Managing Cardiomyopathies in Lysosomal Disorders

John Lynn Jefferies, MD, MBA, MPH, FACC, FAHA, FAAP FHFSA, FESC, FRCPE

Governor, American College of Cardiology, Tennessee Chapter
President, American Heart Association, Mid-South Chapter
Research Member, St Jude Children's Research Hospital
Team Cardiologist, Memphis Grizzlies

Disclosures

- Dr. Jefferies serves on the advisory board of Sanofi Genzyme, Chiesi, Rocket, Amicus, Bristol Myers Squibb and Medtronic. He is also on the speaker bureau of Sanofi Genzyme and Bristol Myers Squibb.
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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 managing cardiomyopathies in lysosomal disorders*
- *Identify best practices to treat cardiomyopathies in lysosomal disorders*

Lysosomal Disorders

- Heterogeneous group of conditions
- Historically, LSDs 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

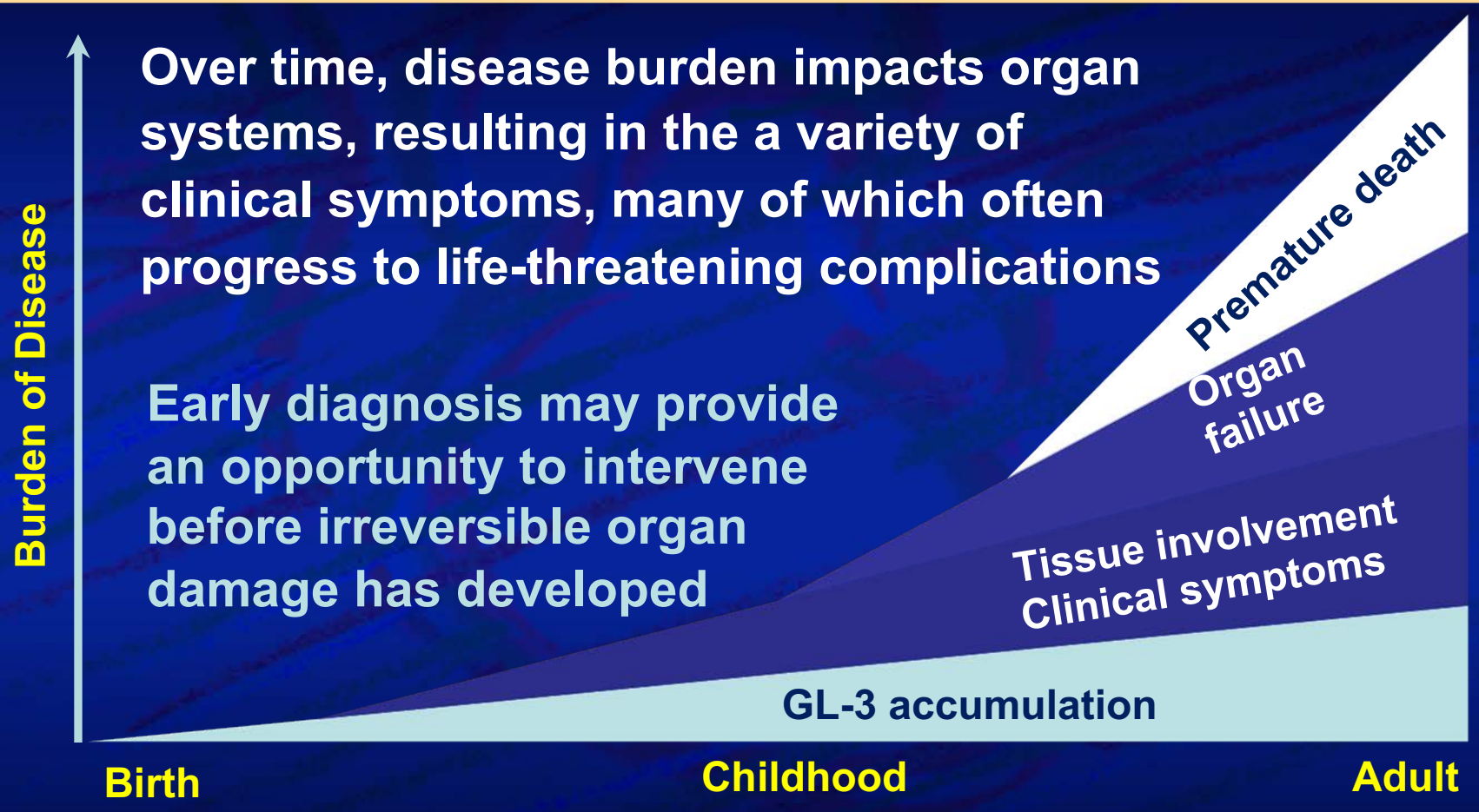
- Cardiovascular implications are significant
- Major driver of morbidity and mortality
- Discussion of cardiologist involvement, testing, and surveillance strategies are translatable across different LSDs
- A proactive and durable approach is needed in patients with LSDs

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

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			●

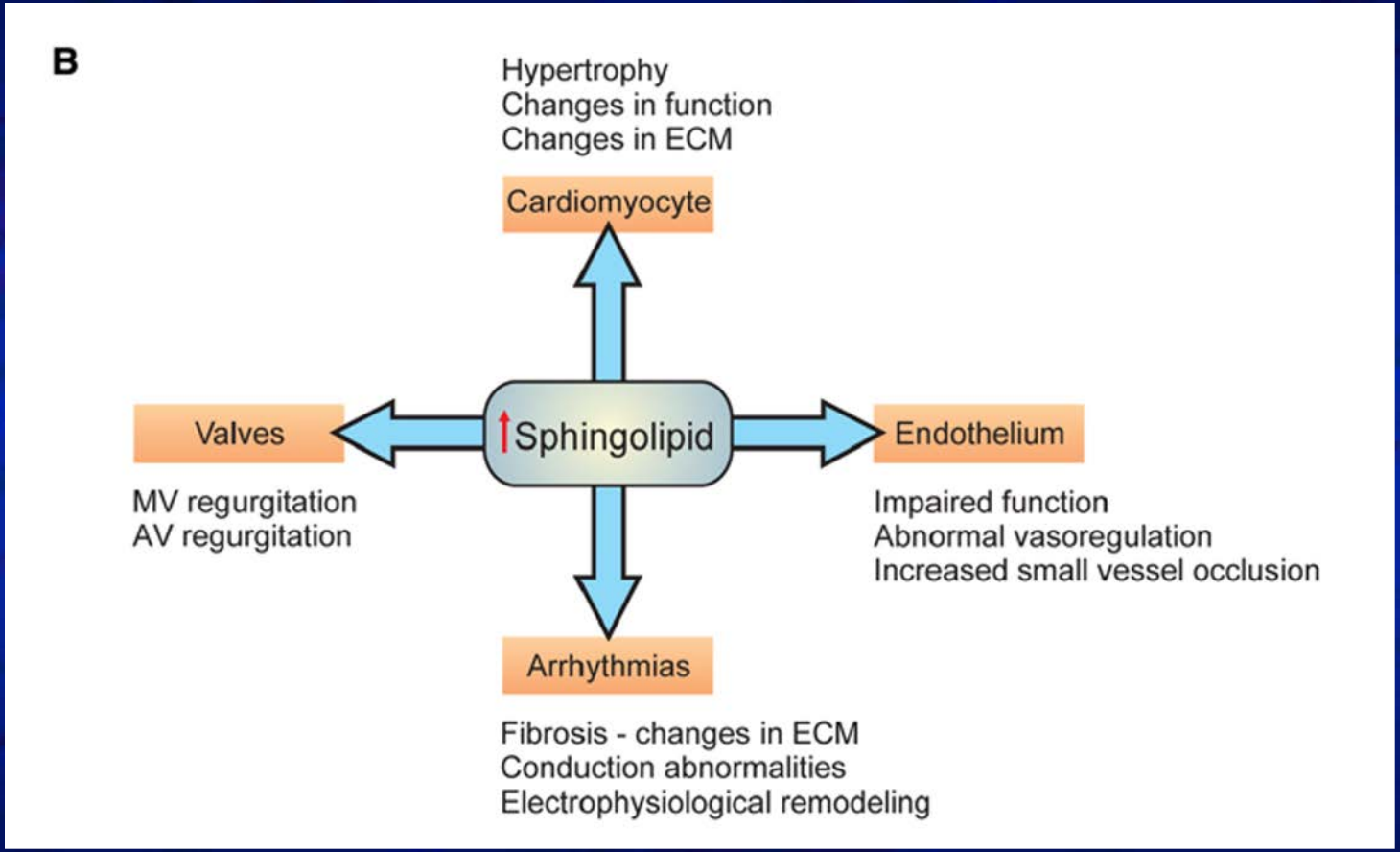
Cardiovascular Findings in Fabry Disease

- 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

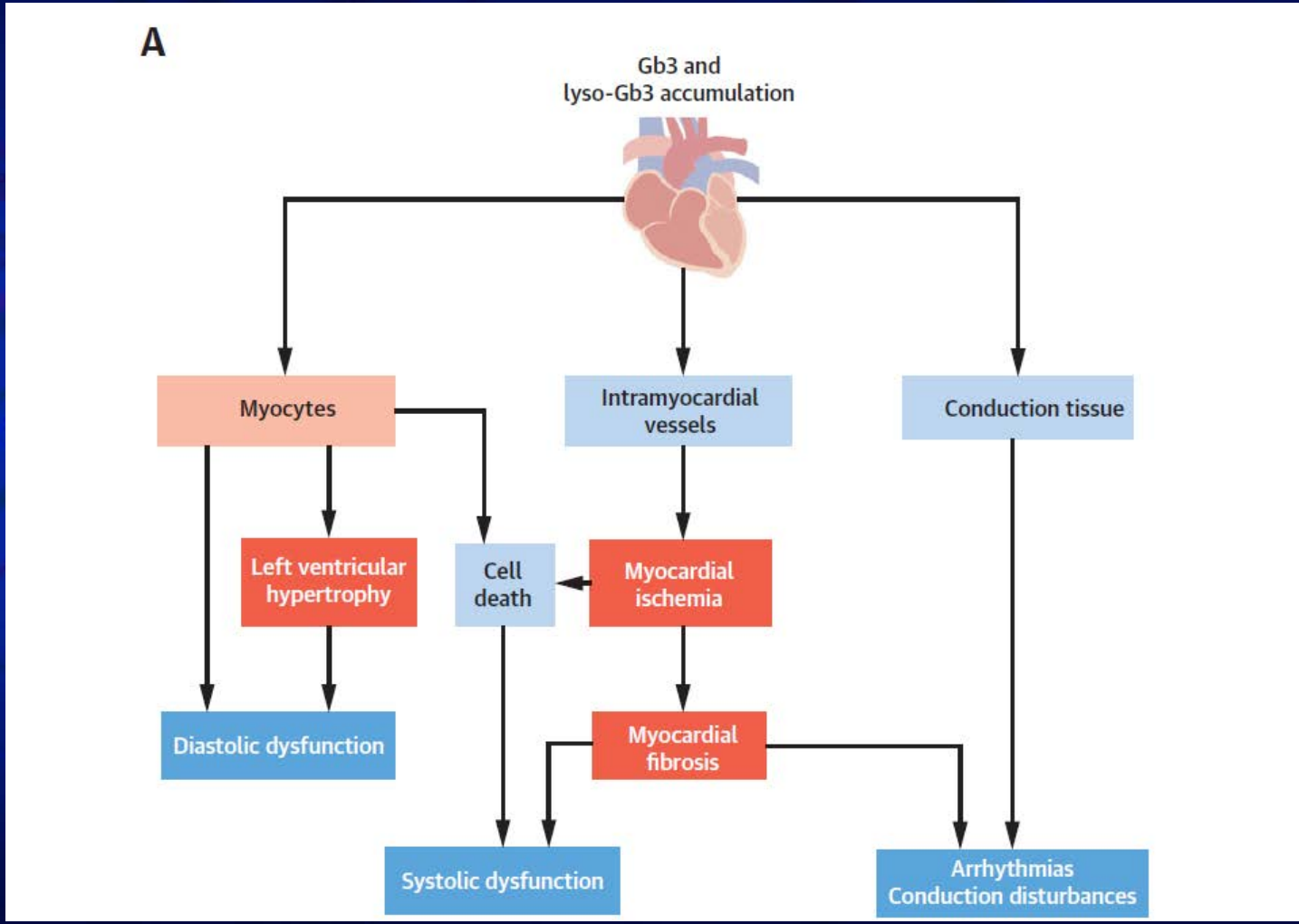
- Member of the multidisciplinary team
- Ideally, the cardiologist is familiar with cardiomyopathy, heart failure, and genetics (adult and pediatric)
- Complex role as multiple phenotypic manifestations
- Beneficial to have other cardiologists with expertise in imaging, electrophysiology, catheterization,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

Cardiovascular Findings in Fabry Disease

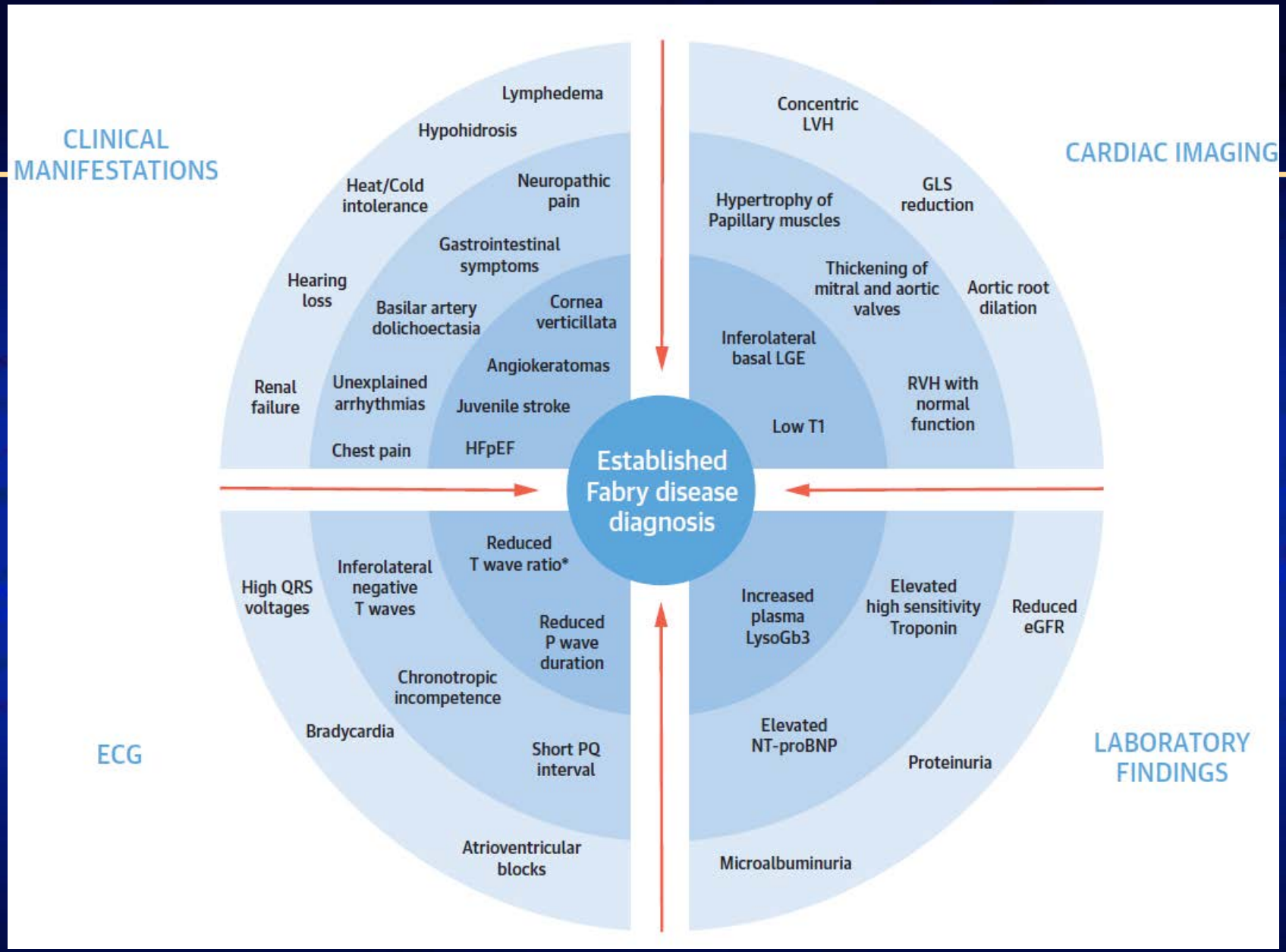


Putko et al. *Heart Fail Rev* 2014; July 17;epub ahead of print.

Pathophysiology

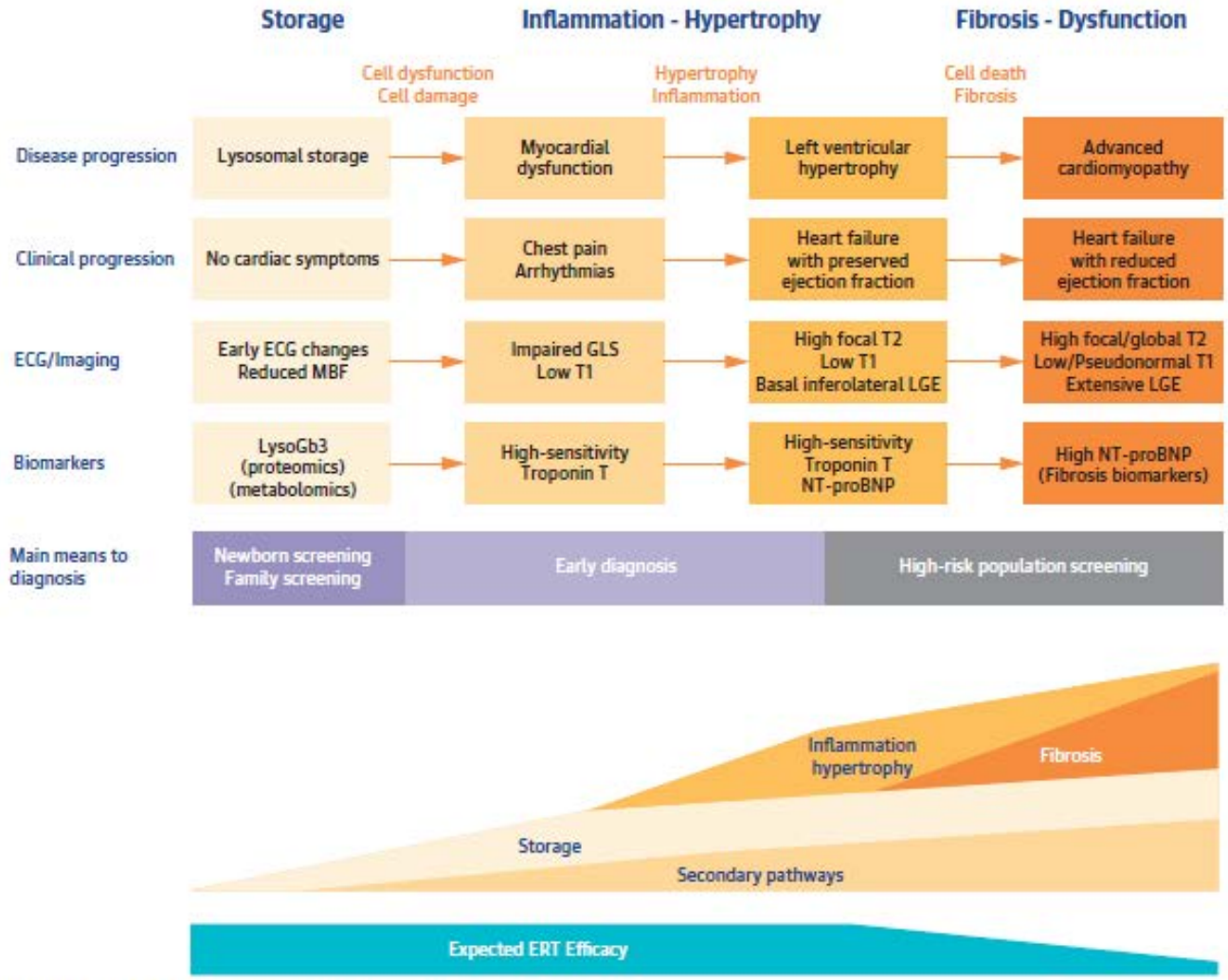


Pieroni et al. *J Am Coll Cardiol* 2021;77:922-36.



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

- 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

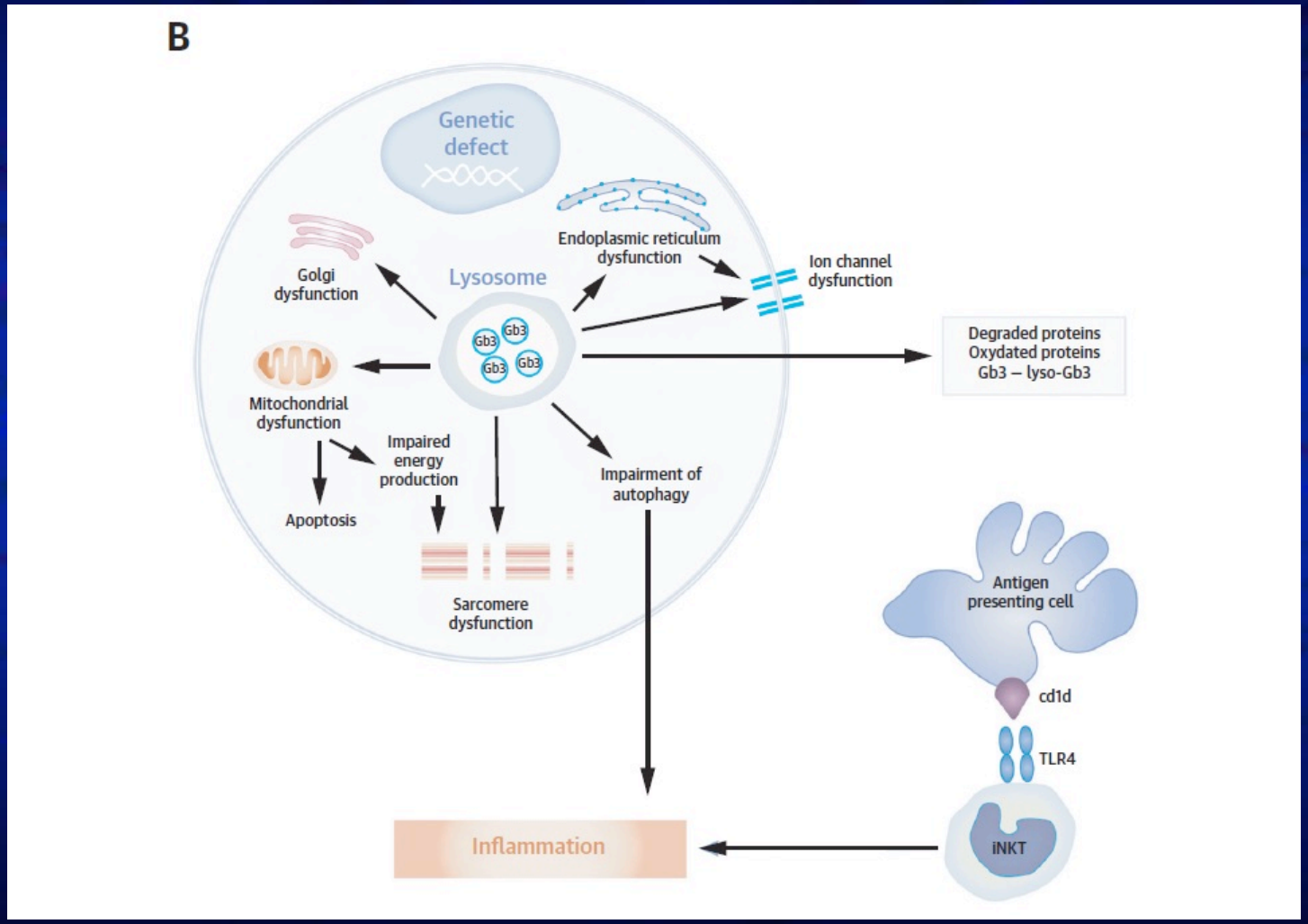
Putko et al. *Heart Fail Rev* 2014; July 17;epub ahead of print.

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

Pathophysiology



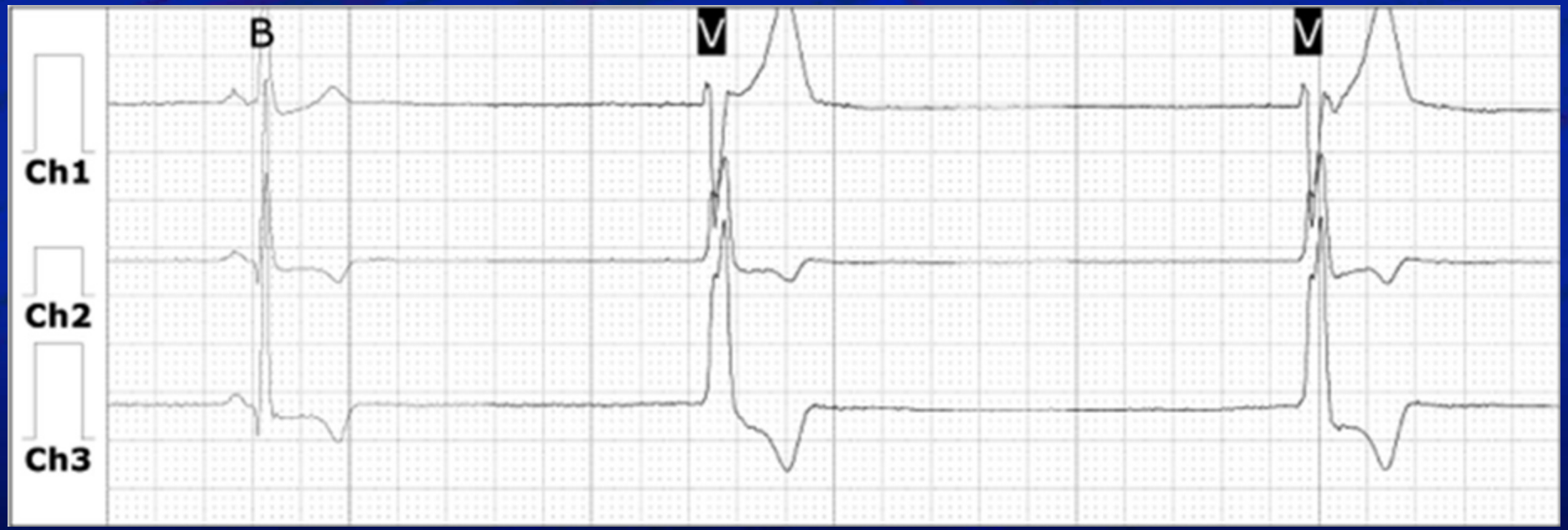
Pieroni et al. *J Am Coll Cardiol* 2021;77:922-36.

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

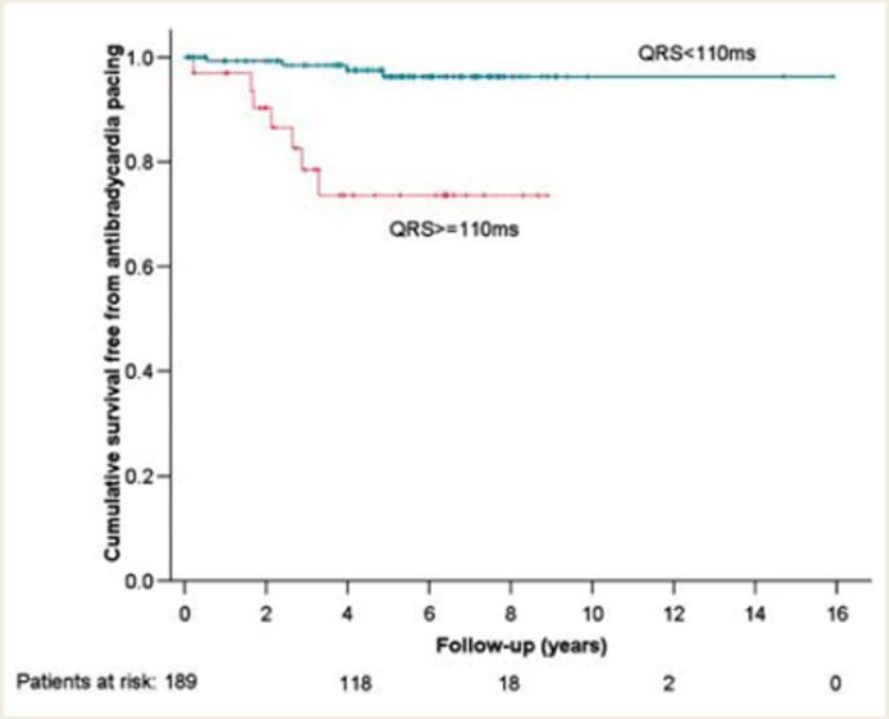
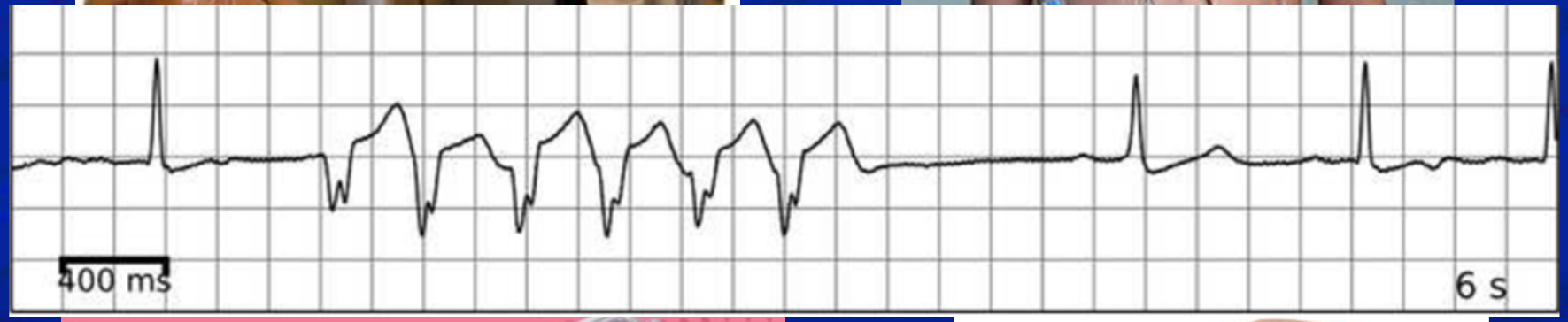


Figure 4 Kaplan–Meier curve for survival free from anti-bradycardia pacing.

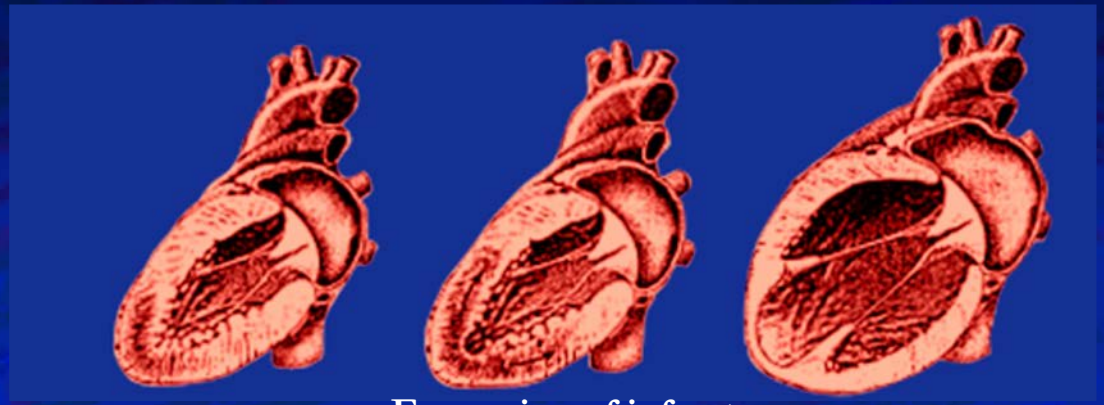
O'Mahony et al. Europace. 2011 Dec;13(12):1781-8.

Arrhythmias and Conduction System Disease



Pathologic Ventricular Remodeling

Ventricular Remodeling

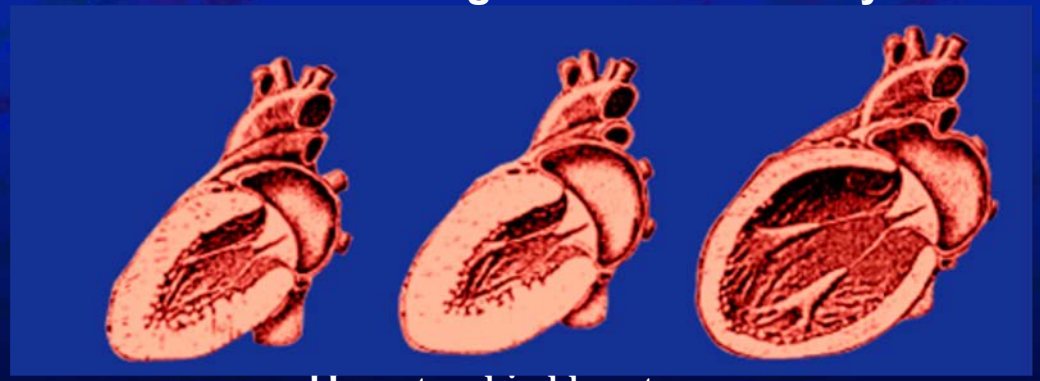


Trigger

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

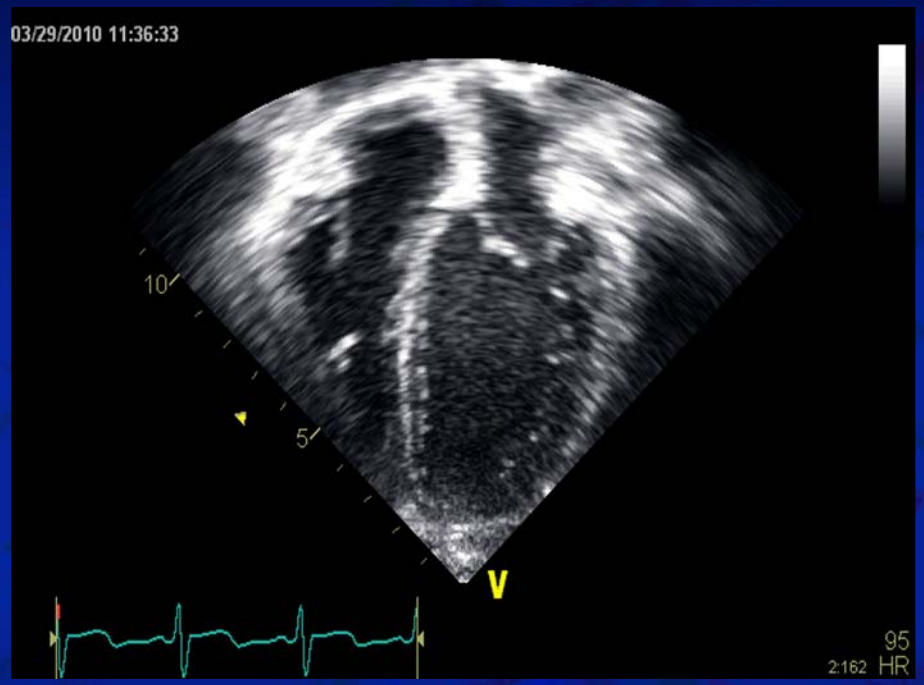
Best Practiced in Managing LSD Related Cardiomyopathies

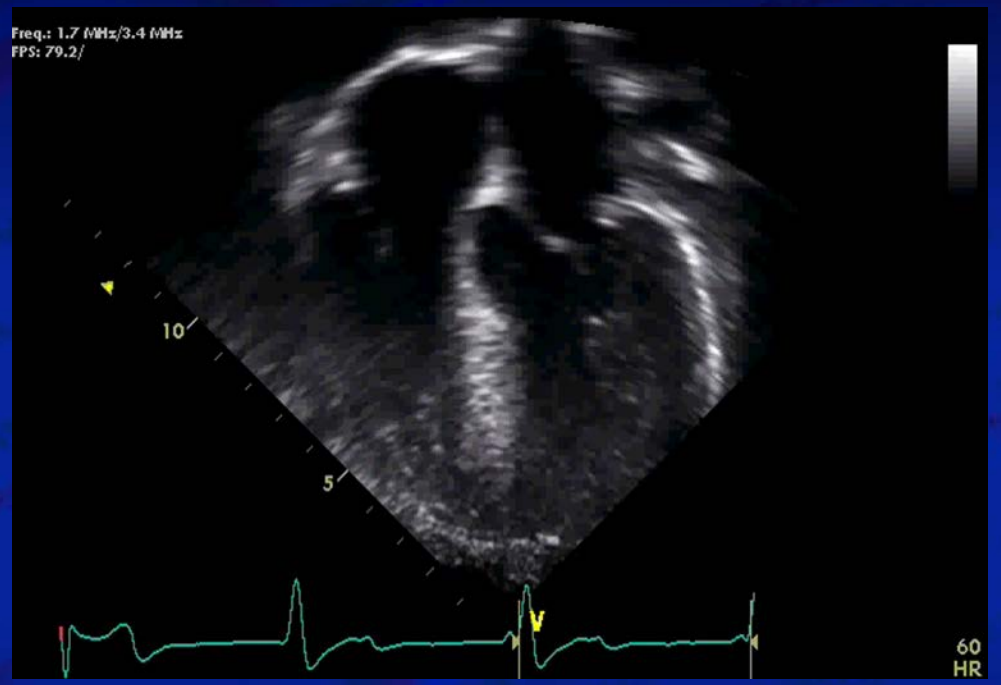
- First step is accurate diagnosis
- Informed by imaging approach
- Phenotype guides treatment pathway
  - Dilated, hypertrophic, restrictive, noncompaction
- Different drug and device options available depending on cardiomyopathy phenotype
  - Can be isolated phenotype or mixed

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

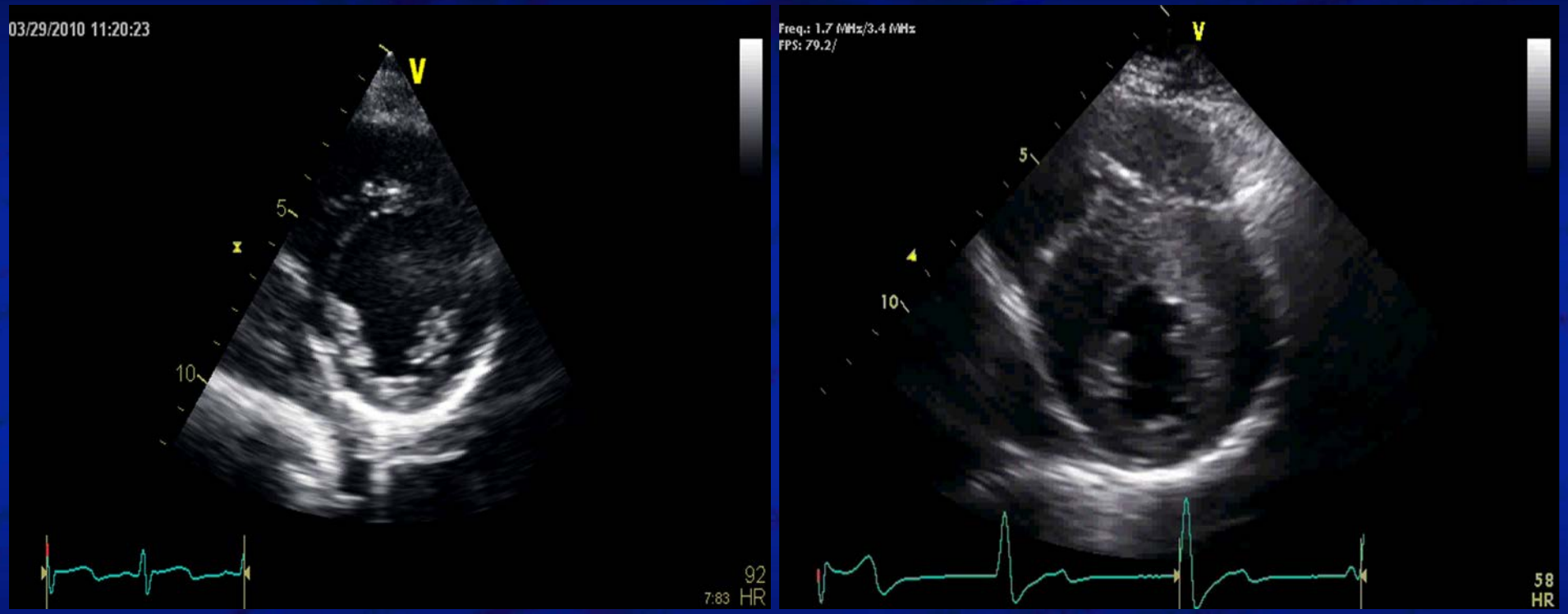
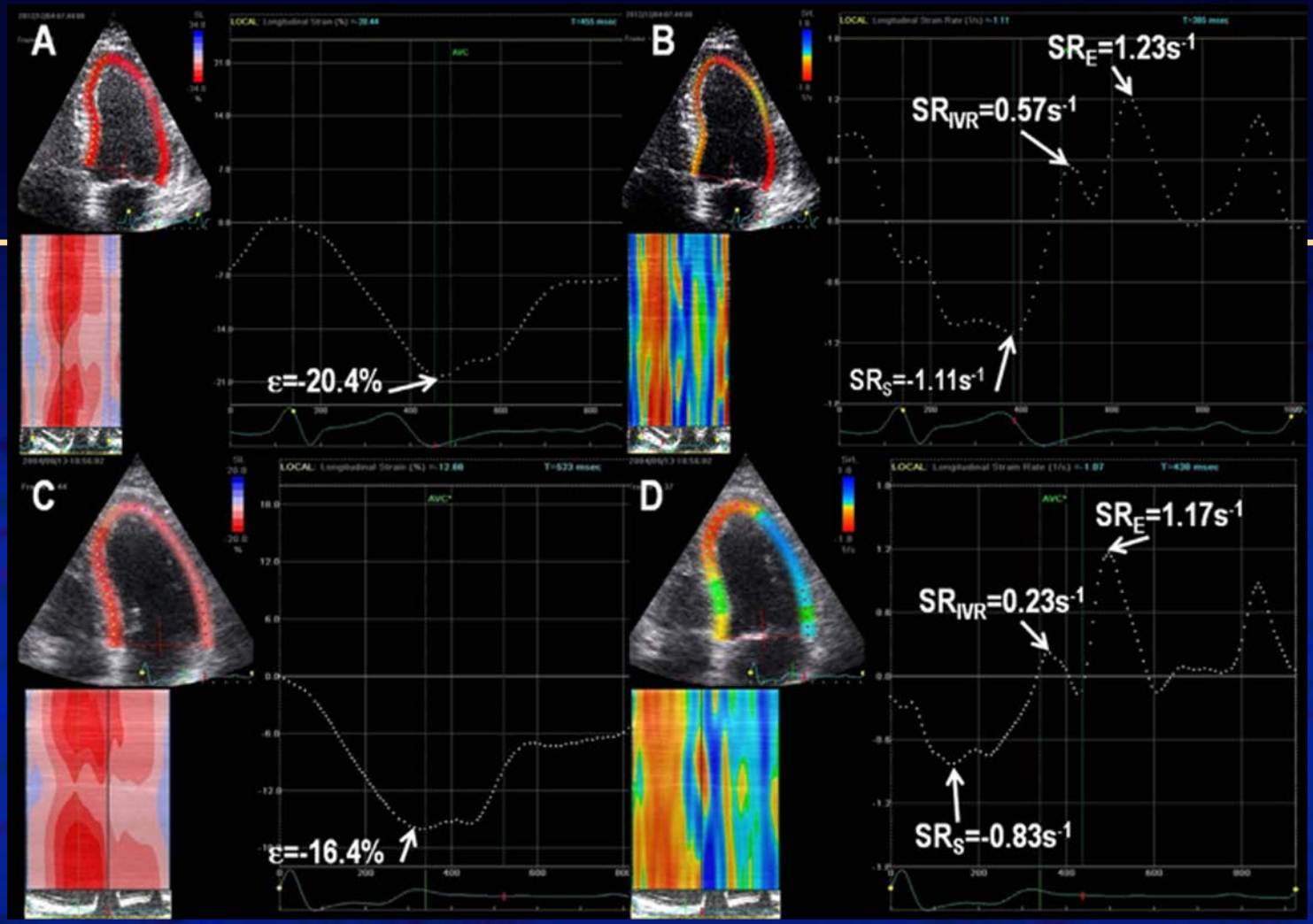


Photo permission on file

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



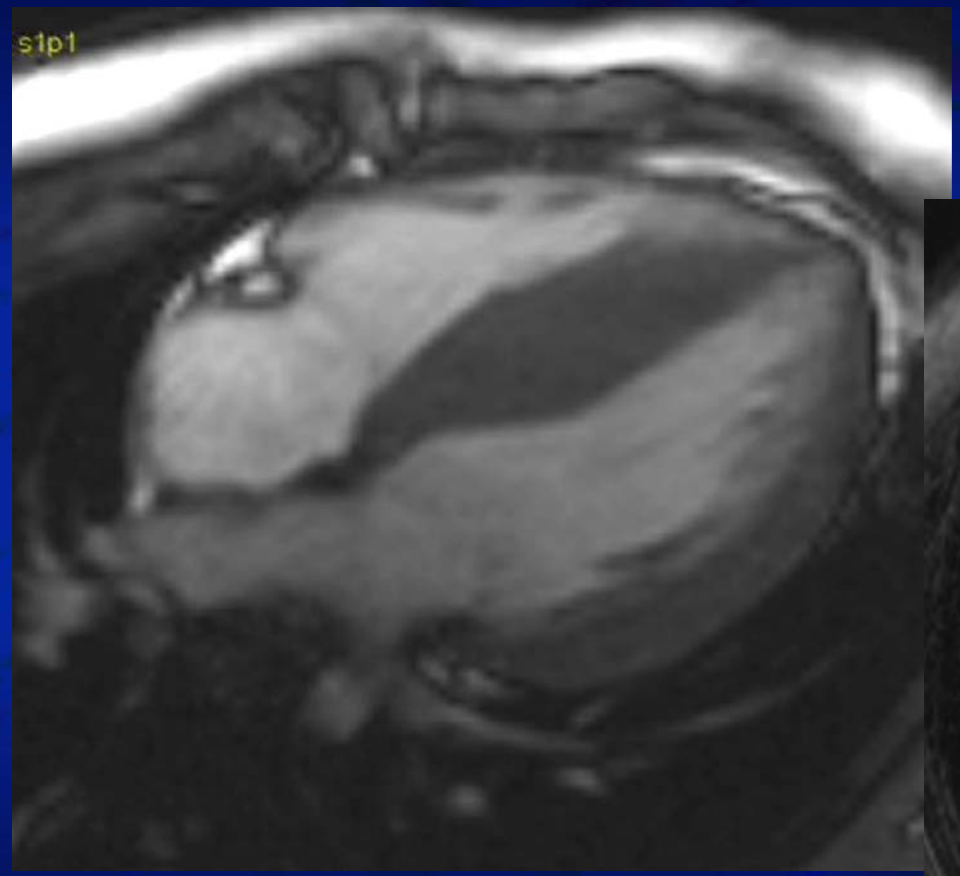
Conclusions: Strain and SR analysis is useful in identifying patients with FD with reduced myocardial function, with longitudinal systolic strain and diastolic isovolumic SR being superior to the other echocardiographic measurements of myocardial contraction and relaxation and independent of LVH. (J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

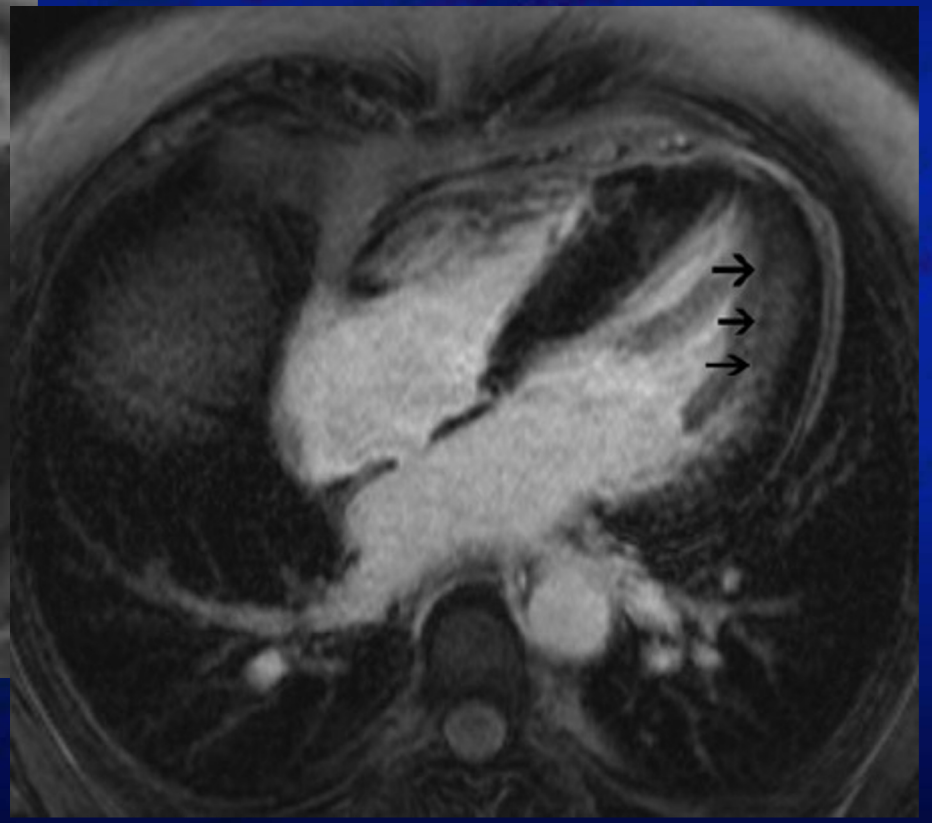
Shanks et al. *J Am Soc Echocardiogr* 2013;26:1407-14.

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

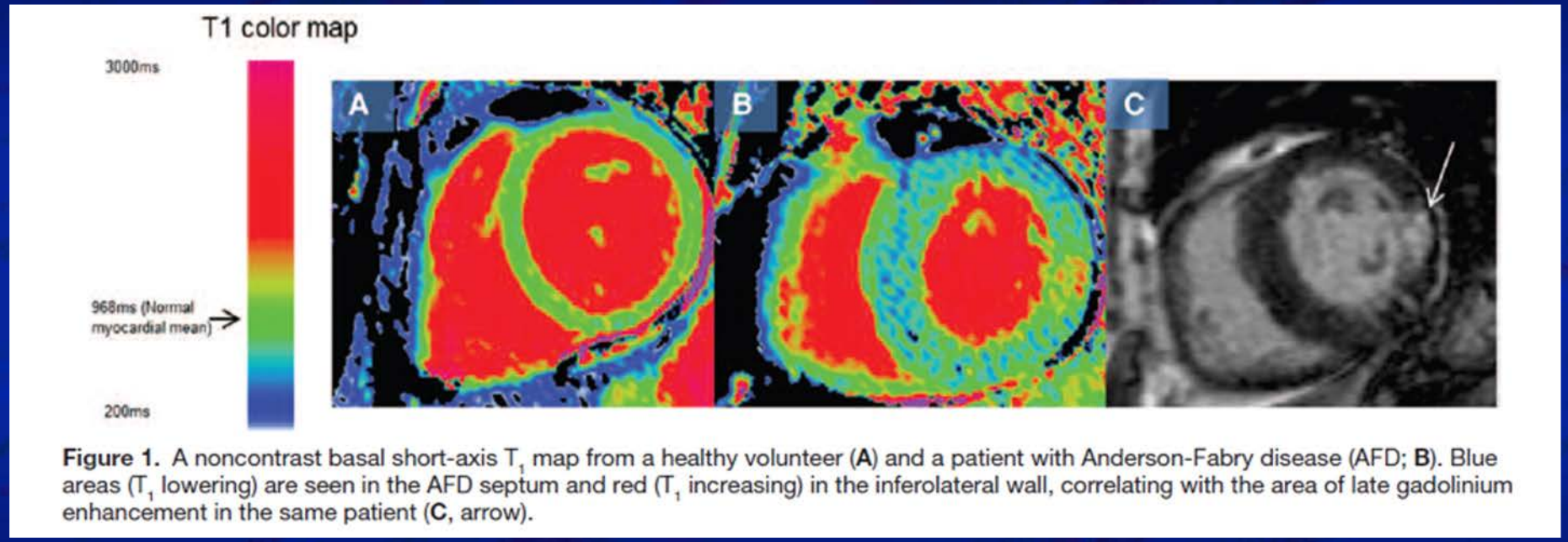
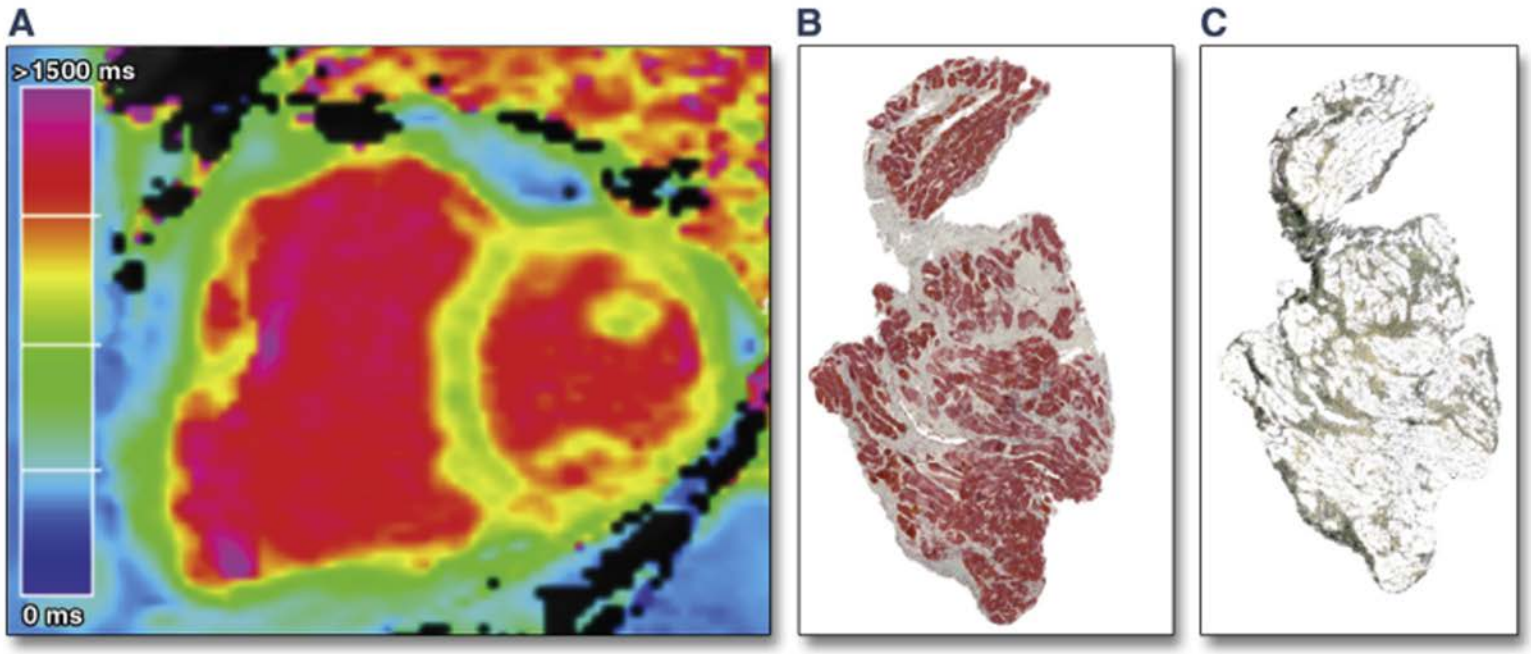


Figure 1. A noncontrast basal short-axis T_1 map from a healthy volunteer (**A**) and a patient with Anderson-Fabry disease (AFD; **B**). Blue areas (T_1 lowering) are seen in the AFD septum and red (T_1 increasing) in the inferolateral wall, correlating with the area of late gadolinium enhancement in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



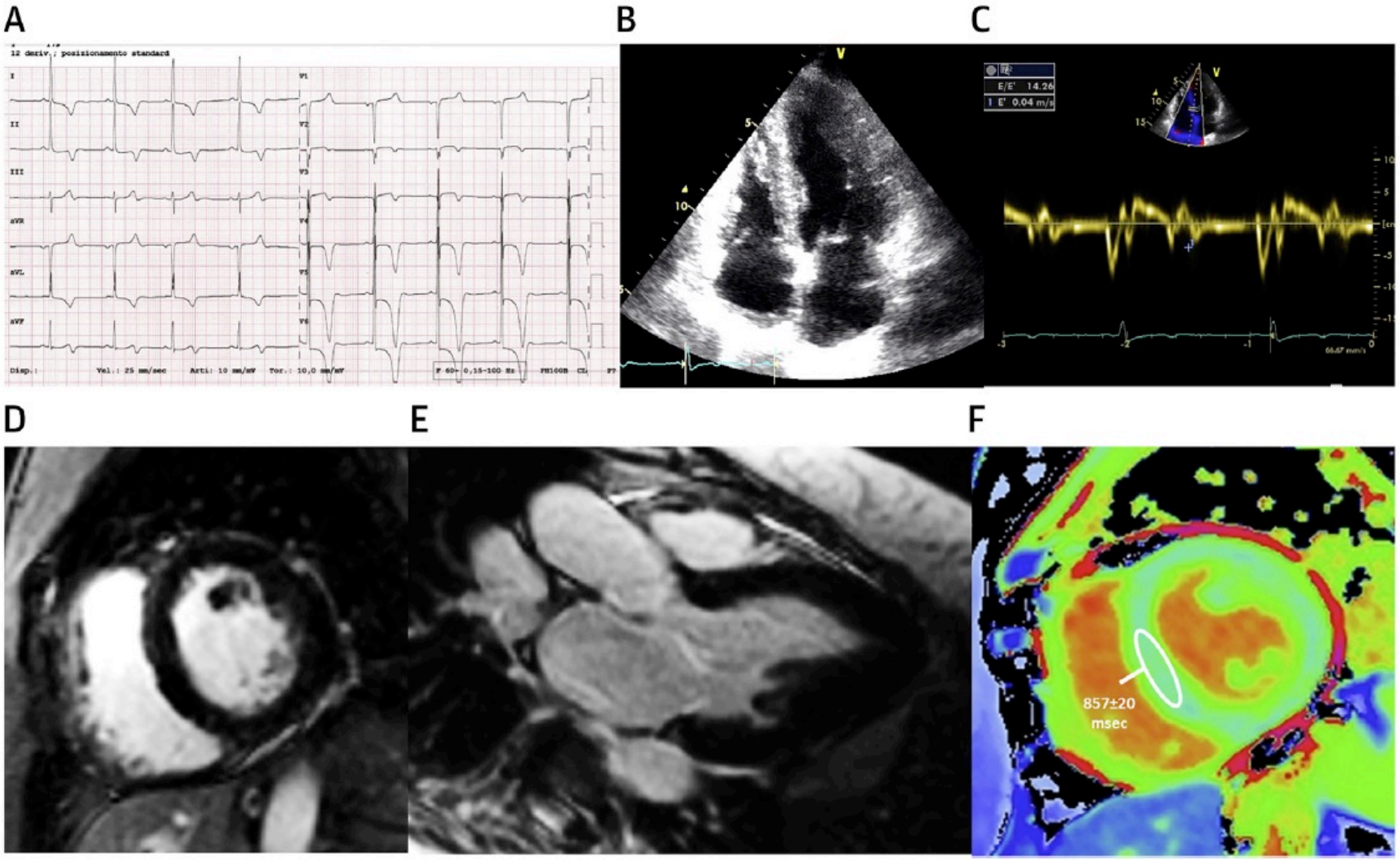
(A) Native T1 map in a patient with heart failure and preserved ejection fraction. Extracellular volume by cardiac magnetic resonance T1 mapping was 26.5%. **(B)** Left ventricular histological specimen of the same patient scanned with TissueFAXS software. **(C)** Same specimen after a color-threshold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

CMR-ECV was calculated with the formula (15)

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

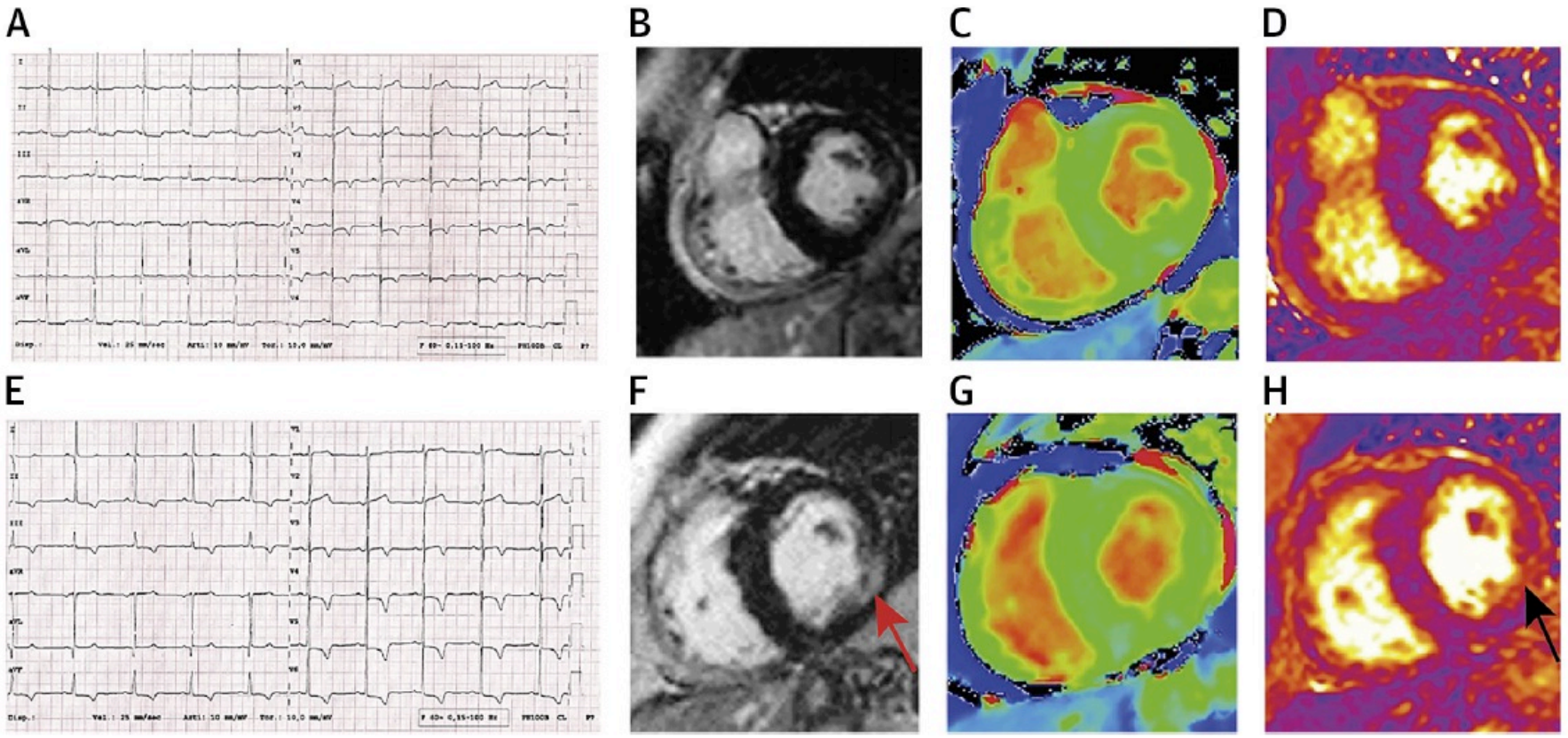
Kammerlander et al. *J Am Coll Cardiol Img* 2016;9:14-23.

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



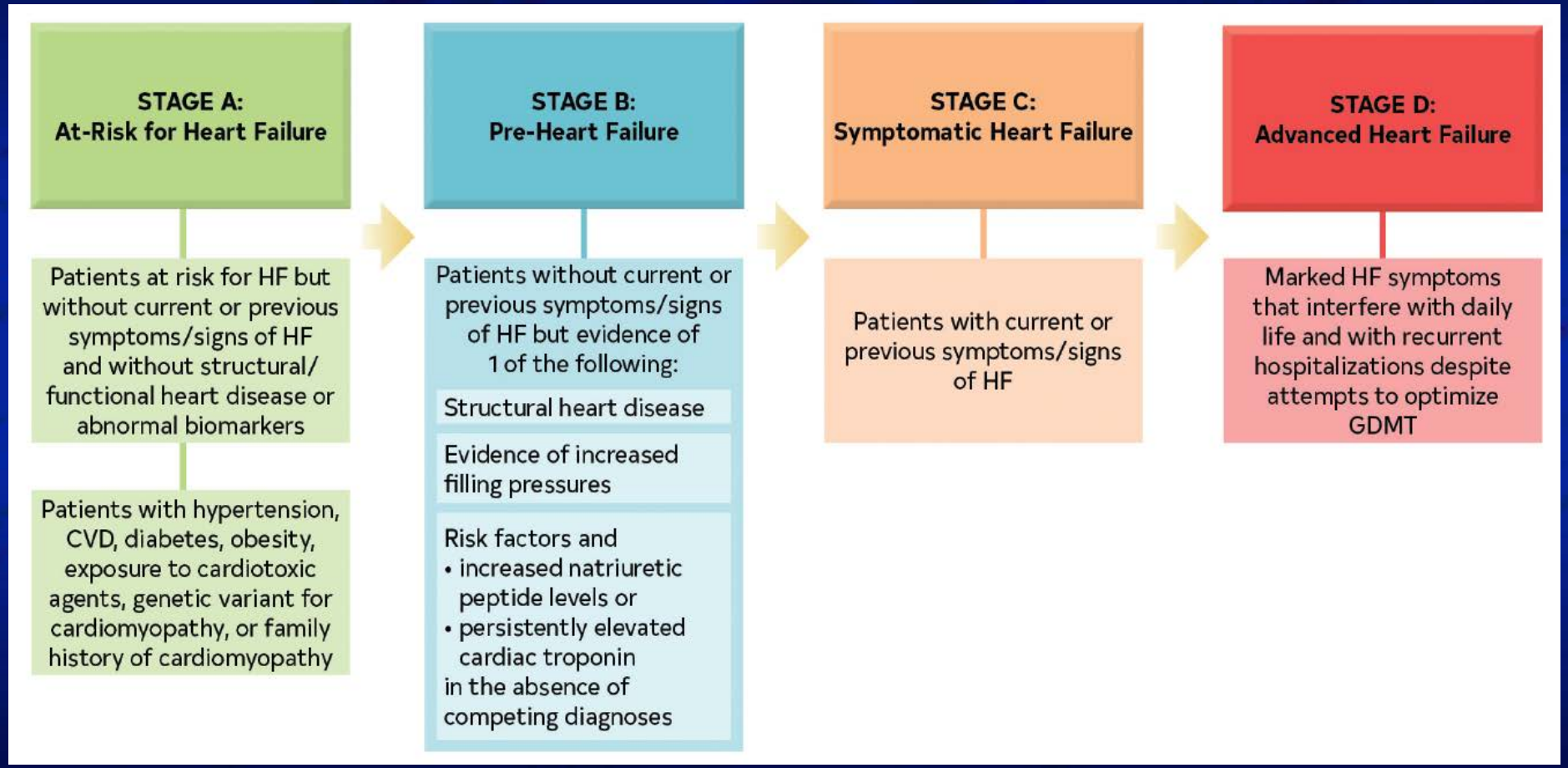
Pieroni et al. *J Am Coll Cardiol* 2021;77:922-36.

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.

ACC/AHA Heart Failure Guidelines



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

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.

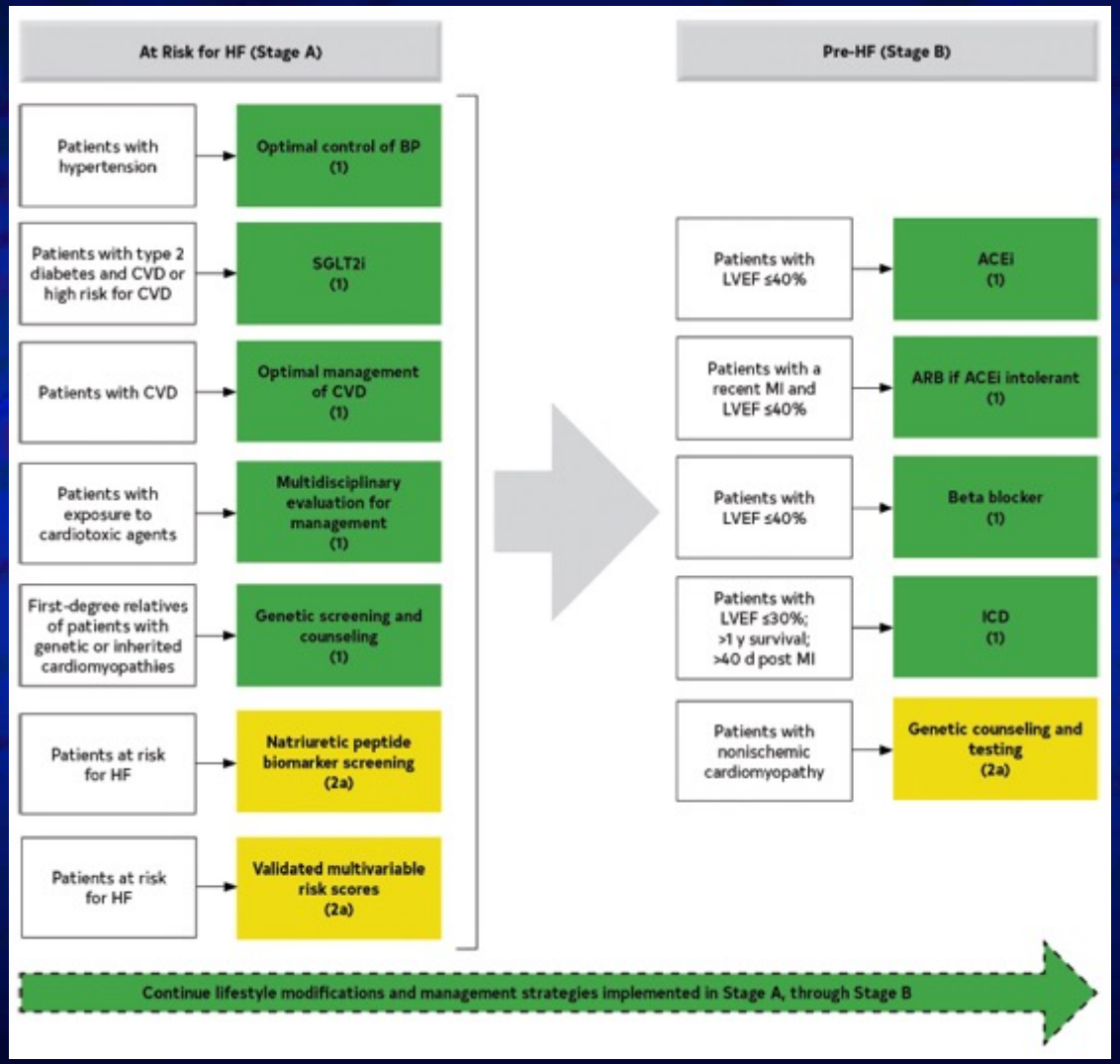
Heidenreich et al. *Circulation*. 2022;145:e895-e1032.

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)

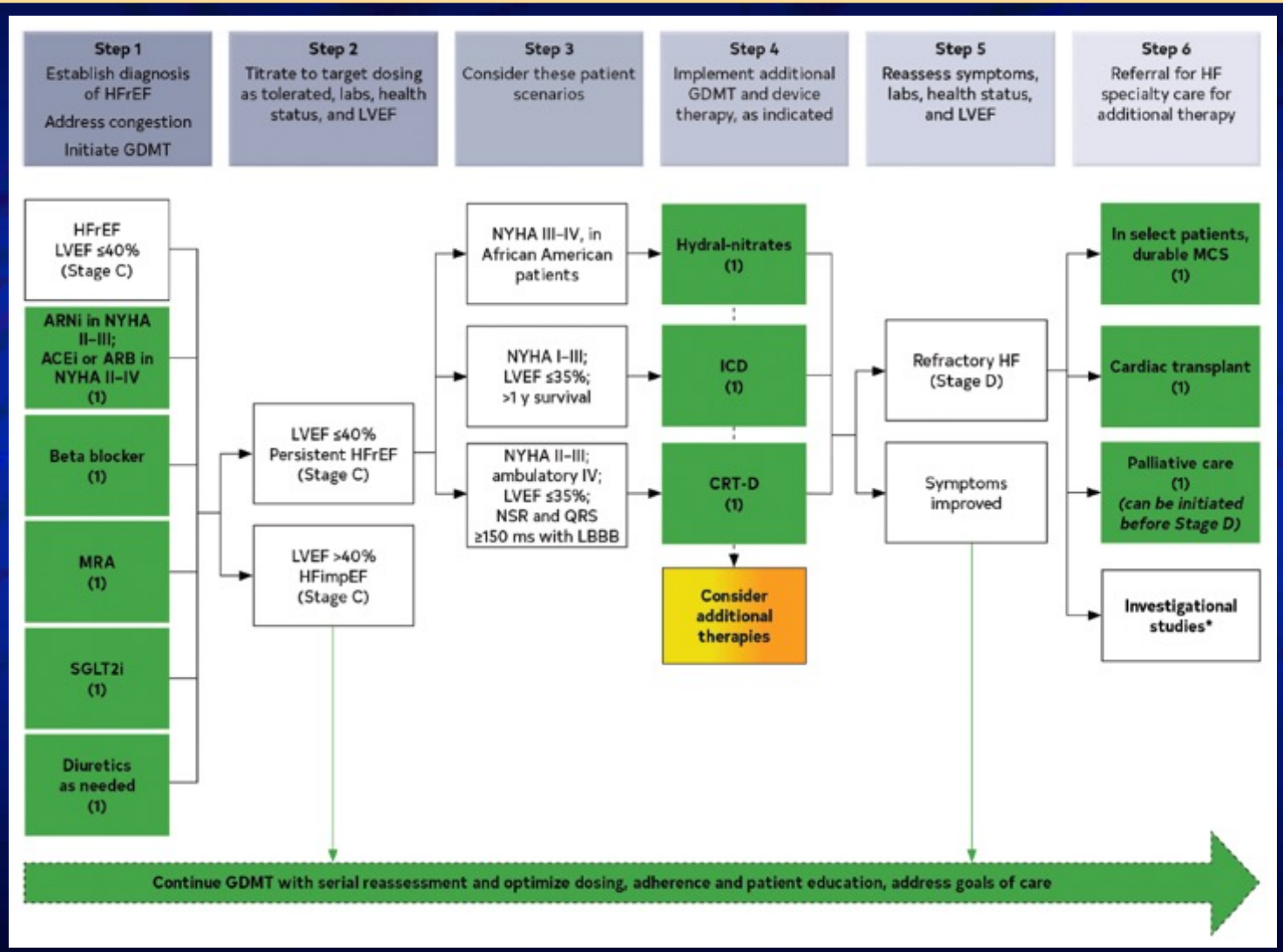
Heidenreich et al. *Circulation*. 2022;145:e895-e1032.

ACC/AHA Heart Failure Guidelines



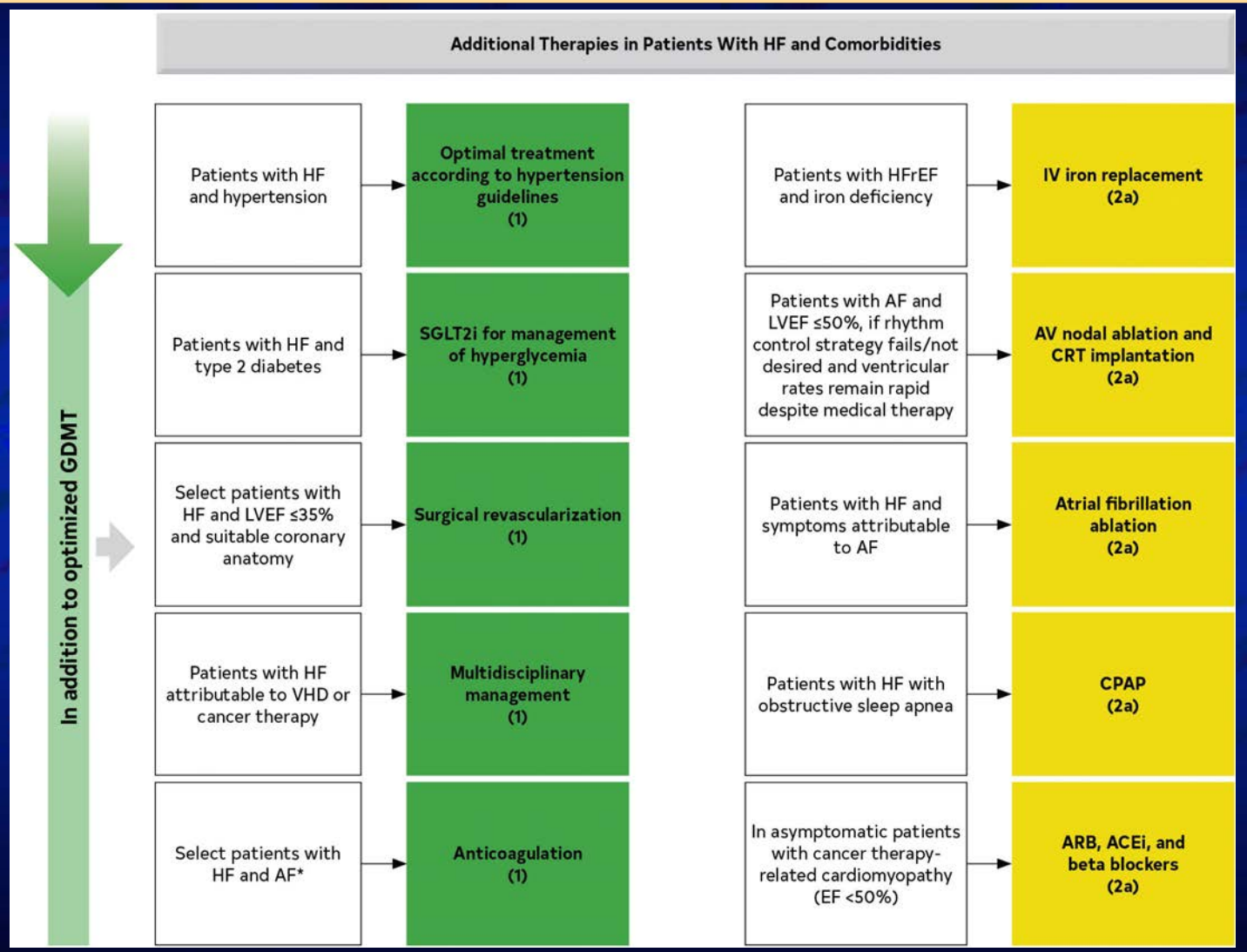
Heidenreich et al. *Circulation*. 2022;145:e895-e1032.

Heart Failure with Reduced Ejection Fraction



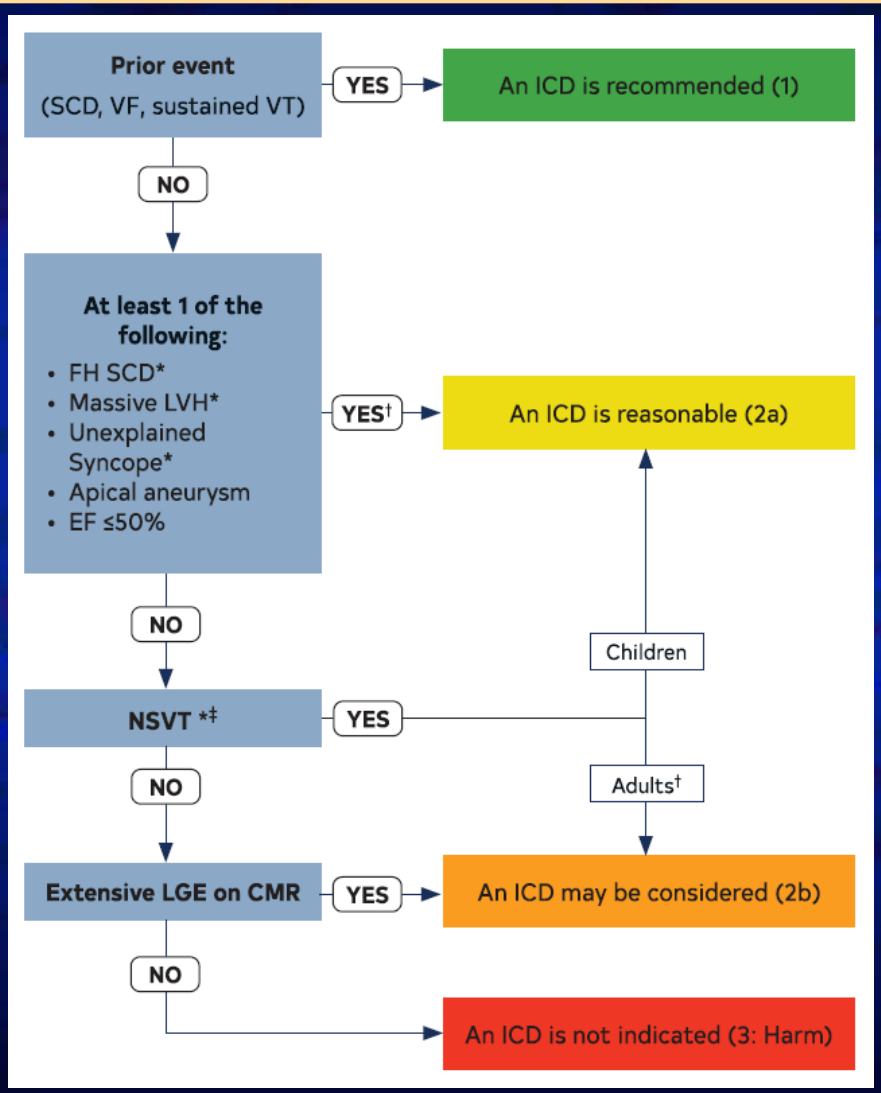
Heidenreich et al. *Circulation*. 2022;145:e895-e1032.

ACC/AHA Heart Failure Guidelines



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

Hypertrophic Cardiomyopathy



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

Lymphedema in Fabry Disease

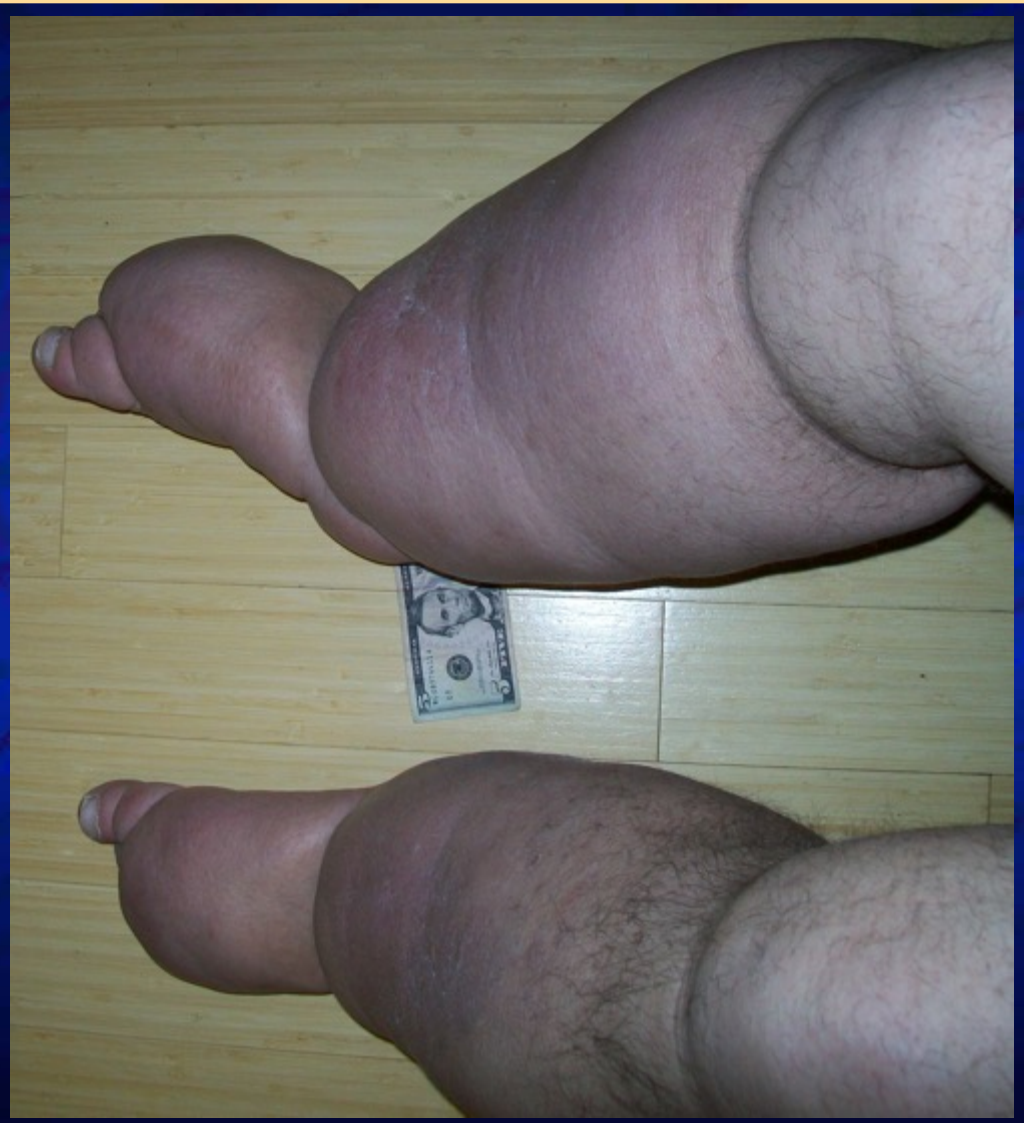
Prevalence of lymphedema among Anderson-Fabry disease patients: A report from the Fabry registry

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.

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

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.

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

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***

John Jefferies
Email: johnljefferiesmd@gmail.com