

Malattia di Anderson-Fabry

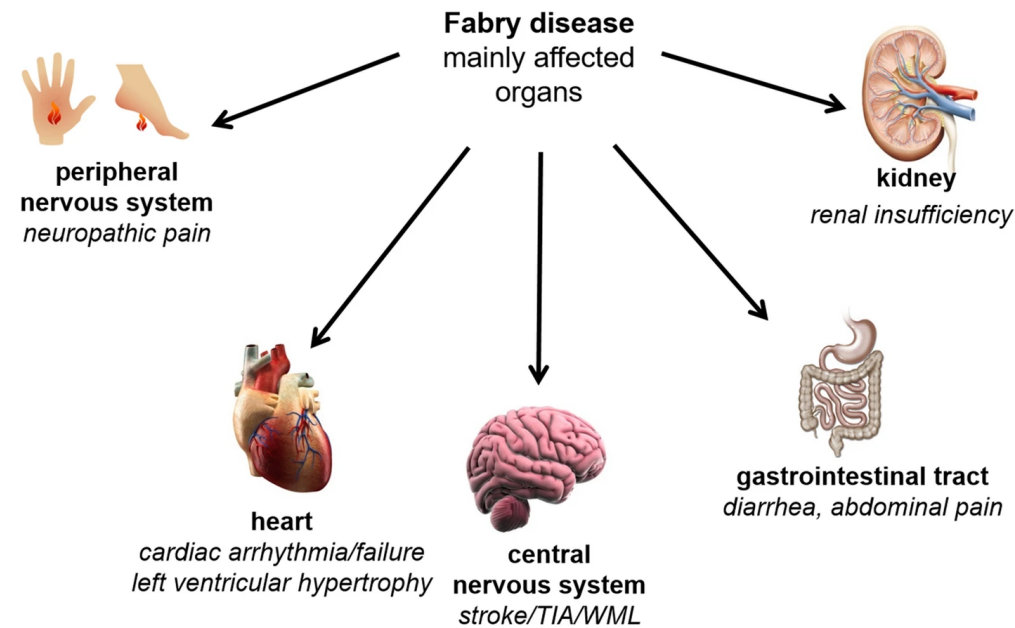
Diagnosi

Alessia Argirò



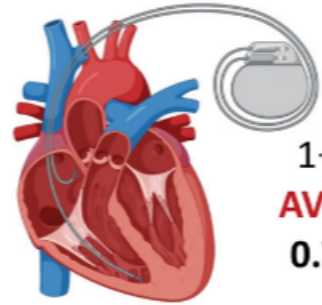
FABRY DISEASE

- Pan-ethnic,
- X-linked lysosomal storage disorder
- caused by pathogenic variants in the *GLA* gene → reduced α -galactosidase A (α -Gal A) enzyme activity.
- Accumulation of lysosomal globotriaosylceramide (Gb3) and related globotriaosylsphingosine (lyso-Gb3 deacylated form of Gb3) in affected tissues, including the heart, kidneys, vasculature, and peripheral and central nervous system.



Pieroni et al. Jacc 2021
Lender et al. Drugs (2021)

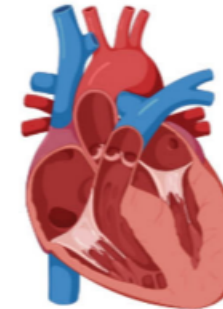
Prevalence: 1 in 40,000 and 1 in 117,000



3 Studies including
1,033 Patients Screened
AVB/SND Requiring PMK:
0.70% (95%CI 0.30-1.40)



15 Studies including
1,108,793 Patients Screened
Newborns:
0.01% (95%CI 0.002-0.079)

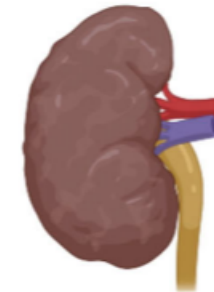


26 Studies including
10,080 Patients Screened
Hypertrophic Cardiomyopathy
1.20% (95%CI 0.80-1.80)

Prevalence of Fabry disease in Screening Studies



3 Studies including
904 Patients Screened
Small-Fiber Neuropathy:
1.00% (95%CI 0.30-3.40)

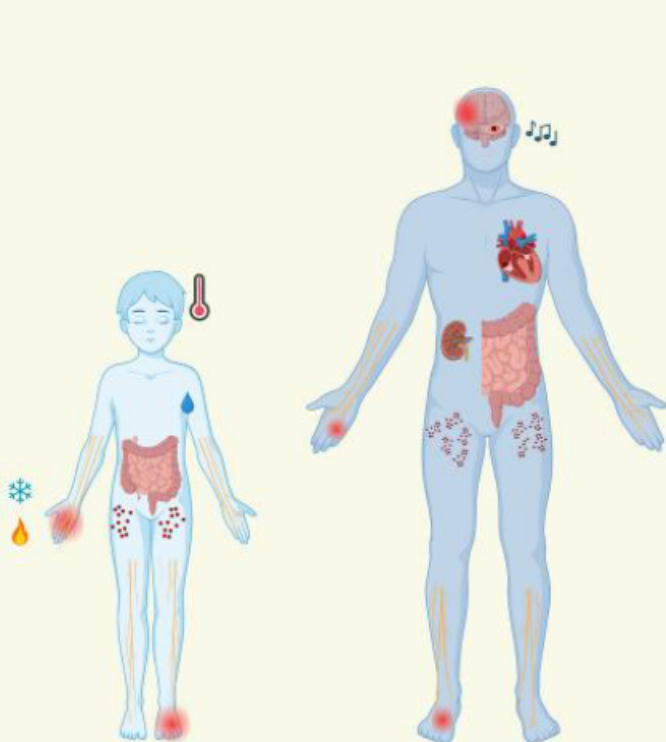


38 Studies including
62,050 Patients Screened
End-Stage Renal Disease:
0.30% (95%CI 0.20-0.40)



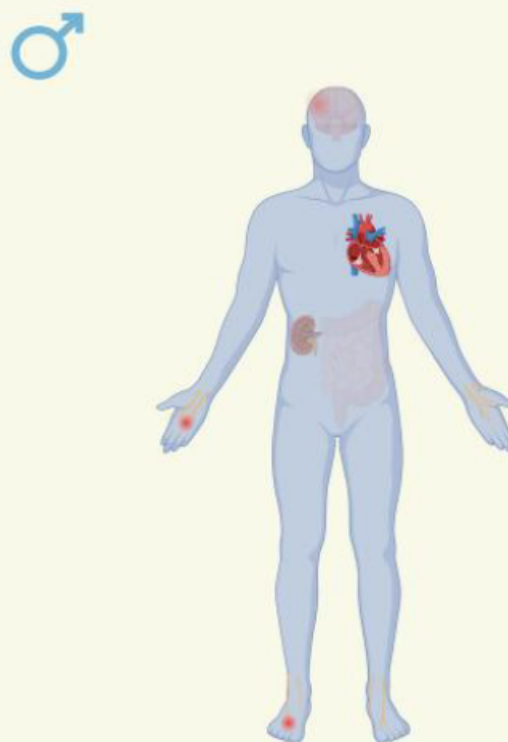
25 Studies including 15,295
Patients Screened
Stroke:
0.70% (95%CI 0.50-1.00)

Monda et. Al circulation genomics
and precision medicine



Classic phenotype

- Absent-very low (<5% of normal) alpha-Gal A activity
- High LysoGb3 plasma levels
- Childhood onset with GI symptoms, neuropathic pain, fever, hypohidrosis, angiokeratomas, hearing loss, corneal opacities (cornea verticillata)
- Development of multi-organ (heart, kidneys, CNS) involvement during adolescence and early adulthood



Non-Classical phenotype

- Low (but >5% of normal) alpha-Gal A activity
- Moderately increased LysoGb3 plasma levels
- 3rd-4th decade onset
- Main cardiac phenotype
- Mild involvement of other tissues possible
 - Proteinuria and eGFR reduction
 - GI symptoms
 - Neuropathic pain

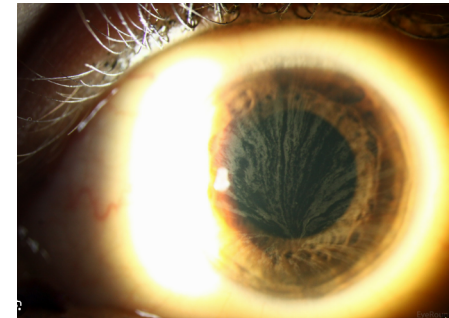


Female heterozygotes

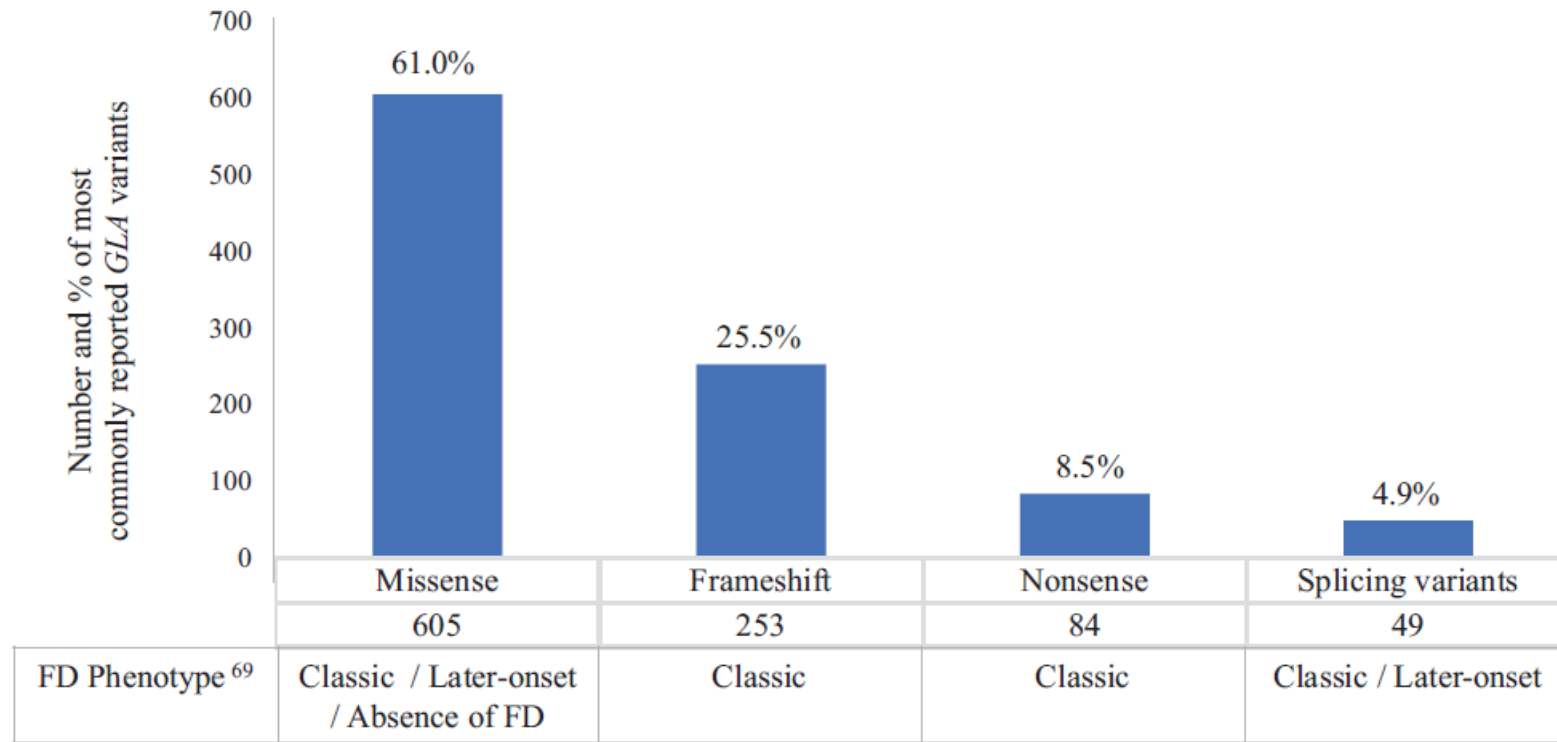
- Variable (low to normal) alpha-Gal A activity
- Normal-moderately increased LysoGb3 plasma levels
- Usually 3rd-4th decade onset
- Phenotype ranging from asymptomatic to severe as in affected male relatives due to random X-inactivation, DNA methylation, other epigenetic factors
- Prevalent cardiac phenotype with wide range of other organs involvement

Cardiac and extra-cardiac red flags for Fabry disease

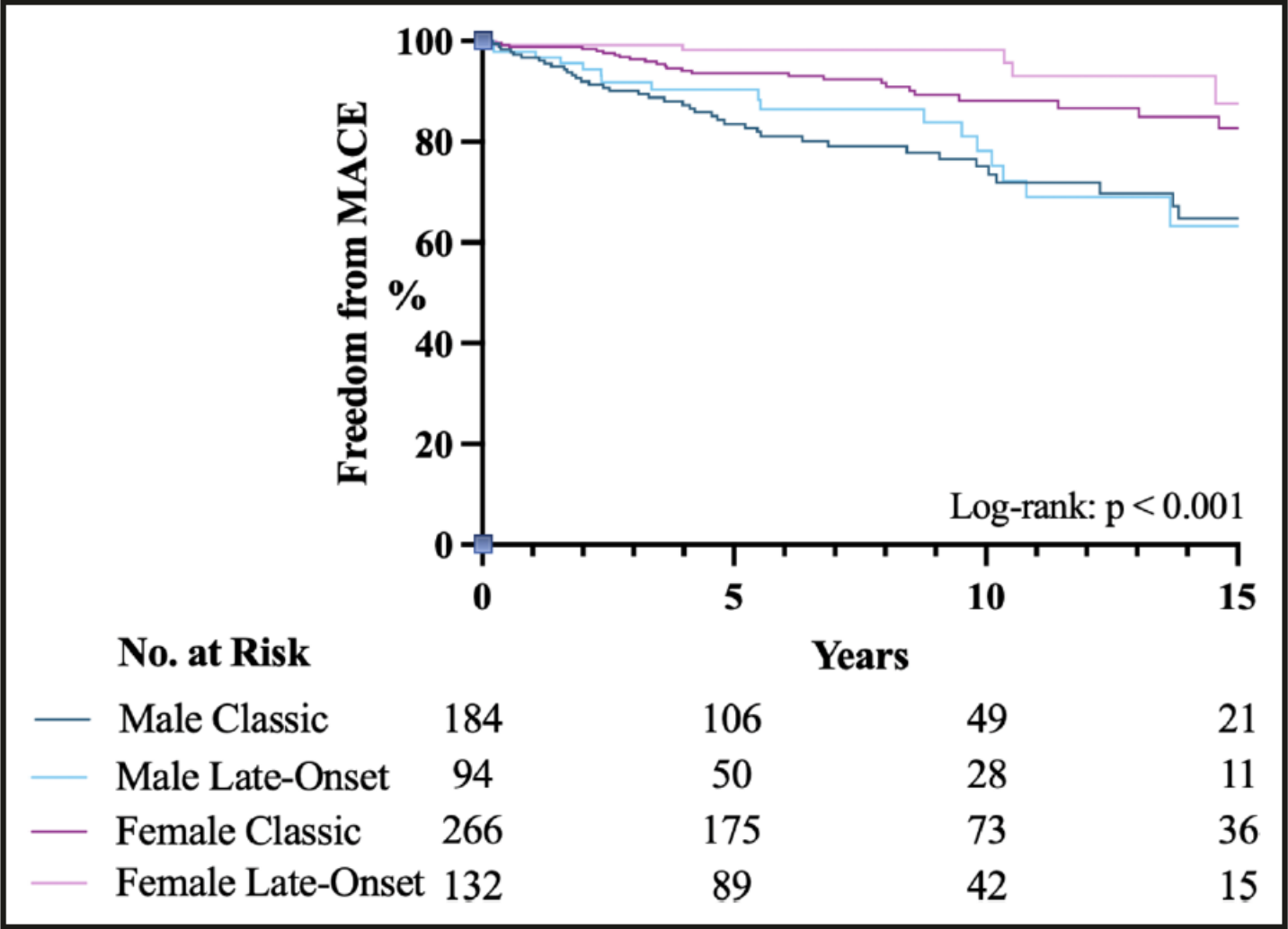
Extra-Cardiac Red Flags			Cardiac Red Flags		
Presenting Decades of Age	Any time	Family history of renal failure and/or stroke	Family history of LVH, particularly if no evidence of male-to-male transmission	History	Diagnostic Tool
	1–2	Neuropathic pain			
	1–2	Gastrointestinal symptoms	Short PQ interval [†]	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		



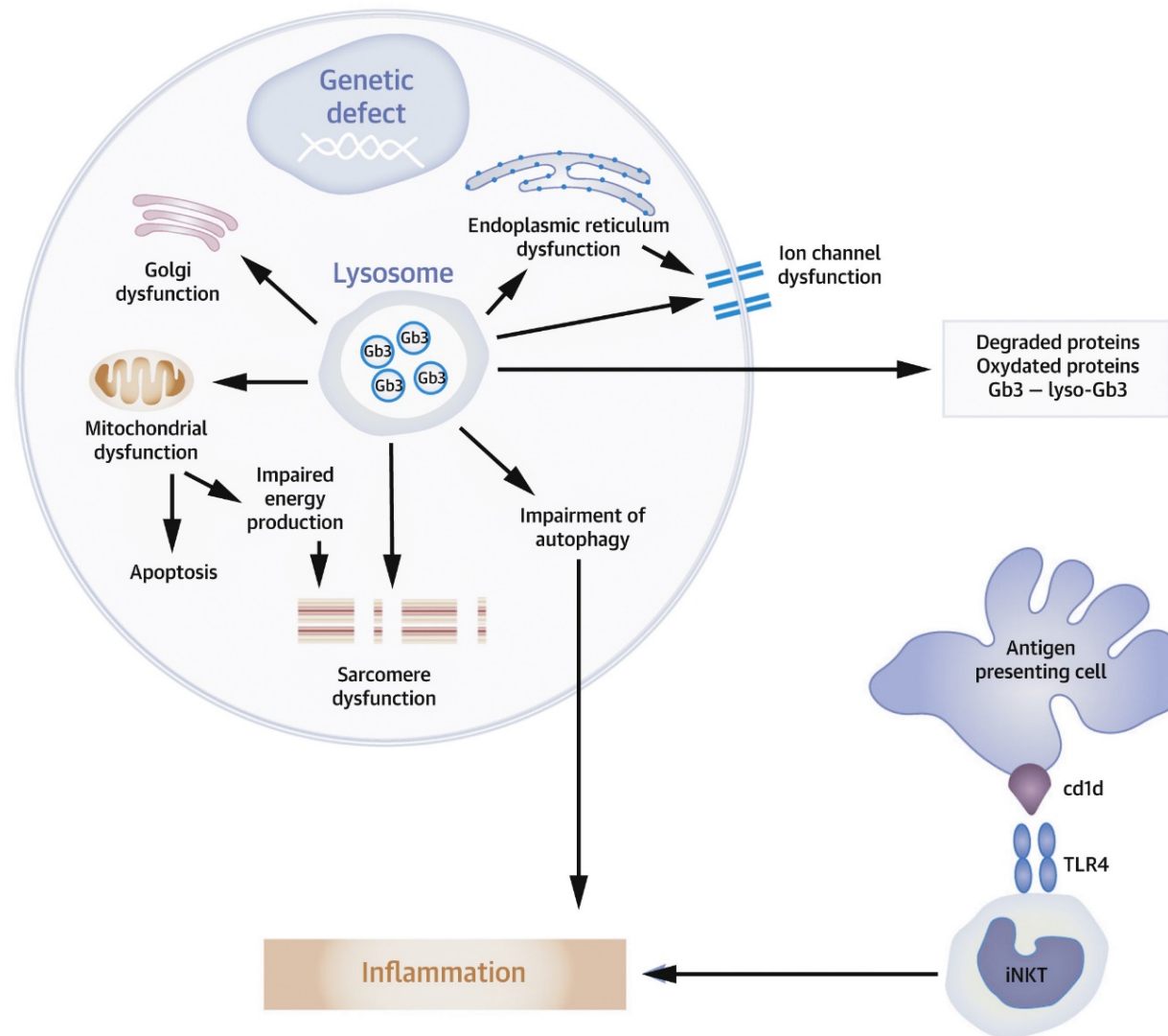
Genetics of Fabry disease



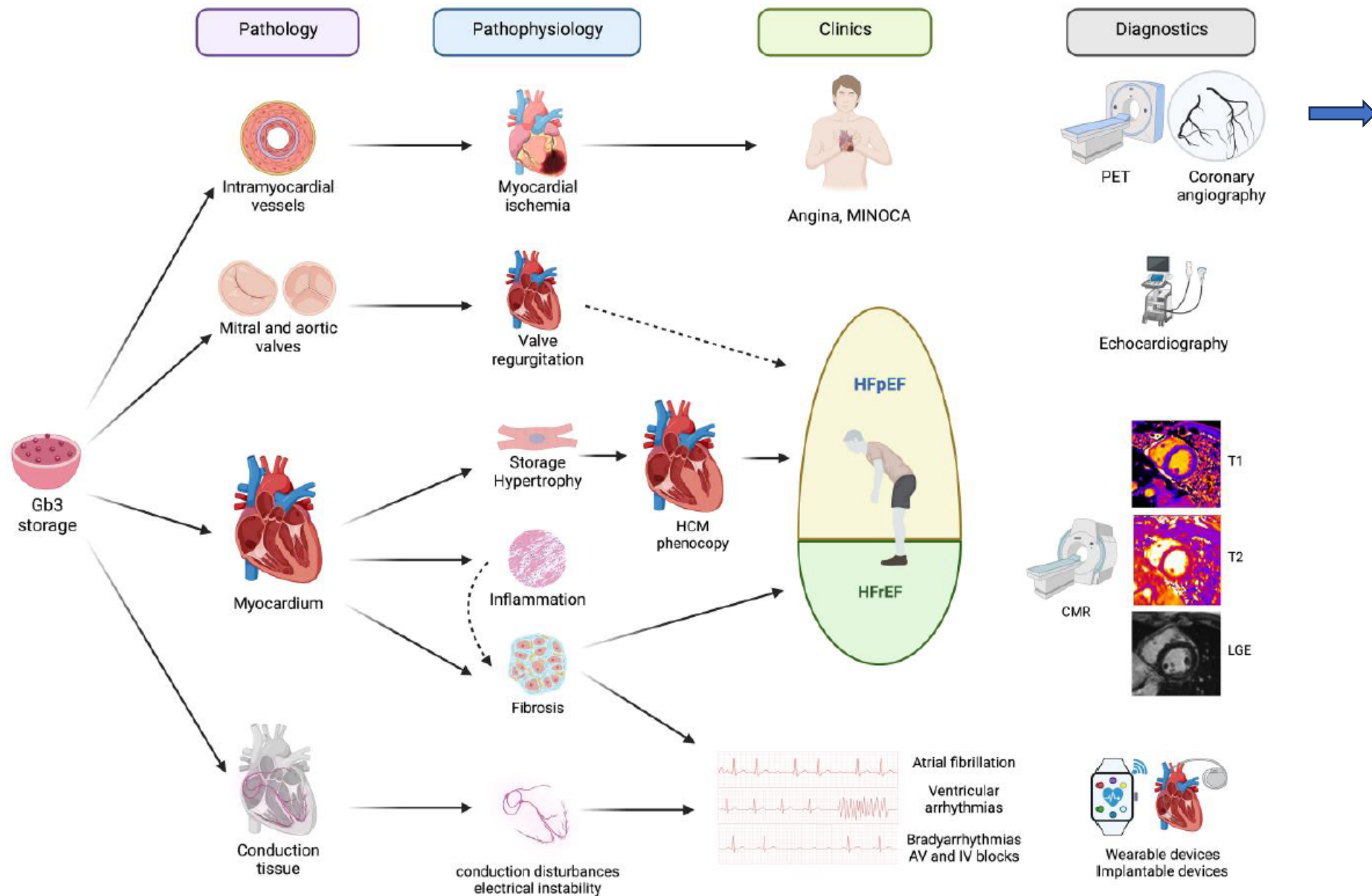
Different natural history of the disease across variants and sex



Pathophysiology of Fabry disease



invariant natural killer T-cells



INOCA
0.15%
(1/663)

Immune-Mediated Myocarditis in Fabry Disease Cardiomyopathy

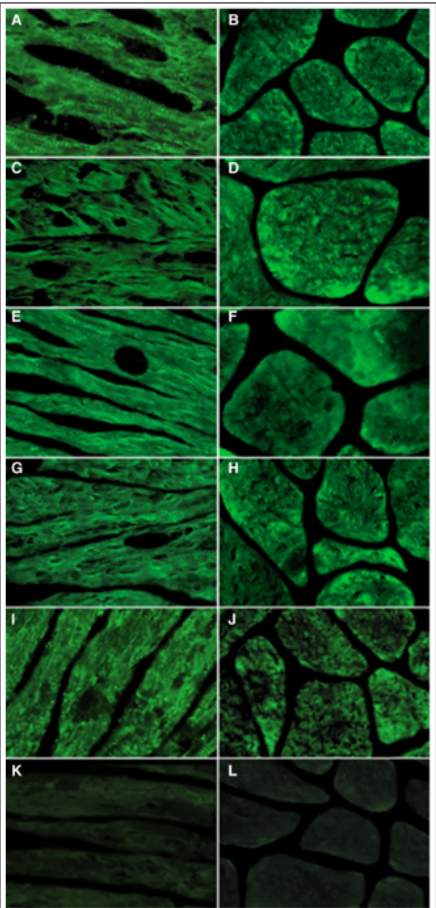
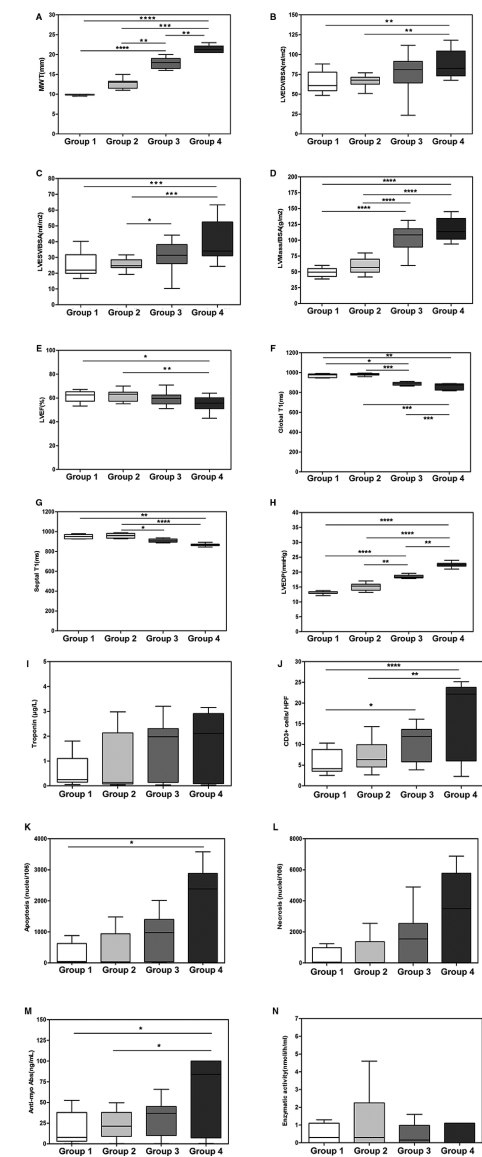
Andrea Frustaci, MD , Romina Verardo, PhD, Claudia Grande, PhD, Nicola Galea, MD, PhD, Pierluca Piselli, ScDMPH, Iacopo Carbone, MD, Maria Alfarano, MD, Matteo Antonio Russo, MD, and Cristina Chimenti, MD, PhD | [AUTHOR INFO & AFFILIATIONS](#)

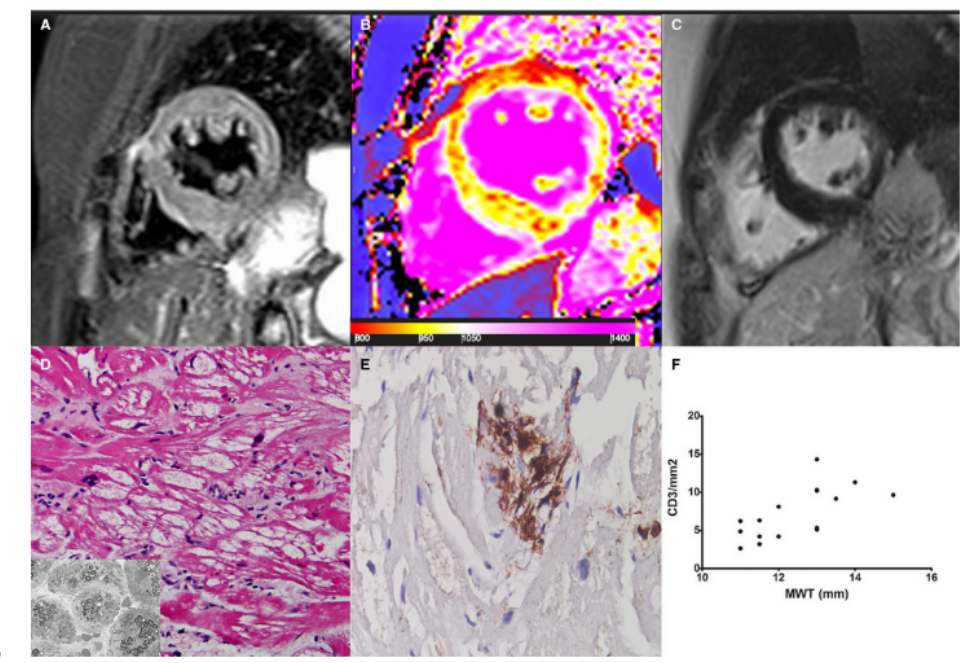
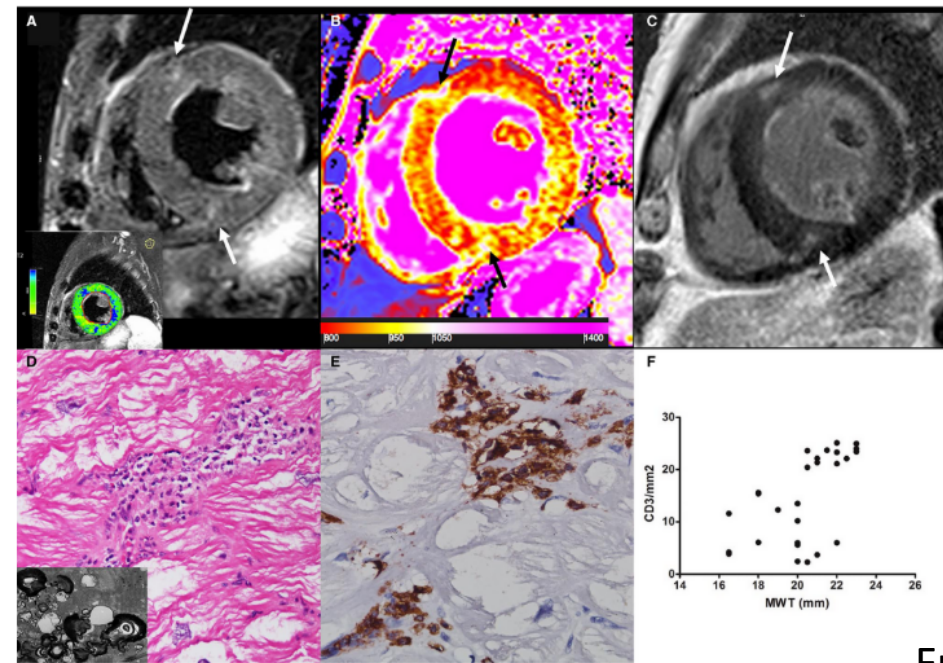
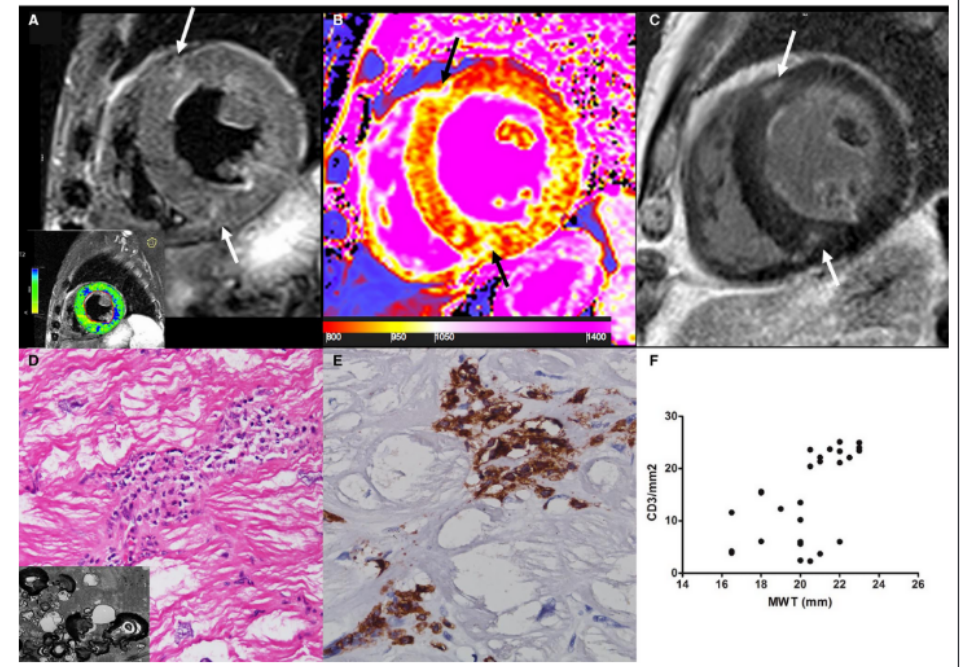
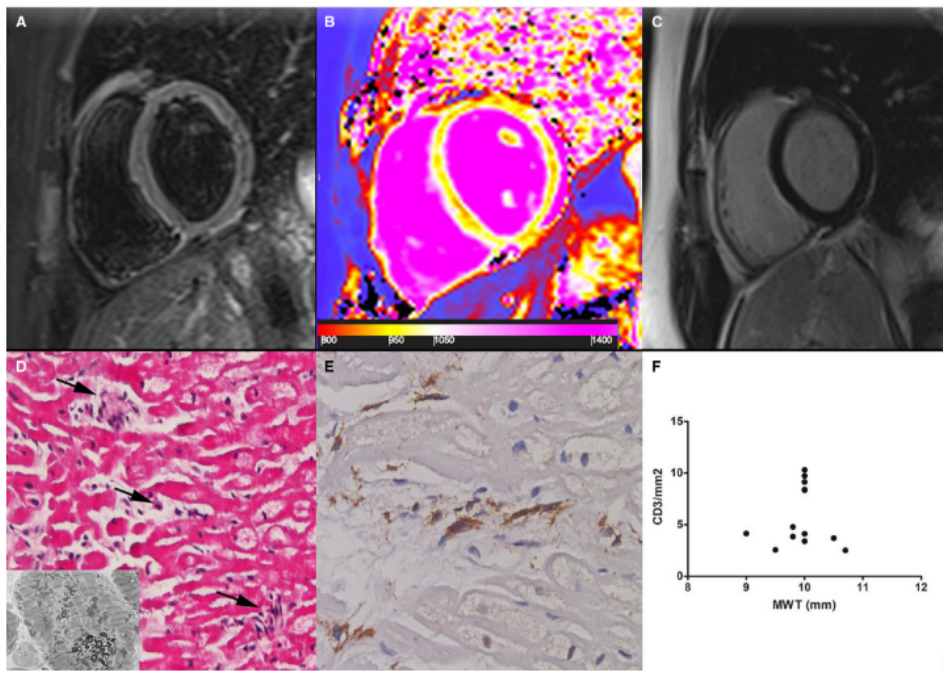
Myocarditis at histology in 48/78 (61%) patients (38% of group 1, 41% of group 2, 66% of group 3, and 72% of group 4).

Myocarditis was characterized by positive antiheart and antimyosin antibodies and negative polymerase chain reaction for viral genomes.

CD3⁺ cells/mm² correlated with myocyte necrosis, antimyosin autoantibody titer, and MWT

Cardiac magnetic resonance showed myocardial edema in 24 of 78 patients (31%): 0% of group 1, 23% of group 2, 37% of group 3, and 50% of group 4.





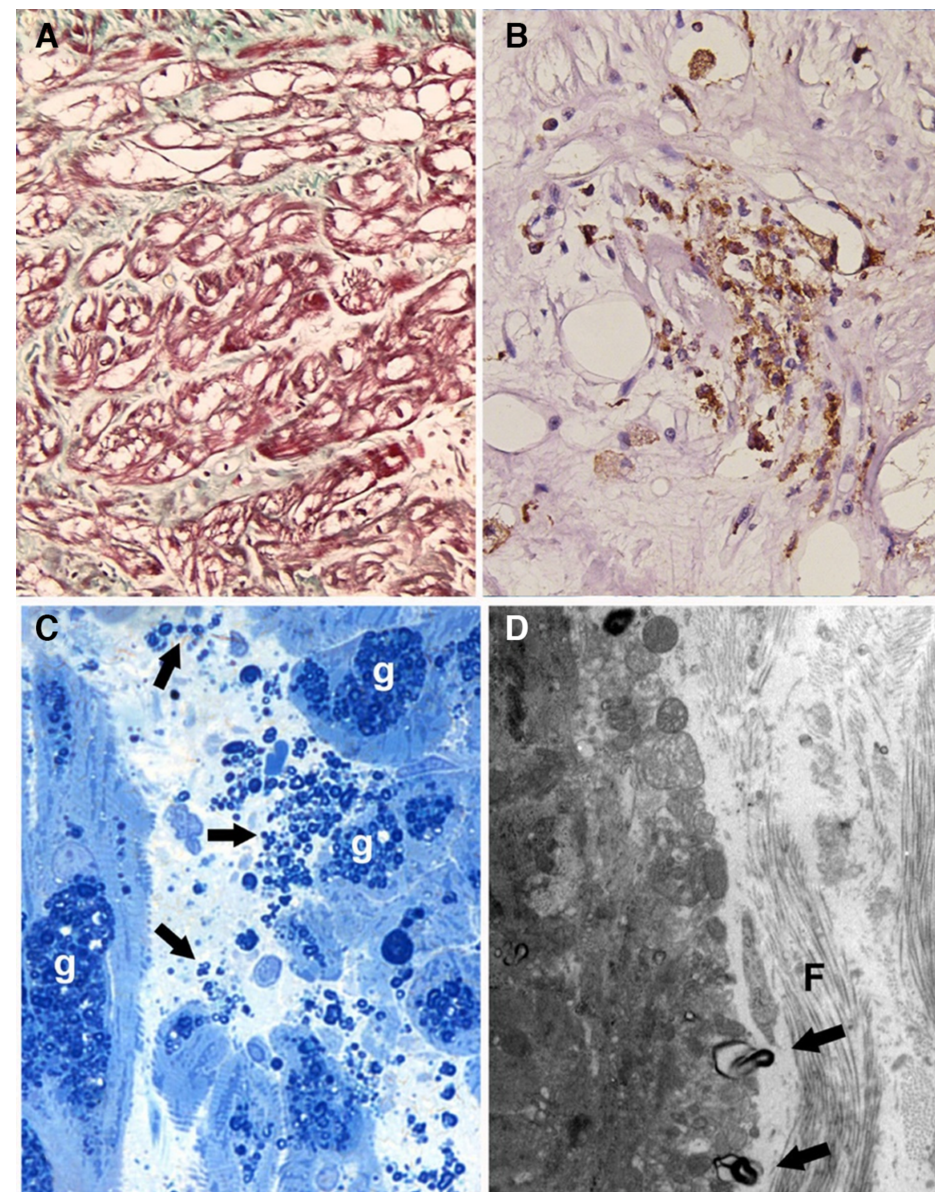
ORIGINAL RESEARCH

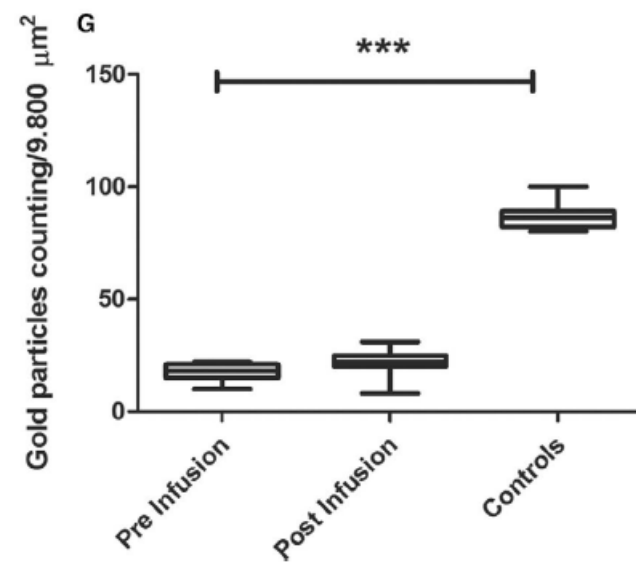
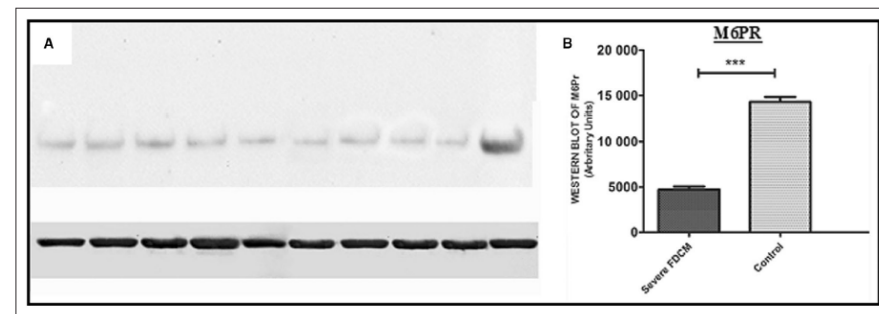
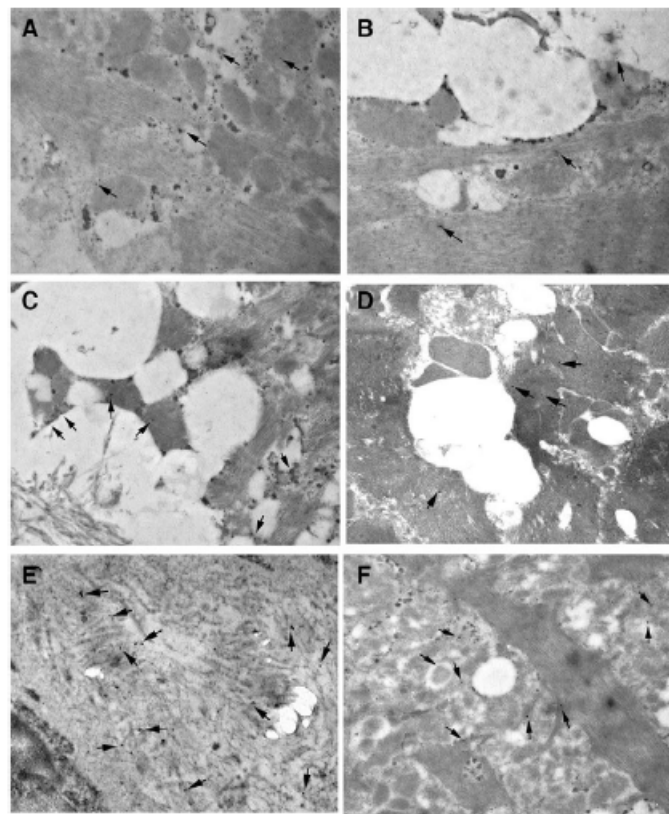
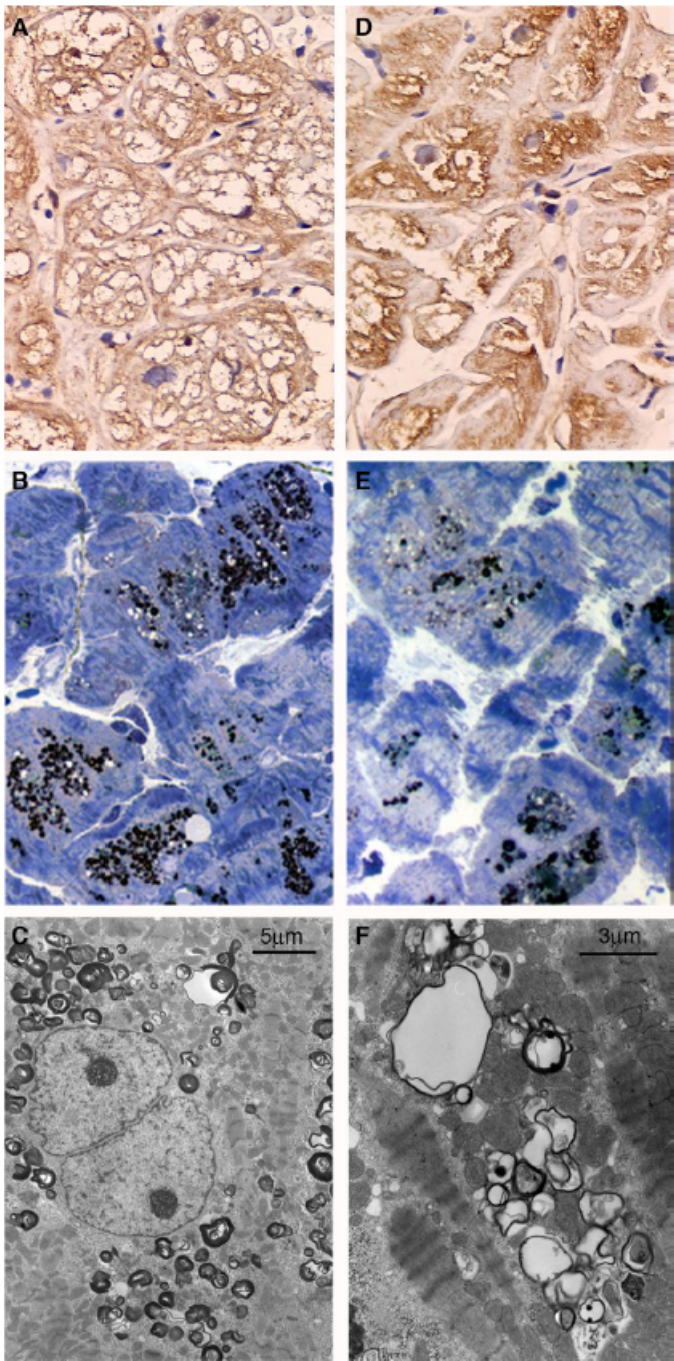
Fabry Cardiomyopathy: Myocardial Fibrosis, Inflammation, and Down-Regulation of Mannose-6-Phosphate Receptors Cause Low Accessibility to Enzyme Replacement Therapy

Andrea Frustaci , MD; Romina Verardo , PhD; Michele Magnocavallo , MD; Emanuela Frustaci , PhD; Matteo Antonio Russo , MD; Cristina Chimenti , MD

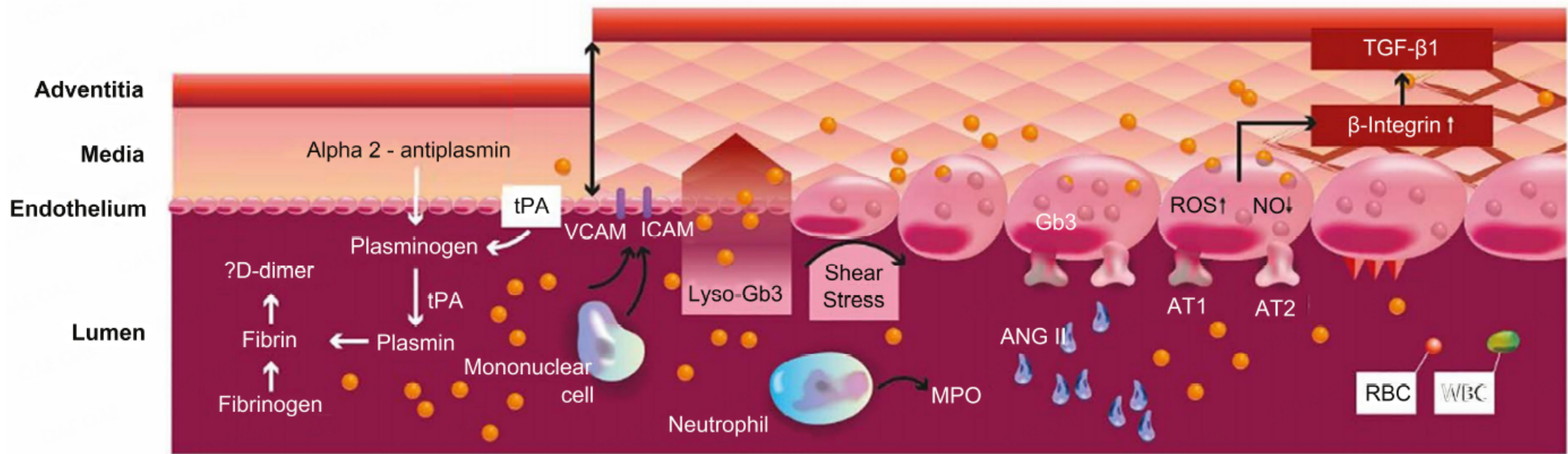
Table 2. Comparison Among Echocardiographic, Morphometric, and Enzymatic Data of Male Patients With Advanced Fabry Disease Cardiomyopathy and Male Controls

Characteristics	Advanced FDCM n=10	Controls n=10	P values
Age, y	45.0±7.3	47.9±7.2	NS
Echocardiography [†]			
MWT, mm	19.3±2.1	10.1±0.9	0.001
EF, %	59.2±5.2	62.4±4.5	NS
Morphometry			
Fibrosis, %	9.8±6.8	3.8±2.0	NS
Interstitial	5.0±2.2	3.1±1.5	NS
Replacement	4.3±3.3	0.8±0.6	0.03
Inflammation, n (%)	7 (70%)	0	0.003
Cardiomyocytes, %	80.7±6.6	90.0±3.8	NS
Other, %	9.5±2.2	6.2±2.7	NS
Myocardial enzymatic activity, nmol/h per mg*			
Before infusion	91.6±27.9	654.5±78.2	<0.001
After infusion	173.6±47.5	...	
IHC for α-Gal A, grade [†]			
Before infusion	0	2.8±0.4	<0.001
After infusion	0.5±0.5	...	
Lysosomal GB3 removal (%) [†]			
Before infusion	49.5±4.2	...	
After infusion	50.2±3.4	...	



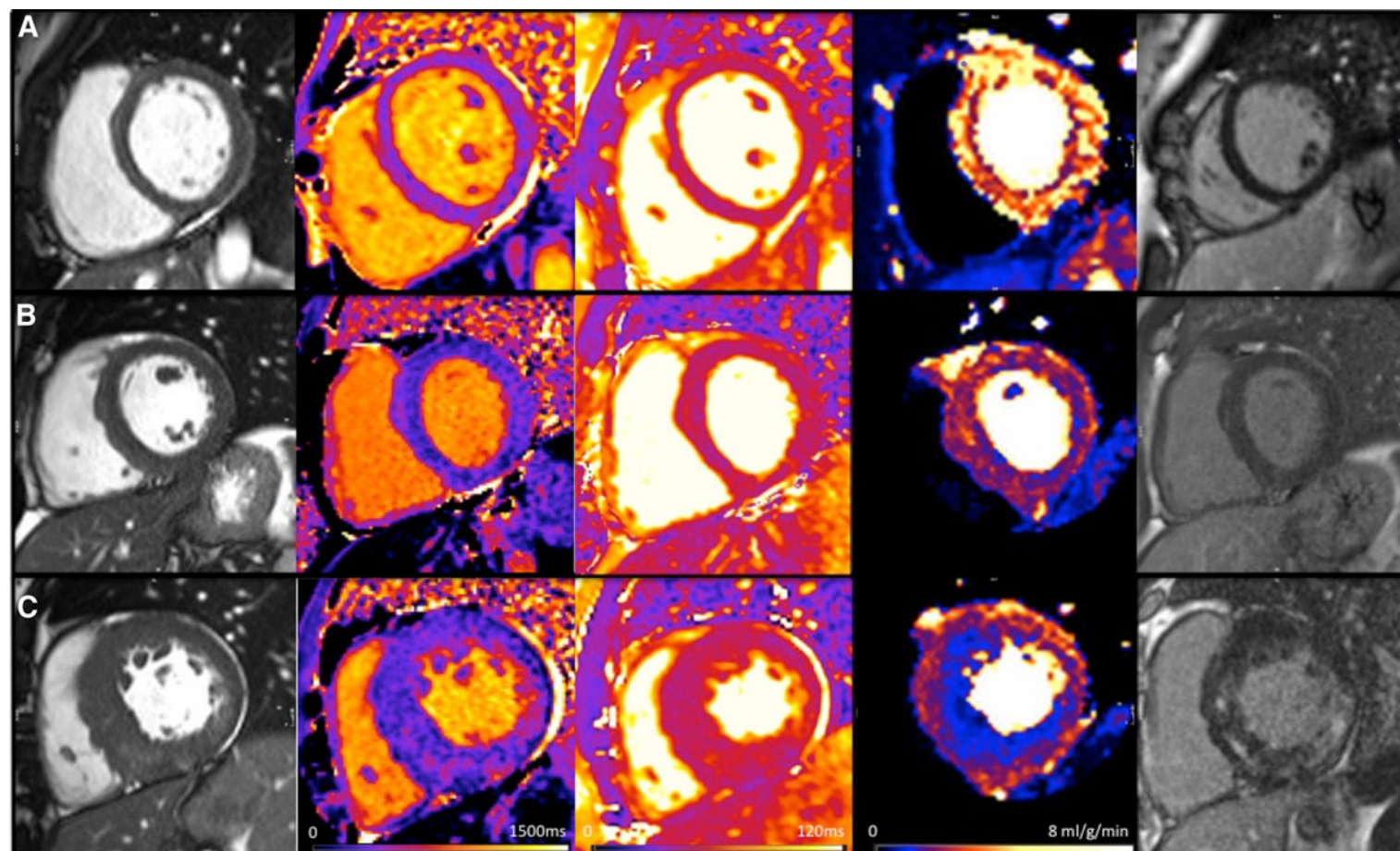


Pathogenesis of vasculopathy in FD



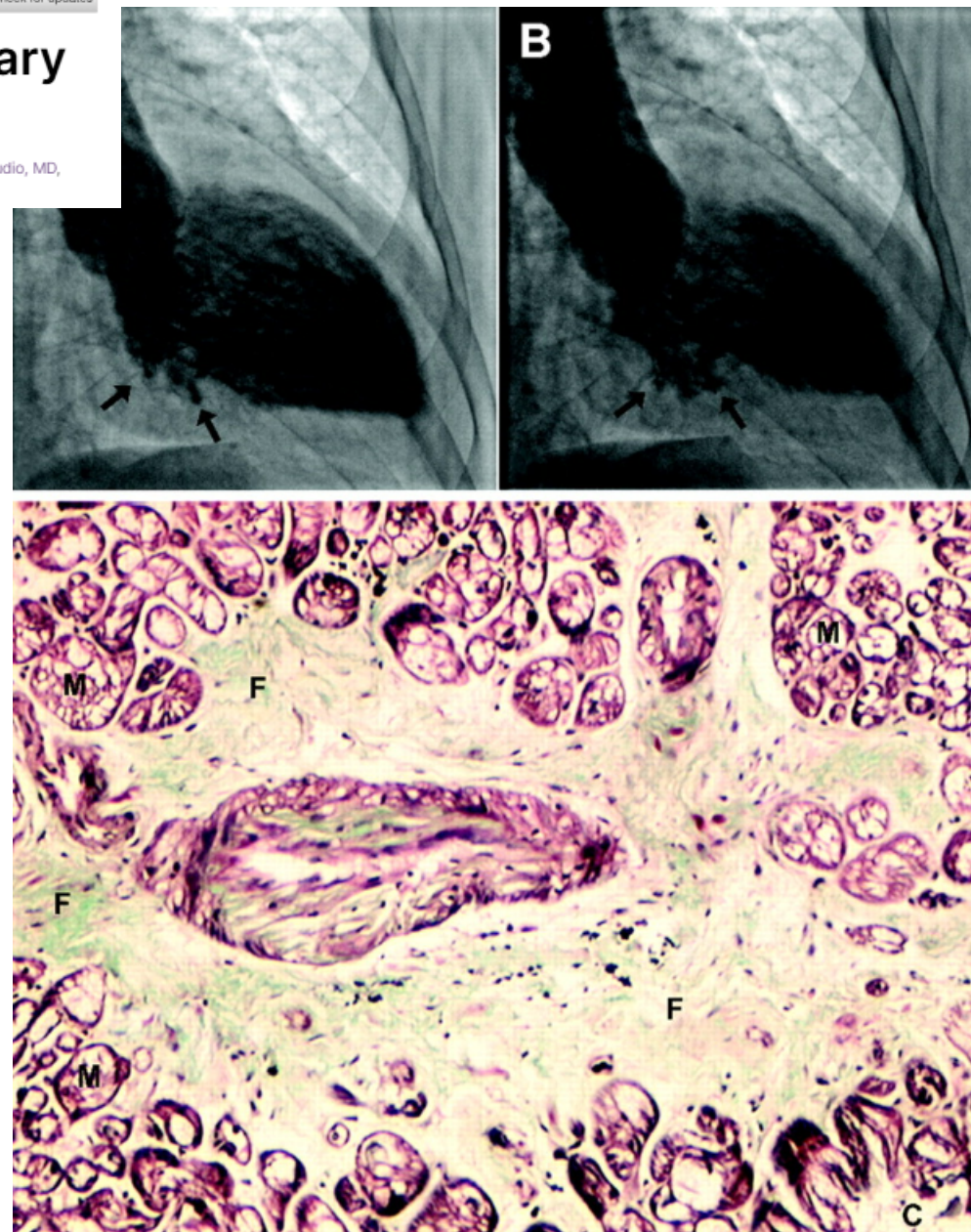
Quantitative Myocardial Perfusion in Fabry Disease

Kristopher D. Knott, MA, MBBS, Joao B. Augusto, MD, Sabrina Nordin, MBBS, Rebecca Kozor, PhD, Claudia Camaioni, MD, Hui Xue, PhD, Rebecca K. Hughes, MBBS, ... [SHOW ALL ...](#) , and James C. Moon, MD  | [AUTHOR INFO & AFFILIATIONS](#)



Angina in Fabry Disease Reflects Coronary Small Vessel Disease

Cristina Chimenti, MD, PhD, Emanuela Morgante, PhD, Gaetano Tanzilli, MD, Enrico Mangieri, MD, Giuseppe Critelli, MD, Carlo Gaudio, MD, Matteo A. Russo, MD, and Andrea Frustaci, MD | [AUTHOR INFO & AFFILIATIONS](#)



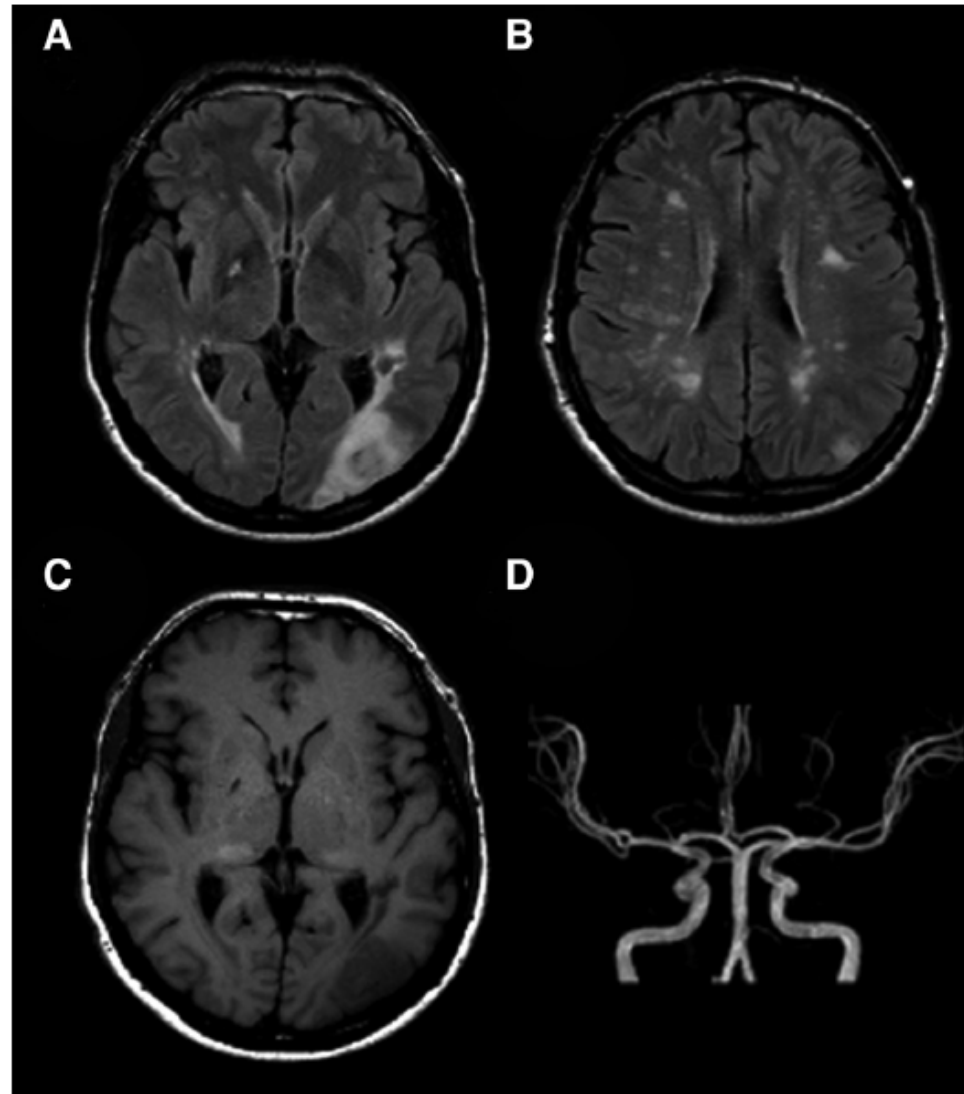
Neurological abnormalities in FD

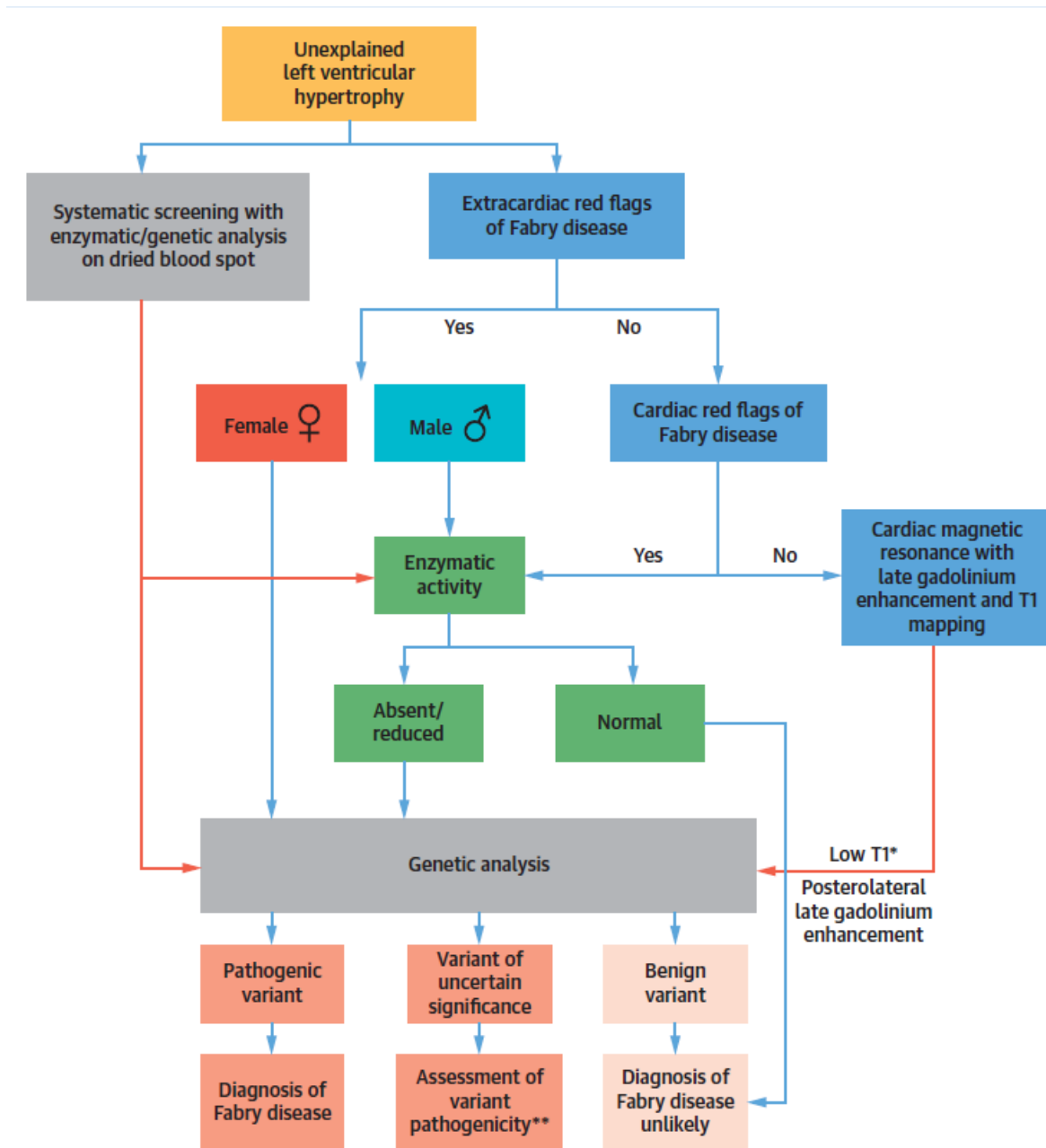
left acute temporo-parietal-
occipital
ischemic stroke and several
lacunar strokes

pulvinar
hyperintensity

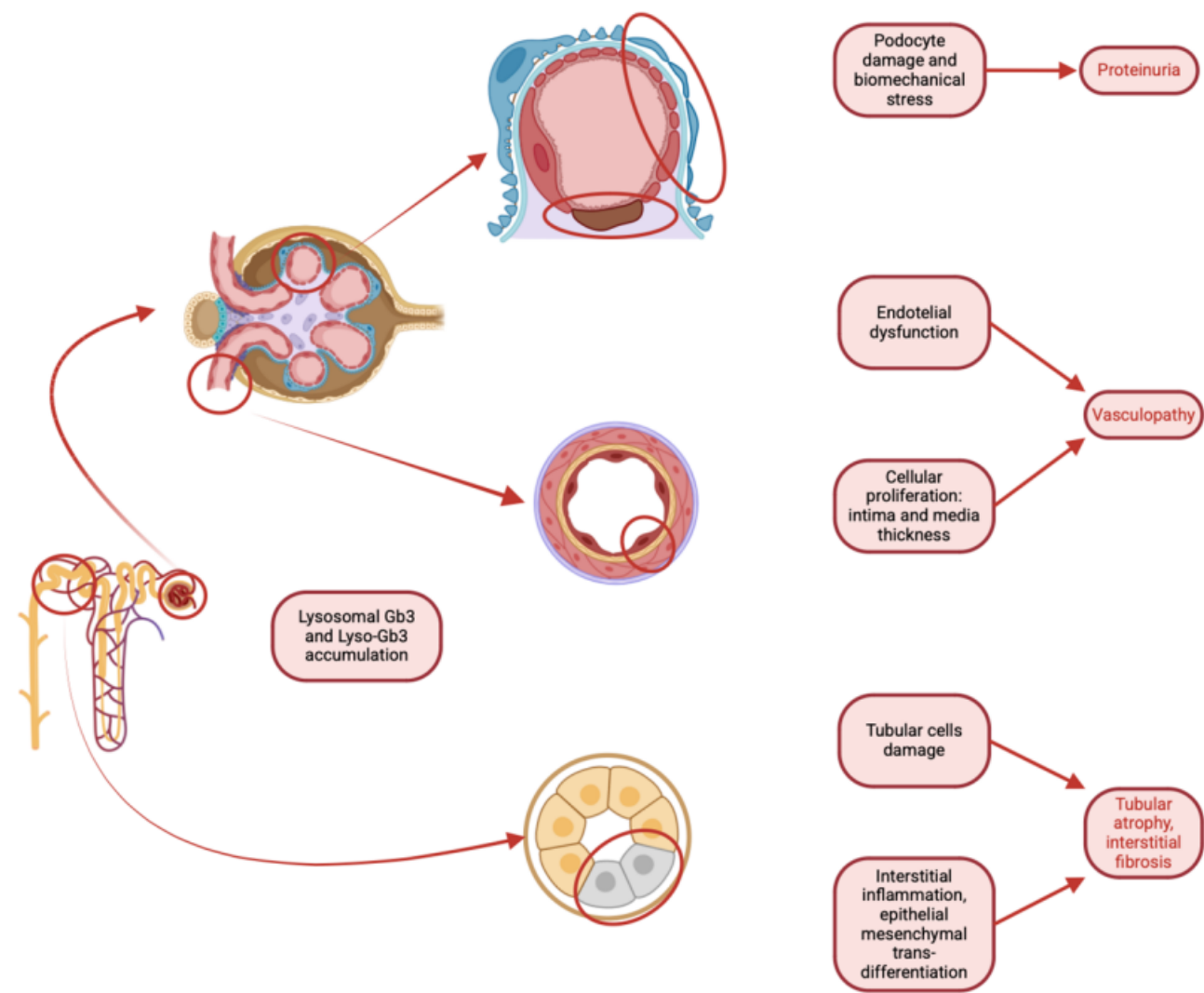
white matter
hyperintensities

basilar artery

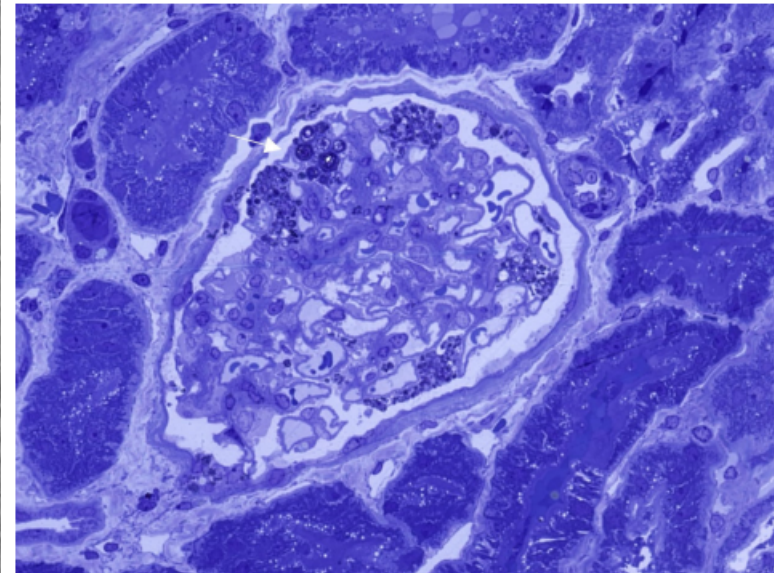
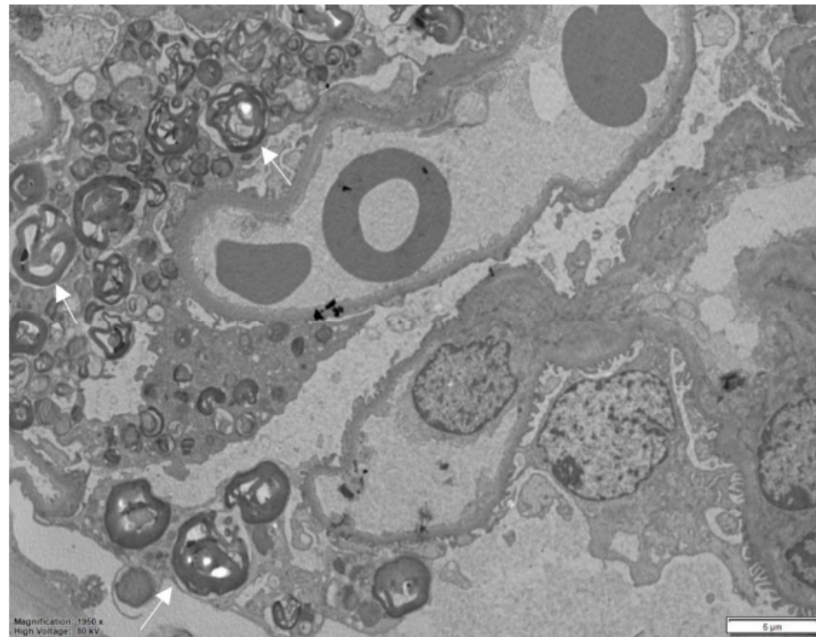
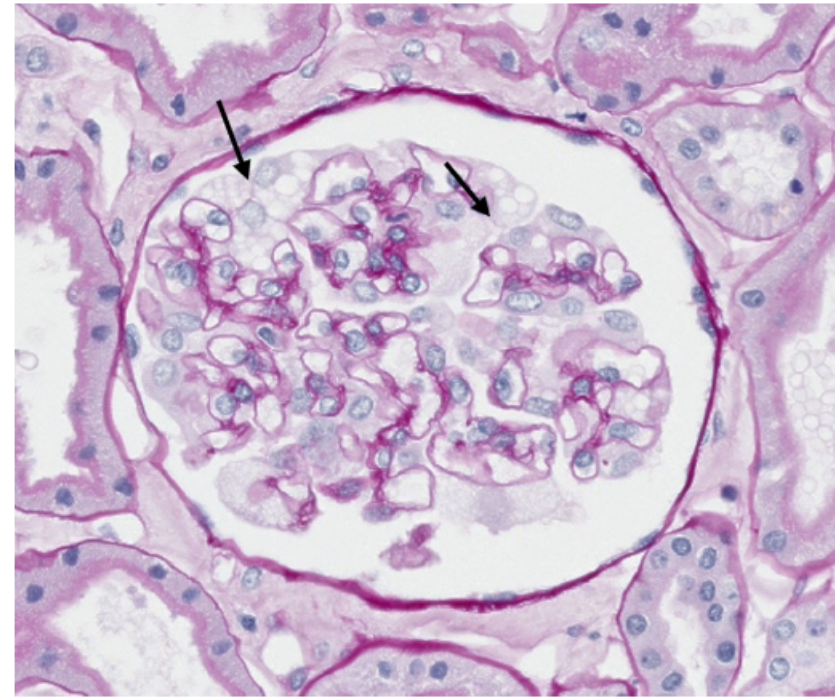
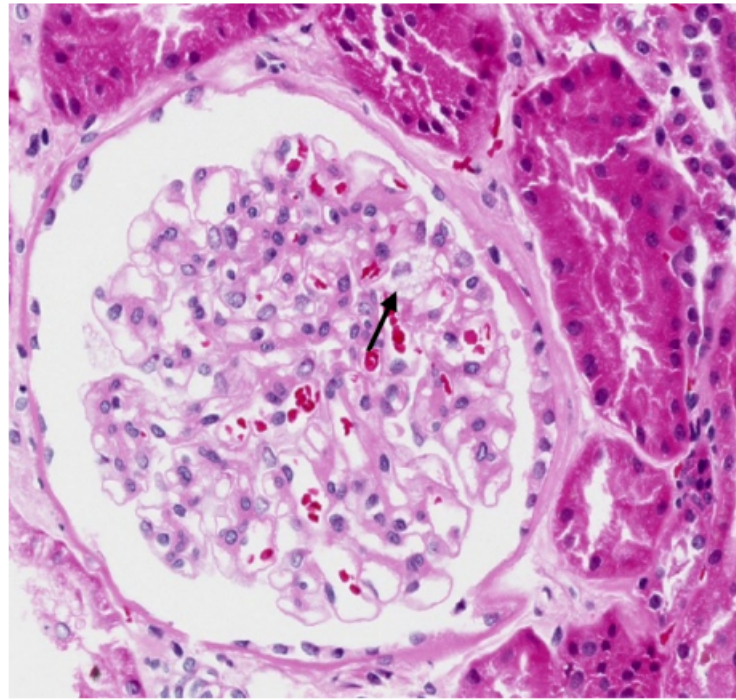




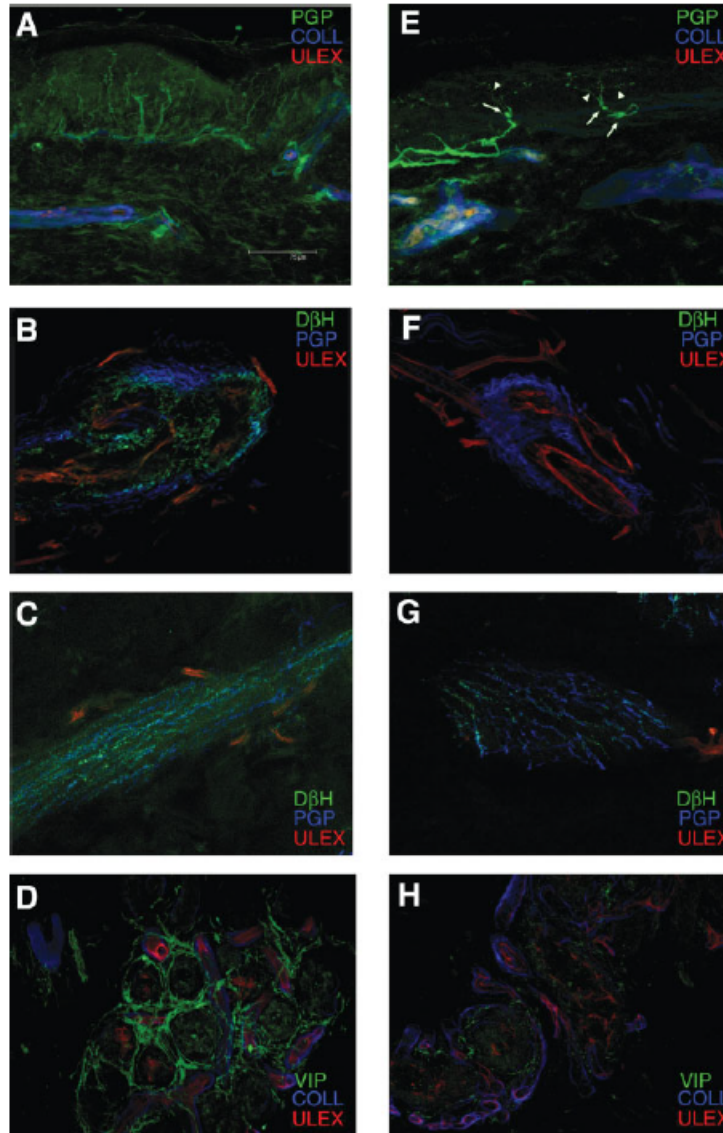
Renal involvement in Fabry disease



Renal biopsy



Small fiber neuropathy



reduced epidermal nerve fiber density

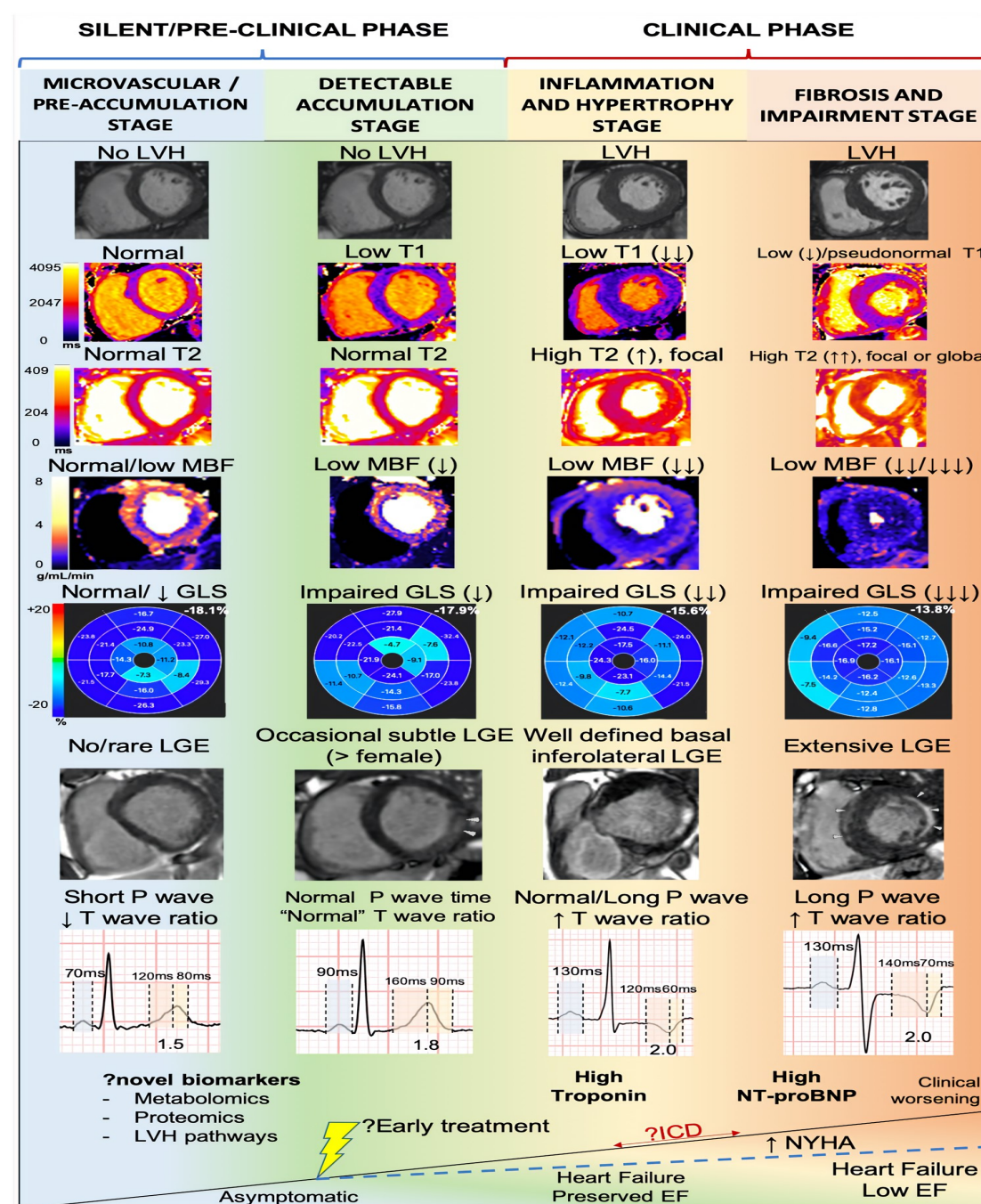
decrease of adrenergic nerve fibers

muscle erector pilorum

loss of cholinergic nerve fibers

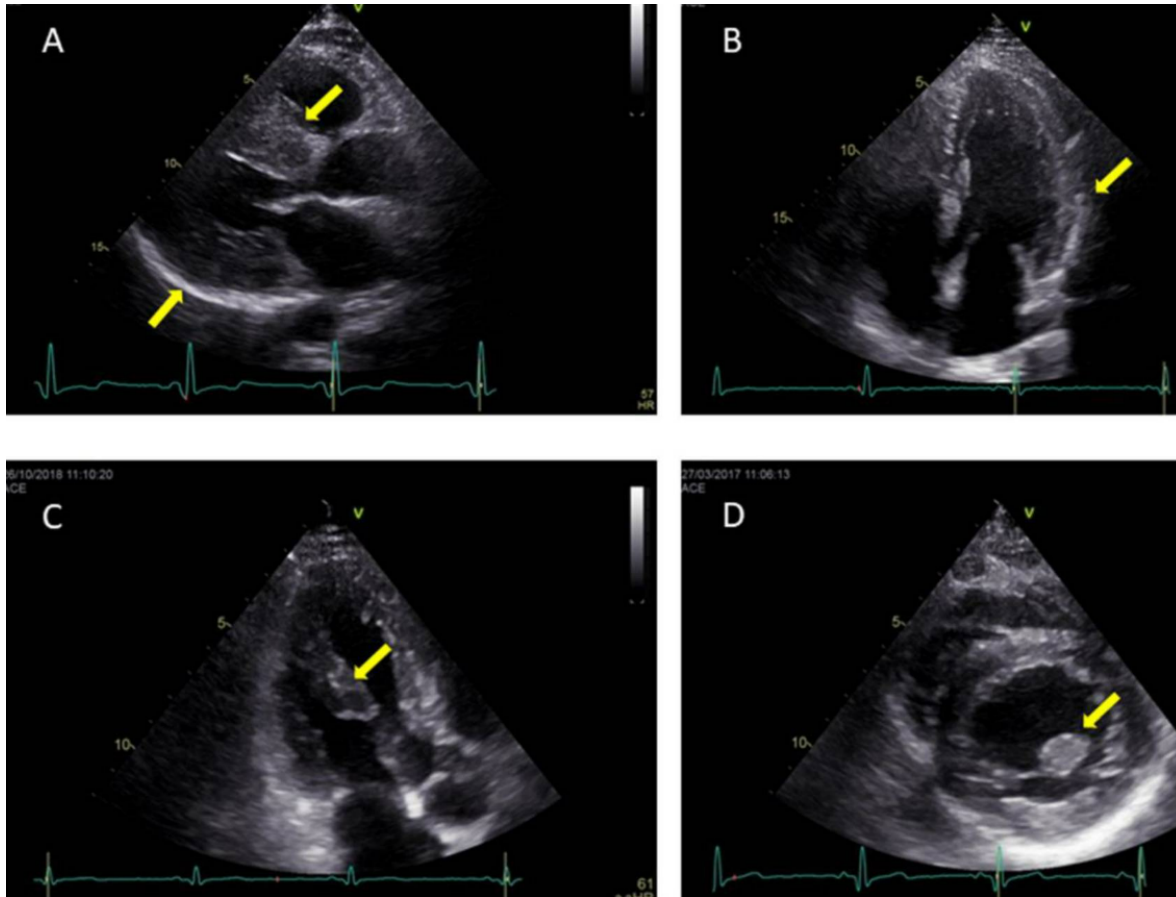
Take home messages

- Fabry disease is a rare condition and the prevalence increases in the presence of red flags
- It's characterized by a complex pathophysiology in which Gb3 accumulation, inflammation, and microvascular dysfunction concur to the tissue damage
- Bioptic exam of involved tissues may be needed in cases of VUSes/uncertain clinical involvement

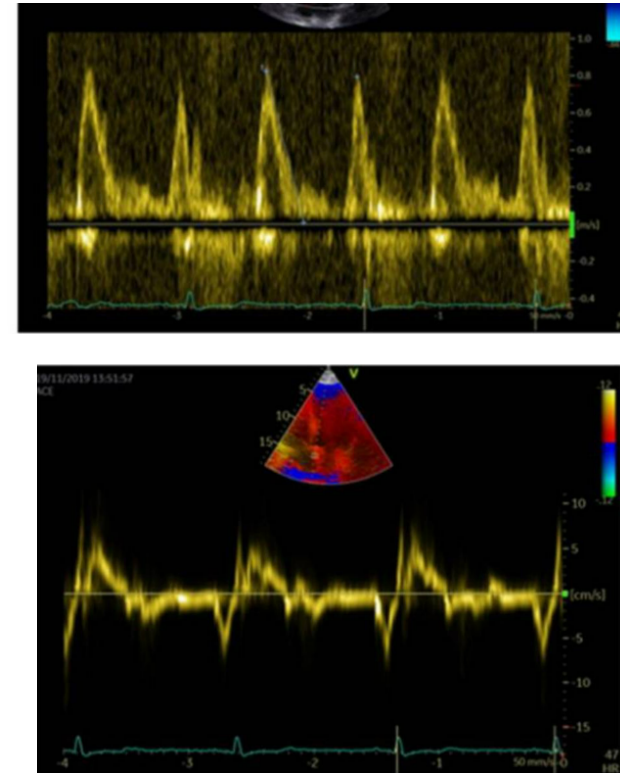


*European Heart Journal -
Cardiovascular Imaging,
Volume 22, Issue 7, July
2021, Pages 790–799*

LV hypertrophy



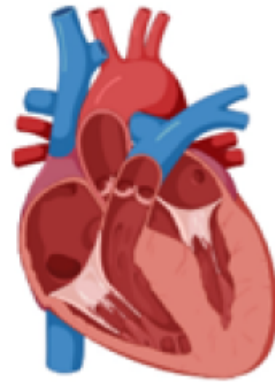
Diastolic Dysfunction



RV hypertrophy



Hypertrophic Cardiomyopathy/Left Ventricular Hypertrophy



LVH/HCM

Patients Screened
(n = 10,080)



Patients Diagnosed with FD
(n = 94)

Pooled Prevalence 1.4%



ACMG Criteria
(n = 80)

1.2%

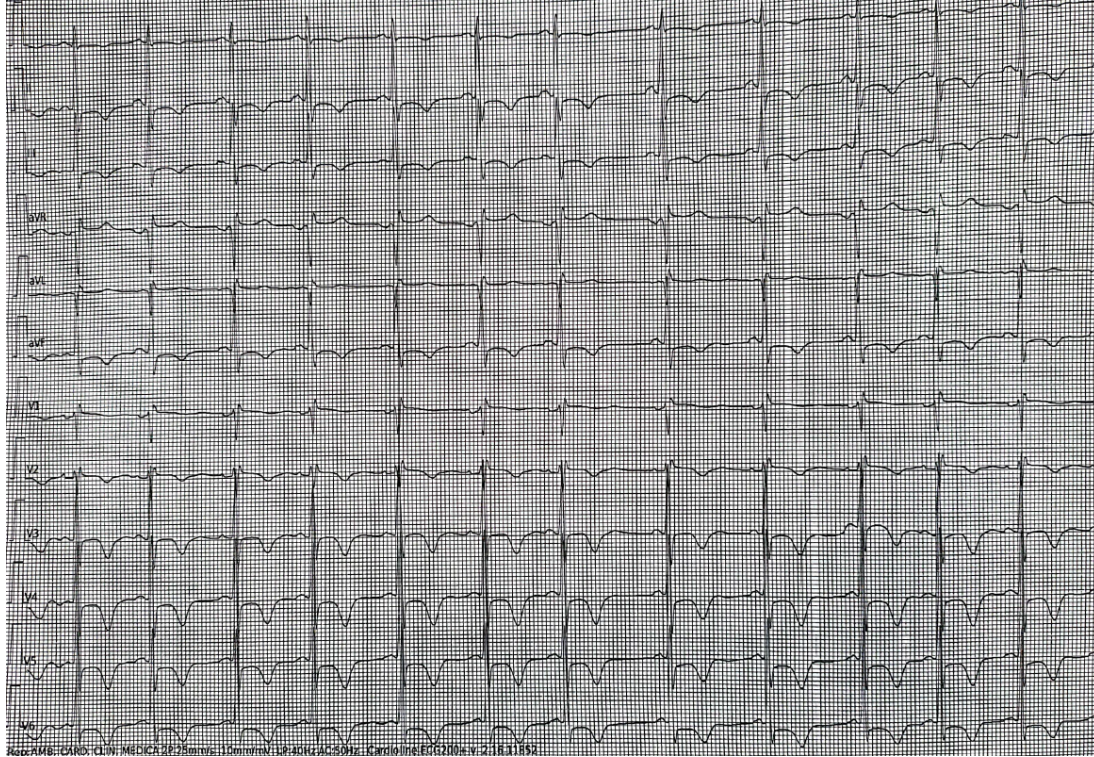


Clinvar
(n = 57)

0.9%

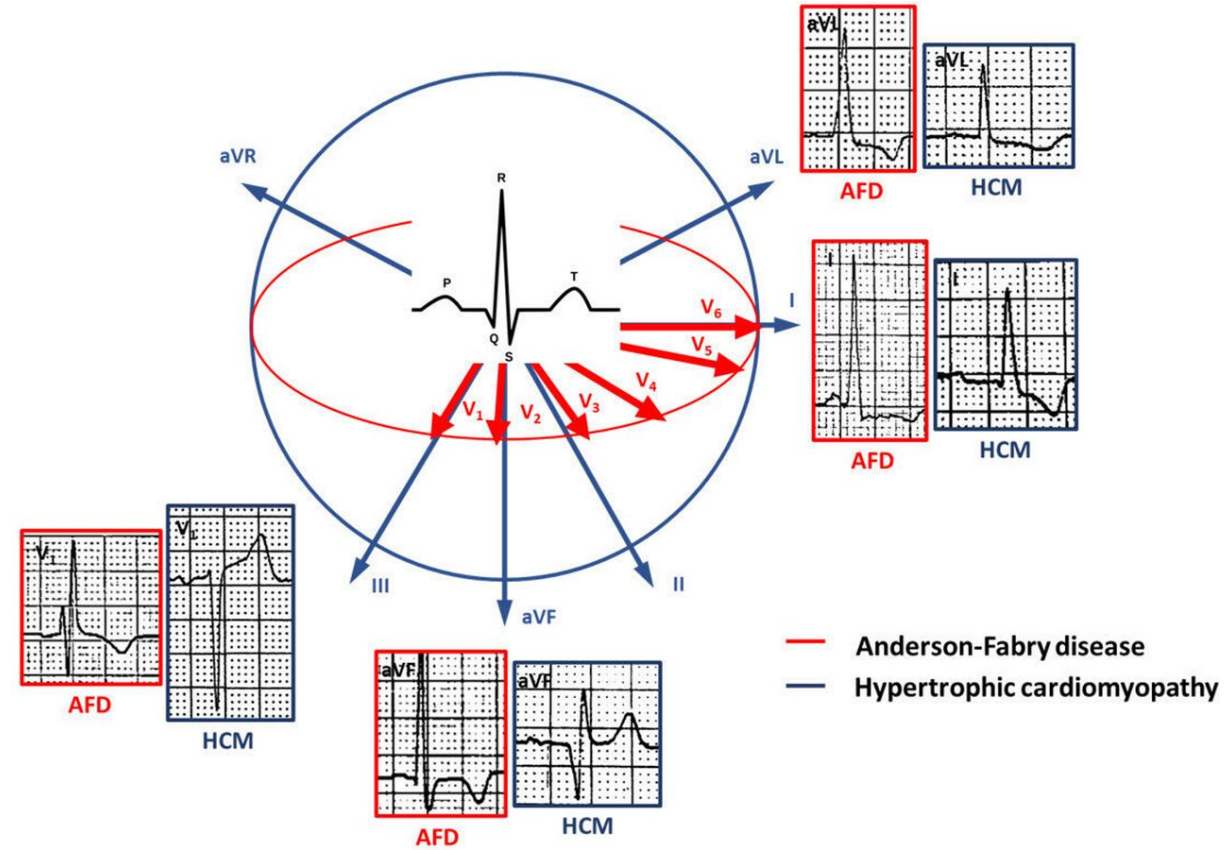
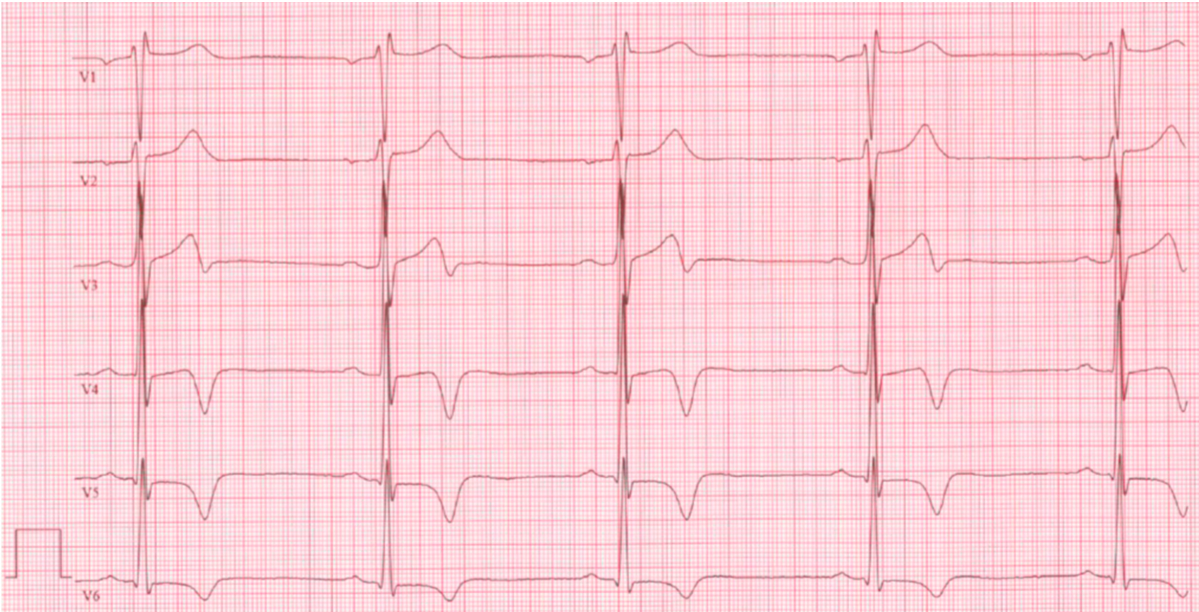
Pooled Prevalence

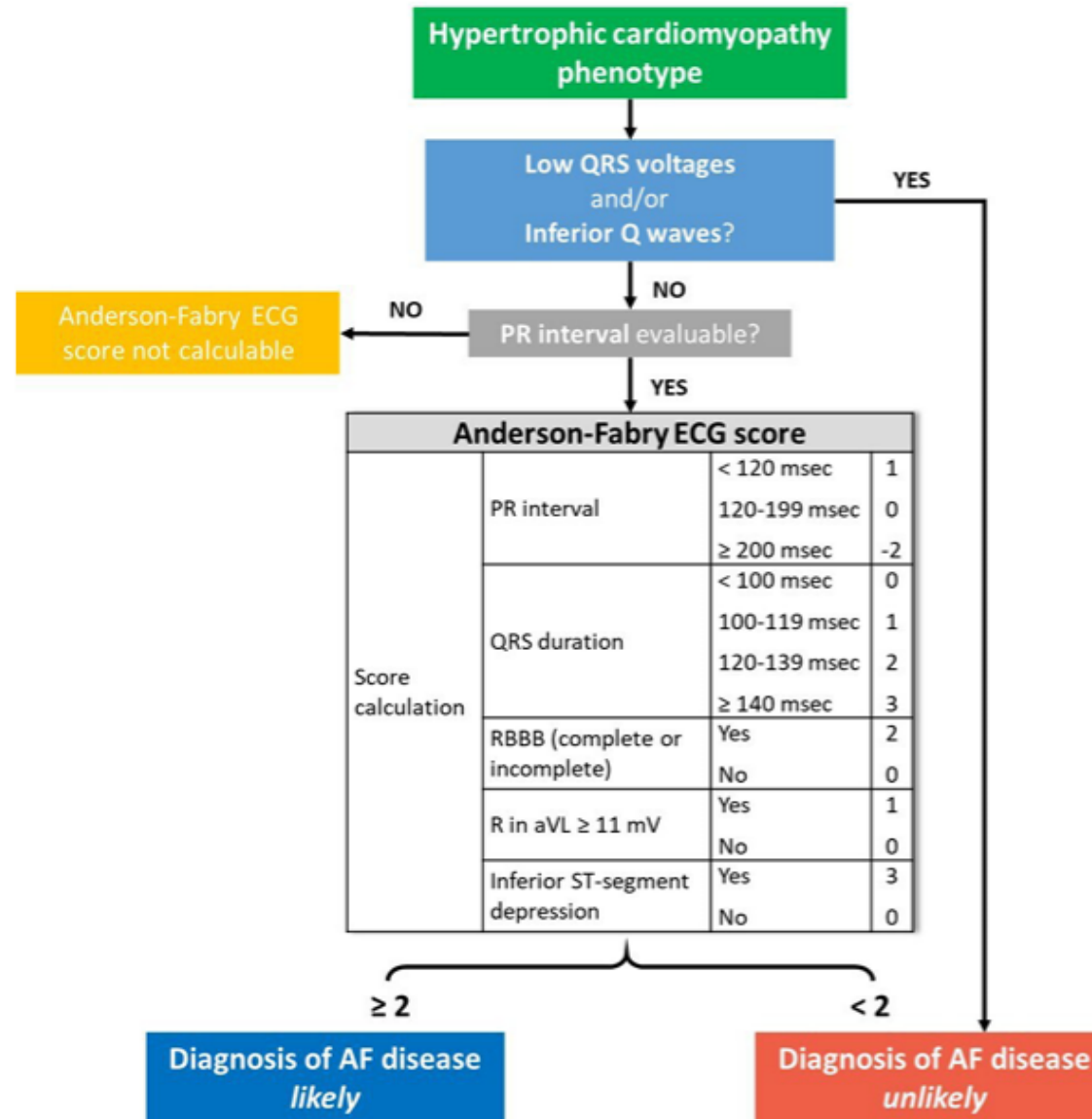
Apical HCM in Fabry disease



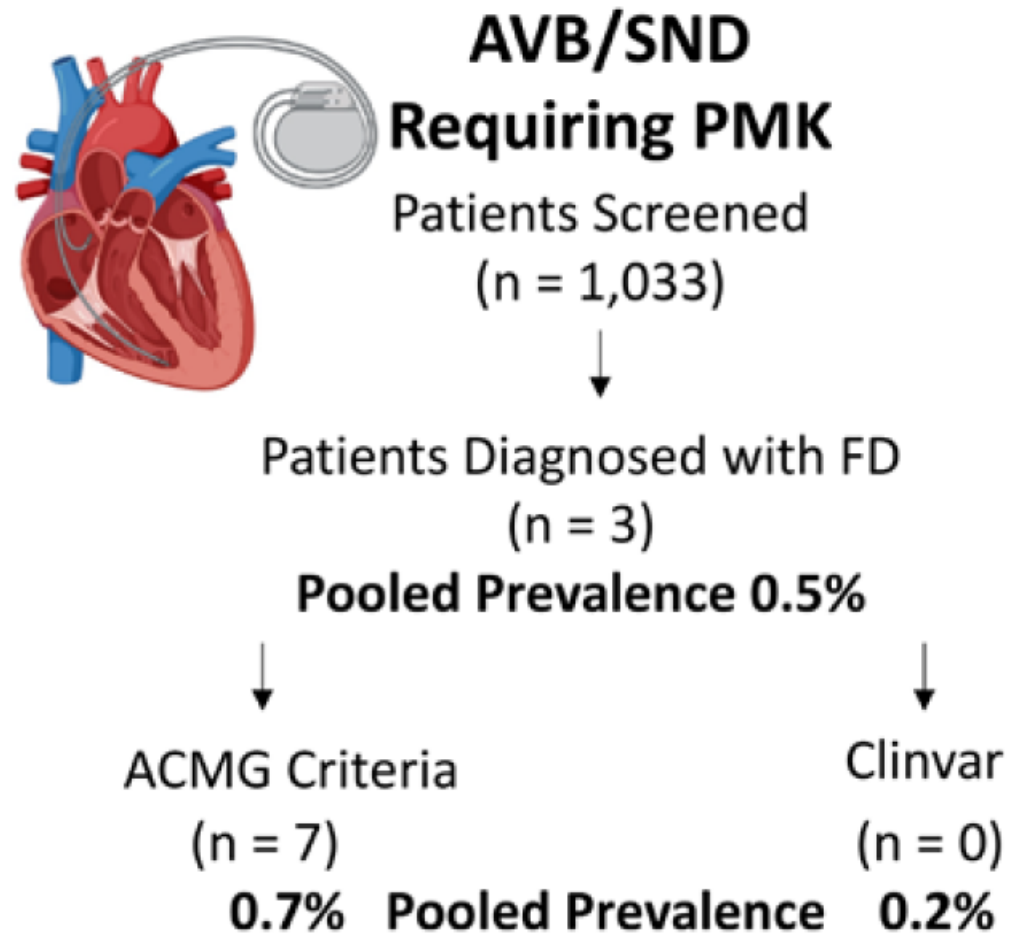
Atypical Subendocardial Late Gadolinium Enhancement in Anderson-Fabry Cardiomyopathy

Electrocardiography





Atrioventricular Block/Sinus Node Dysfunction



Prevalence and predictors of bradyarrhythmias requiring permanent pacing in patients with Anderson-Fabry disease

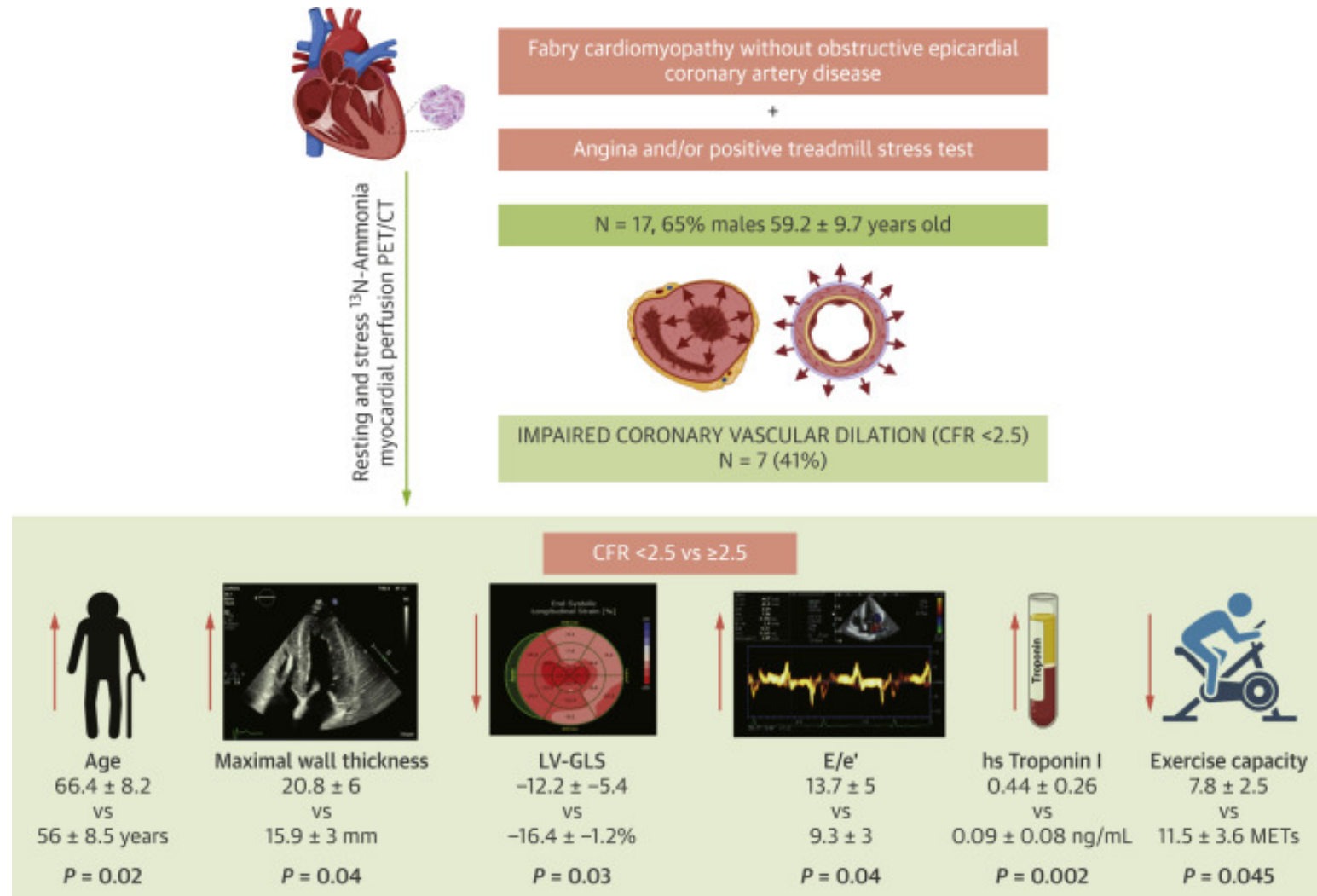
	PM requirement (N = 5)	No PM requirement (N = 77)	p value
ECG			
Baseline PR duration (ms)	160 [130–199]	140 [126–160]	.357
Baseline QRS duration (ms)	125 [120–135]	92 [84–102]	.030
Baseline PR < 120 ms	1 (20%)	10 (13%)	.449
Baseline PR > 200 ms	2 (40%)	3 (3.9%)	.018
Baseline QRS > 120 ms	4 (80%)	5 (6.5%)	.003
Baseline LVH	3 (60%)	22 (28.5%)	.163
Final PR duration (ms)	218 [189–221]	150 [132–164]	.024
Final QRS duration (ms)	160 [166–180]	100 [88–111]	.004
Final PR < 120 ms	0	7 (9.1%)	.576
Final PR > 200 ms	2 (40%)	7 (9.1%)	.035
Final QRS > 120 ms	4 (80%)	11 (14.3%)	.003
Final LVH	3 (60%)	27 (35.1%)	.350
ΔPR (base-FU, ms)	20 [10–32]	4 [0–17]	.314
ΔQRS (base-FU, ms)	31 [21–36]	4 [1–8]	.001
Echocardiography			
Baseline EF (%)	62 [59–65]	64 [60–68]	.585
Baseline LVMWT (mm)	17 [11–21]	10 [9–15]	.041
Baseline LVH	3 (60%)	24 (31.2%)	.325
Final EF (%)	52 [50–60]	63.5 [60–65.5]	.009
Final LVMWT (mm)	21 [16–23]	12 [9–15]	.002
Final LVH	5 (100%)	34 (44.2%)	.021
ΔLVMWT (base-FU, ms)	4 [0–5]	0 [0–3]	.324

Note: Continuous variable expressed as a median and IQR. LVH at ECG was defined according to Sokolow–Lyon criteria. LVH at echocardiography was defined as maximal wall thickness ≥13 mm. P values with statistical significance are indicated as bold values.

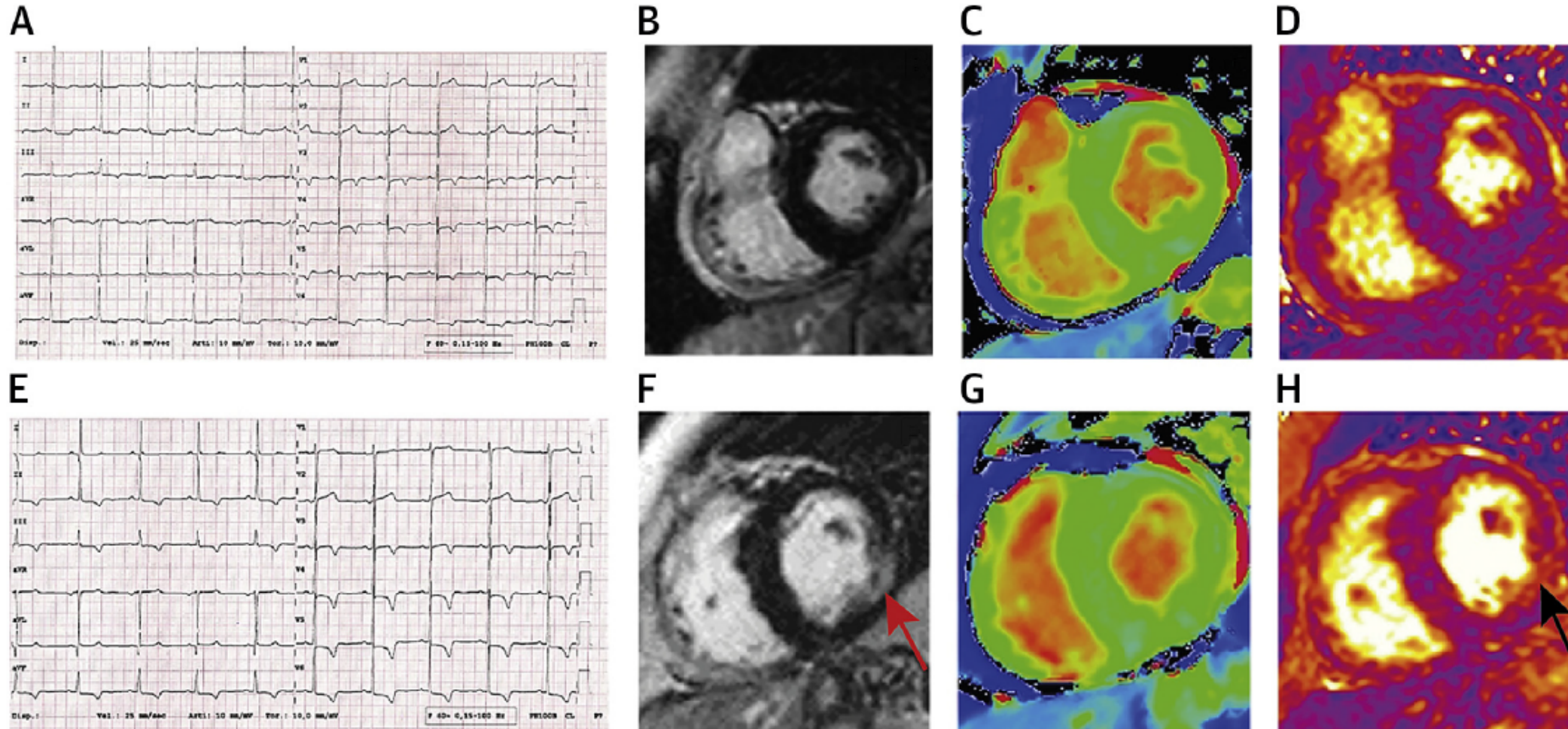
Abbreviations: ECG, electrocardiography; EF, ejection fraction; FU, follow-up; IQR, interquartile range; LVH, left ventricular hypertrophy; LVMWT, left ventricular maximal wall thickness; LVOTO, left ventricular outflow tract obstruction; PM, pacemaker.

T
P
A

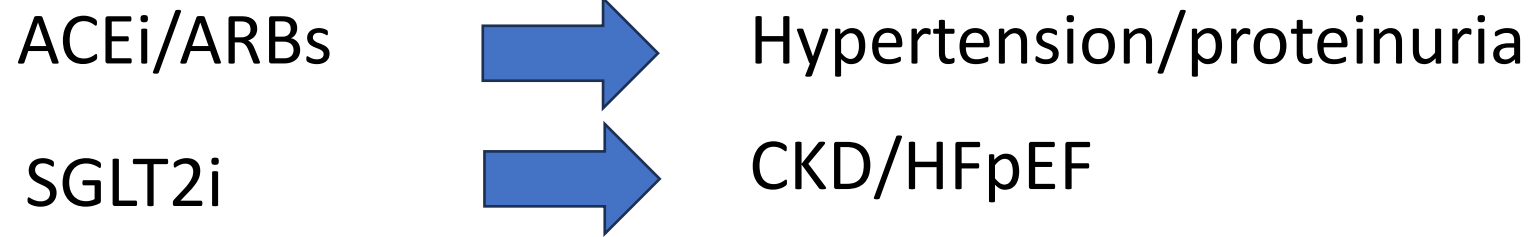
Coronary Microvascular Dysfunction Is Associated With a Worse Cardiac Phenotype in Patients With Fabry Disease



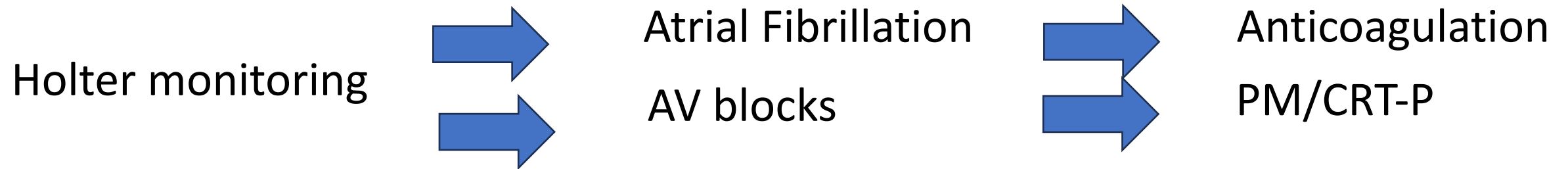
Progression of cardiological abnormalities in 2 years



Management of cardiac complications



Beta blockers are poorly tolerated due to chronotropic incompetence



Therapeutic landscape in Fabry disease

Therapeutical indication: laboratory, histological, or imaging evidence of injury to the heart, kidney, or central nervous system, even in the absence of typical Fabry symptoms -> the earlier the better.

Enzyme replacement therapy:

Agalsidase alfa: Intravenous 0.2 mg/kg/every other week (half life 2 h)

Agalsidase beta: Intravenous 1.0 mg/kg/every other week (half life 2 h)

Pegunigalsidase alfa: Intravenous 1 mg/kg/every other week (pegylated form of α -Gal A) -> longer circulatory half-life (80h), increased heart and kidney uptake compared with current ERTs, reduced immunogenicity, pre-existing anti-drug antibodies against agalsidase alfa and agalsidase beta seem to have less affinity and enzymatic inhibitory effects against pegunigalsidase alfa.

Chaperone:

Migalastat: Oral 123 mg/every other day ->indicated only for adult patients with migalastat-amenable α -galactosidase variants

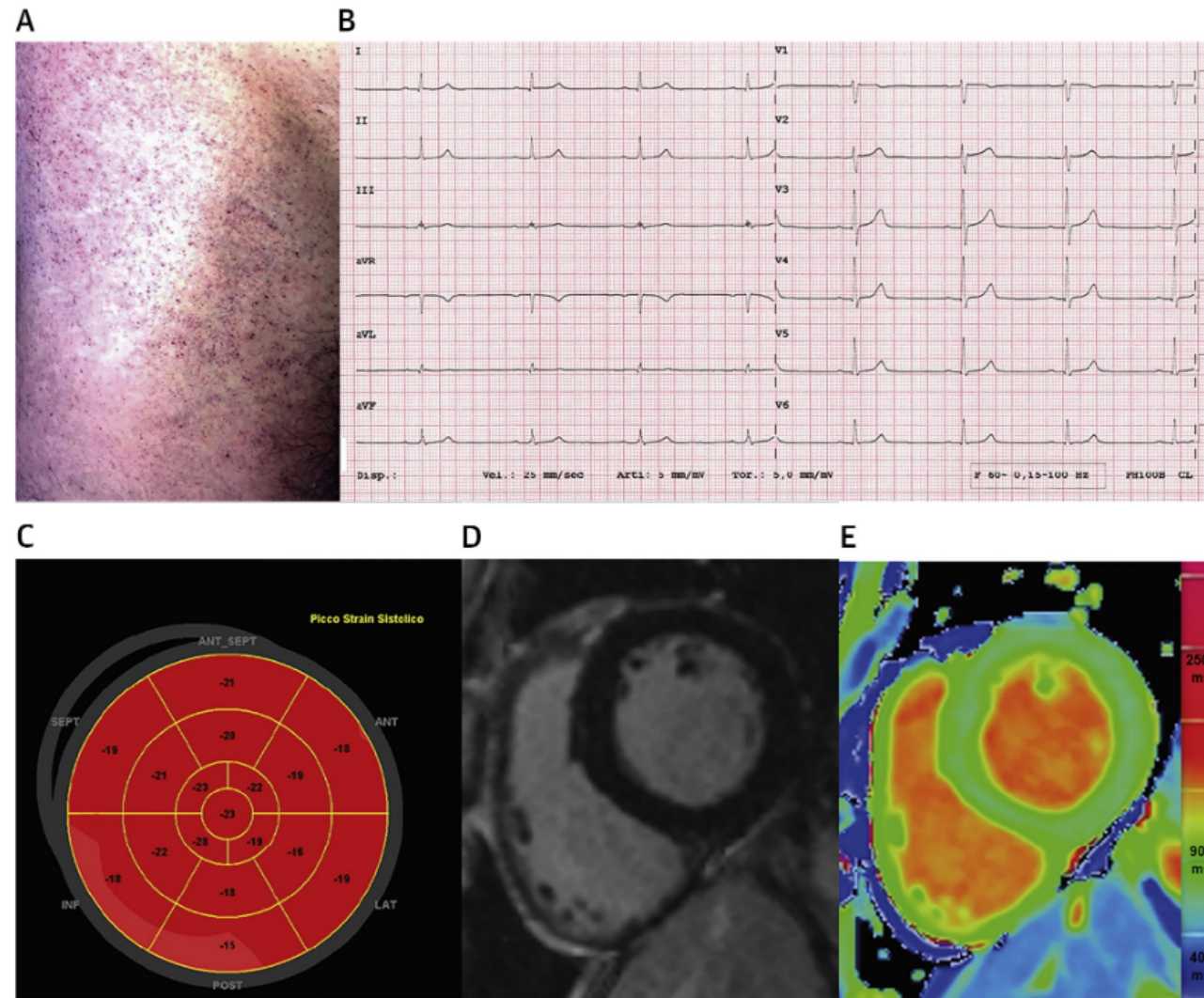
Gene therapy:

Adenoviral-based transduction of liver or cardiac cells -> ongoing clinical trials (Sangamo, 4D)

Pieroni et al. Jacc 2021

Long term treatment

FIGURE 8 Long-Term Effect of Early ERT



A 42-year-old man with classic FD (c.946delG) after 19 years of ERT. **(A)** Angiokeratomas in bathing-trunk region. **(B)** Normal electrocardiogram with sinus bradycardia. **(C)** Echocardiography showing mild reduction of longitudinal strain in postero-inferior basal segment. **(D and E)** CMR with no evidence of LVH nor LGE **(D)** but with low myocardial T1 values (820 ms; normal reference value 959 ± 20 ms) **(E)**. Abbreviations as in [Figures 2, 3, 5, and 7](#).

Pieroni et al. Jacc 2021



***Thanks for your
attention!***



CARDIOMIOPATIE PEDIATRICHE E DELL'ADULTO

CORSO PERFEZIONAMENTO POST-LAUREA

III° EDIZIONE - A.A. 2024/2025

1. Basic Science & Genetic-Metabolic

- 1.1 Fisiopatologia del miocardio e modificazioni associate alle principali cardiomiopatie
- 1.2 Indicazioni, aspetti tecnici ed interpretazione del test genetico
- 1.3 Inquadramento delle malattie metaboliche associate a cardiomiopatie

2. Quadri clinici in età pediatrica

- 2.1 Forme Genetiche
- 2.2 Errori congeniti del Metabolismo
- 2.3 Quadri Sindromici

3. Quadri clinici nell'adulto

- 3.1 Miocarditi
- 3.2 Cardiomiopatia Ipertrofica
- 3.3 Cardiomiopatia Dilatativa
- 3.4 Malattia di Anderson Fabry
- 3.5 Cardiomiopatia aritmogena
- 3.6 Amiloidosi
- 3.7 Quadri non classificati

4. Imaging multimodale nelle Cardiomiopatie

- 4.1 Ecocardiogramma - Ecostress
- 4.2 TAC
- 4.3 Risonanza magnetica nucleare

5. Aritmologia Clinica nelle Cardiomiopatie

- 5.1 Principi generali di stratificazione del rischio aritmico
- 5.2 ICD transvenoso e sottocutaneo
- 5.3 Approccio alla fibrillazione atriale
- 5.4 Approccio alle aritmie ventricolari

6. Valutazione funzionale e biomarcatori

- 6.1 Test cardiopolmonare
- 6.3 Utilizzo dei biomarcatori nelle Cardiomiopatie

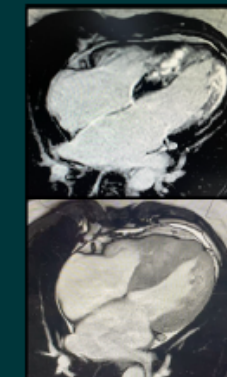
7. Approccio Terapeutico medico-chirurgico alle Cardiomiopatie

- 7.1 Principi di farmacologia generale applicata alle cardiomiopatie
- 7.2 Nuovi approcci farmacologici
- 7.3 Opzioni terapeutiche interventistiche
- 7.3 Opzioni terapeutiche chirurgiche
- 7.4 Algoritmi di trattamento per patologia

8. Bioetica - Innovazione e Ricerca

- 8.1 Bioetica e fine vita
- 8.2 Organizzazione di un Centro Cardiomiopatie; associazione pazienti AICARM
- 8.3 Innovazione terapeutiche e prospettive future

Per ulteriori informazioni sul corso scrivere a:
alberto.marchi@meyer.it



DIRETTORI:

Prof. Iacopo Olivetto
Dott.ssa Silvia Favilli

RESPONSABILE SCIENTIFICO:

Dott. Alberto Marchi



FABRY DISEASE THERAPY

DISEASE MODIFYING THERAPY

Enzyme replacement therapy

Chaperone therapy

SUPPORTIVE TREATMENT

Heart failure

Arrhythmias

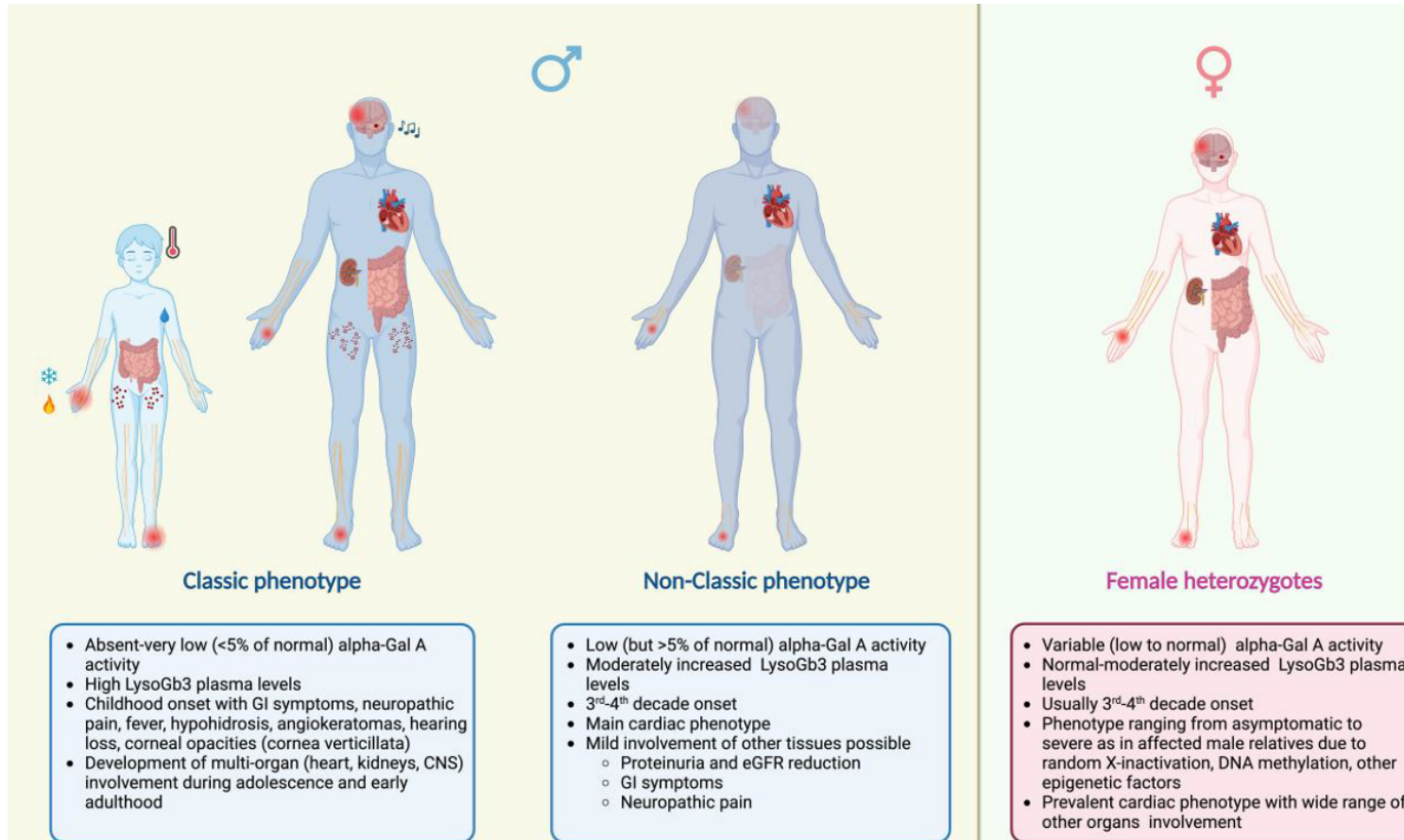
CKD

Neuropathic pain symptoms

Drug	Type of therapy	Route of administration	Half life	Source
Agalsidase beta	ERT	IV, 1.0 mg/kg every two weeks.	45s-100 min	Ovary cells of Chinese Hamster
Agalsidase alfa	ERT	IV, 0.2 mg/kg every two weeks	108 +- 17 minutes	Human fibrosarcoma cells HT-1080
Pegunigalsidase alfa	ERT	IV, 1 mg/kg every two weeks.	53-134 hours	Nicotiana tabacum cells (ProCellEx)
Migalastat	chaperone	Orally, 123 mg every two days.	3-5 hours	Fermentation product of <i>Streptomyces lydicus</i> (Strain PA-5726)

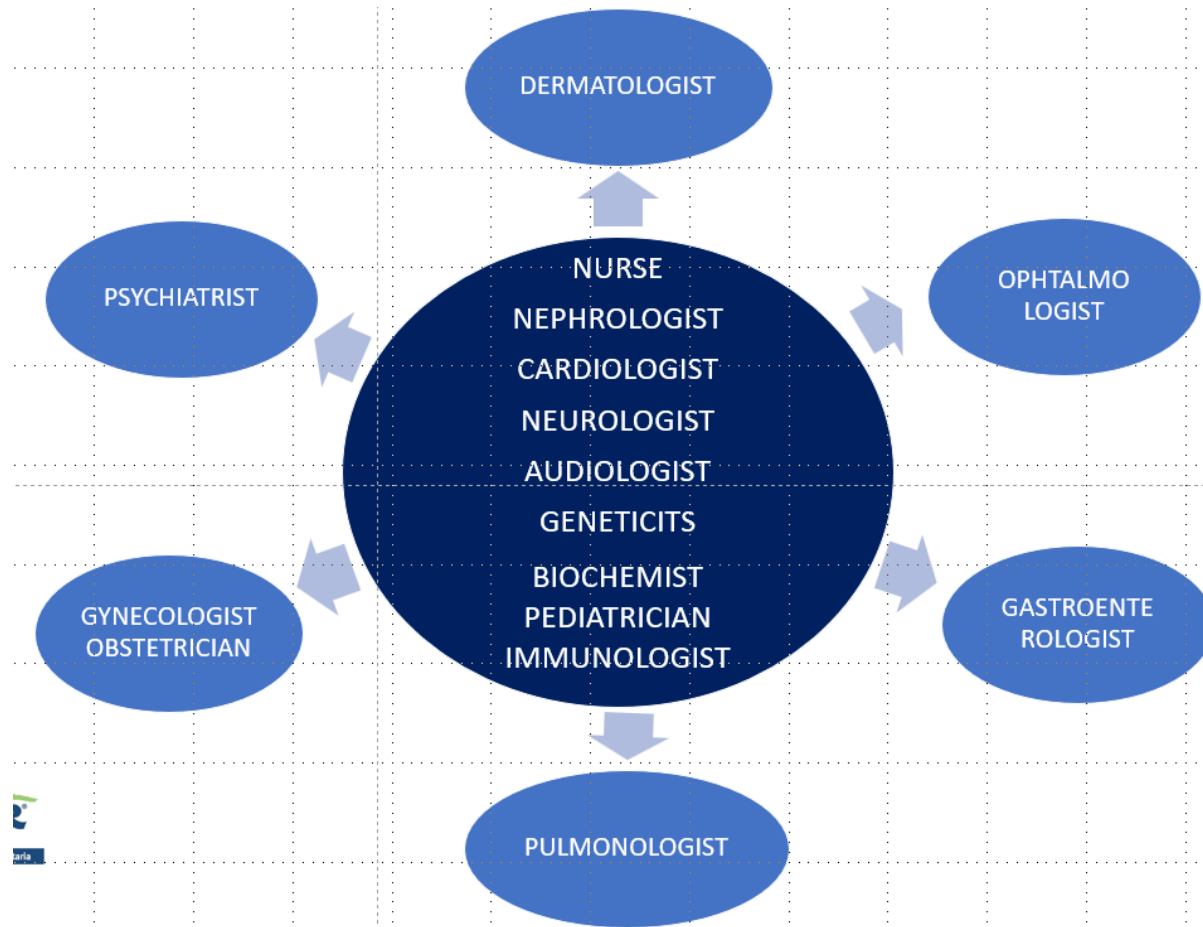
Who should start the treatment?

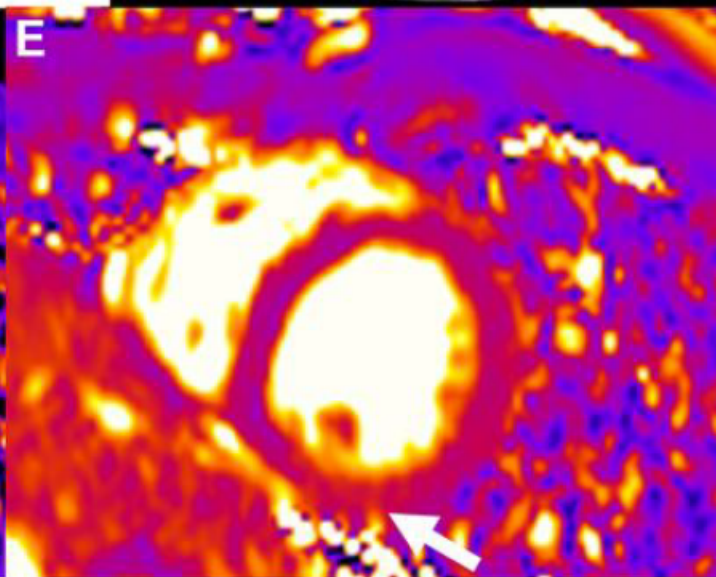
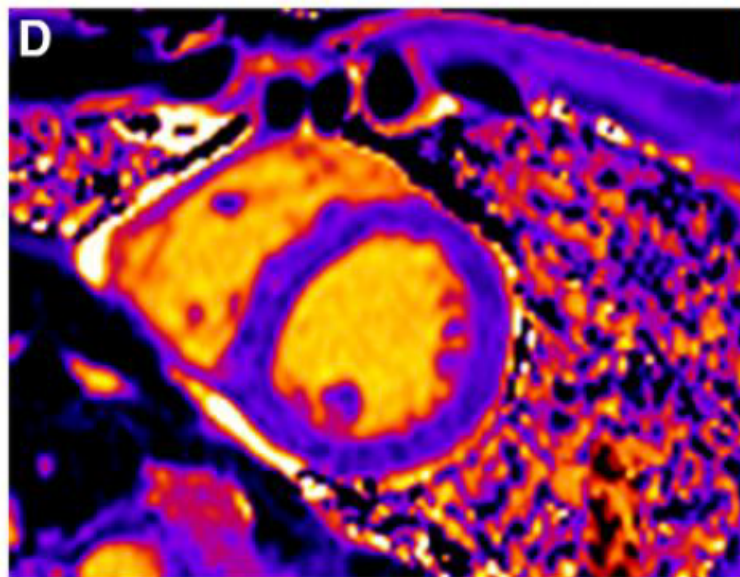
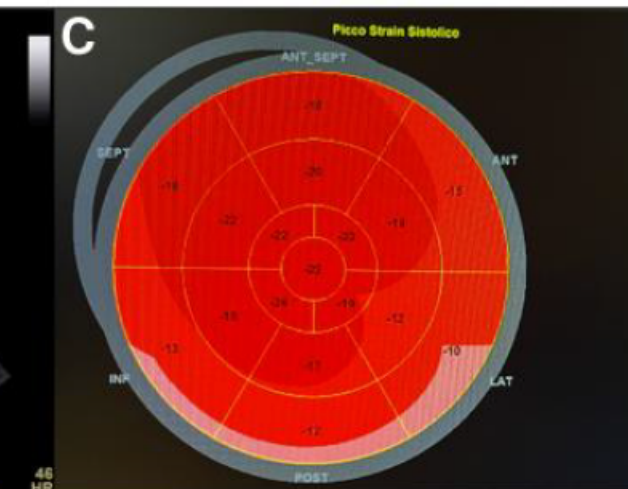
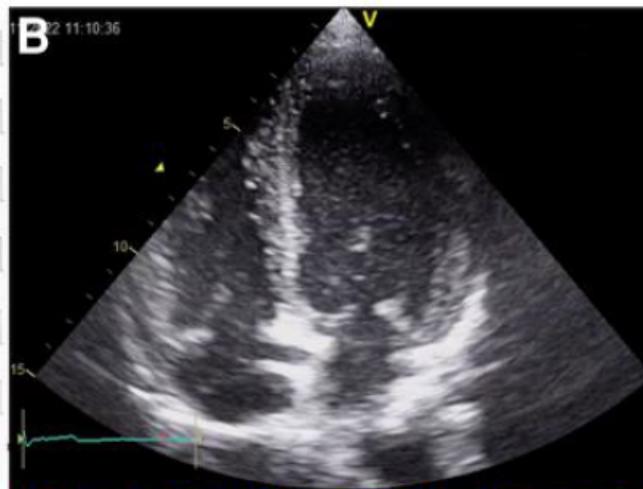
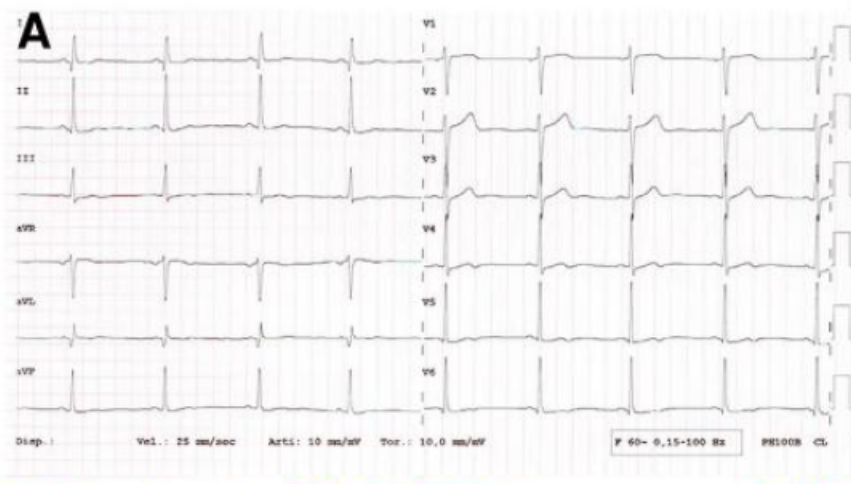
Children with classic disease at any age of presentation irrespective of symptoms.



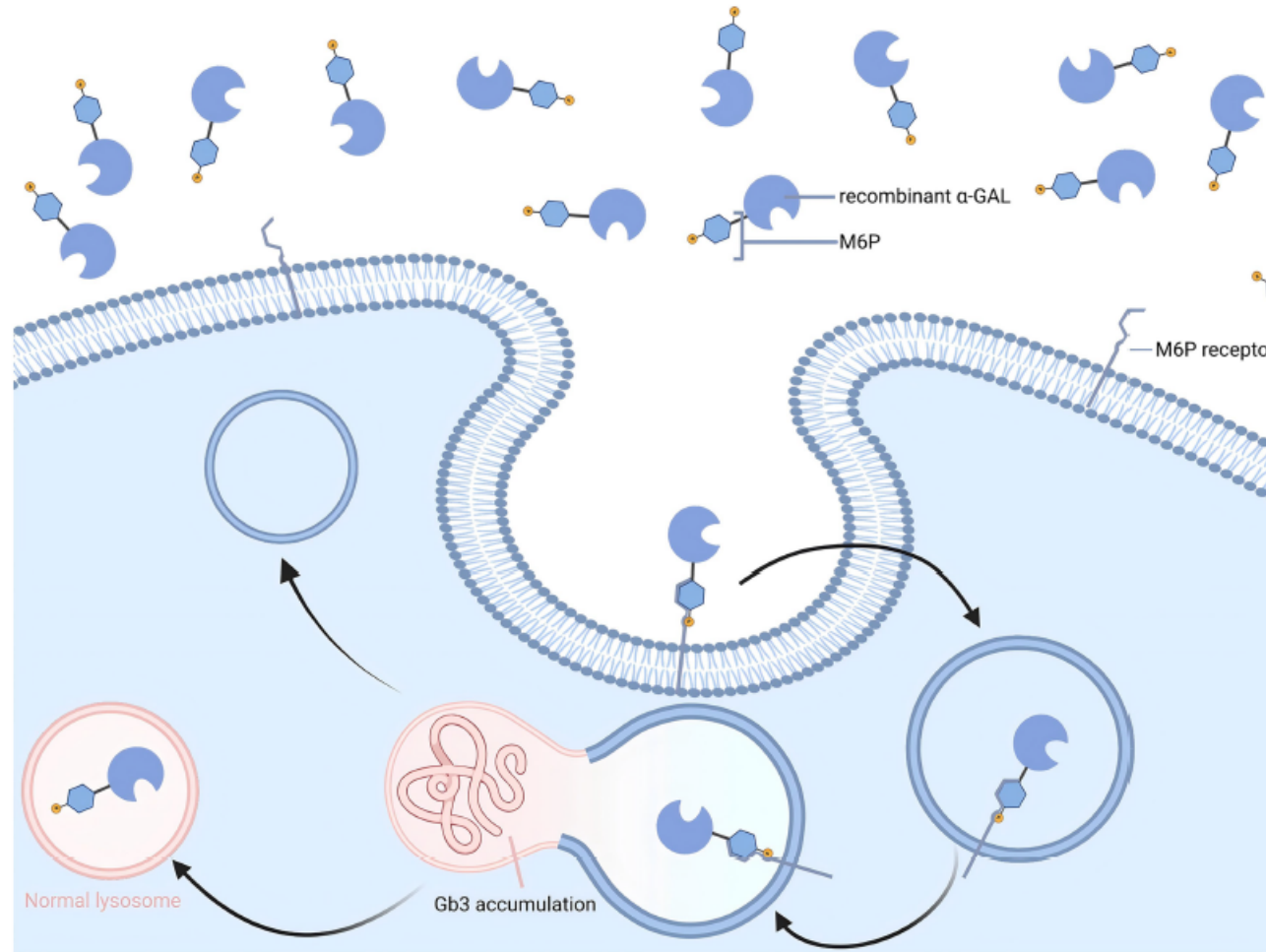
Non-classic phenotype and heterozygous females suggests starting ERT or chaperone treatment whenever signs and/or symptoms of AFD become evident

Patients can be prescribed ERT or chaperone therapy based on shared-decision making.



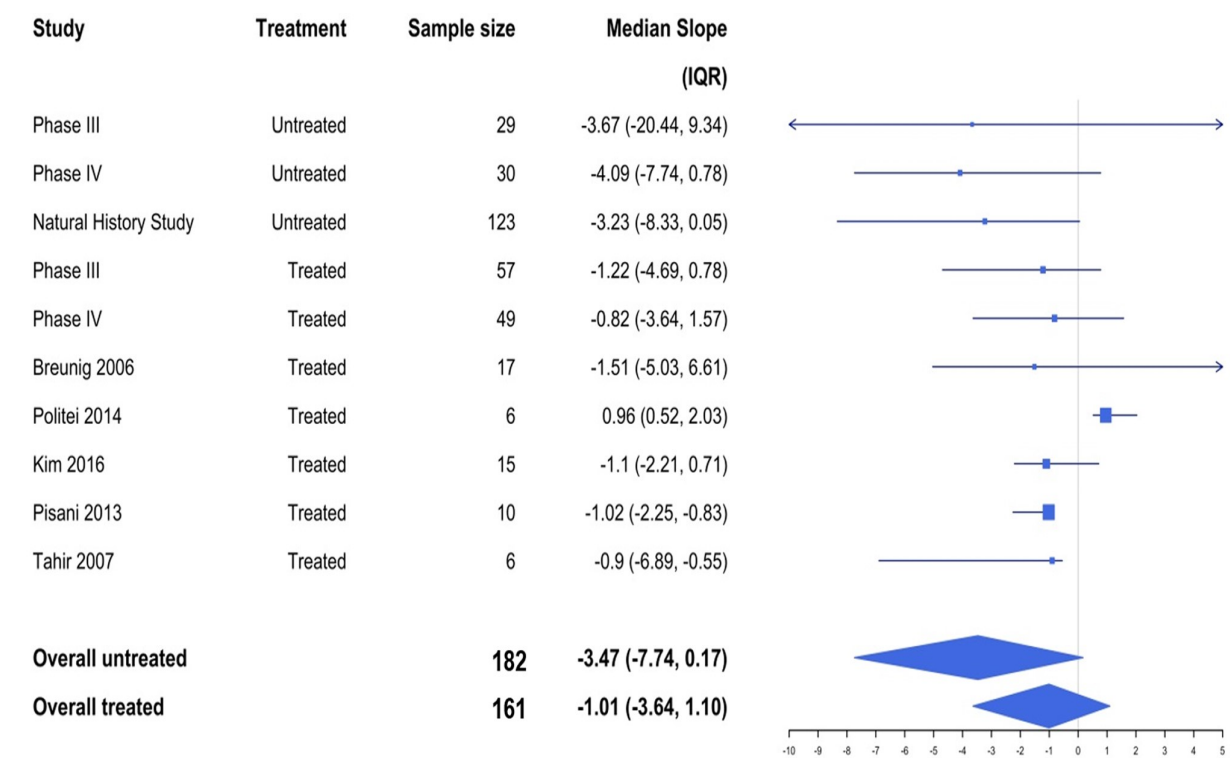


Enzyme replacement therapy

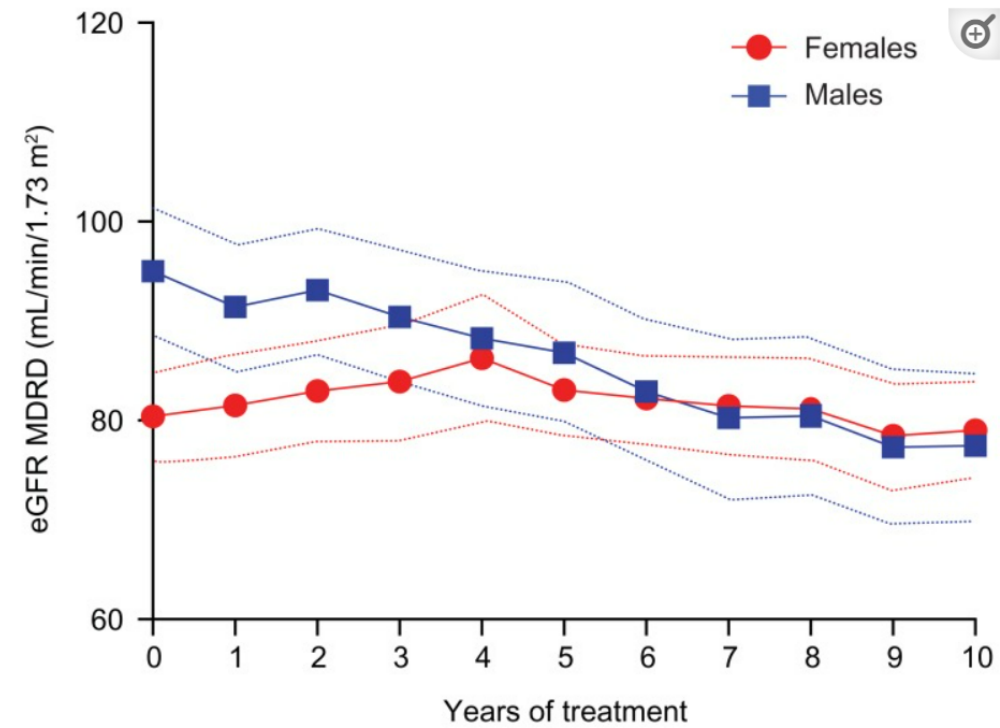


ERT effects: prevent pathological progression of kidney disease

BETA



ALFA



relatively stable in females ($n = 52$; -0.55) and slightly declined in males ($n = 79$; -1.99)

Switch criteria

eGFR and response to treatment in adult Fabry patients



Fabry disease

Main criteria:

Adult FD patients, age 18–60 years



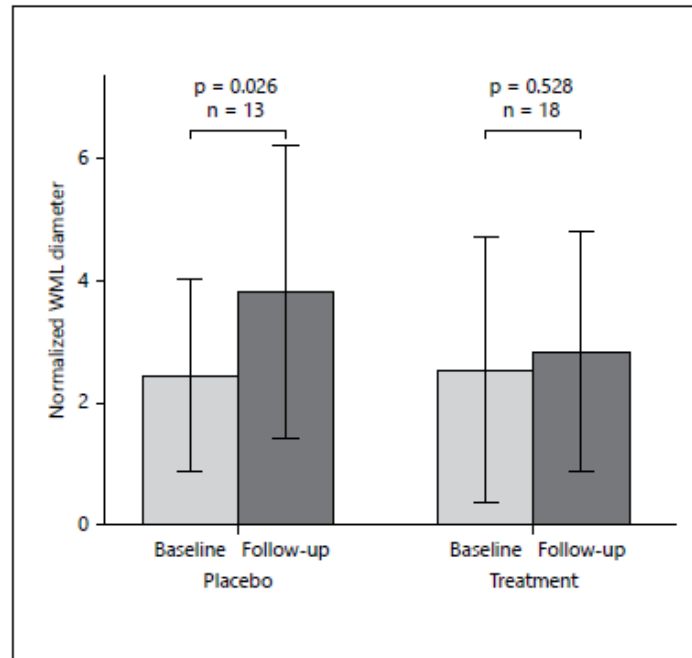
eGFR 45 to 90 mL/min/1.73 m²



Treatment with a stable dose of ERT per infusion every 2 weeks for at least one year and at least 80% over the last 3 years

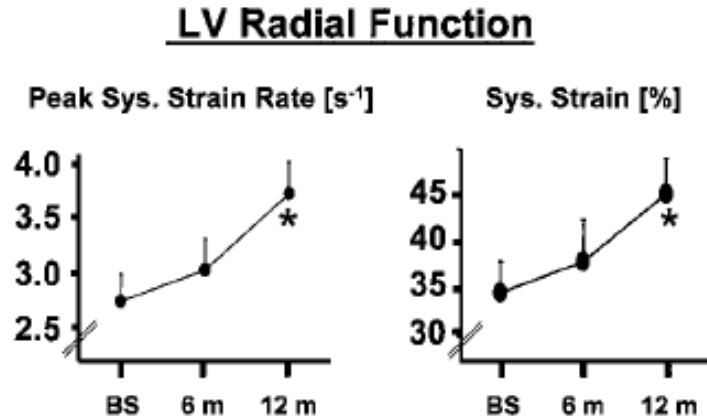
	Therapeutic goal achieved	Therapeutic goal not achieved
	eGFR decline	eGFR decline
ERT  Over 56 w	< 3 ml/min/1.73 m ² per year	≥ 3 ml/min/1.73 m ² per year
ERT  Over 56 w	< 2.5 ml/min/1.73 m ² per year	≥ 2.5 ml/min/1.73 m ² per year
	Continue therapy	Consider switch

ERT effects: prevent pathological progression of neurological manifestations

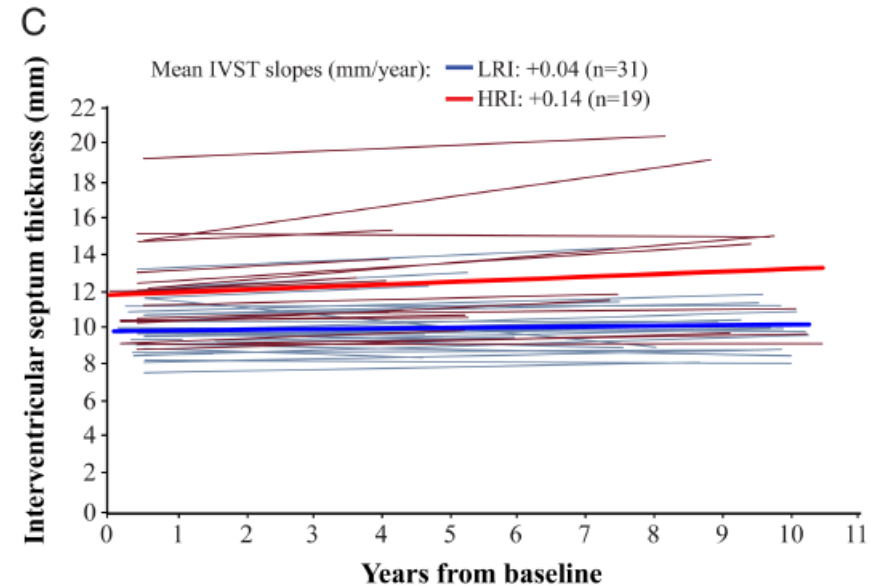


the proportion of patients with stable WML burden was significantly greater among patients receiving ERT than in those receiving placebo

ERT effects: prevent pathological progression of cardiological manifestations



In Fabry patients, myocardial mass at study entry (n10) averaged 201 ± 18 g and decreased significantly after 12 months of ERT by 10% (180 ± 21 g; $P < 0.05$).



LVPWT and IVST remained within normal ranges in patients aged < 40 years (with no LVH at baseline)

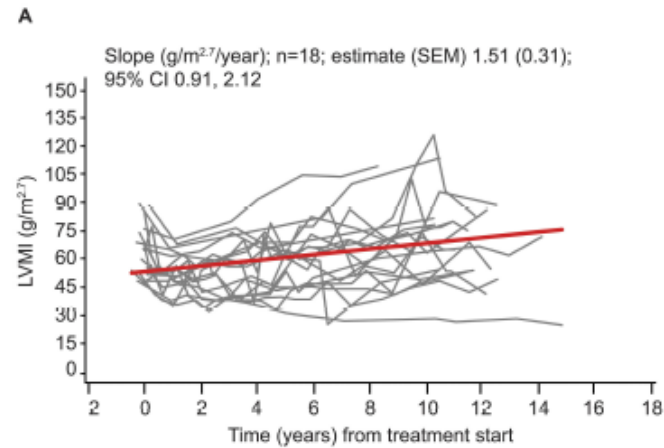
Patients aged > 40 years (with LVH at baseline), had a significant increase in LVH despite receiving agalsidase beta (mean slope $+0.23$ mm/year, $p = 0.028$)

Weidemann et al. Circ 2003

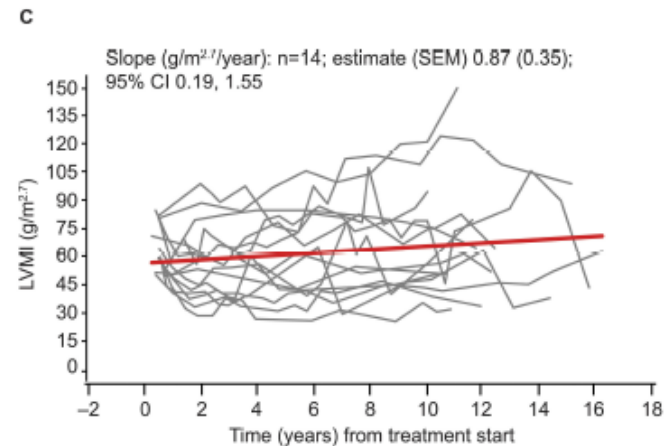
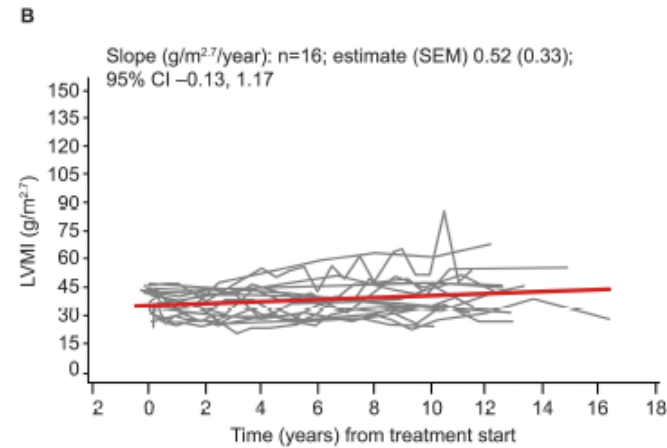
Germain DP, et al. J Med Genet 2015

ERT effects: prevent pathological progression of cardiological manifestations

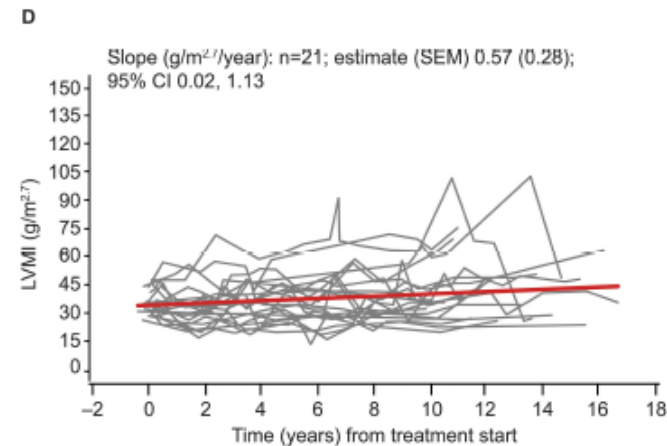
female population, LVH at baseline



female population, no LVH at baseline



male population, LVH at baseline

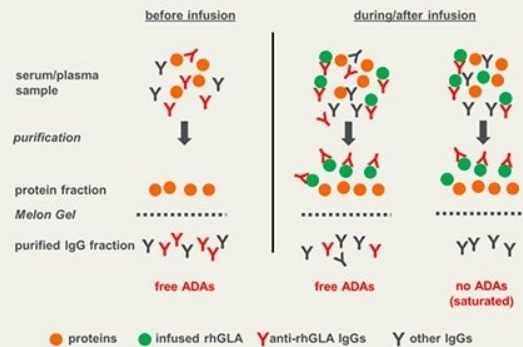


male population, no LVH at baseline

Enzyme replacement therapy and antidrug antibody

Dose-dependent Impact of Enzyme Replacement Therapy on Neutralizing Anti-drug Antibody Titers and Clinical Outcome in Patients with Fabry Disease

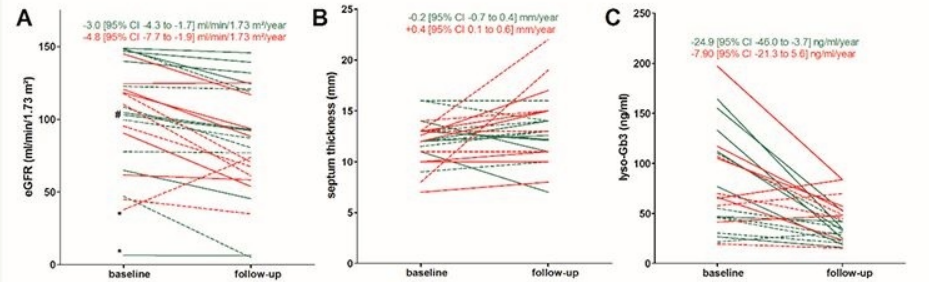
METHODS



Neutralizing anti-drug antibodies from 26 male patients were measured before and after infusions. Longitudinal clinical data were retrospectively assessed and analyzed.

RESULTS

Neutralizing anti-drug antibodies can be saturated during infusions, allowing to differentiate between “saturated” (agalsidase excess) and “not saturated” (antibody excess) patients.



Comparison of eGFR (A), interventricular septum thickness (B), and (C) plasma lyso-Gb3 levels between saturated (green) and not saturated (red) patients.

CONCLUSION

A not saturated antibody status (antibody excess) during infusion is associated with a progressive loss of eGFR, ongoing cardiac hypertrophy, and reduced plasma lyso-Gb3 decline over time.

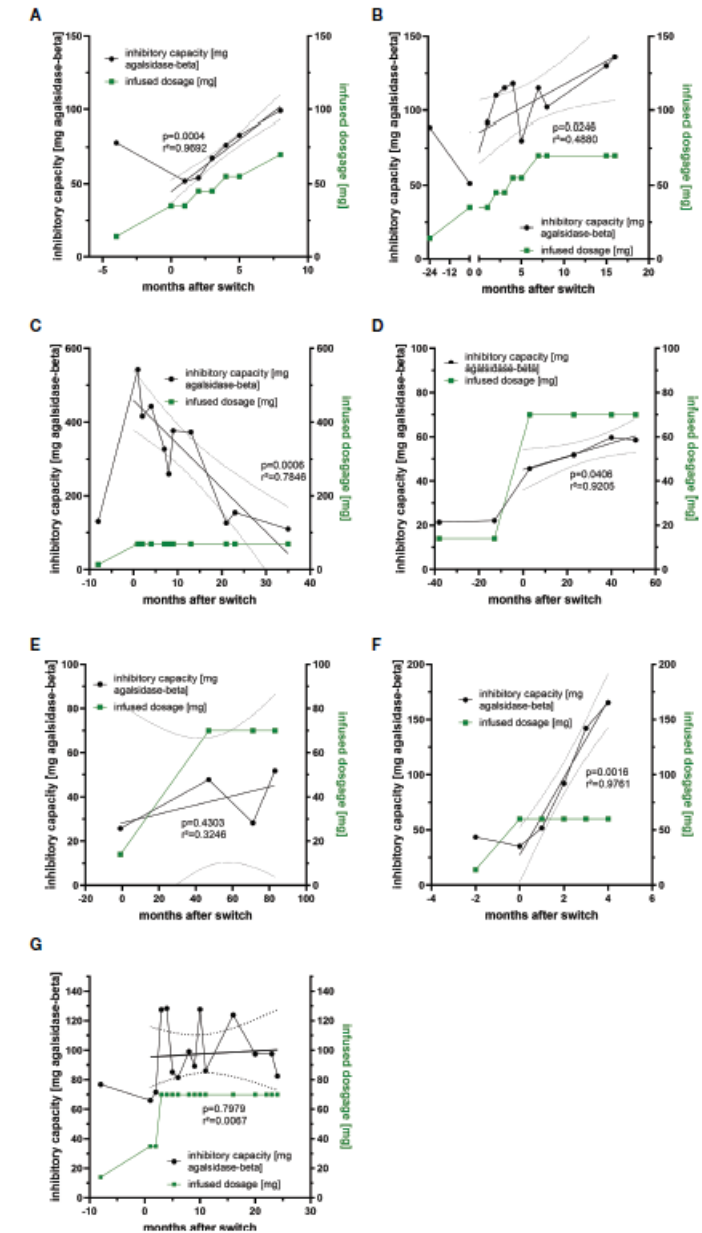
30% alfa
40% beta

ADAs demonstrate a high cross-reactivity for both recombinant enzymes

Assessment and impact of dose escalation on anti-drug antibodies in Fabry disease

70 (35%) of the male patients on ERT were ADA-positive

7 patients were switch from alfa to beta-> in 2 patients although ADA titers increased, infused dosages were sufficient to saturate all free ADAs



Lenders et al 2022

Pegulsidase alfa: BRIDGE TRIAL: phase 3 open-label, switch-over study designed to assess safety and efficacy of pegunigalsidase alfa (1 mg/kg) administered every 2 weeks (E2W) to adults with FD previously receiving agalsidase alfa (0.2 mg/kg E2W) for ≥ 2 years

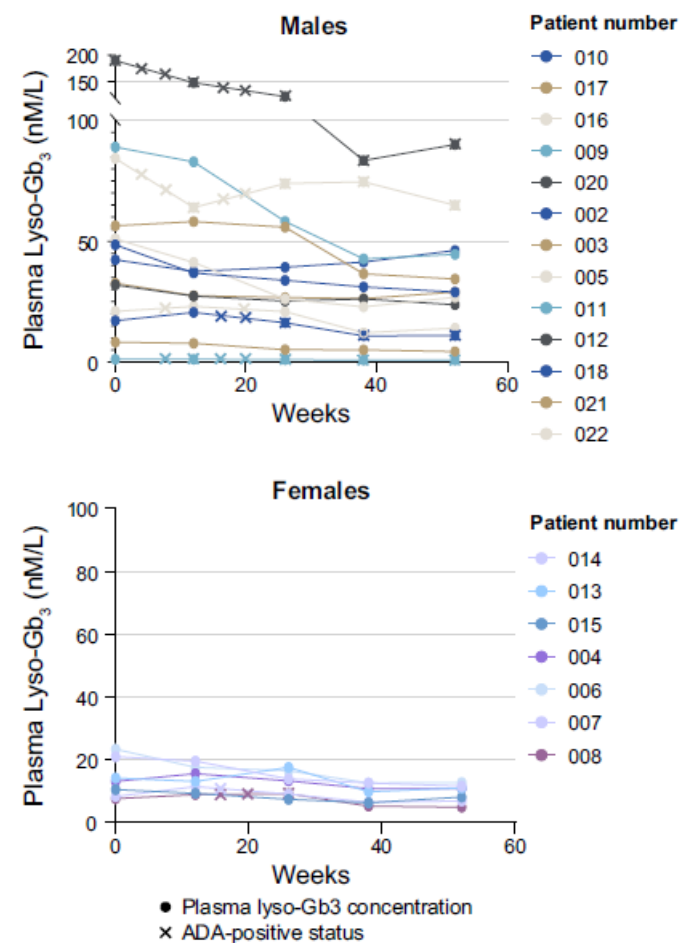


Fig. 1 Change in plasma lyso-Gb₃ in males and females (efficacy population). Anti-pegunigalsidase alfa ADA assessment was conducted at baseline, Weeks 4, 8, 12, 16, 20, 26, 38, and 52; positive status is shown with an x. ADA, antidrug antibody

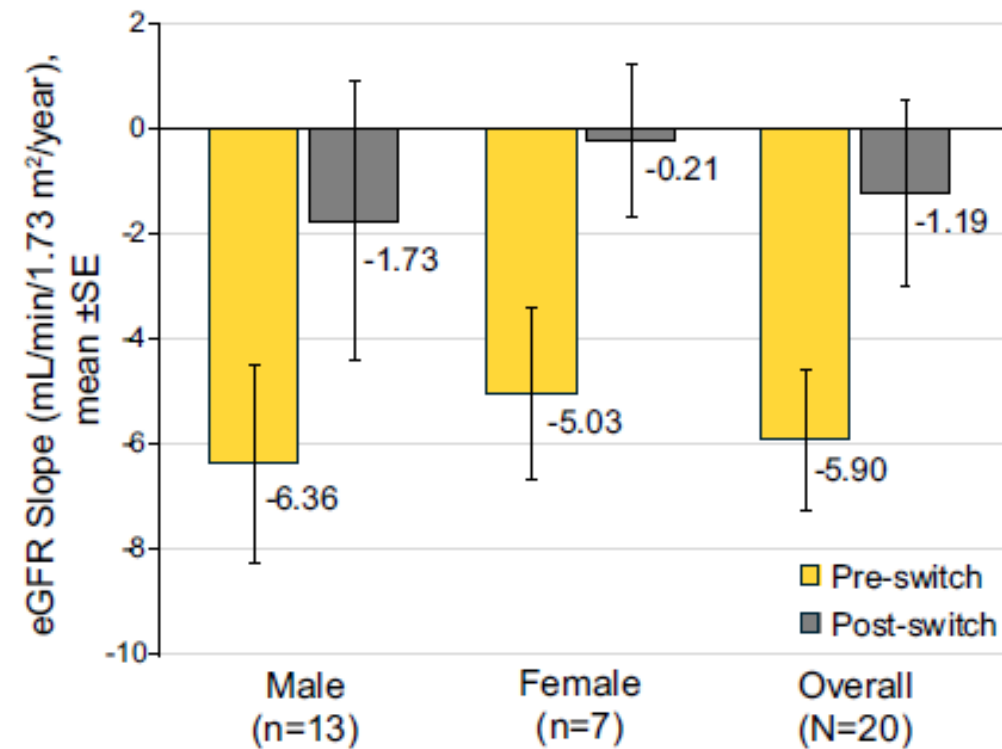


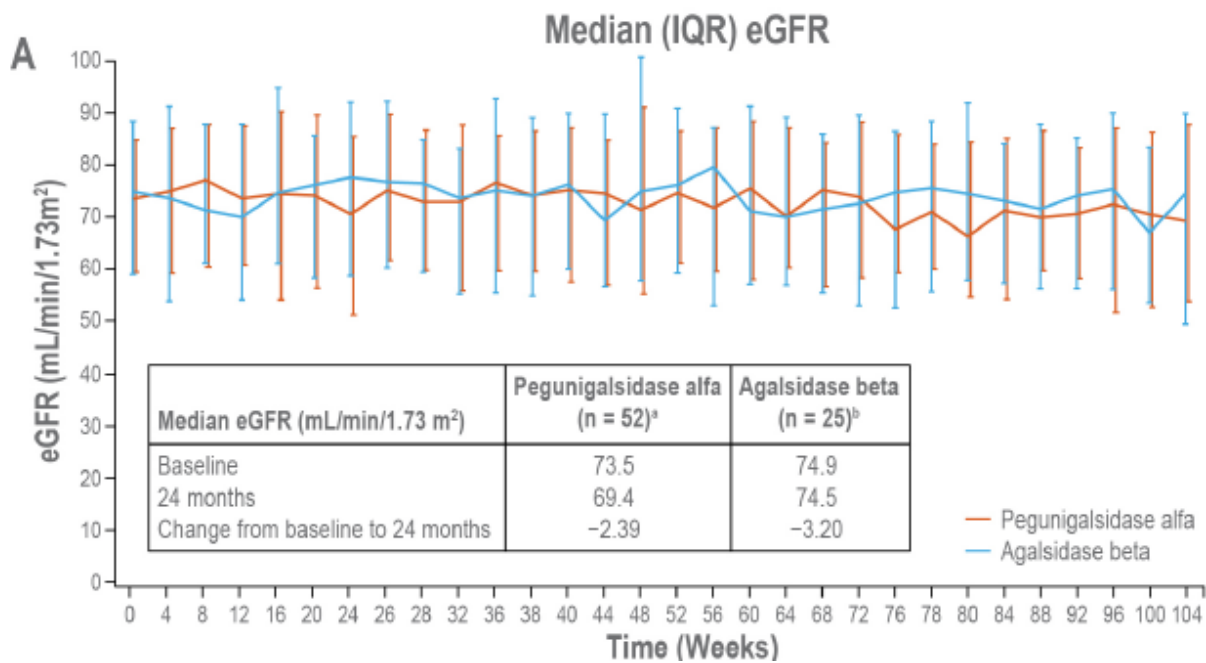
Fig. 2 eGFR annualized slope in males, females, and overall study population (efficacy population). eGFR estimated glomerular filtration rate, SE standard error

Pegulsidase alfa: BALANCE STUDY

Patients were randomly assigned 2:1 to receive 1 mg/kg pegunigalsidase alfa or agalsidase beta every 2 weeks for 2 years. The primary efficacy analysis assessed non-inferiority based on median annualised eGFR slope differences between treatment arms.

the difference between median eGFR slopes was -0.36 mL/min/1.73 m²/year, meeting the prespecified non-inferiority margin.

neutralising antibodies were detected in 7 out of 47 (15%) pegunigalsidase alfa-treated patients and 6 out of 23 (26%) agalsidase beta-treated patients.



Migalastat therapy

Compared to ERT, Migalastat:

- ➔ it is nonimmunogenic, escaping antibody-related tolerability;
- ➔ It is an oral treatment (123 mg/every other day);
- ➔ it may lead to sustained enzyme levels that more closely mimic the endogenous enzyme
- ➔ Administered only in amenable variants: monitor patients' clinical symptoms and laboratory markers during treatment to comprehensively assess the actual therapeutic efficacy of migalastat

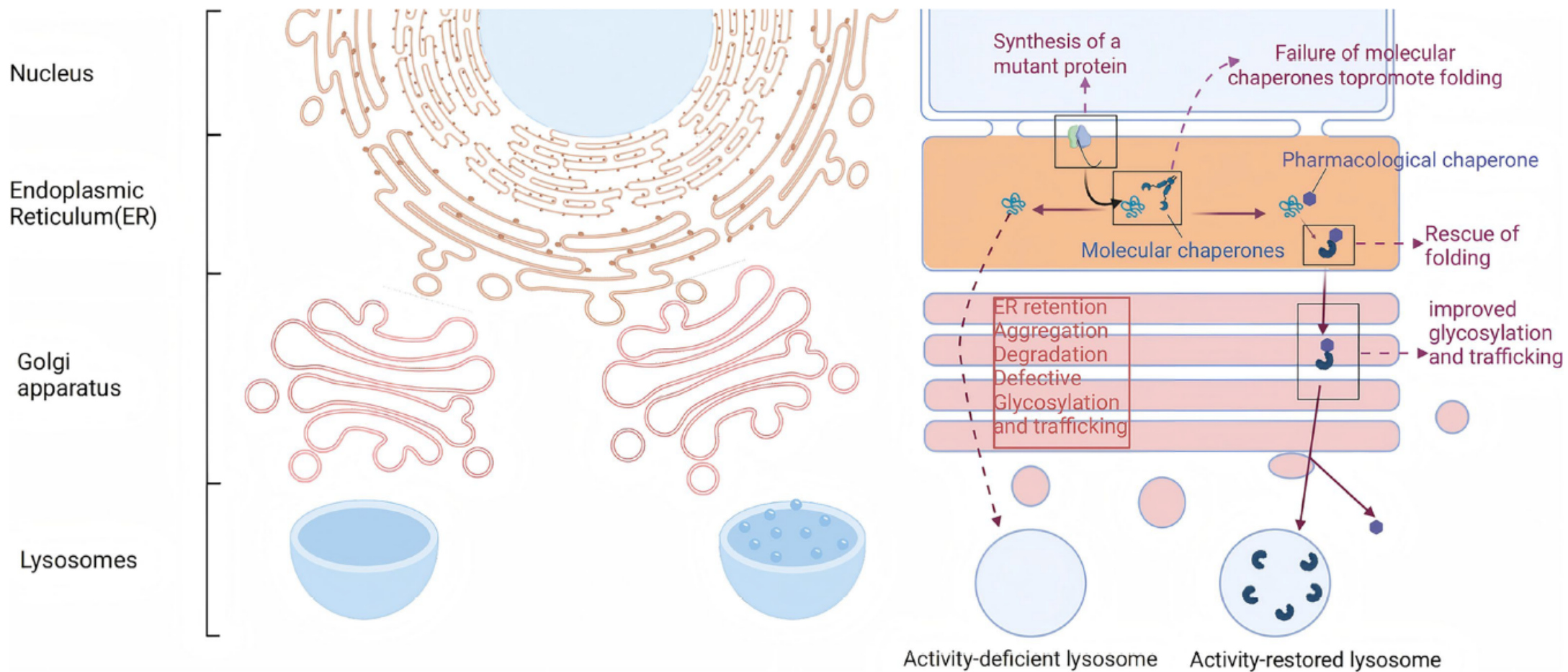
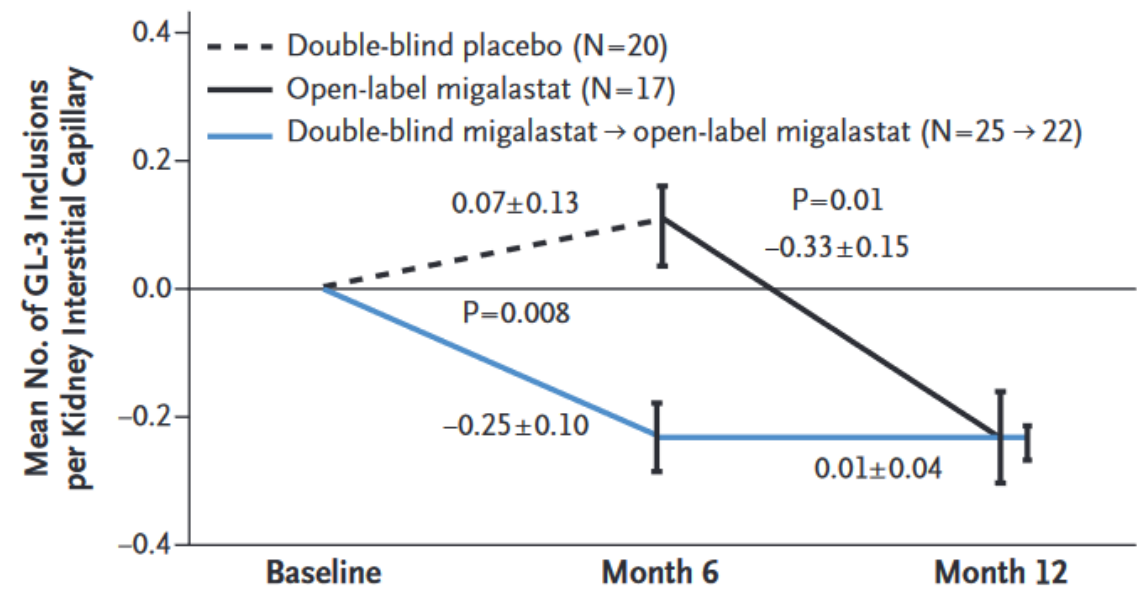


FIGURE 2
Migalastat stabilizes mutated α -Gal A enzymes to enhance enzymatic activity.

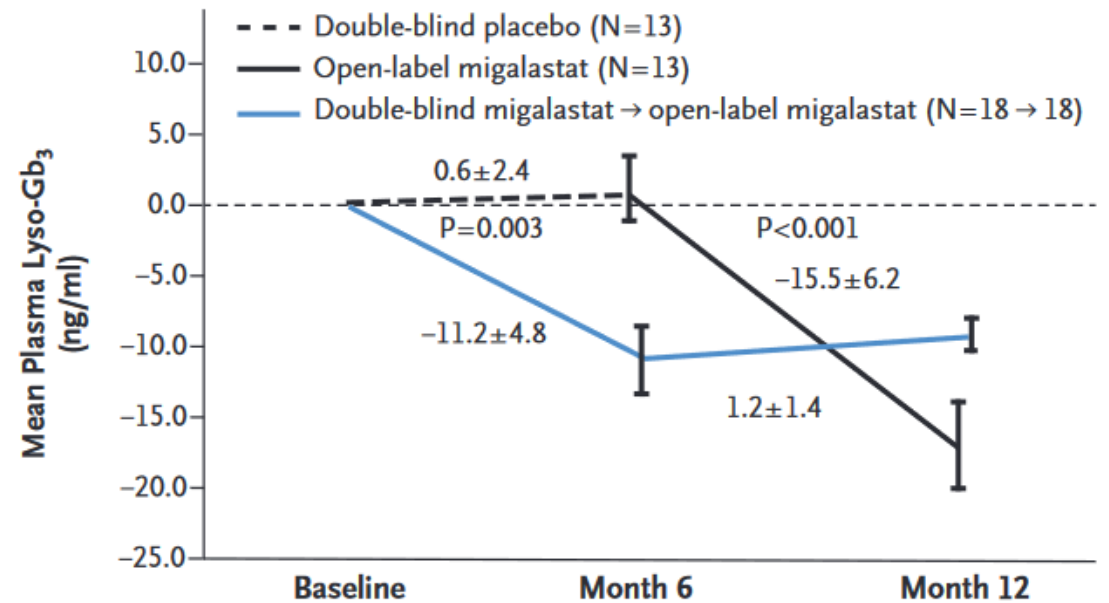
Migalastat in clinical trials: FACETS trial

Double blind, randomized, placebo controlled trial

67 patients were randomized to six months double-blind Migalastat or placebo, followed by open-labeled Migalastat for six to 12 months.



Patients with responsive mutant α -galactosidase showed decreases in GL-3 in glomerular podocytes (5 of 23 samples, 22%), endothelial cells (6 of 23 samples, 26%), and mesangial cells (11 of 23 samples, 48%).



Among migalastat-treated patients in the ITT population with suitable mutant α -galactosidase, symptoms decreased in three domains (diarrhea, reflux, and indigestion) of five domains in the Gastrointestinal Symptom Rating Scale

N Engl J Med 2016;375:545-55.

Table 2. Changes in Echocardiographic-Derived Left-Ventricular-Mass (LVM) Index from Baseline to Month 18 or 24.*

Population	LVM Index at Baseline <i>g/m²</i>	Change in LVM Index from Baseline to Month 18 or 24† <i>g/m² (95% CI)</i>
Patients with suitable mutant α -galactosidase		
No. of patients	44	27
Mean value	96.5±5.0	−7.7±3.7 (−15.4 to −0.01)‡
Patients with suitable mutant α -galactosidase and LVH at baseline		
No. of patients	11	8
Mean value	138.9±11.0	−18.6±8.3 (−38.2 to 1.0)



A total of 125 patients with Fabry disease and amenable variants were treated with at least 3 years of migalastat...

n=75
male

58 years
Median age

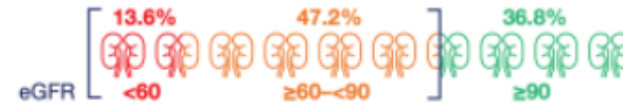
n=50
female



Migalastat
(123 mg every other day)

At enrollment:
61%

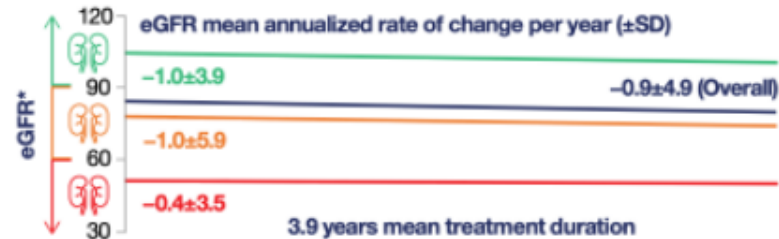
of patients had
renal involvement



of patients had
multiorgan involvement



Renal function
remained stable
over 3.9 years
of migalastat
treatment



Despite population age
and baseline morbidity,
80% of patients did
not experience a
Fabry-associated
clinical event (FACE)



19.2%
experienced
cardiac events



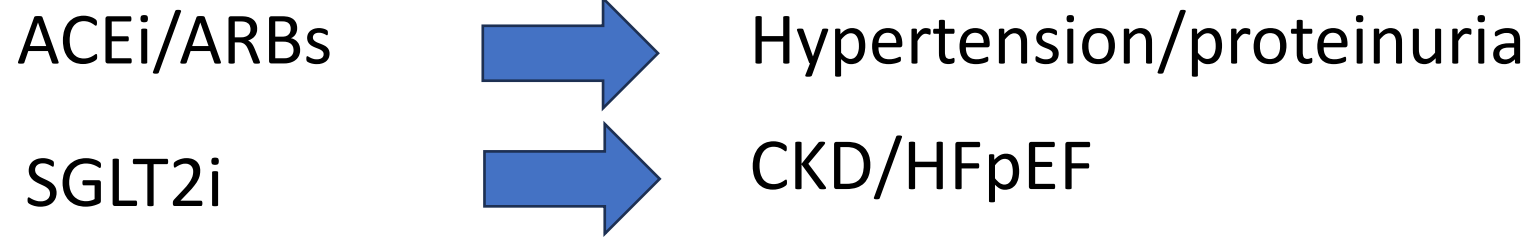
0.8%
experienced
renal events



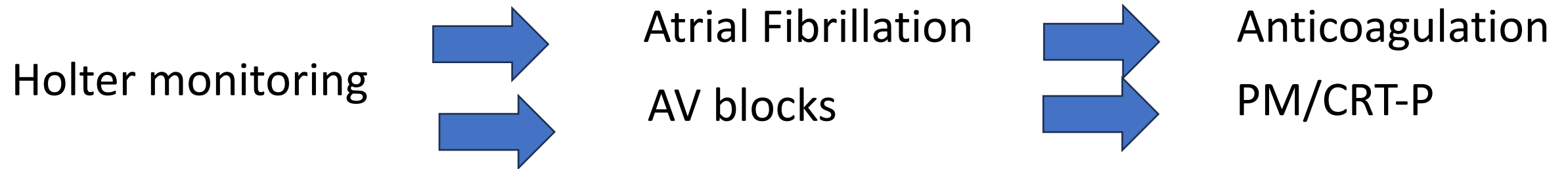
1.6%
experienced
cerebrovascular events

Findings reinforce the multisystem treatment benefits of migalastat, including preserved renal function and low incidence of FACES, in this older, geographically diverse Fabry population with significant disease

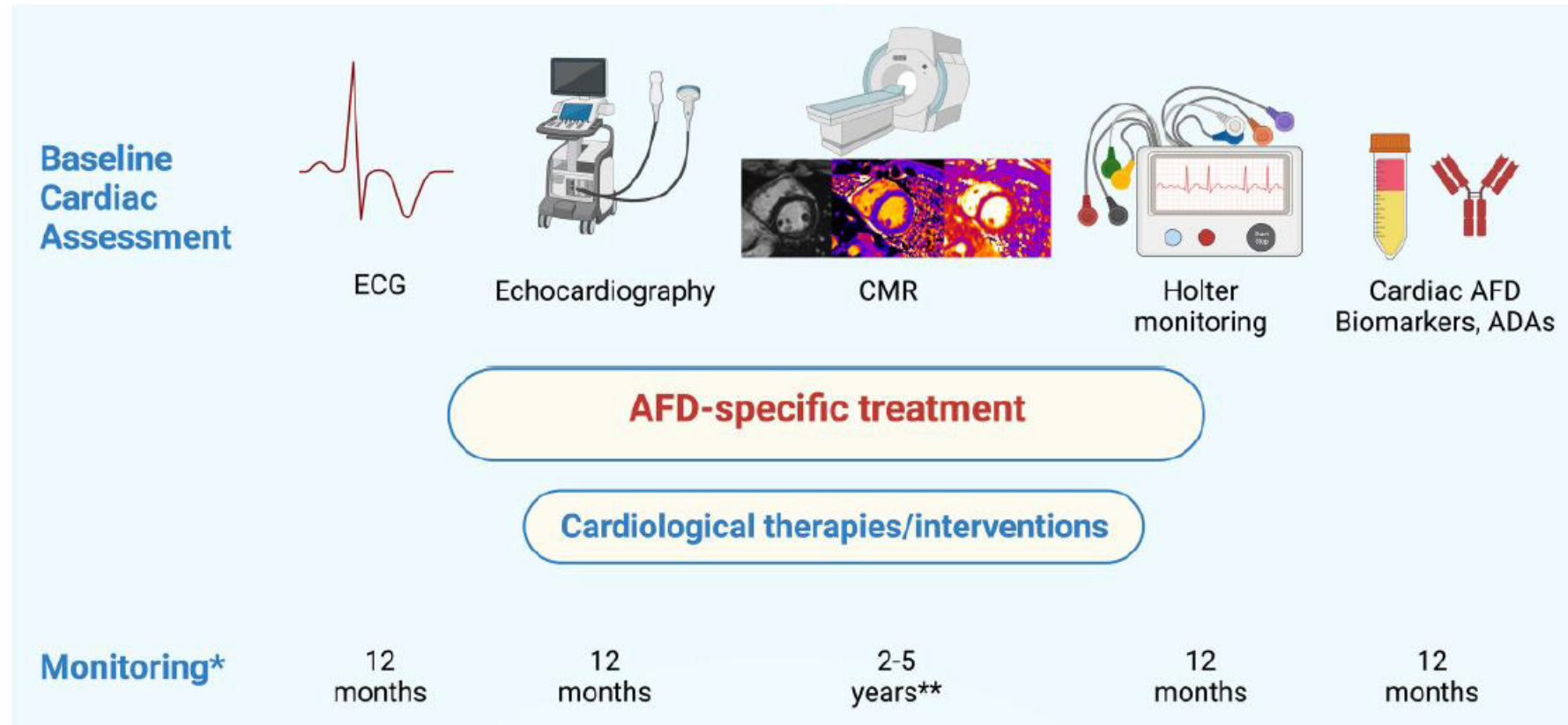
Management of cardiac complications



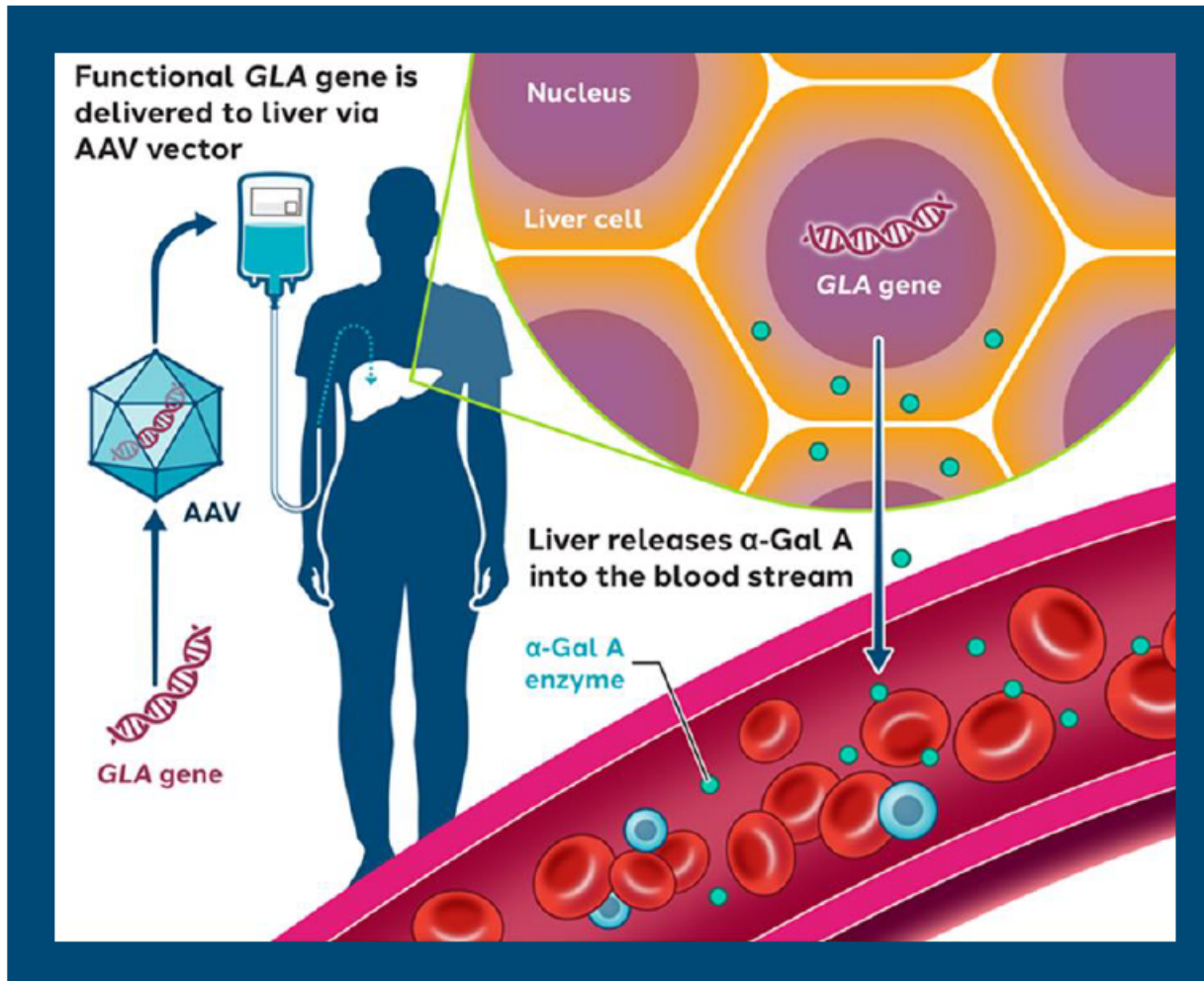
Beta blockers are poorly tolerated due to chronotropic incompetence



Disease monitoring



— Isargalgene civaparvovec (ST-920) for Fabry Disease Treatment



Potential Advantages

- Safe, one-time administration
- Eliminate ERT infusions
- Durable efficacy
- Low immunogenicity
- No prophylaxis with steroids or other immunomodulating agents

– Dose escalation phase: classic Fabry disease males baseline characteristics

		FOS-MSSI								
vg/kg		Age (years)	ERT	Total Max 65.5	General Max 14.5	Neuro Max 15 	Cardiac Max 18 	Renal Max 18 	GLA Mutation	Length of Follow up
Cohort 1 0.5×10^{13}	1	48	Agalsidase beta	Moderate 30.5	6.5	7	13	4	G261D	26 M
	2	25	Pseudo naïve	Mild 12	4	8	0	0	T141I	25 M
Cohort 2 1×10^{13}	3	42	Pseudo naïve	Moderate 20.5	8.5	9	3	0	W340R	21 M
	4	22	Agalsidase beta	Mild 10	4	6	0	0	S297Y	17 M
Cohort 3 3×10^{13}	5	39	Agalsidase beta	Moderate 23	5	8	6	4	Q283X	12 M
	6	42	Agalsidase beta	Mild 18.5	8.5	2	8	0	N215S	9 M
	7	51	Agalsidase beta	Severe 40.5	11.5	12	13	4	c.801+3A>G	6 M
Cohort 4 5×10^{13}	8	49	Naïve	Moderate 20	2	1	9	8	P362L	6 M
	9	40	Naïve	Mild 18.5	3.5	6	9	0	T141I	6 M

Data cut-off date: October 20, 2022

Participants in the dose escalation phase are representative of males with classic Fabry disease

- Participants generally had mild to moderate disease severity
 - Mild = 44.4% (4/9)
 - Moderate = 44.4% (4/9)
 - Severe = 11.1% (1/9)
- Range of organ involvement is variable among participants
 - Renal involvement present in 44% at baseline (4/9)
 - Cardiac manifestations present at baseline in 78% (7/9)

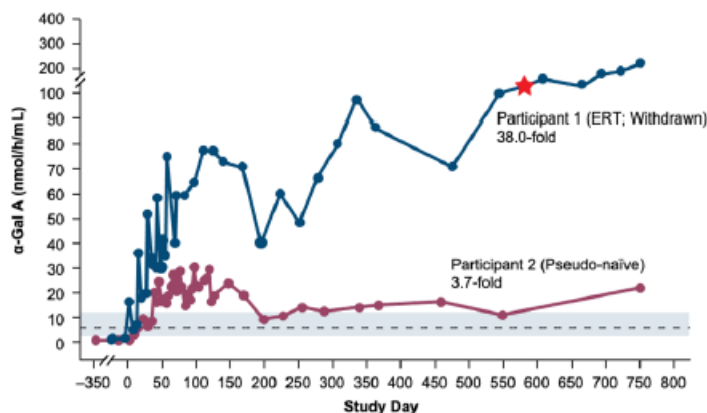
— Expansion phase: baseline characteristics
all treated with 5×10^{13} vg/kg

		FOS-MSSI								
		Age (years)	ERT	Total Max 65.5	General Max 14.5	Neuro Max 15 	Cardiac Max 18 	Renal Max 18 	GLA Mutation	Length of Follow up
Cardiac	12	67 Female	Agalsidase beta	Mild 17.5	5.5	3	9	0	D266N	4 W
α-Gal A Ab Positive Males	10	34	Pseudo naïve	Moderate 32.5	7.5	7	14	4	N34S	10 W
	11	49	Agalsidase beta	Moderate 28	12	9	3	4	Y134S	9W
	13	38	Agalsidase beta	Mild 17.5	6.5	5	6	0	A348Gfs X27 insertion	2 W

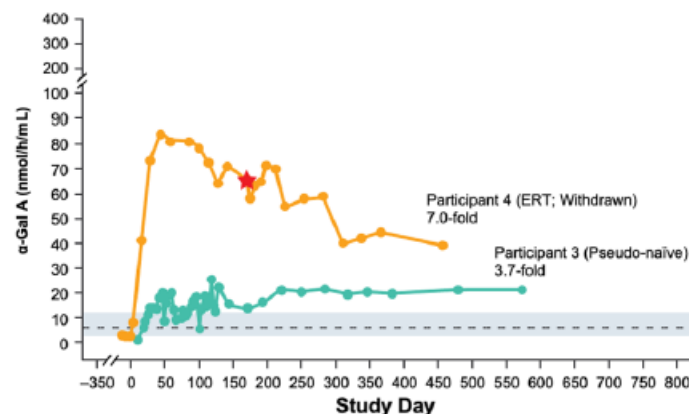
- To date, Expansion Phase participants treated with ST-920 had mild or moderate disease severity
 - Mild = 50% (2/4)
 - Moderate = 50% (2/4)

Rapid, predictable and stable expression of α -Gal A activity occurred in all Dose Escalation cohorts

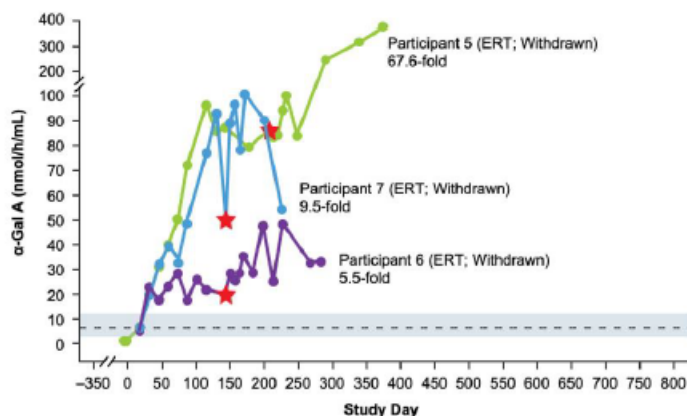
Cohort 1: 0.5×10^{13} vg/kg, N = 2



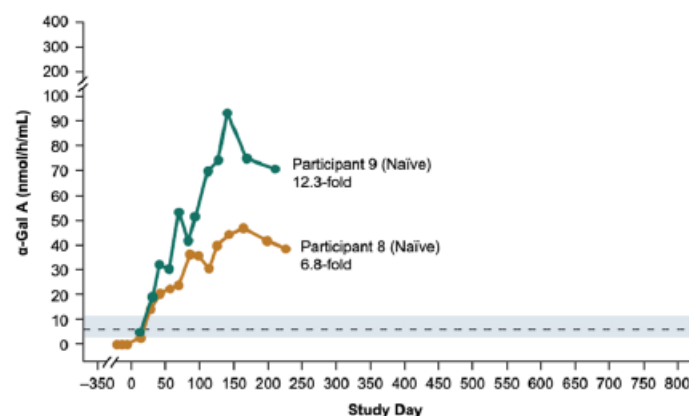
Cohort 2: 1×10^{13} vg/kg, N = 2



Cohort 3: 3×10^{13} vg/kg, N = 3



Cohort 4: 5×10^{13} vg/kg, N = 2



■ Normal range (2.45 - 11.37) --- Mean Normal 5.70 ★ ERT Withdrawal

Data cut-off date: November 15, 2022

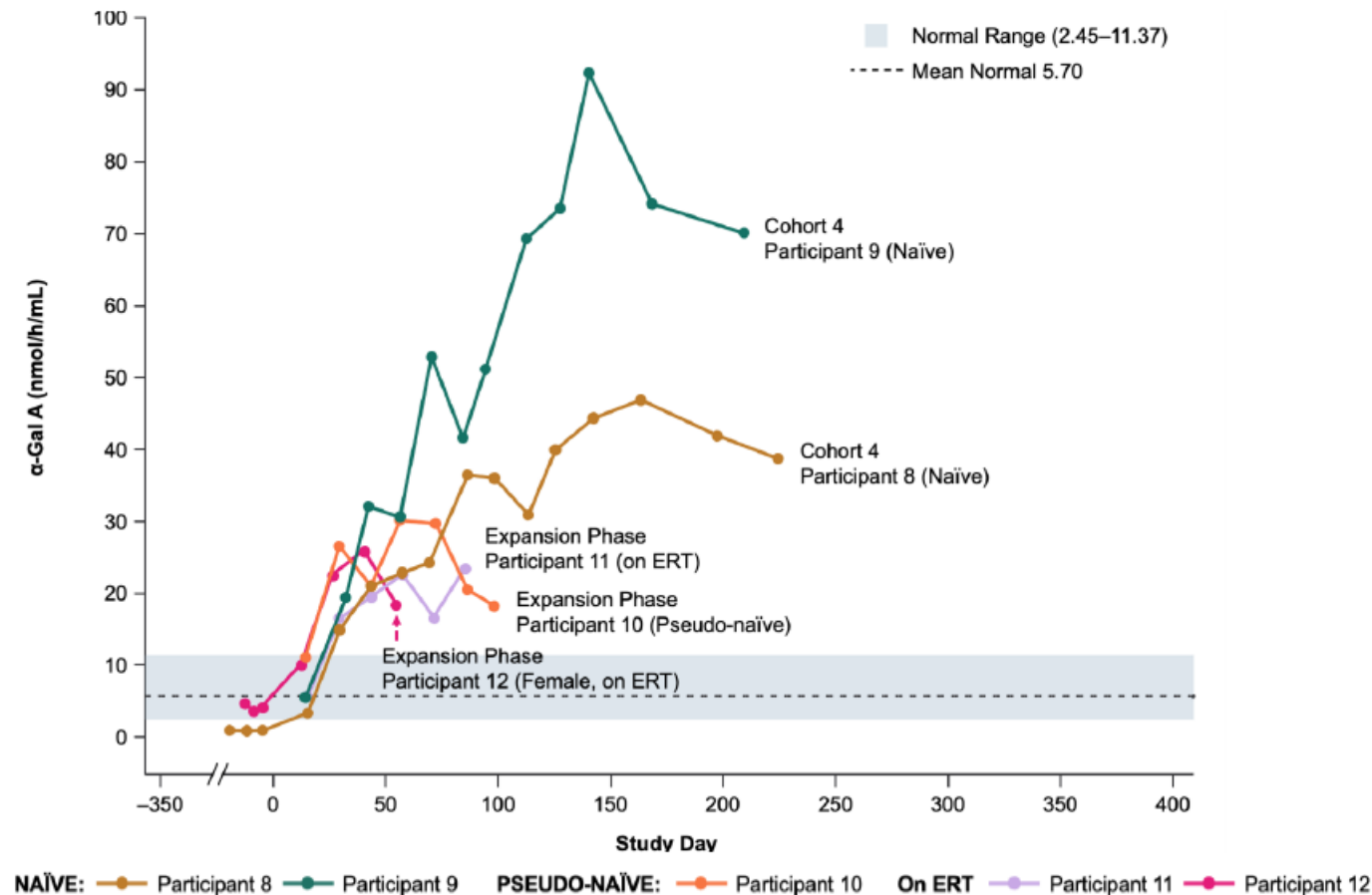
α -Gal A activity measured using 3-hour reaction time. Normal range determined in healthy males.

Fold change from normal mean was calculated at last measured time point. Long Term Follow-up Data: Data points > Study Day 365.

α -Gal A, alpha-galactosidase A; ERT, enzyme replacement therapy

- Rapid and predictable increase in α -Gal A activity observed in all participants 4-8 weeks after dosing
- Supraphysiological α -Gal A activity maintained in all participants
- ERT withdrawal completed for all 5 participants – with continued supraphysiological activity following withdrawal
- ST-920 expression observed was durable, with α -Gal A activity at supraphysiological levels maintained in all participants, up to more than two years

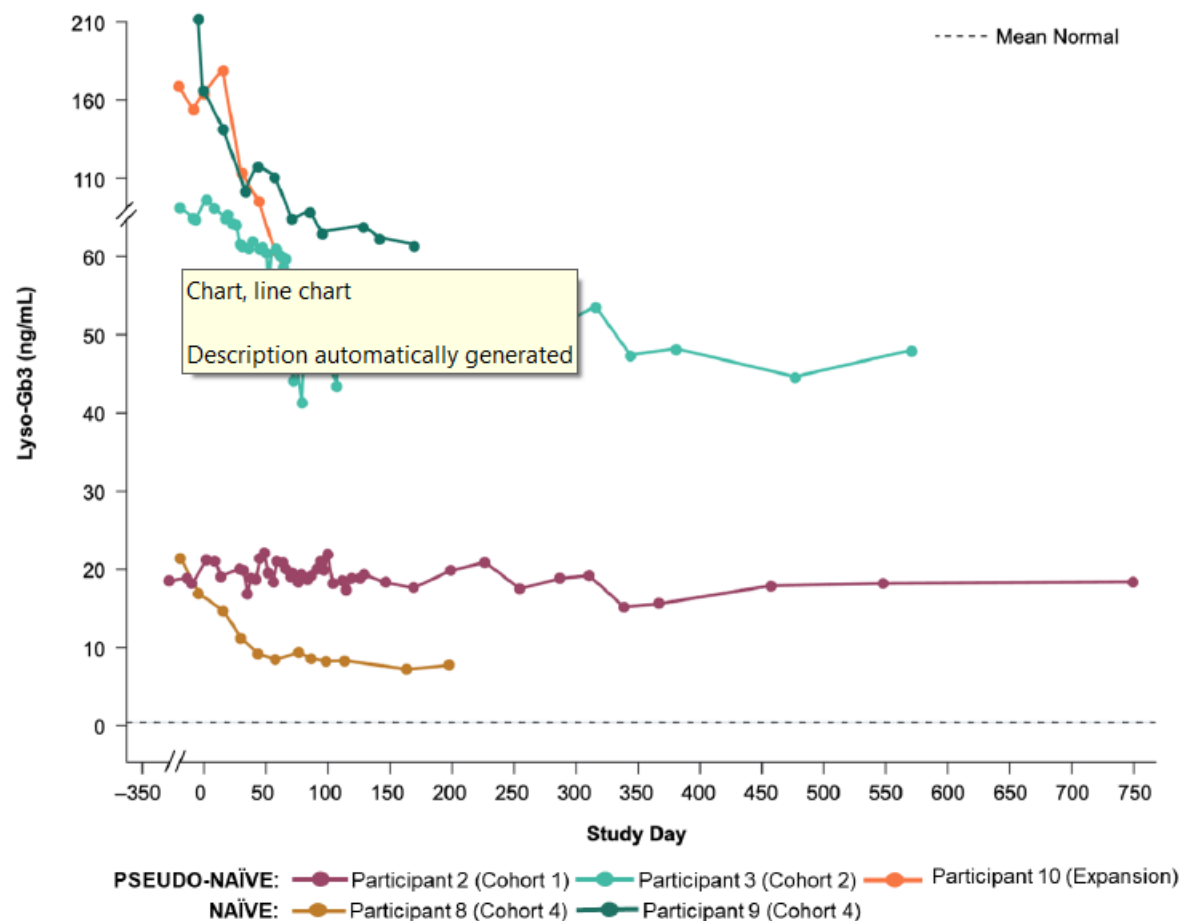
— The proposed Phase 3 clinical trial dose (5×10^{13} vg/kg) produced rapid, sustained increases in α -Gal A activity in Dose Escalation (Cohort 4) and Expansion Phase participants



Data cut-off date: November 15, 2022
 Participant 13: Week 6: 3.97 nmol/h/mL.
 α -Gal A activity measured using 3-hour reaction time. Normal range determined in healthy males.
 Long Term Follow-up Data: Data points > Study Day 365
 α -Gal A, alpha-galactosidase A; ERT, enzyme replacement therapy

- The highest dose (5×10^{13} vg/kg) produced rapid, predictable and durable increases in plasma α -Gal A activity across all participants as of the data cut-off
- The female participant has demonstrated a similar response profile to males as of the data cut-off

ST-920 effectively lowered plasma Lyso-Gb3 in naïve and pseudo-naïve participants across Dose Escalation and Expansion Phases



Data cut-off date: October 20, 2022

Lyso-Gb3 normal range determined in healthy males and females

Normal range for males and females combined 0.32 to 0.63 ng/mL

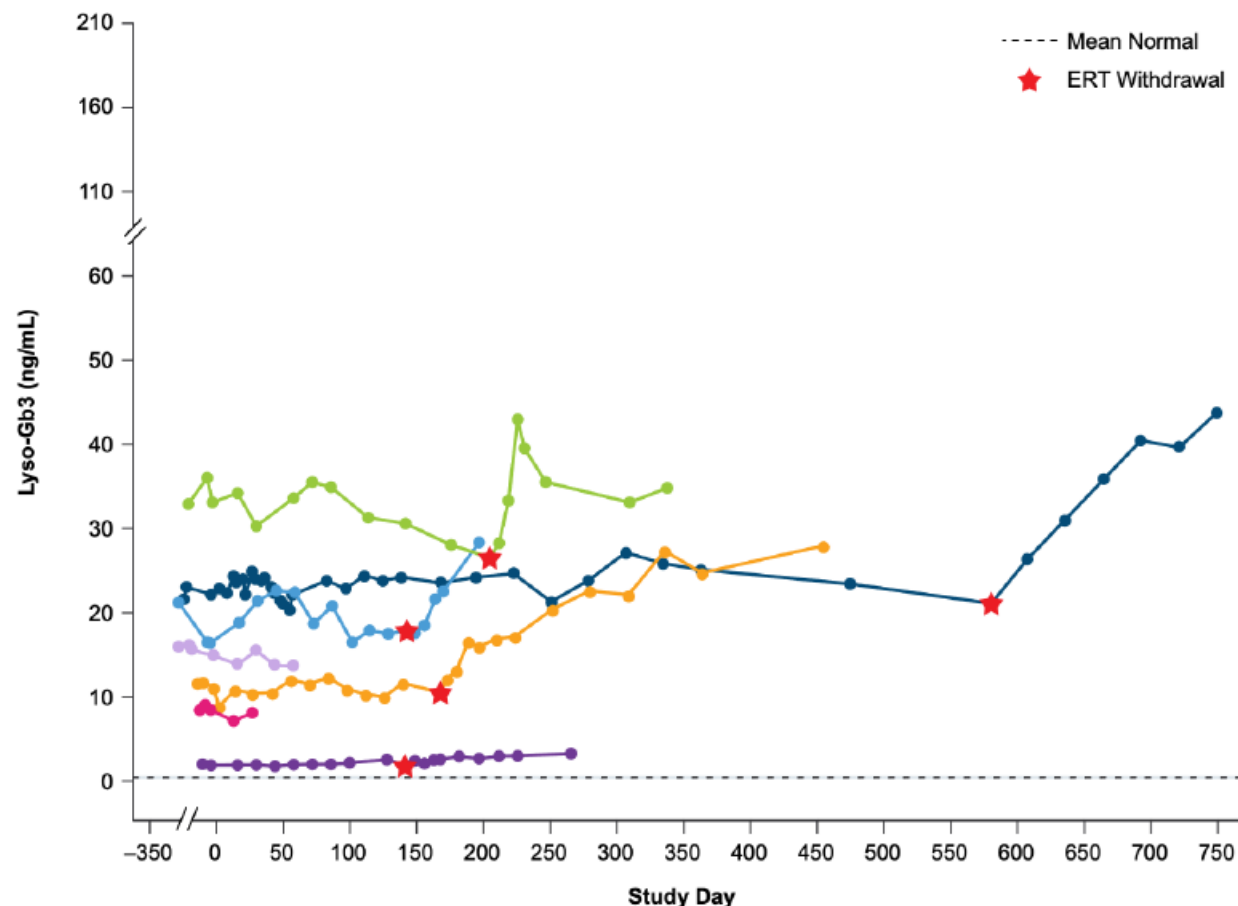
*The time point immediately preceding ST-920 administration was presented as the baseline value and used to calculate percent reduction

Long Term Follow-up Data: Data points > Study Day 365

Lyso-Gb3, globotriaosylsphingosine

- Where baseline levels of Lyso-Gb3 started high (>80 ng/mL), participants experienced a 40% to 65%* reduction in plasma levels
- For the first time, at the high dose, we observed a further reduction (54%) in Lyso-Gb3 where baseline plasma levels started lower (<25 ng/mL)
- Plasma Lyso-Gb3 continued to decrease in two participants
- Plasma Lyso-Gb3 levels were stable up to 25 months

Plasma Lyso-Gb3 in ERT-treated dose escalation and expansion phase participants



ESCALATION PHASE — Participant 1 (Cohort 1) — Participant 4 (Cohort 2) — Participant 5 (Cohort 3) — Participant 6 (Cohort 3) — Participant 7 (Cohort 3)

EXPANSION PHASE — Participant 11 — Participant 12

Data cut-off date: October 20, 2022

Participant 13: Week 2 34.5 ng/mL

Lyso-Gb3 normal range determined in healthy males and females

Normal range for males and females combined 0.32 to 0.63 ng/mL

Long Term Follow-up Data: Data points > Study Day 365

Lyso-Gb3. *globotriaosylsphingosine*: ERT, enzyme replacement therapy

Dose Escalation Phase

- ERT withdrawal was successful in all ERT-treated participants
- Lyso-Gb3 levels following ERT withdrawal remained within the range of levels and variability normally observed in participants treated with ERT^{1, 2, 3}
- In these participants, α -Gal A activity remained elevated, and no participant has experienced symptoms requiring the resumption of ERT

Expansion Phase

- At this data cut, ERT withdrawal had not yet been initiated for any participant

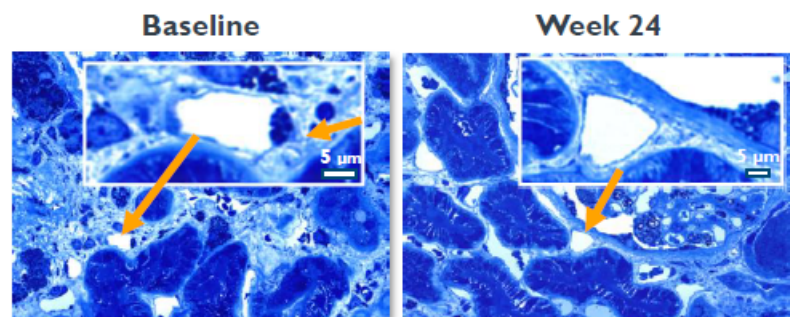
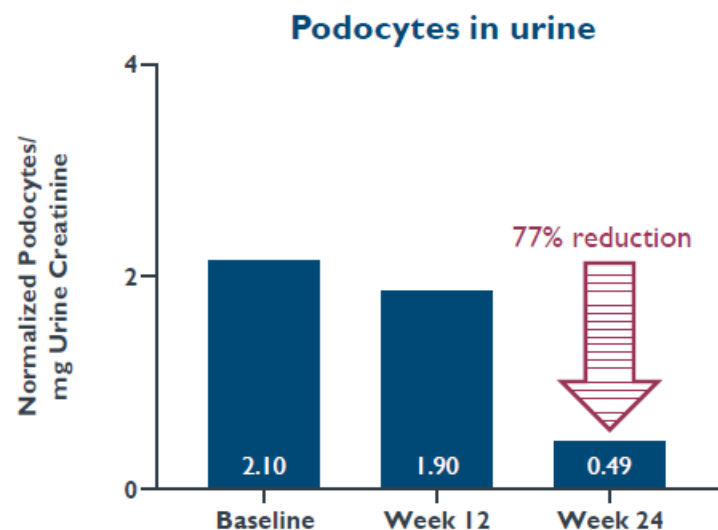
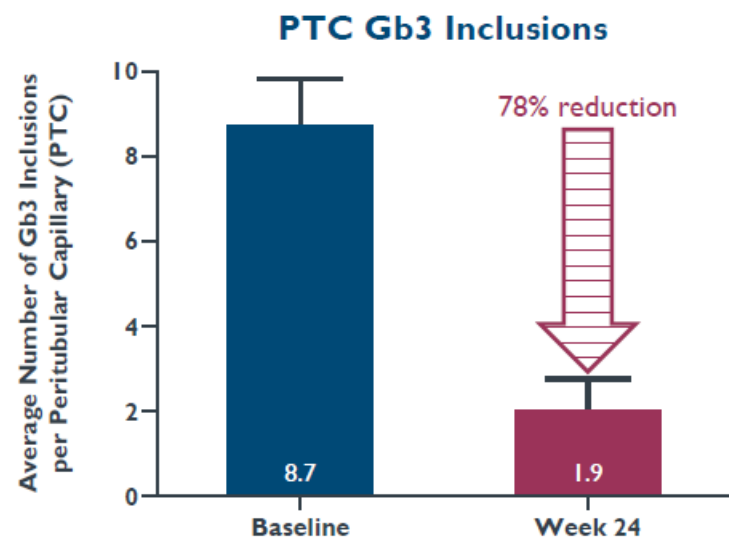
1. Arends, M., M et al. 2018. *J Med Genet*, 55: 351-58.

2. Nowak, A., F. et al. 2022. *J Med Genet*, 59: 287-93.

3. Kramer, J., M. et al. 2018. *Nephrol Dial Transplant*, 33: 1362-72.

Participant 9: biomarkers of nephropathy significantly improved. Reduced renal Gb3 inclusions and podocyuria

Cohort 4 (5×10^{13} vg/kg) - high number of Gb3 inclusions and lyso-Gb3 at baseline



Representative PTC Images

	Baseline	Week 24	Change
Plasma α -Gal A activity (nmol/h/mL)	Below LOQ	74.2	13 $\times$ Mean Normal
Plasma lyso-Gb3 (ng/mL)	167	66.8	60% $\downarrow$

- ST-920 cleared 78% of Gb3 inclusions from peritubular capillaries
- ST-920 also reduced urinary podocyte loss by 77%
- This participant exhibited significant increase in α -Gal A activity and reduction in lyso-Gb3 after dosing with ST-920
- The significant decrease in renal Gb3 inclusions and the reduction in urine podocyte loss support a potential favorable impact on progression of Fabry nephropathy

Data cut-off date: October 20, 2022

Podocyte quantification was performed via immunofluorescence with urine creatinine normalization.

The Barisoni Lipid Inclusion Scoring System (BLISS) was used in a blinded manner by 3 independent pathologists to quantify PTC Gb3 inclusions. Lines above the bars indicate standard deviation.

α -Gal A, alpha-galactosidase A; ERT, enzyme replacement therapy; PTC, peritubular capillary; lyso-Gb3, globotriaosylsphingosine; Gb3, globotriaosylceramide

– Conclusion | Isaralgagene civaparvovec (ST-920)



EVIDENCE OF EFFICACY IN FABRY DISEASE

- Clearance or stabilization of renal Gb3 inclusions along with reductions in urine podocyte loss suggest a favorable impact on progression of Fabry nephropathy
- Stable expression of α -Galactosidase A activity in 13 participants for over two years for the longest treated participant
- All participants in the Dose Escalation phase who commenced the study on ERT have been successfully withdrawn from ERT and remain off ERT with sustained supraphysiological levels of α -Galactosidase A activity
- 40% to 65% plasma Lyso-Gb3 reduction in naïve/pseudo-naïve participants with high plasma Lyso-Gb3
- Lyso-Gb3 levels following ERT withdrawal remained within the range of levels and variability normally observed in participants treated with ERT
- Clinically meaningful and statistically significant increase in mean general health scores



FAVORABLE SAFETY PROFILE TO DATE

- Generally well tolerated at all doses (0.5×10^{13} to 5×10^{13} vg/kg)
 - Classic males (n=12) and a female (n=1)
 - ERT-treated and ERT-naïve participants



LOW AAV2/6 CAPSID IMMUNOGENICITY

- No requirement for prophylactic corticosteroids or other immune modulating agents



THE PROPOSED PHASE 3 STUDY DOSE IS 5×10^{13} VG/KG

- The Phase 1/2 STAAR study Expansion Phase is ongoing, with a further four participants dosed since the October 20, 2022 cut-off date. Phase 3 preparation is in progress.

2023 Update

24 patients dosed 13 (54%) were on ERT and 10 (42%) had mild to moderate renal dysfunction at baseline.

Safety:

- Isaralgagene civaparvovec was well-tolerated. Most common adverse events were pyrexia, headache, COVID-19, fatigue and nasopharyngitis (majority Grade 1/2, with one Grade 3 pyrexia).

- No LFT elevations post-dosing requiring steroids occurred. No prophylactic steroids or other immunomodulatory agents were administered, as per protocol.

Efficacy (all dosed patients):

- In dose escalation and dose expansion phases: exhibited sustained, elevated expression of α -Gal A activity for up to three years in the longest treated patient.

- The ERT naïve or pseudo-naïve patients receiving the highest dose (2.63×10^{13}) showed sustained supraphysiological α -Gal A activity up to nearly 500 days, with the largest reductions in plasma globotriaosylsphingosine (lyso-Gb3) levels seen in those subjects with the highest levels at baseline.

- All 12 patients who began the study on ERT and have subsequently been withdrawn from ERT, remained off ERT as of the September 19, 2023 data cutoff date.

- Seven patients had measurable titers of total antibodies (Ab) or neutralizing antibodies (Nab) against α -Gal A associated with ERT at baseline. Following dosing, total Ab or NAb titers decreased markedly in all seven patients and became undetectable in five. Isaralgagene civaparvovec did not induce anti- α -Gal A antibodies in seronegative patients.

Efficacy (13 patients followed for 12 months or more):

- Renal function remained stable, as evidenced by a mean annualized estimated glomerular filtration rate (eGFR) slope of -0.915 mL/min/1.73m²/year.
- Statistically significant improvements in disease severity were reported in the Fabry Outcome Survey adaptation of the Mainz Severity Score Index (FOS-MSSI) age-adjusted score at week 52 (p=0.0269).
- Four patients improved their overall FOS-MSSI disease category (e.g., improving from 'Moderate' to 'Mild' categorization of Fabry disease compared to their baseline category) at week 52. Three of these individuals were on ERT at baseline, demonstrating the potential clinical benefit of isaralgagene civaparvovec over the currently approved standard of care.
- Significant improvements in the short form-36 (SF-36) QoL scores were reported, with mean changes in the General Health and Physical Component scores of 10.5 (p=0.0158) and 4.395 (p=0.0140), respectively, at week 52. For context, a 3- to 5-point change on any SF-36 score is the minimally clinically important difference.
- Significant improvements in the gastrointestinal symptom rating scale (GSRS) compared to baseline were also reported at week 52 (p=0.0226).
- Collectively, we believe these data support the potential for isaralgagene civaparvovec to be a promising new treatment option for previously treated and untreated patients with Fabry disease.

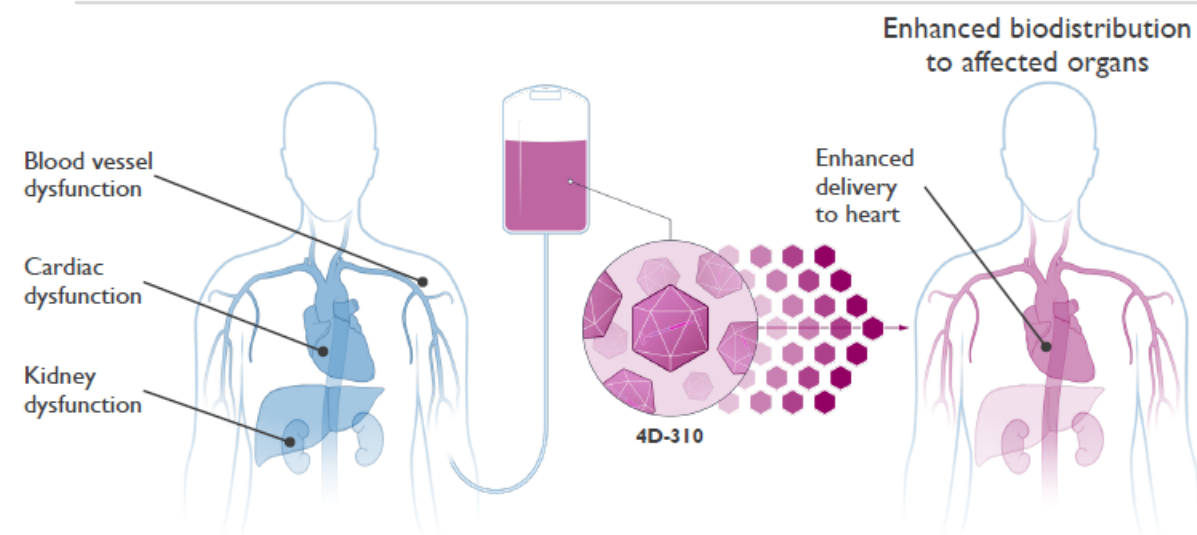
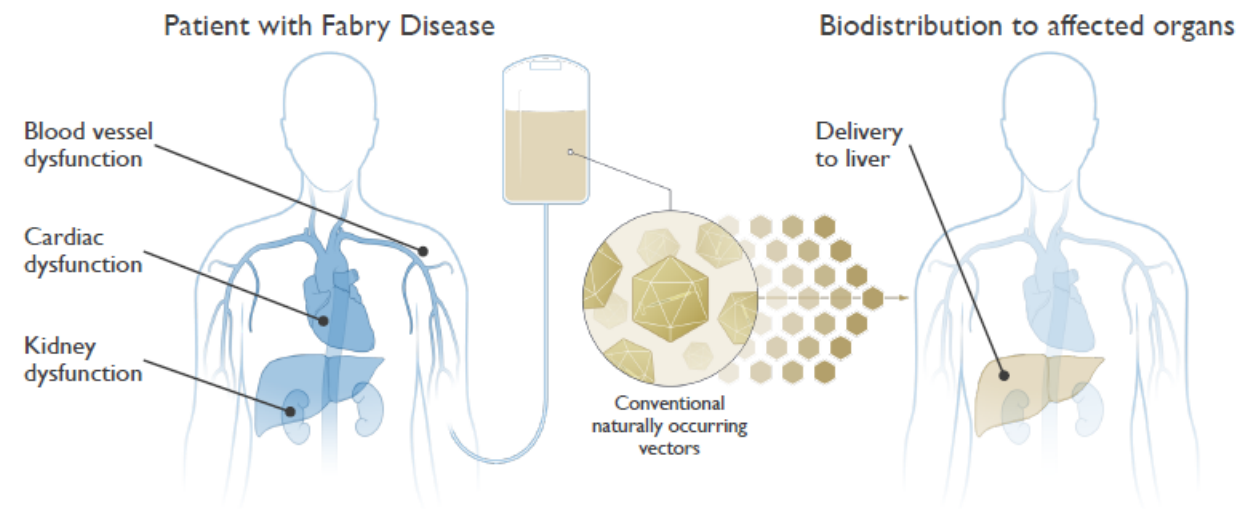
2024 update

Sustained elevated expression of alpha-galactosidase A (α -Gal A) activity maintained for up to three years for the longest-treated patient as of the data cutoff date.

- All 12 patients withdrawn from enzyme replacement therapy (ERT) remain off ERT, with sustained elevated α -Gal A activity observed for up to 19 months as of the data cutoff date.*
- Total antibody (Ab) or neutralizing antibody (Nab) titers against α -Gal A decreased markedly in all seven patients with antibodies associated with ERT at baseline, and became undetectable in five.*
- In the 13 patients followed for 12 months or more after treatment, renal function remained stable and significant improvements in overall disease severity, quality of life (QoL) and gastrointestinal symptoms compared to baseline were reported.*
- Continued favorable safety profile, with no liver function test (LFT) elevations requiring steroids post-treatment.*
- Since the data cutoff date, four additional patients have been dosed. Enrollment in Phase 1/2 STAAR study is now complete, with dosing of remaining patients expected in the first half of 2024.*

4D-310 Product Design & C102 Target Vector Profile for Heart

INVENTED FOR LOW DOSE IV DELIVERY TO THE HEART IN NHP & HUMANS



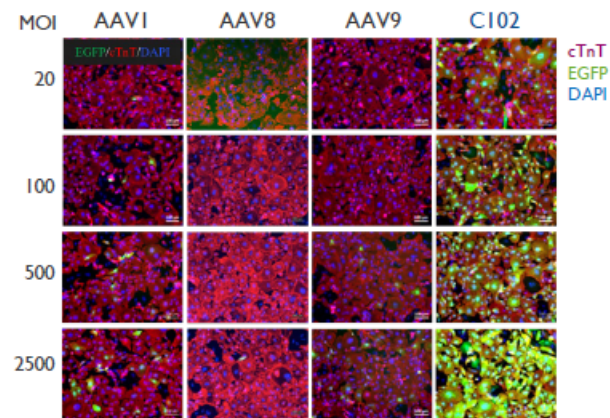
Our Product



PRODUCT DESIGN

- **Vector:** C102
- **Transgene:** *GLA* (encodes AGA enzyme)
- **Promoter:** Ubiquitous

Improved Transduction: Human Cardiomyocytes



Human ventricular cardiomyocytes EGFP immunofluorescence in vitro

Baseline Characteristics: INGLAXA-1 & INGLAXA-2

COHORT 1 (IEI3 vg/kg + CORTICOSTEROID IMMUNE REGIMEN; N=6)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age, years	51	32	26	19	57	69
Race/ethnicity	Hispanic/Latino	White	White	NR	Asian	White
Disease classification	Classic	Classic	Classic	Late onset	Late onset	Late onset
Variant	c.1023A>C	c.708G>T	c.974G>A	c.671A>G	c.639+919G>A	c.644A>G
Serum AGA activity, nmol/hr/mL*	0.42	0.00	0.30	0.06	1.62	0.18
Serum lyso-Gb3, ng/mL†	6.28	101.0	8.78	45.0	3.79	2.03
ERT experience	Yes	Yes	Yes	No	Yes	Yes
ERT status at enrollment	On	Off	On	ERT naïve‡	On	Off‡
Anti-AGA antibody titer	1:947 (l)	1:99,900 (h)	1:13,900 (m)	Negative	Negative	Negative
Peak VO ₂ mL/kg/min % predicted	21.4 (wk 26) 72.0 (wk 26)	14.0 33.0	23.0 66.1	19.1 30.3	24.8 76.0	28.2 120.2
Global longitudinal strain, %	-17.10	-22.17	-18.83	-23.27	-21.95	-20.63
eGFR, mL/min/1.73m ² ¶	107	130	125	142	77	62

Cardiac Assessments: Improvement in All FIVE Cardiac Endpoints (4 Patients)

SIGNIFICANT IMPROVEMENTS IN ALL 5 CARDIAC ENDPOINTS

		ERT Natural History (12 months)	4D-310 IE13 vg/kg 12 months (n=3) Biopsy wk 6 (n=1)
Exercise capacity (peak VO ₂) <i>FDA-recommended primary endpoint</i>	CPET*	Worsened ¹	Improved in 2 of 3
Cardiac quality of life (physical limitations, symptoms) <i>FDA-recommended primary endpoint</i>	KCCQ	n.a.	Improved in 2 of 2, stable in 3rd
Cardiac contractility (global longitudinal strain) <i>FDA-recommended supportive endpoint</i>	Echocardiogram*	Worsened ²	Improved in 3 of 3
Substrate accumulation (native T1 signal) <i>Exploratory endpoint</i>	Cardiac MRI*	Worsened ²	Improved in 2 of 3
Transgene delivery & expression <i>Exploratory endpoint (INGLAXA-2)</i>	Cardiac Biopsy (INGLAXA-2 trial only)	Negative ³	Widespread delivery & expression

*Assessed by independent central reading center. CPET, cardiopulmonary exercise test; KCCQ, Kansas City Cardiomyopathy Questionnaire; MRI, magnetic resonance imaging;

1. Lobo et al. *Intern Med J* 2008;38:407. 2. Nordin et al. *Circ Cardiovasc Imaging* 2019:e009430. 3. Thurberg et al. *Circulation* 2009;119:2561–7.

Global Longitudinal Strain (ECHO): 3 of 3 Responders

Global Longitudinal Strain (%)

Patient	Screening	Week 52	Change
1	-17.10 (Borderline)	-19.6	-2.5
2*	-22.17 (Normal)	-23.27	-1.1
3	-18.83 (Borderline)	-22.1	-3.3
ERT†	-13.2‡	-12.1‡	+1.1‡

GLS was measured in 3 apical views (4-, 3- and 2-chamber); the average value is shown.

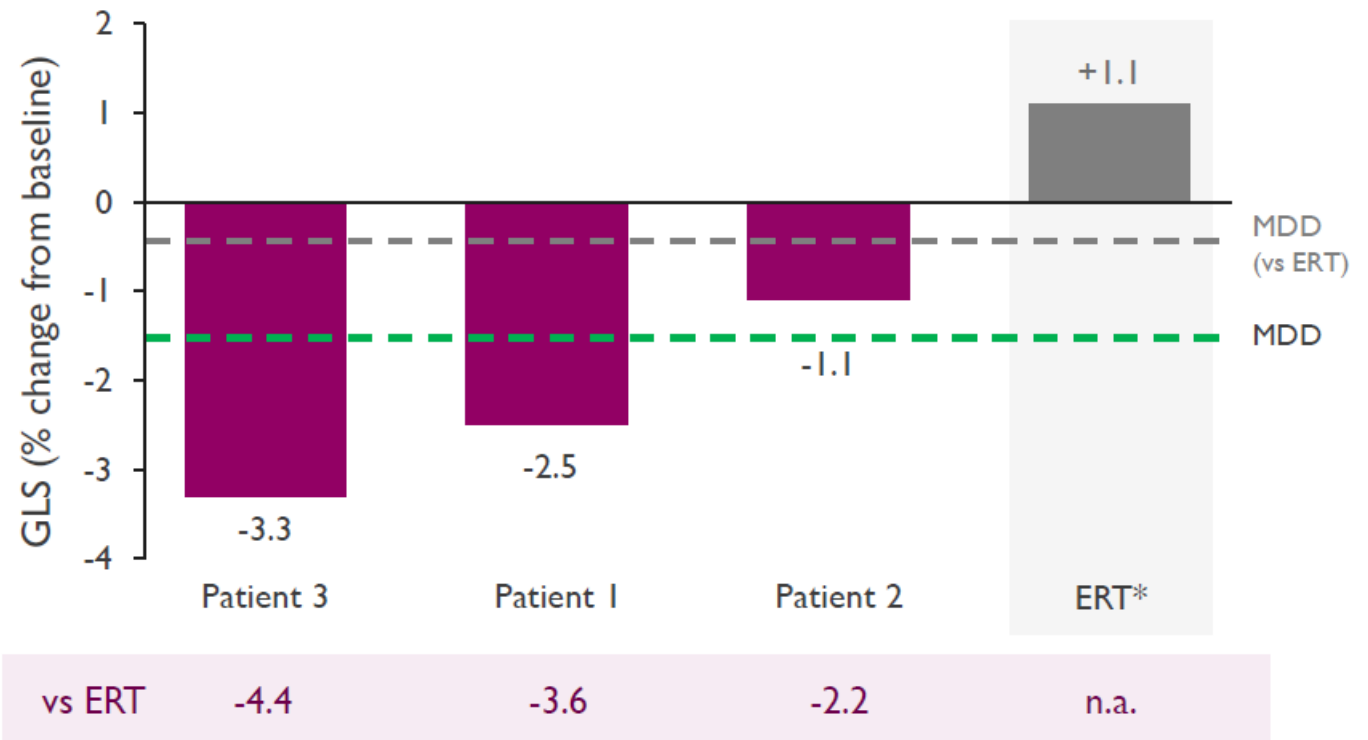
GLS range (borderline), -16.0 to -18.0% [1]; (low), >-15.9%. Minimal detectable difference, 1.5% [2].

*High antibody titer, entered study off ERT.

†Historical control (N=18); median duration of ERT, 4.2 years (range, 1.4–12.2) [3].

‡Mean value.

Change from Baseline to Week 52 (Responders)



*Historical control (N=18); median duration of ERT, 4.2 years (range, 1.4–12.2) [3].

Peak VO₂ (Cardiopulmonary Exercise Testing): 2 of 3 Responders

Peak VO₂ Measurements

Pt	Peak VO ₂	Screening	Week 26	Week 52	Change
1	mL/kg/min	na	21.4	23.4	+2.0*
	% predicted	na	72.0	78.3	+6.3*
2†	mL/kg/min	14.0	na	21.0	+7.0
	% predicted	33.0	na	50.0	+17.0
3	mL/kg/min	23.0	23.4	20.8	-2.2
	% predicted	66.1	65.8	58.3	-7.8
ERT‡	VO ₂ max (mL/kg/min)	24.1 [¶]	NR	22.4 [¶]	-1.8 [¶]

Minimal clinically important difference, 1.5 mL/kg/min [1].

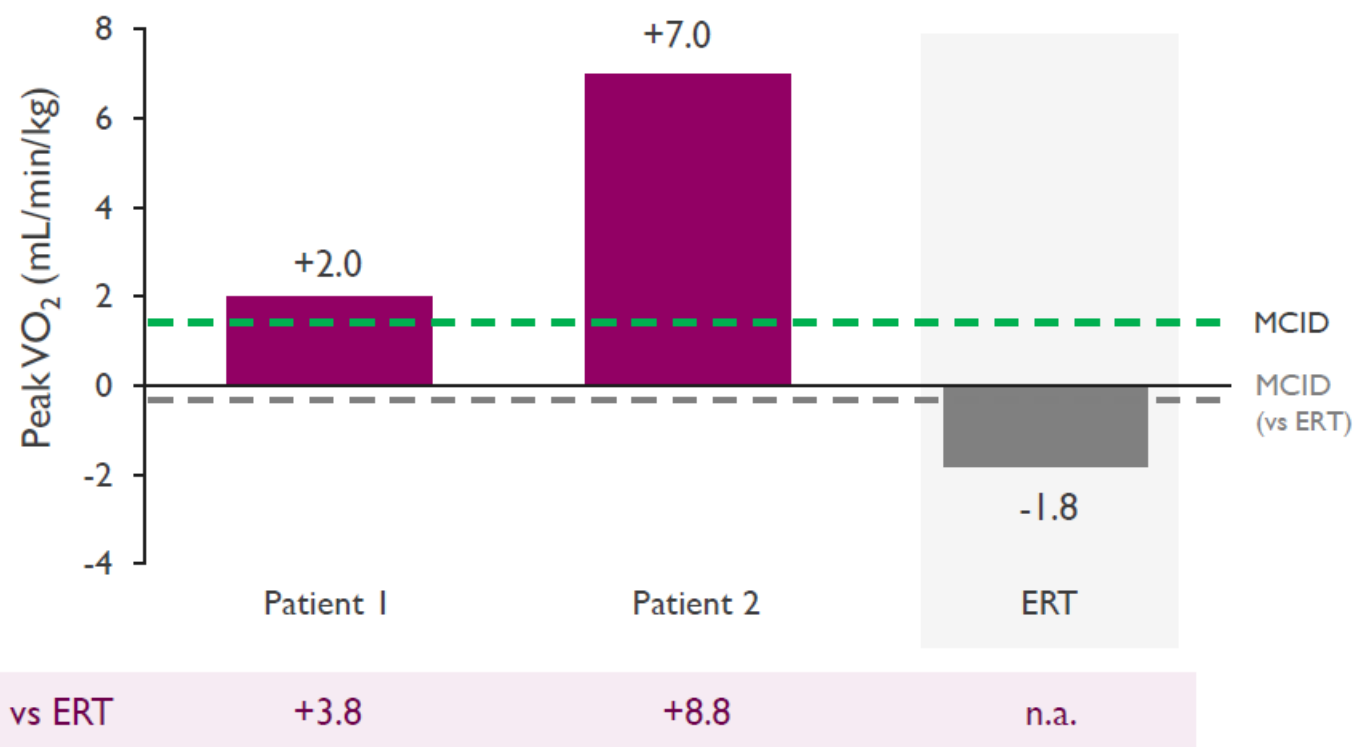
*Calculated as change from Week 26 to Week 52.

†High antibody titer, entered study off ERT.

‡Historical control (N=14); median duration of ERT, 48 months [2].

¶Mean value.

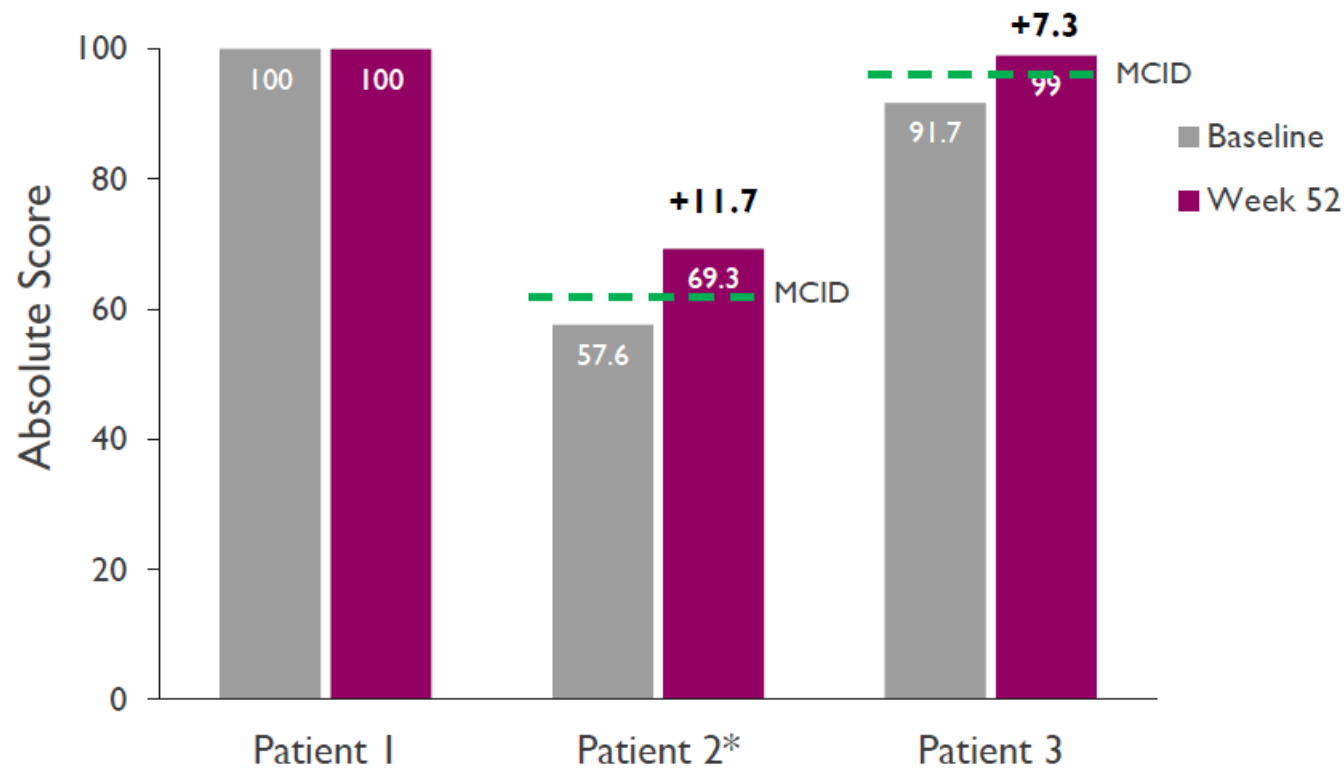
Change from Baseline to Week 52 (Responders)



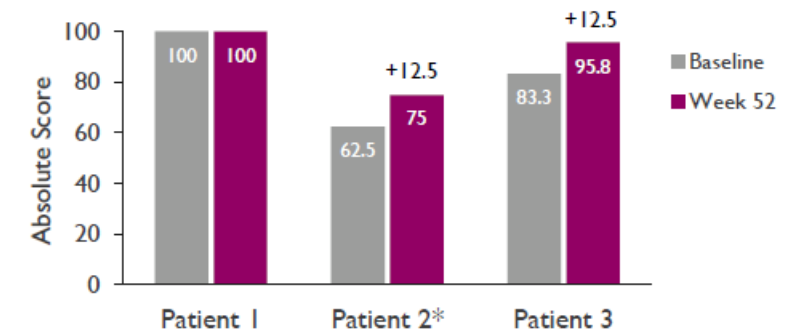
Cardiomyopathy QOL (KCCQ): 2 of 2 Responders; 1 Retained 100%

CHANGE CORRELATES WITH PEAK VO₂, 6-MINUTE WALK, HOSPITALIZATION & MORTALITY¹

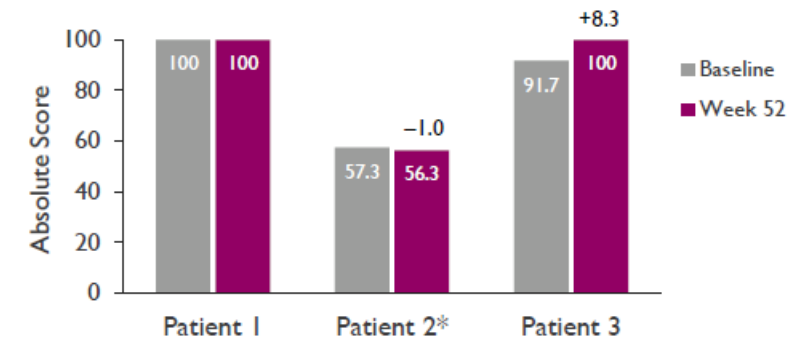
Overall Summary Score



Physical Limitation Score



Total Symptom Score



Scores range from 0 to 100 (higher scores = less severe); minimal clinically important difference (overall summary score), 5 points [1]. *High antibody titer; entered study off ERT. Abbreviations: ERT, enzyme replacement therapy.

1. Spertus JA et al. JACC 2020;76:2379–90.

4D-310 Cardiac Biopsy (Week 6): High-level Transgene Expression

FIRST PATIENT IN INGLAXA-2 CLINICAL TRIAL (1E13 VG/KG)*

Histology

- Healthy tissue, no inflammation
- 4 of 4 samples (+): cardiomyocytes only (ISH)
- **Est. 50% of cardiomyocytes (+) by ISH**
- 4 of 4 samples (+): AGA protein (IHC)

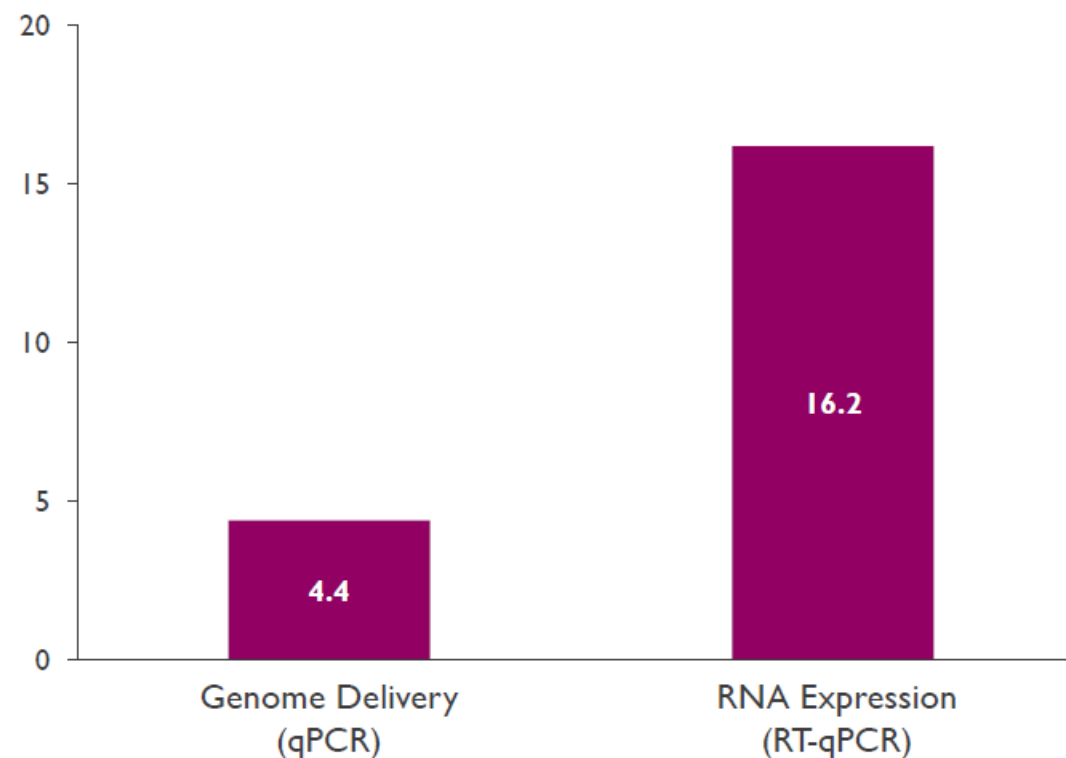
Genome Delivery (qPCR)

- 1.2 vector copies per cell
- **4.4 vector copies per cardiomyocyte**

RNA Expression (ISH & RT-qPCR):

- 4.3 transcript copies per cell
- **16.2 transcript copies per cardiomyocyte**

Cardiomyocyte Genome Delivery & RNA Expression**



*Male (57 y) with late onset Fabry disease (GLA variant: IVS4 + 919G>A); **As calculated based on cardiomyocyte to heart cell ratio (est. 30% of all cells); baseline anti-AGA antibody titer negative; baseline serum AGA activity, 1.62 nmol/hr/mL; baseline serum lyso-Gb3 concentration, 3.79 ng/mL; entered study on ERT. †Endogenous AGA protein observed in commercially acquired cardiac tissue samples. AGA, α -galactosidase A, ERT, enzyme replacement therapy; IHC, immunohistochemistry; ISH, *in situ* hybridization.

Interim Safety & Tolerability: aHUS & NO Liver, Cardiac, DRG Tox

COHORT 1, INGLAXA-1 & -2: 1E13 VG/KG & CORTICOSTEROID IMMUNE REGIMEN

- Total n=6 dosed
- Generally well-tolerated after aHUS “window”
Dorsal root ganglia
- **NO liver, heart or DRG toxicity observed**
- **Transient acute aHUS** (n=3): admission & observation
 - Active aHUS process: ~Day 3-7 onset; resolution started within ~1-4 days
 - No intervention (n=1): discharge ~4 days
 - Eculizumab (n=1): discharge ~1 week
 - **Eculizumab & temporary dialysis (n=1): discharge ~1 week**
 - **DLT (Gr 4) - 4DMT hold on enrollment f/b FDA hold**
- 69 y.o. pt with DLT (Gr 4 aHUS) investigation

Summary: 4D-310 Phase 1/2 Clinical Trial Cardiac Proof-of-Concept

SIX PATIENTS (1E13 vg/kg) WITH CORTICOSTEROID PROPHYLAXIS

- **Cardiac activity demonstrated at 12 months:**
 - LV function (ECHO): 3 of 3
 - Exercise capacity (CPET): 2 of 3
 - Quality of life (KCCQ): 2 of 2 (1 SD 100%)
 - Activity despite Ab to AGA & C102 capsid
 - **Positive cardiac biopsy:** Transgene delivery & expression in cardiomyocytes*
 - **Generally well-tolerated:** No liver, heart or DRG toxicity observed
 - **Transient acute aHUS on corticosteroids (n=3):**
 - Resolved in all 3
 - Investigation identified:
 - Pre-dosing: complement activation
 - Post-dosing: heightened production of IgM contributing to accelerated complement activation
 - C102 shown to not activate the complement pathways directly
-

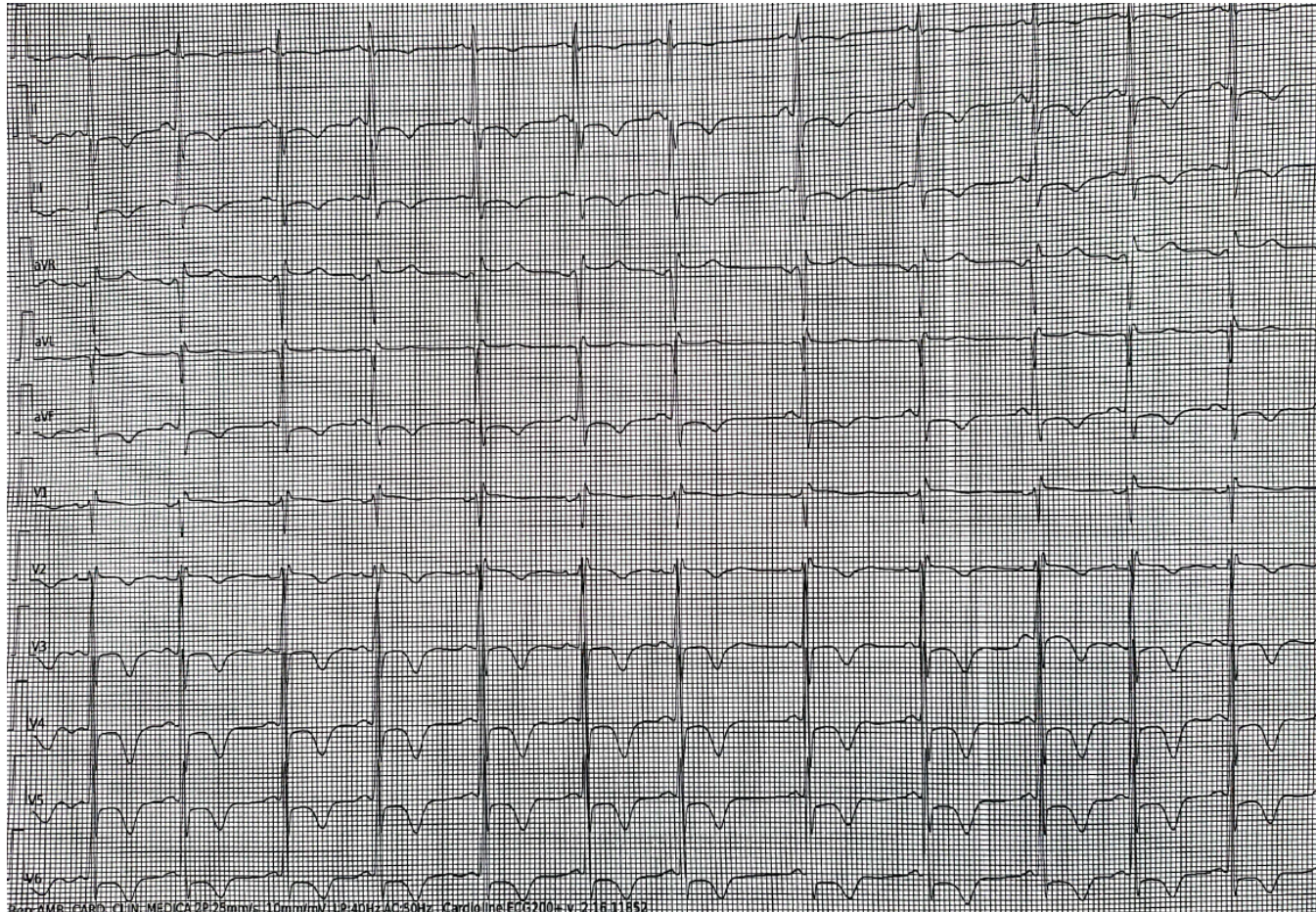
- 4D-310 demonstrated clinically meaningful cardiac endpoint improvements through 12-24 months in contractility (echocardiography), peak VO_2 (cardiopulmonary exercise testing) and/or cardiac quality of life (KCCQ) in all five evaluable patients
- Cardiac biopsies were obtained from a patient at week 6 and 24 and showed robust and durable delivery, transgene expression and clearance of Gb3 substrate in cardiomyocytes
- No new treatment-related adverse events > Grade 1 since last interim update and through 12-33 months; previously reported cases of atypical hemolytic uremic syndrome (aHUS) (n=3) fully resolved
- FDA LIFTED THE CLINICAL HOLD with implementation of rituximab/sirolimus immunosuppressive regimen and the exclusion of patients with predosing complement activation.

Storia clinica

BB, 62 AA

Ex sportiva a livello agonistico (maratona), nel 2013 riscontro di TWI in sede antero-laterale eseguita RM riferita nei limiti

Nel 2019 visita cardiologica con conferma di alterazioni ECG e riscontro di ipertrofia apicale, consigliata cine RM del cuore



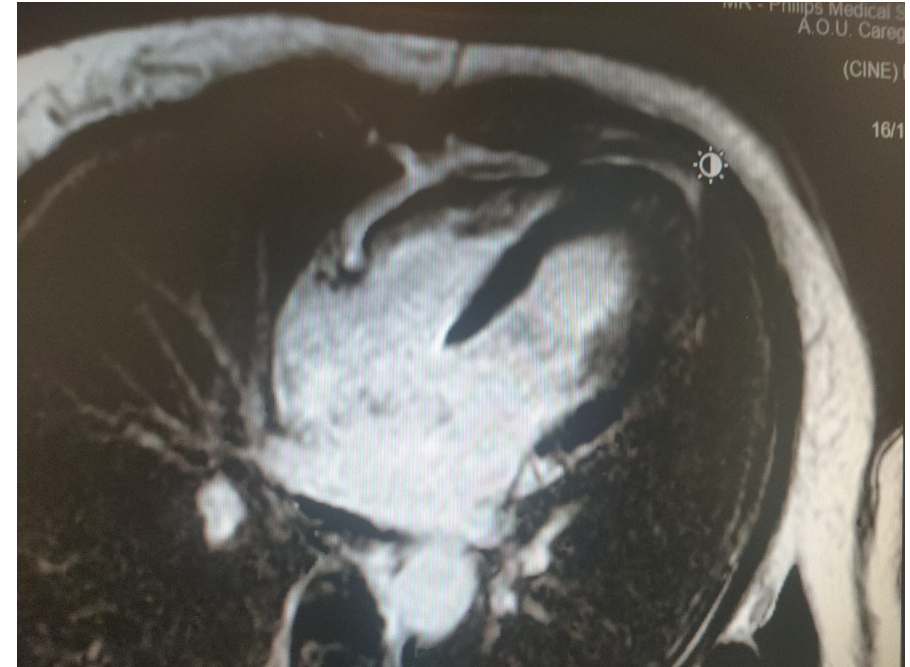
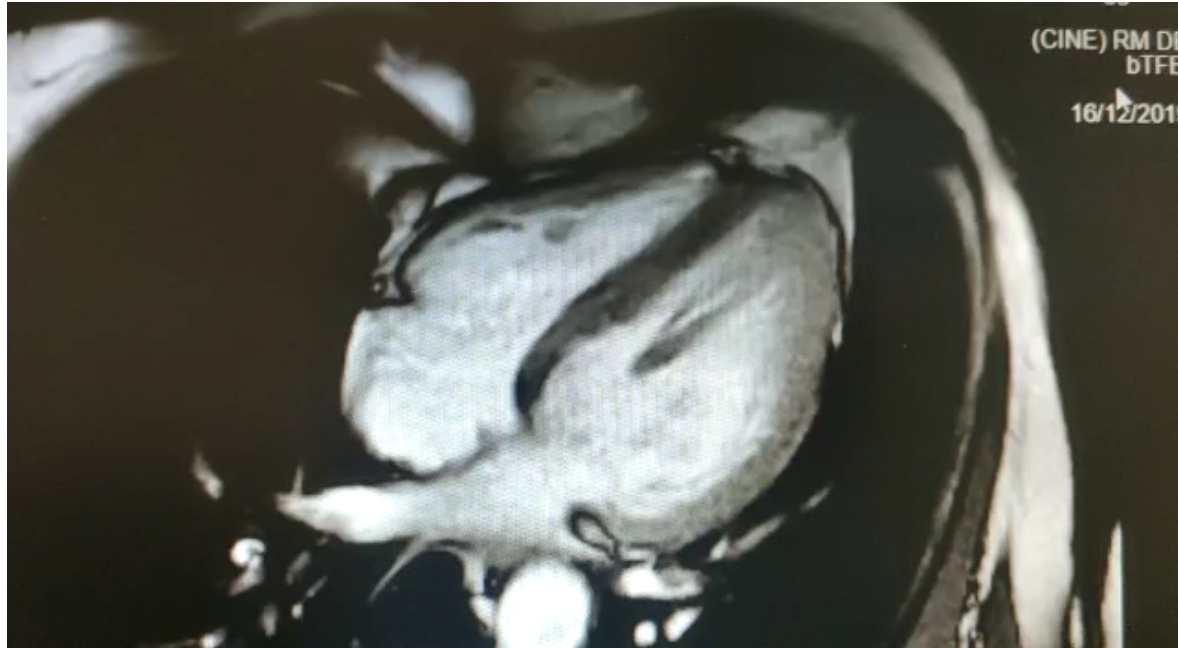
Ecocardiogramma



SIV 11, PP 10
Apice 15 mm



CMR



Normorappresentato il tessuto adiposo epi-pericardico
Non aree di edema in T2
Parcellare versamento pericardico

VS nei limiti per dimensioni, cinetica conservata; ipertrofia asimmetrica dell'apice parete laterale
setto giunzione posteriore, tratto apicale 8-10 mm con lieve accentuazione della trabecolatura
AS nei limiti per dimensioni, parcellare artefatto da rigurgito mitralico
VD ispessimento della parete laterale, lieve accentuazione della trabecolatura nei limiti per
dimensioni la cavita' ventricolare, cinetica conservata
AD nei limiti

in LGE limitata chiazza di enhancement meso-subepicardico a carico della parete anteriore
apice ventricolare di aspetto non ischemico

Dalle immagini Cine-RM in asse corto si sono ottenuti i seguenti parametri funzionali:

Ventricolo	SINISTRO	DESTRO			
Frazione d'eiezione	73%	62 %	Stroke Volume	116ml	100 ml
			Stroke Index	69 ml/mq	56 ml/mq
			Gettata cardiaca	7.9 l/min	5.3 l/min
			Indice cardiaco	4.7 l/min/mq	3.0 l/min
			Volume telediastolico	160 ml	161 ml
			Volume telesistolico	43 ml	34 ml
			Massa	133 (99+papilalri) , 79 g/mq (vn=25-44 gr/,mq)	
			BSA 1.68 mq(Mostellar)		
			FC 68 bpm		

cr: segni di CMI asimmetrica tratto apicale VS con LGE meso-subepicardica non ischemica ,
ipertrofia parete laterale VD

[illegible]

Test genetico:

c.335G>A (p.Arg112His) → Pathogenic/Likely pathogenic for Anderson-Fabry disease late-onset phenotype



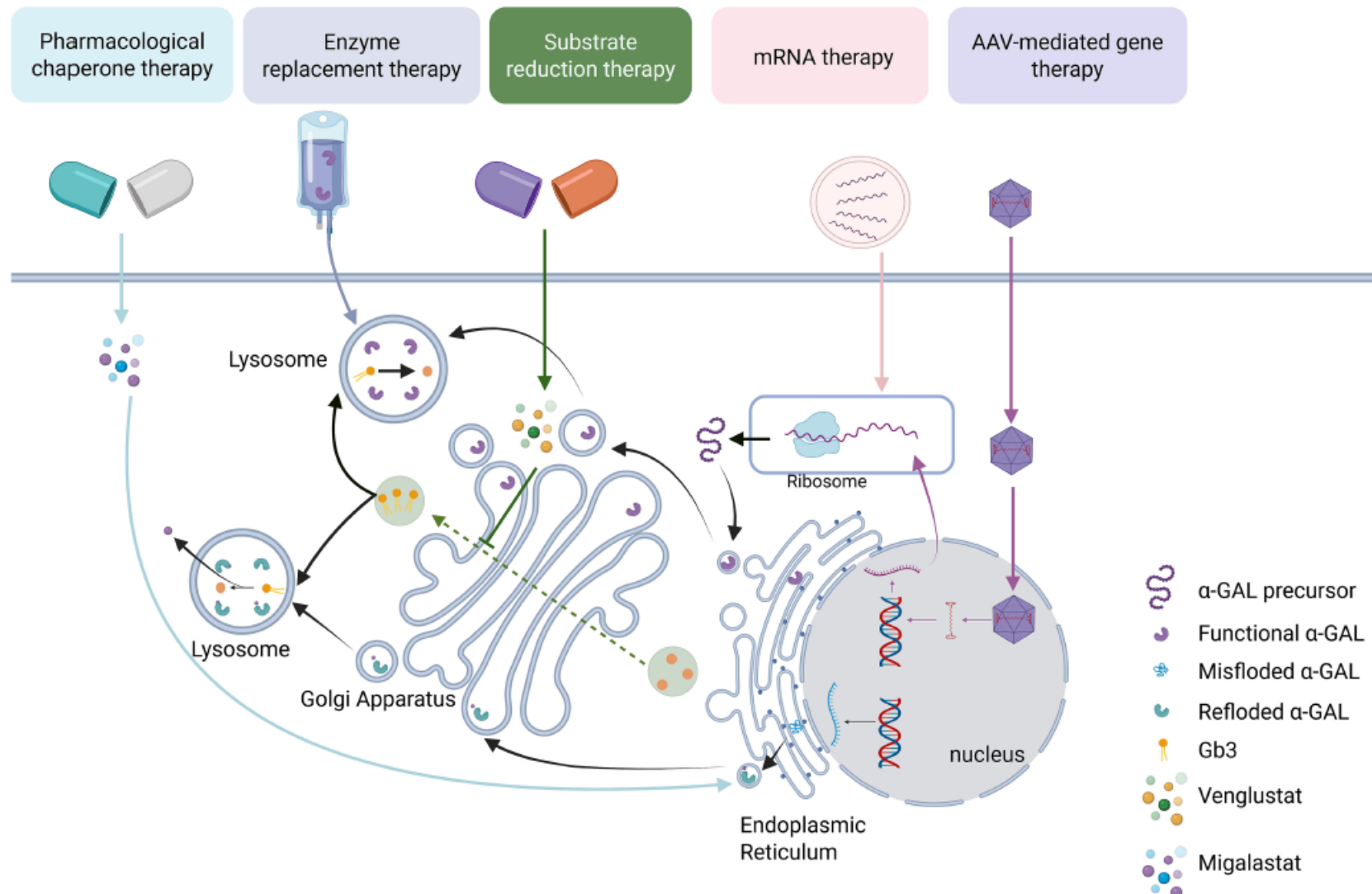
DIAGNOSI MALATTIA DI FABRY



Iniziata ERT



Screening familiare: una figlia di 30 anni portatrice di mutazione



GRAPHICAL ABSTRACT