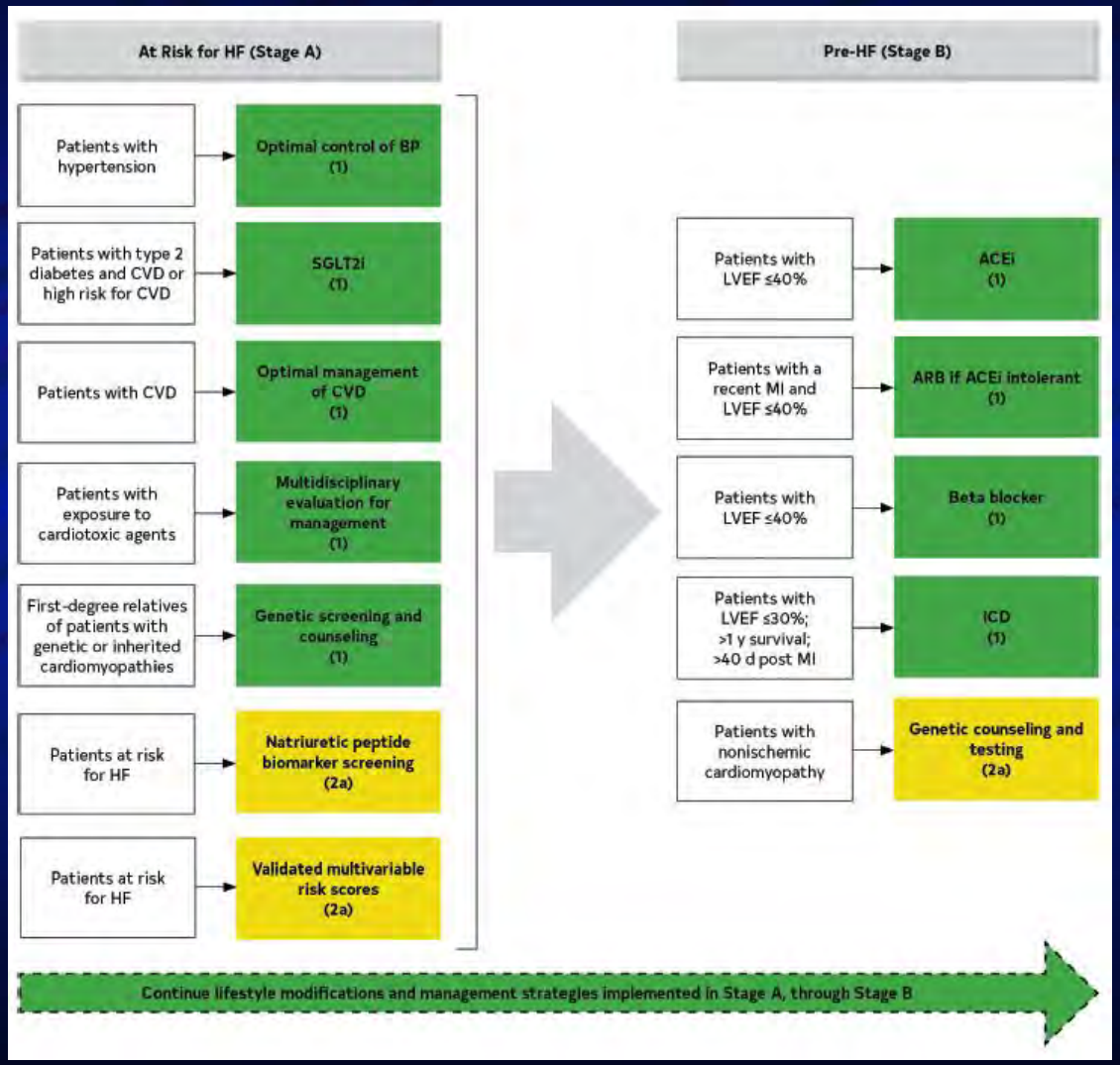
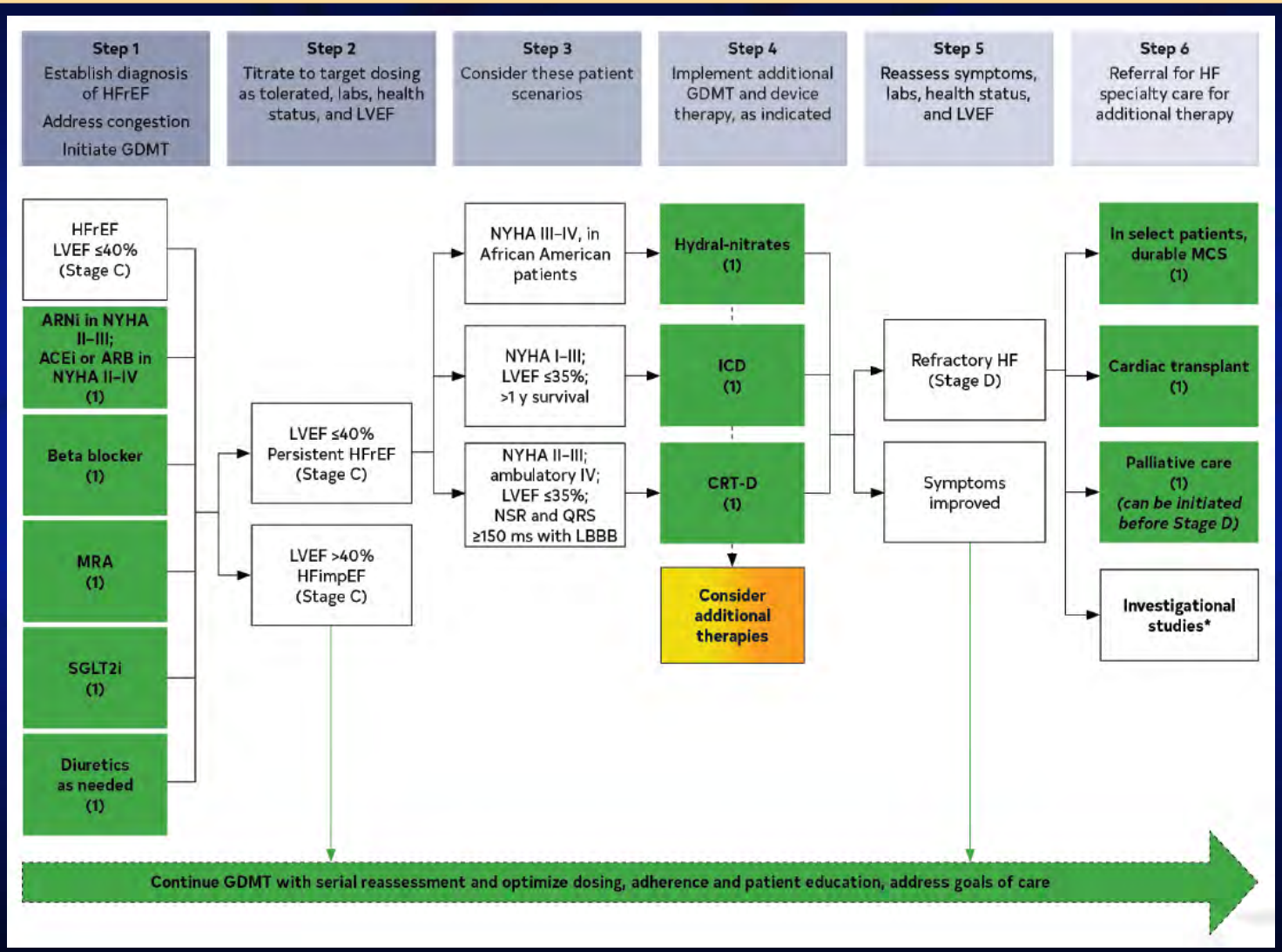
ACC/AHA Heart Failure Guidelines



Heidenreich et al. *Circulation*. 2022;145:e895-e1032.

Heart Failure with Reduced Ejection Fraction



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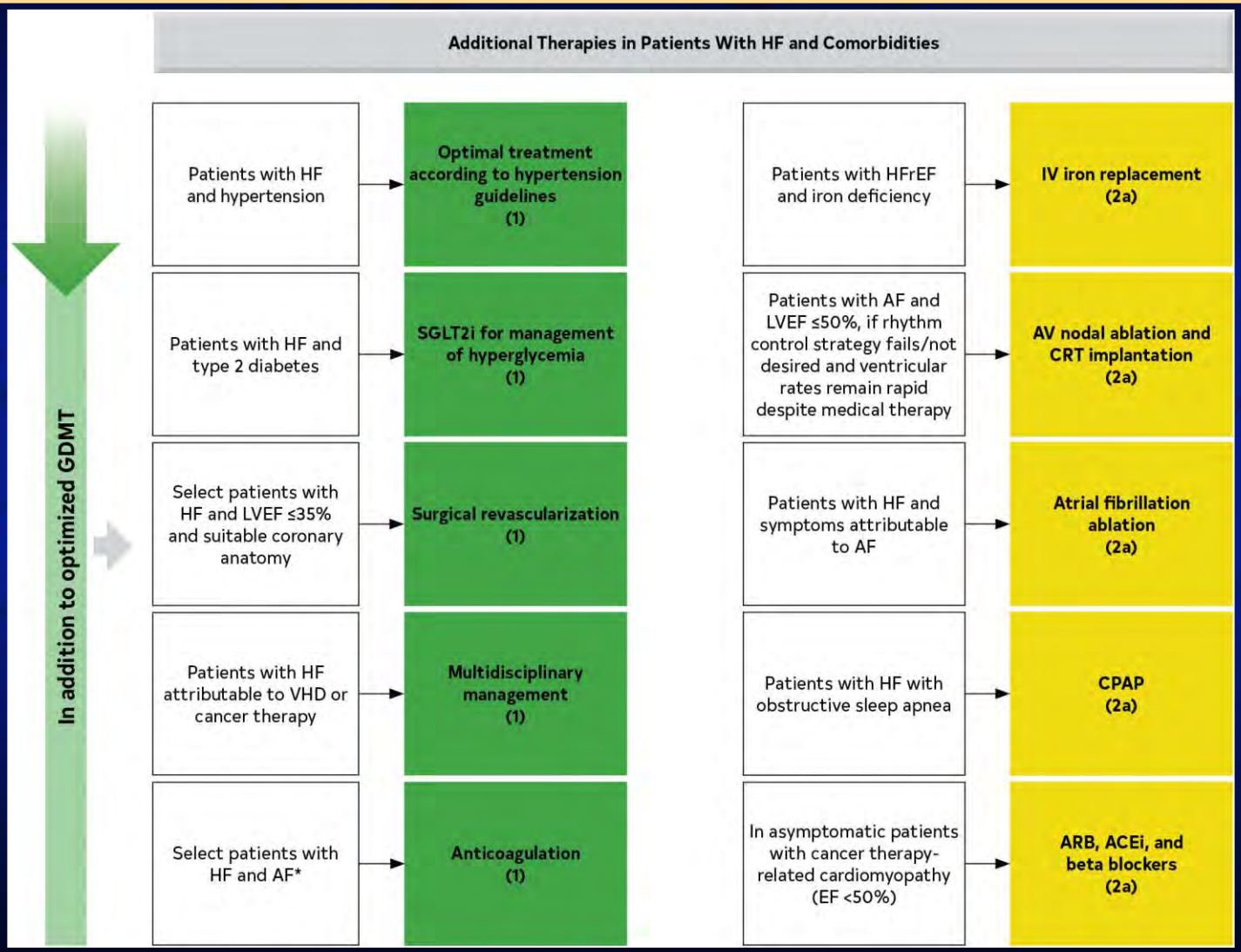
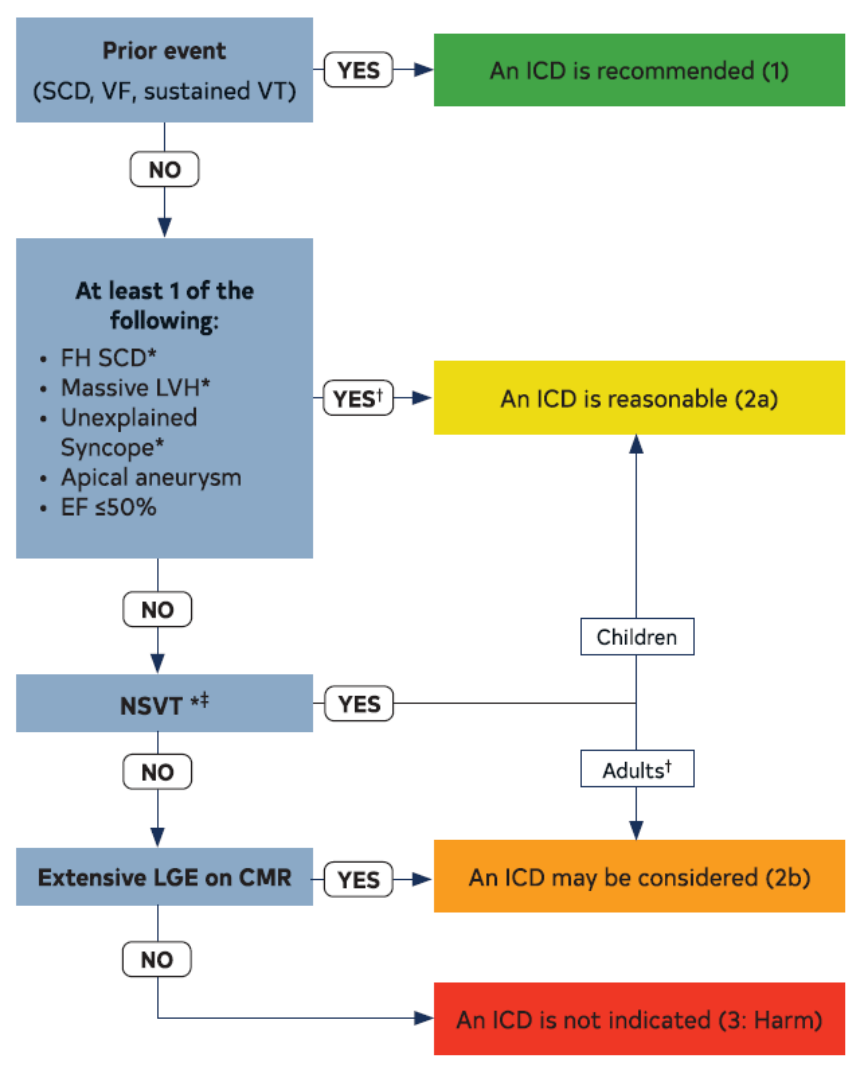
ACC/AHA Heart Failure Guidelines



Heidenreich et al. *Circulation*. 2022;145:e895-e1032.

Hypertrophic Cardiomyopathy



Ommen et al. *Circulation.* 2020;142:e558-e631.