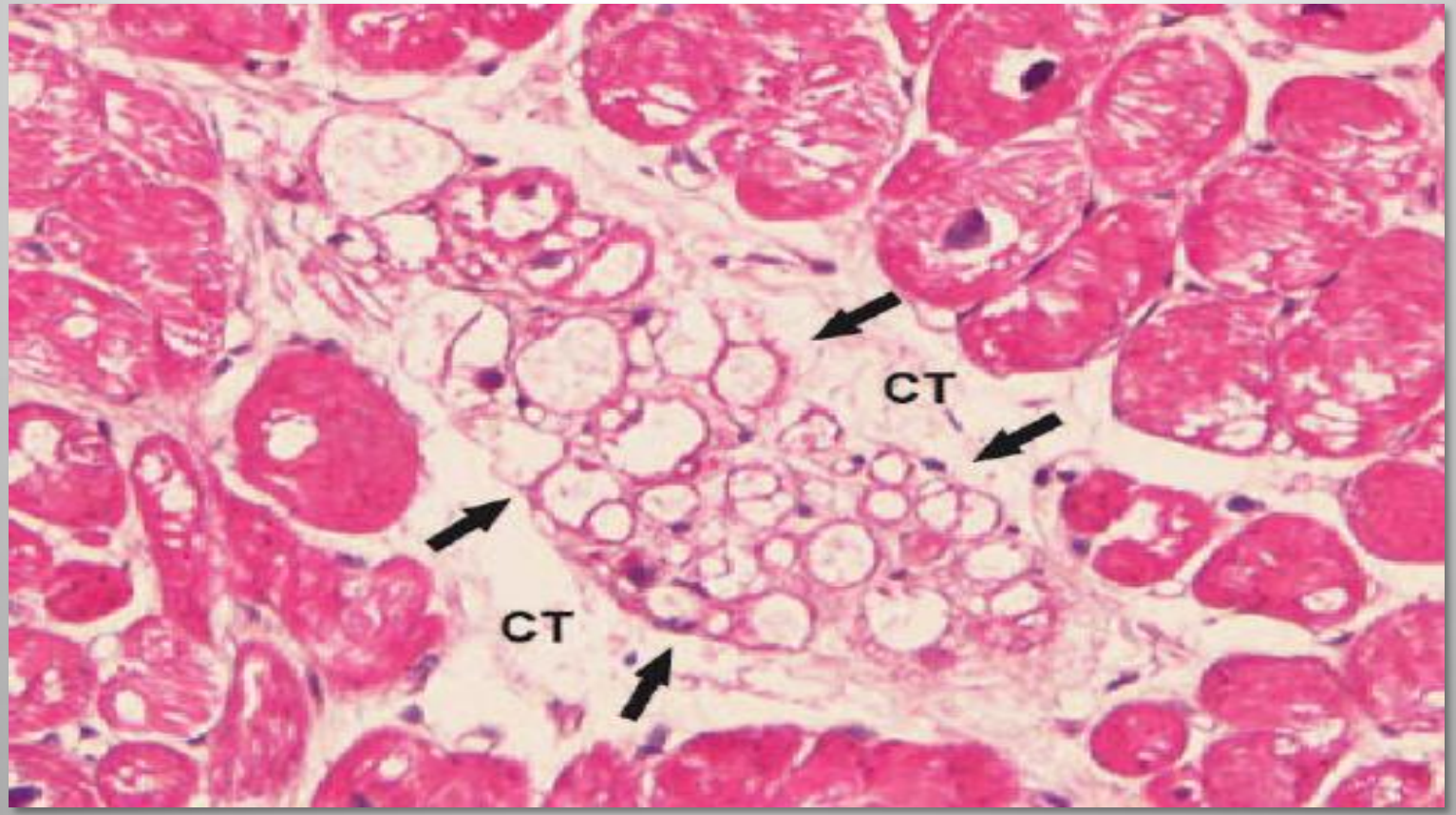



# La maladie de Fabry et l'implication du coeur

Mehdi Namdar, MD, PhD, PD, Médecin Adjoint Agrégé, Service de Cardiologie – HUG

Bern, 04.05.2019

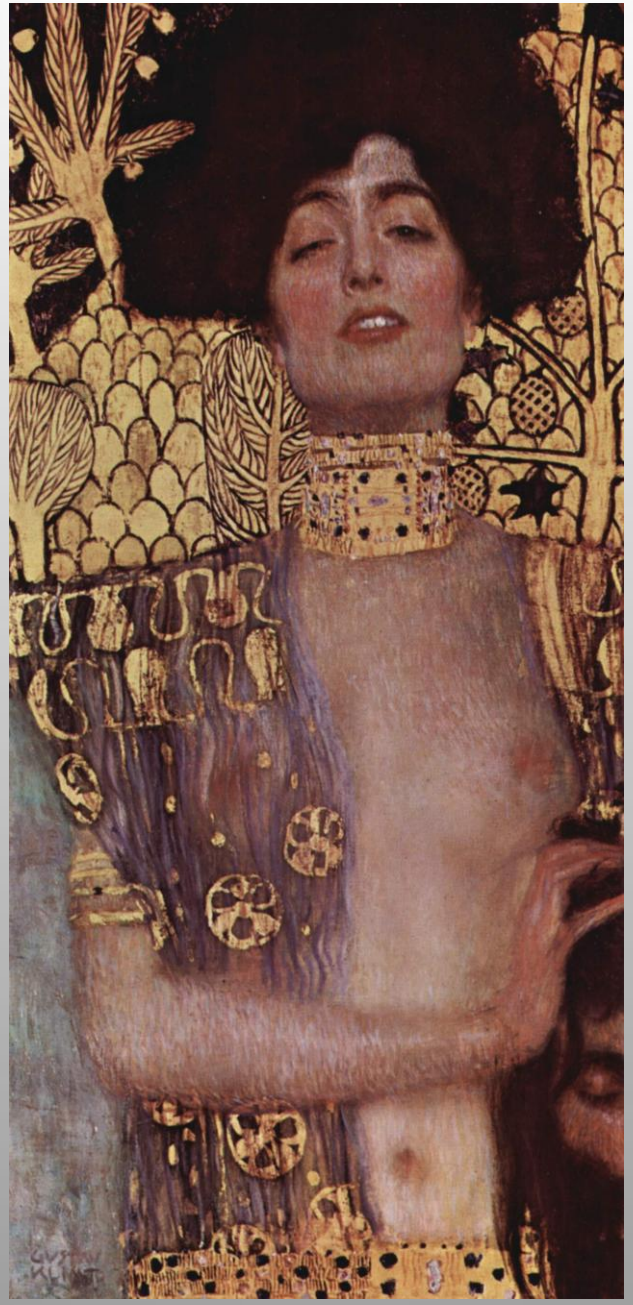
# Disclosures

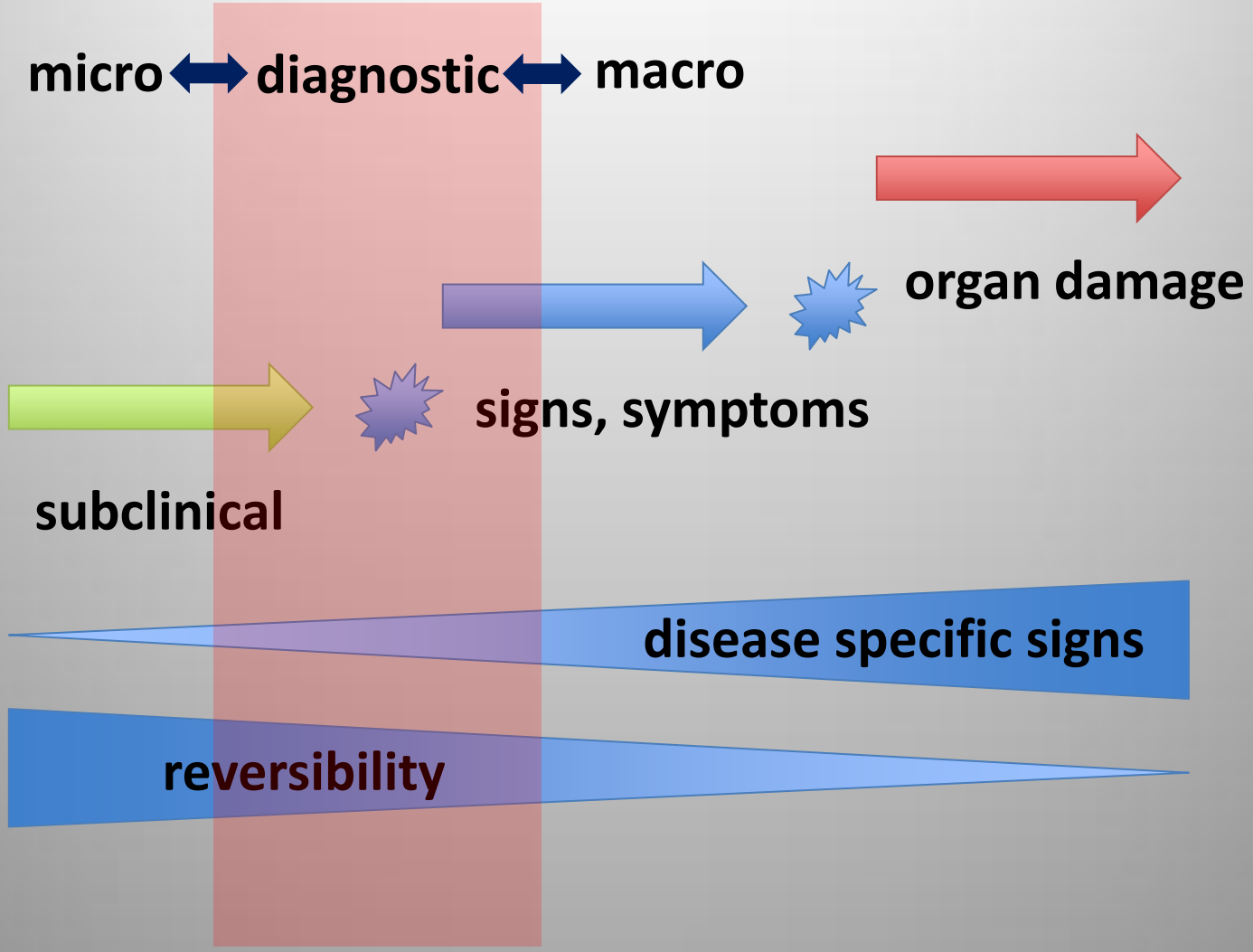
- **Speakers fees/honoraria/travel grants**
  - Bayer, Biosense-Webster, Biotronik, Boston-Scientific, Daiichi-Sankyo, Medtronic, Sanofi Genzyme, Takeda
- **Advisory Boards**
  - Amicus, Bayer, Biotronik, Boston-Scientific, Daiichi-Sankyo, GBc, Sanofi Genzyme, Takeda
- **Investigatorships**
  - Biotronik, Daiichi-Sankyo, Biosense-Webster, Boston-Scientific, Sanofi Genzyme,
- **Research/fellowship grants**
  - Abbott, Biotronik, Biosense-Webster, Sanofi Genzyme, Takeda
- **Presidency**
  - CHAR – Swiss Arrhythmia Foundation

# HOW TO DIAGNOSE

## AWARENESS

SEEING  LOOKING






Namdar M (2016) Front. Cardiovasc. Med. 3:7.

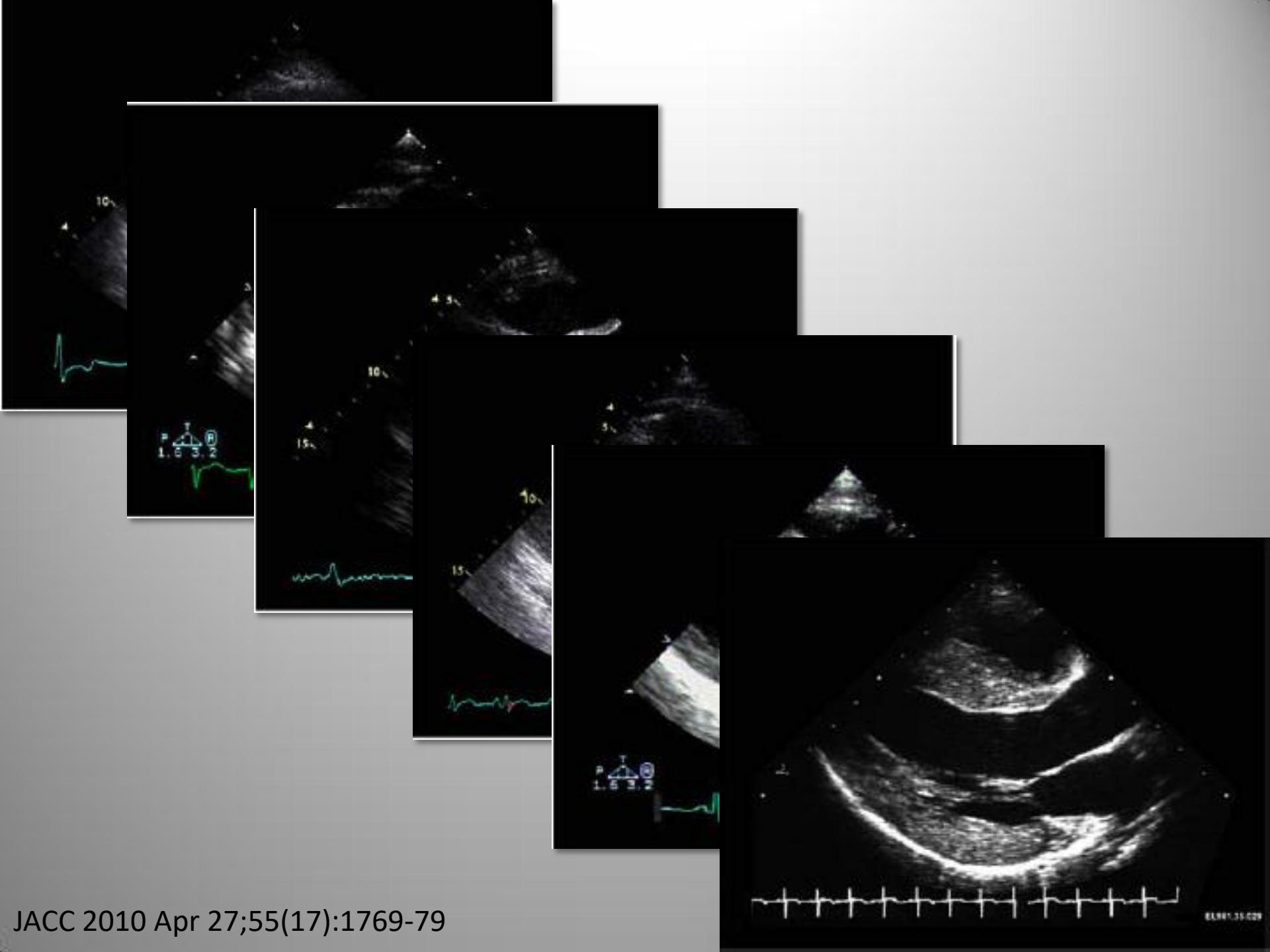
# *MACROSCOPIC* DIAGNOSTIC TOOLS

**ECHOCARDIOGRAPHY**

**DIASTOLIC DYSFUNCTION**

**LEFT VENTRICULAR HYPERTROPHY**

**FIBROSIS**



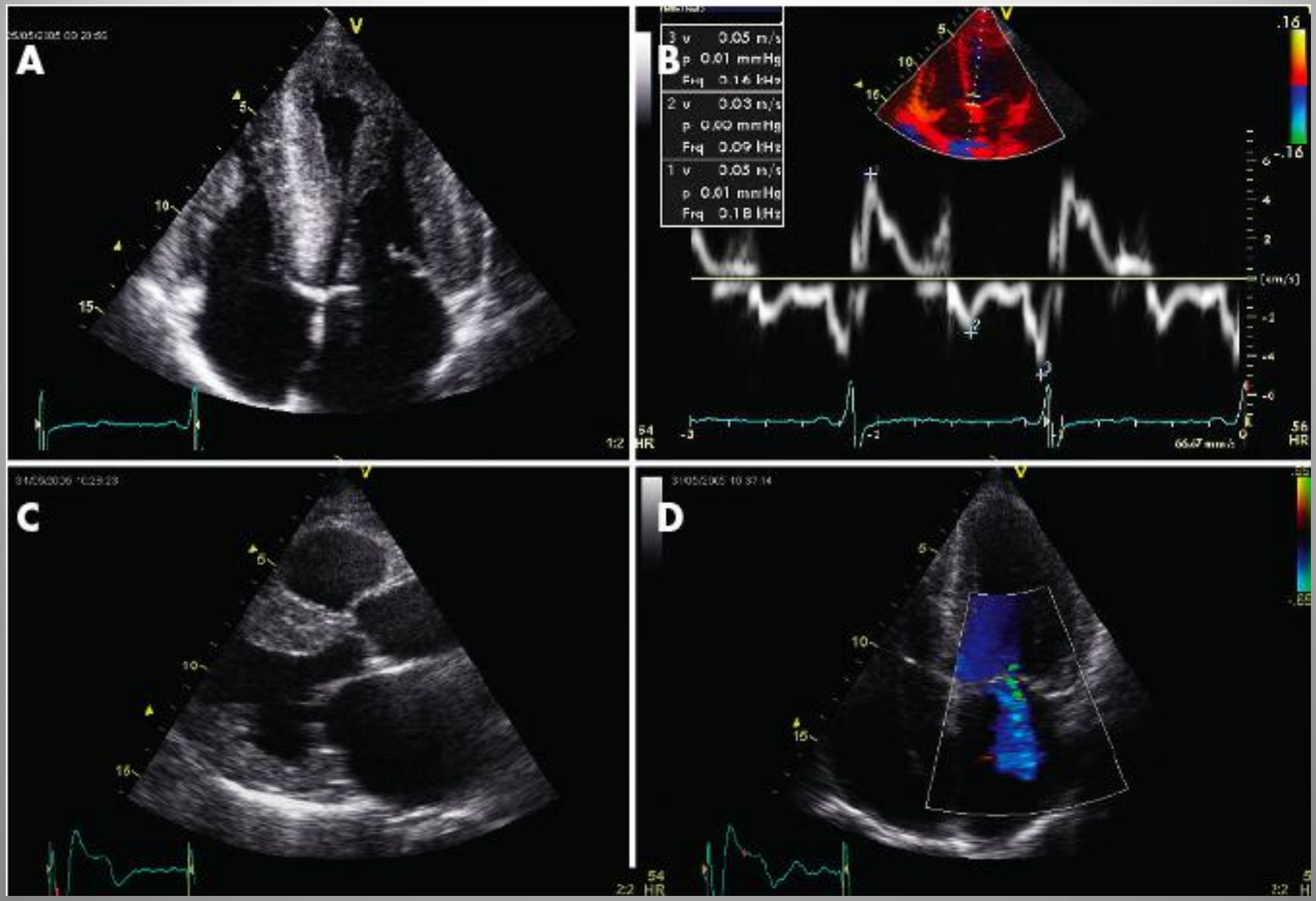
JACC 2010 Apr 27;55(17):1769-79

# Diagnostic criteria HCM

- In an adult, HCM is defined by a wall thickness ≥15 mm in one or more LV myocardial segments—measured by any imaging technique (echo/MRI/CT)—that is not explained solely by loading conditions.

- Genetic and non-genetic disorders can present with lesser degrees of wall thickening (13–14 mm) → diagnosis of HCM requires evaluation of other features including family history, non-cardiac symptoms and signs, electrocardiogram (ECG) abnormalities, laboratory tests and multi-modality cardiac imaging.

- Challenged by HCM phenocopies (e.g., Fabry disease, lysosomal associated membrane protein-2 (LAMP2) cardiomyopathy, or amyloidosis)




*Heart* 2007;**93**:528–535.

| Finding | Specific diseases to be considered |
|---|---|
| Increased interatrial septum thickness | Amyloidosis |
| Increased AV valve thickness | Amyloidosis; Anderson-Fabry disease |
| Increased RV free wall thickness | Amyloidosis, myocarditis, Anderson-Fabry disease, Noonan syndrome and related disorders |
| Mild to moderate pericardial effusion | Amyloidosis, myocarditis |
| Ground-glass appearance of ventricular myocardium on 2D echocardiography | Amyloidosis |
| Concentric LVH | Glycogen storage disease, Anderson-Fabry disease, PRKAG2 mutations |
| Extreme concentric LVH (wall thickness ≥30 mm) | Danon disease, Pompe disease |
| Global LV hypokinesia (with or without LV dilatation) | Mitochondrial disease, TTR-related amyloidosis, PRKAG2 mutations, Danon disease, myocarditis, advanced sarcomeric HCM, Anderson-Fabry disease |
| Right ventricular outflow tract obstruction | Noonan syndrome and associated disorders |

European Heart Journal (2014) **35**, 2733–2779

# LGE (replacement fibrosis) in females independent of LVH

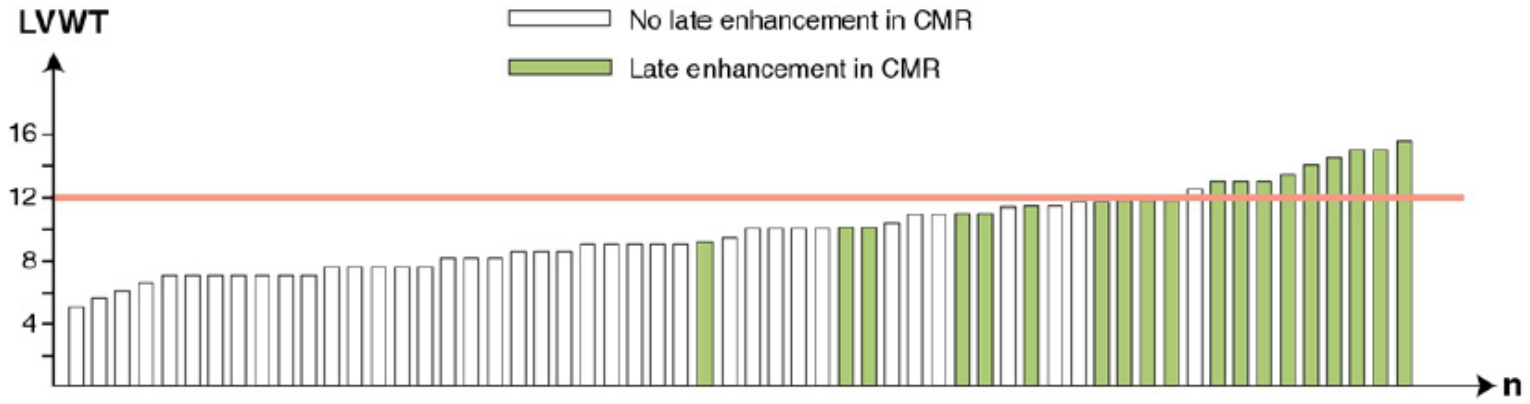



**Figure 1.** Distribution of LE Depending on LVWT in Female Patients With Fabry Disease

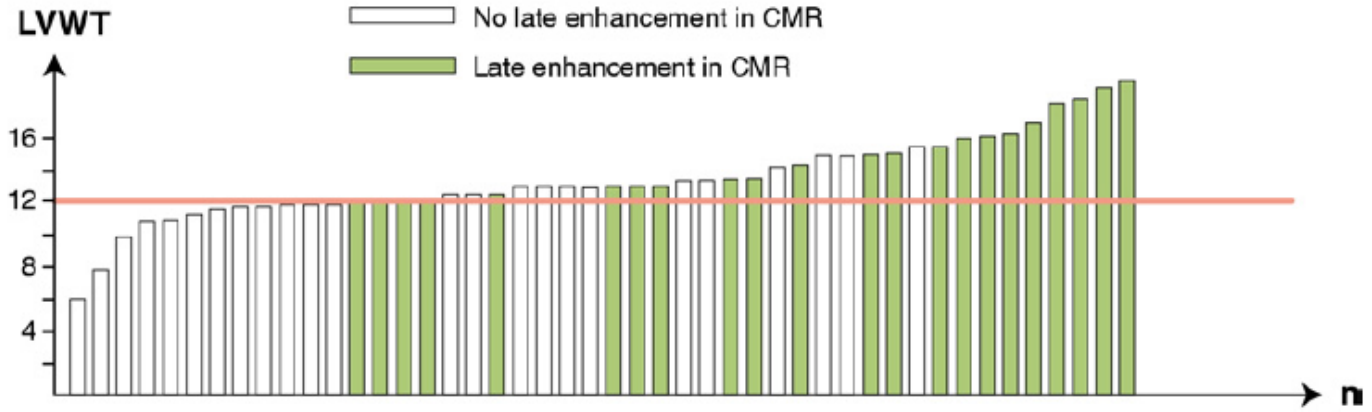



**Figure 2.** Distribution of LE Depending on LVWT in Male Patients With Fabry Disease

JACC: CARDIOVASCULAR IMAGING, VOL. 4, NO. 6, 2011
JUNE 2011:592–601

# T1 MRI – Mapping for early recognition

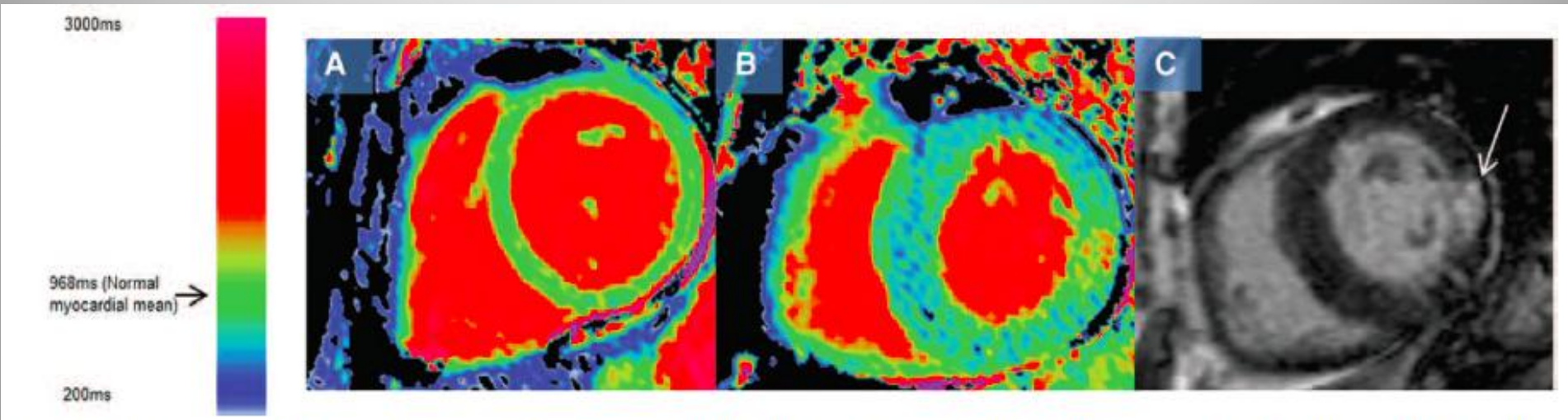
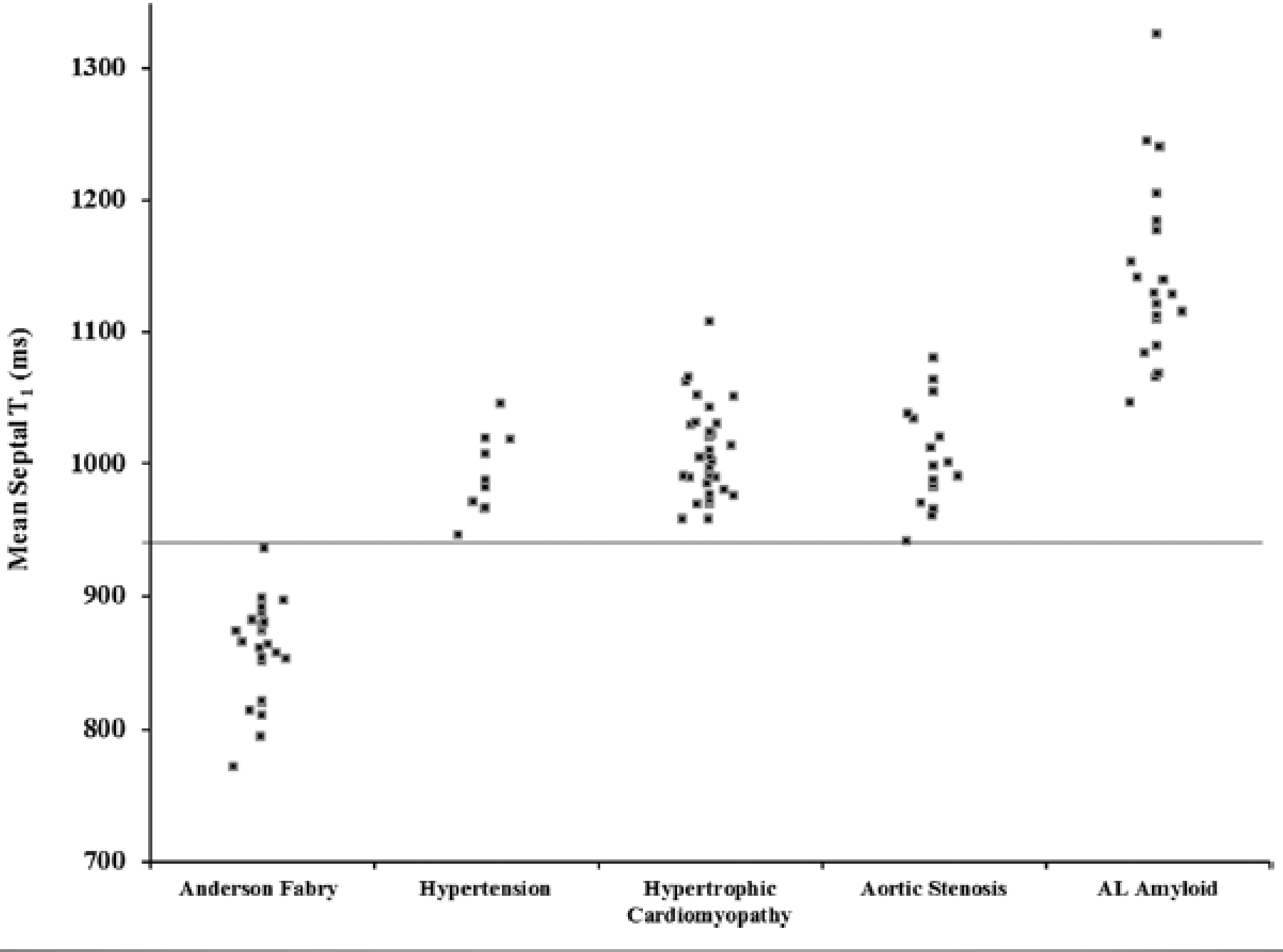



**Figure 1.** A noncontrast basal short-axis $T_1$ map from a healthy volunteer (**A**) and a patient with Anderson-Fabry disease (AFD; **B**). Blue areas ($T_1$ lowering) are seen in the AFD septum and red ($T_1$ increasing) in the inferolateral wall, correlating with the area of late gadolinium enhancement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

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




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

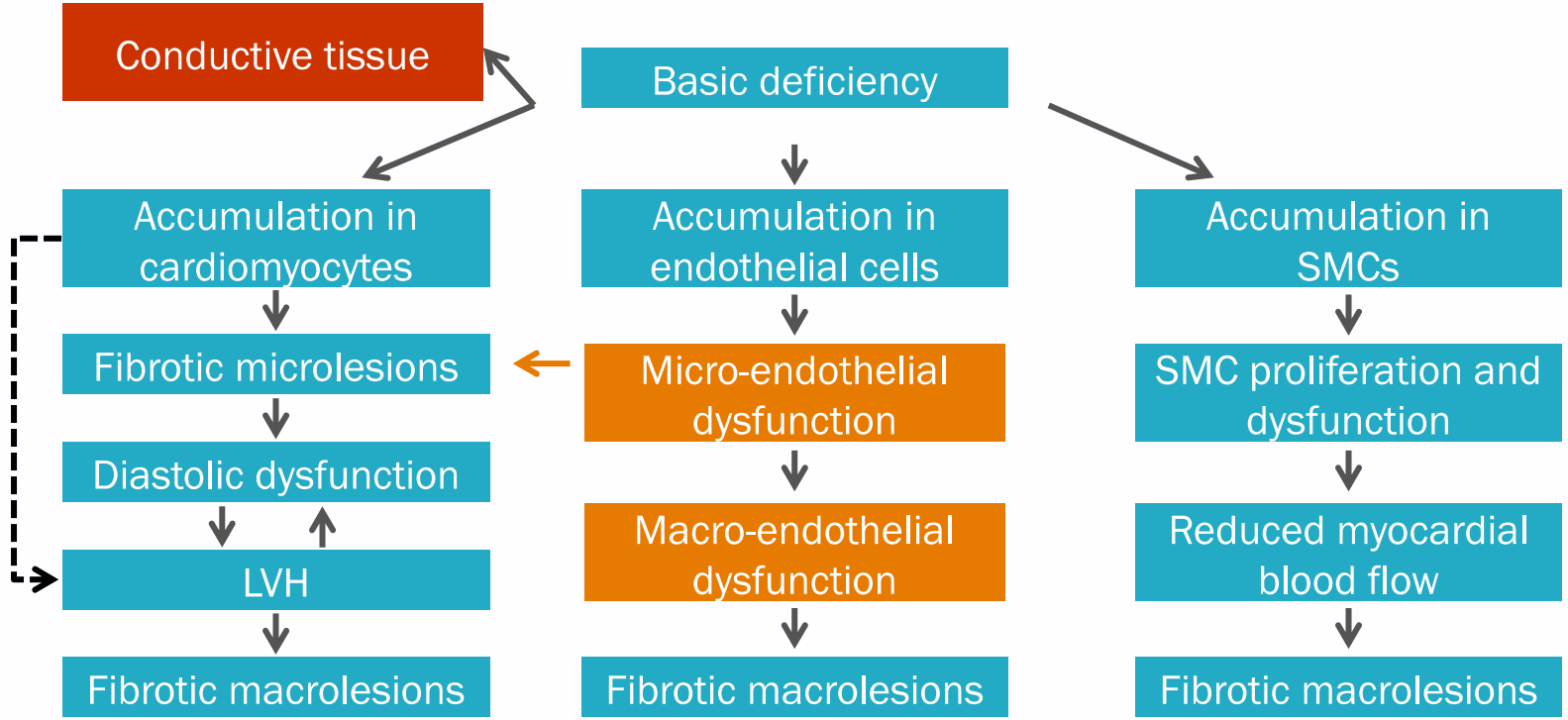
# *MICROSCOPIC* DIAGNOSTIC TOOLS

**BIOPSIES**

**ELECTROCARDIOGRAM**

**MRI**

# Simplified course of disease pathogenesis in Fabry disease

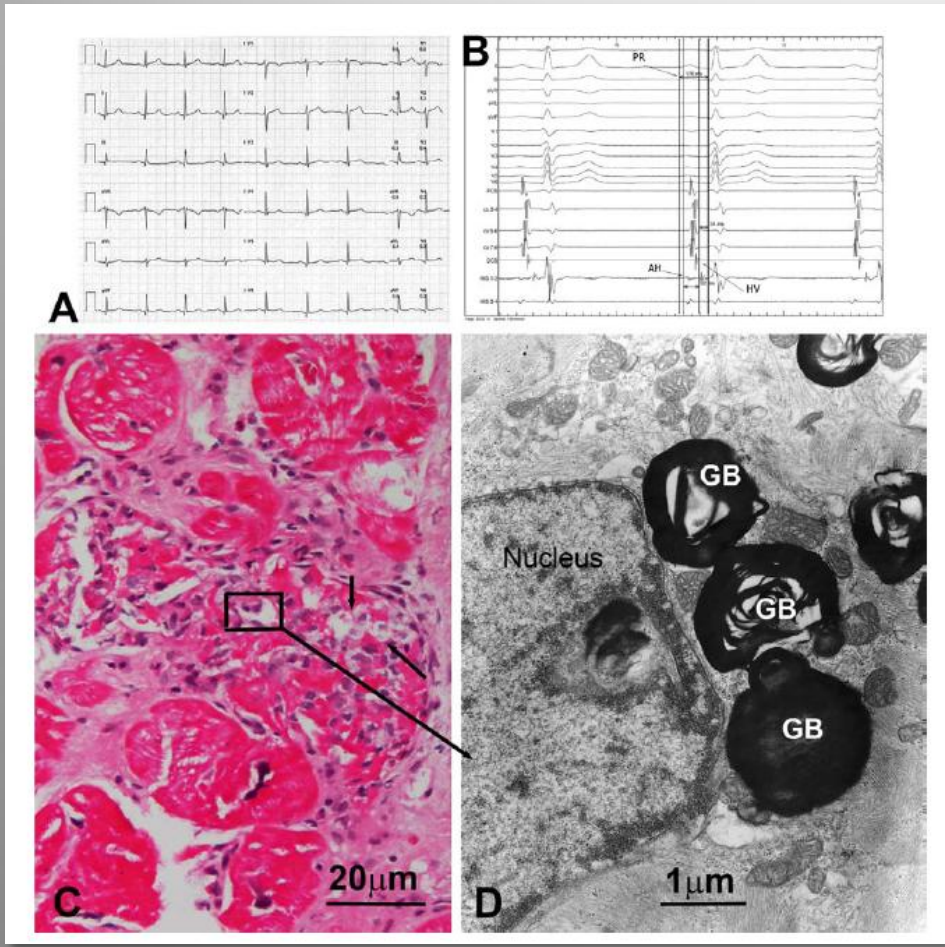



SMC, smooth muscle cell.

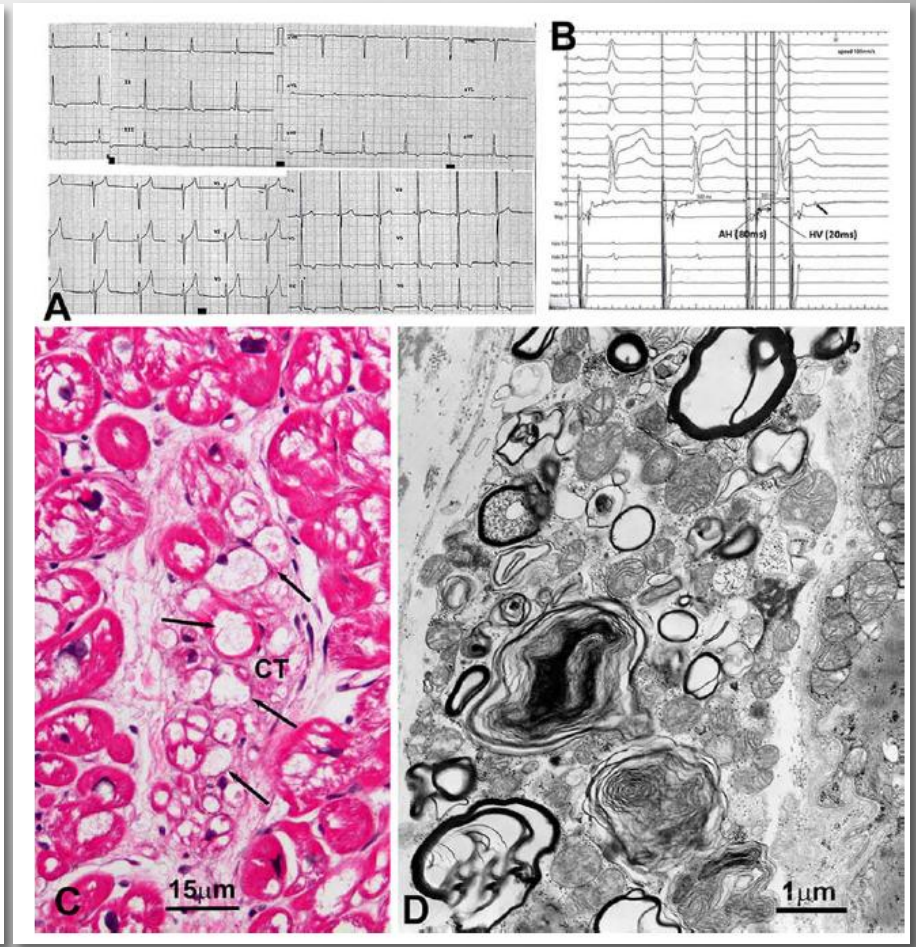
Namdar M. Front Cardiovasc Med. 2016;3:7.

# PATHOLOGY AND CONDUCTION TISSUE INVOLVEMENT

## FEMALE

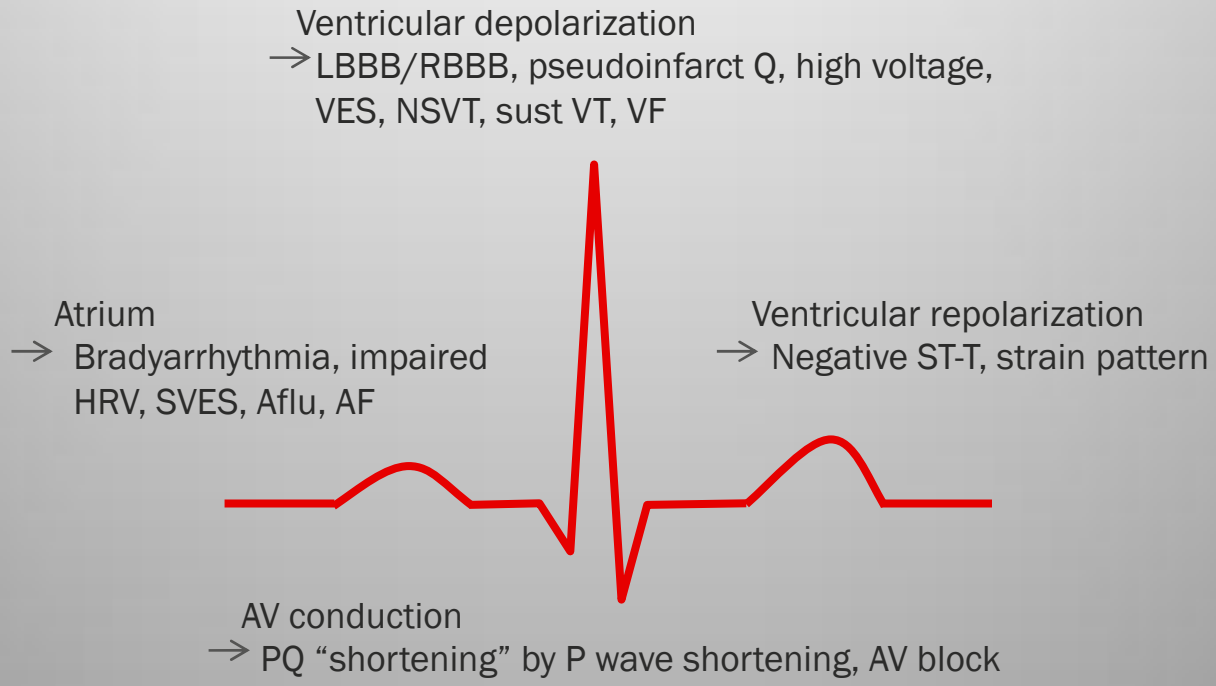



## MALE



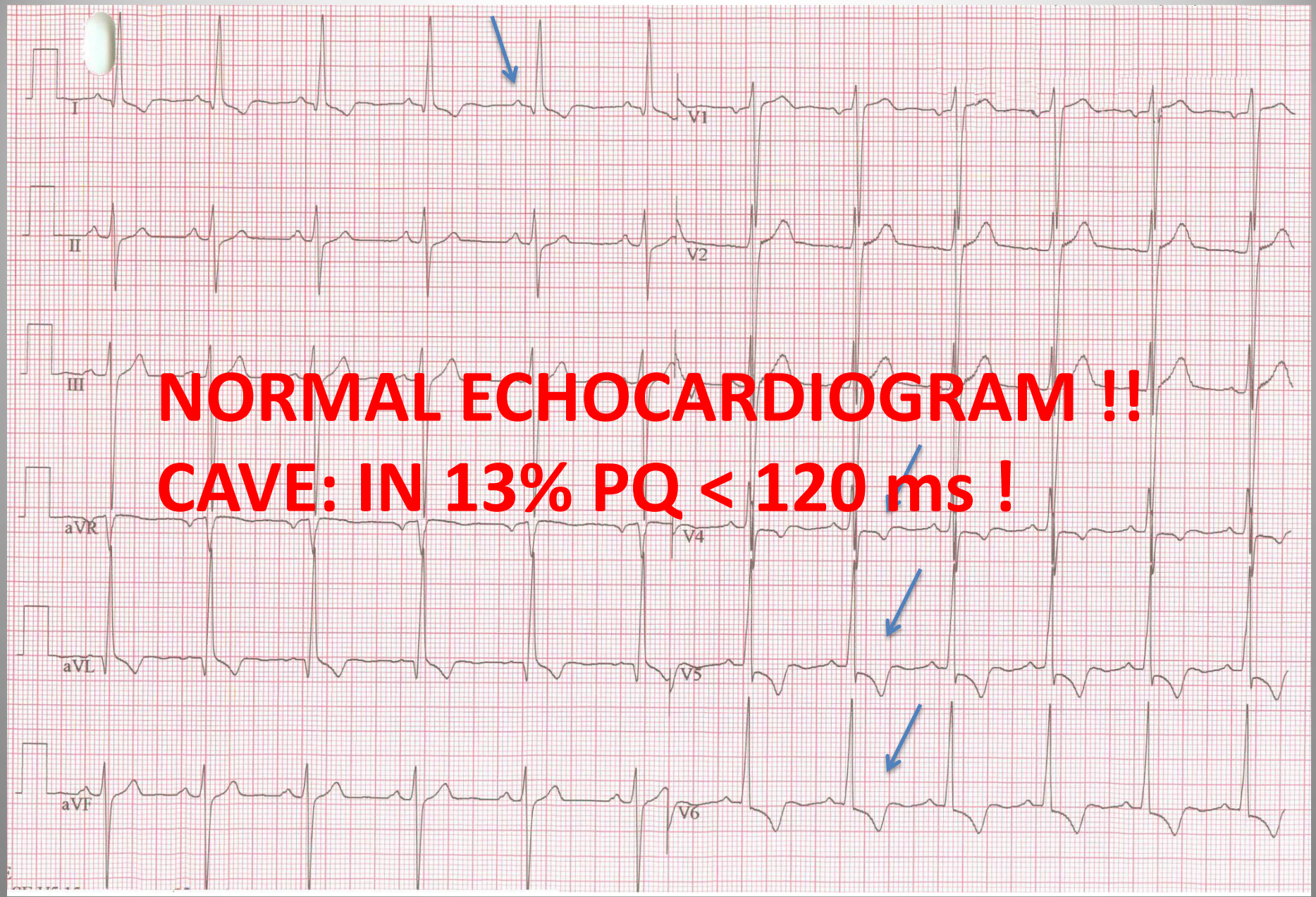

Circ Arrhythm Electrophysiol. 2015;8:799-805.

# Most prevalent conduction abnormalities and arrhythmia

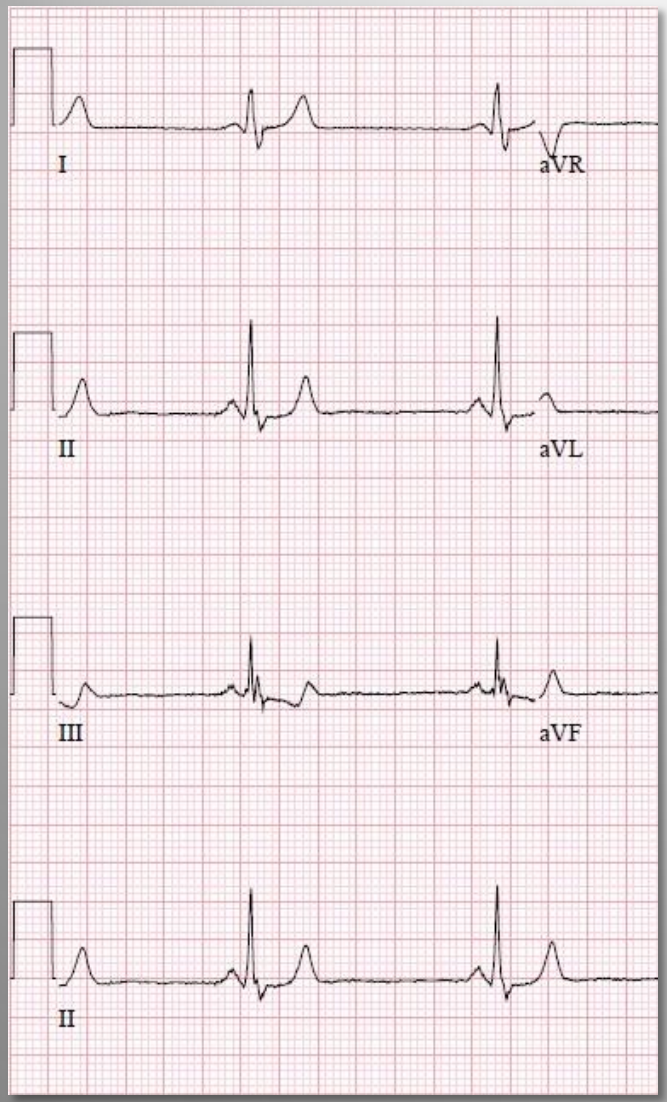



AF, atrial fibrillation; Aflu, atrial flutter; AV, atrioventricular; HRV, heart rate variability; LBBB, left bundle branch block; NSVT, non-sustained ventricular tachycardia; RBBB, right bundle branch block; sust VT, sustained ventricular tachycardia; SVES, supraventricular extrasystole; VES, ventricular extrasystole; VF, ventricular fibrillation.

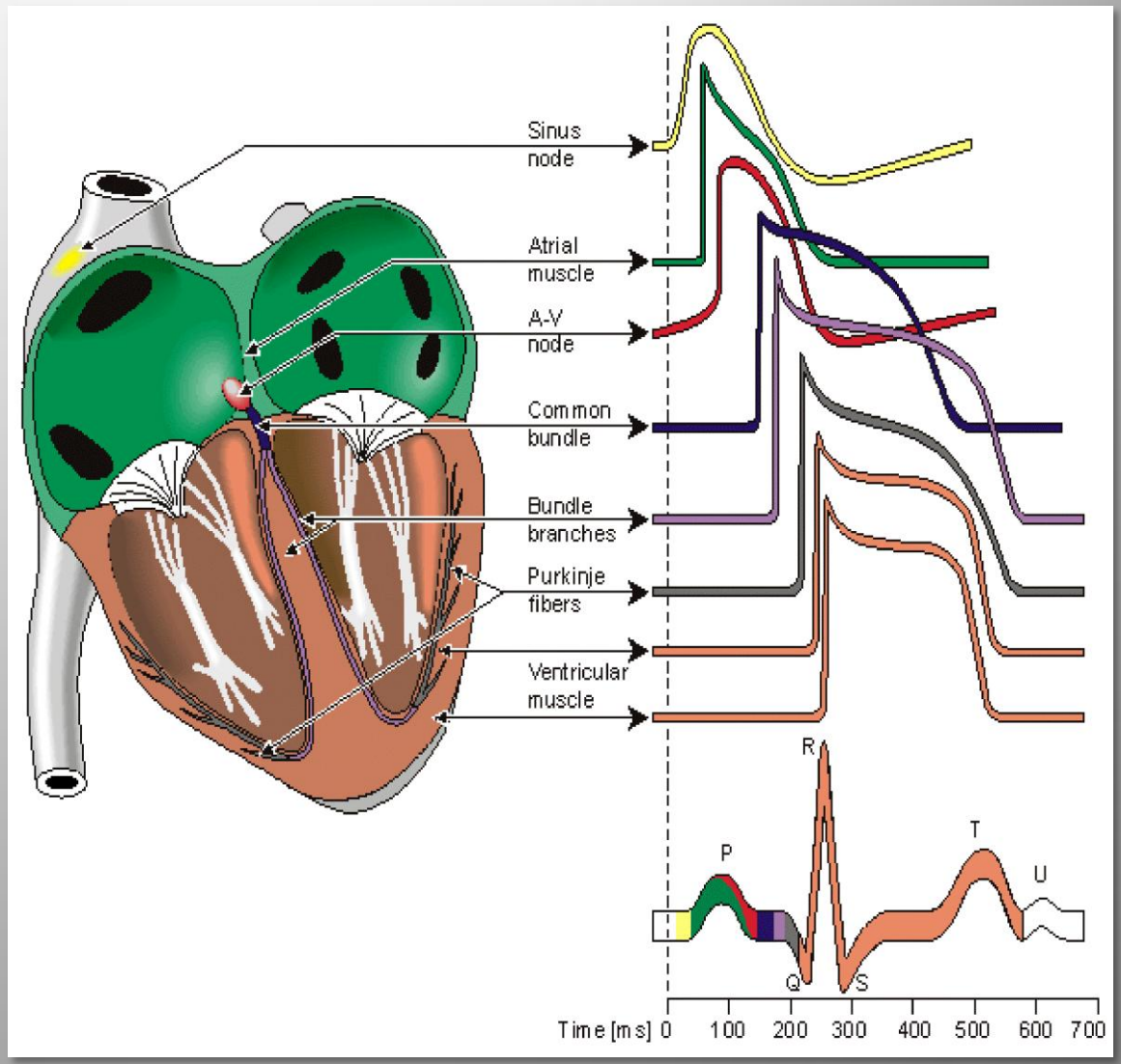
Namdar M. Front Cardiovasc Med. 2016;3:7.


I
II
III
aVR
aVL
aVF
V1
V2
V4
V5
V6
NORMAL ECHOCARDIOGRAM !!
CAVE: IN 13% PQ < 120 ms !

# FABRY



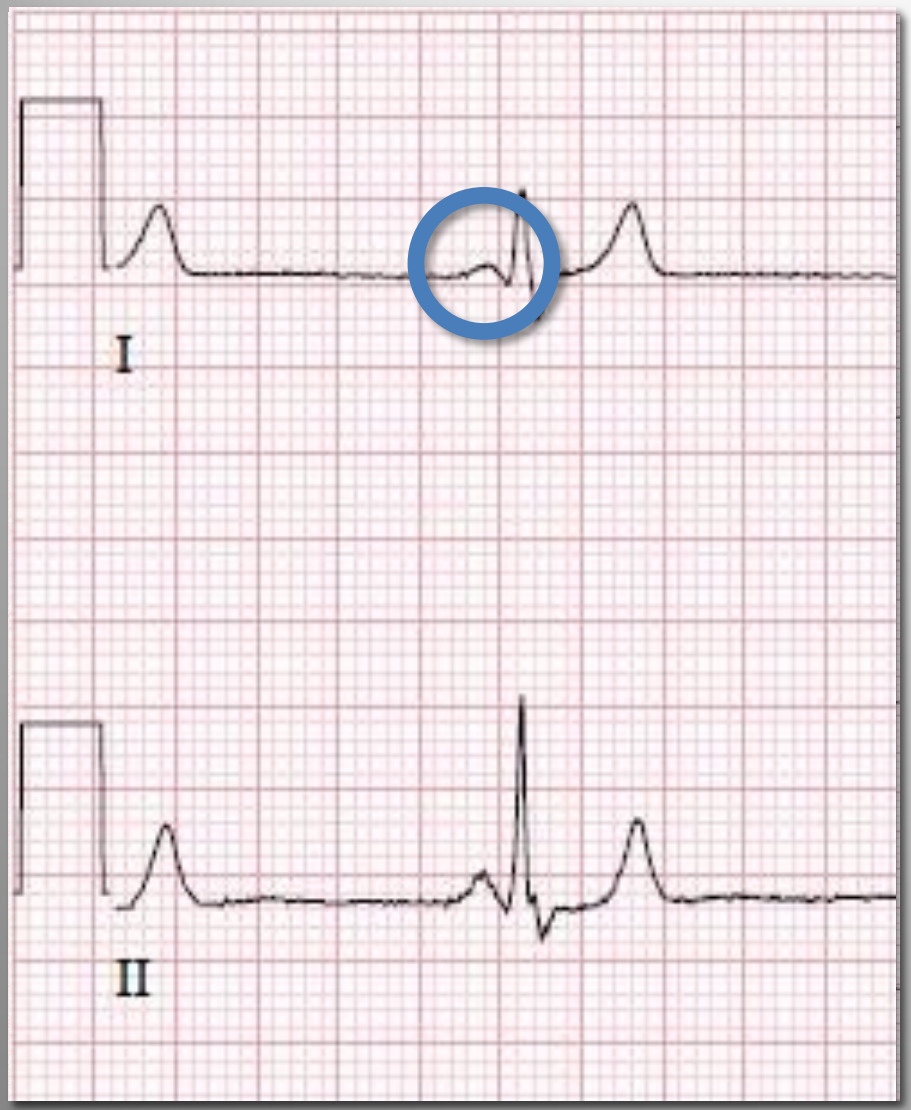

# NORMAL



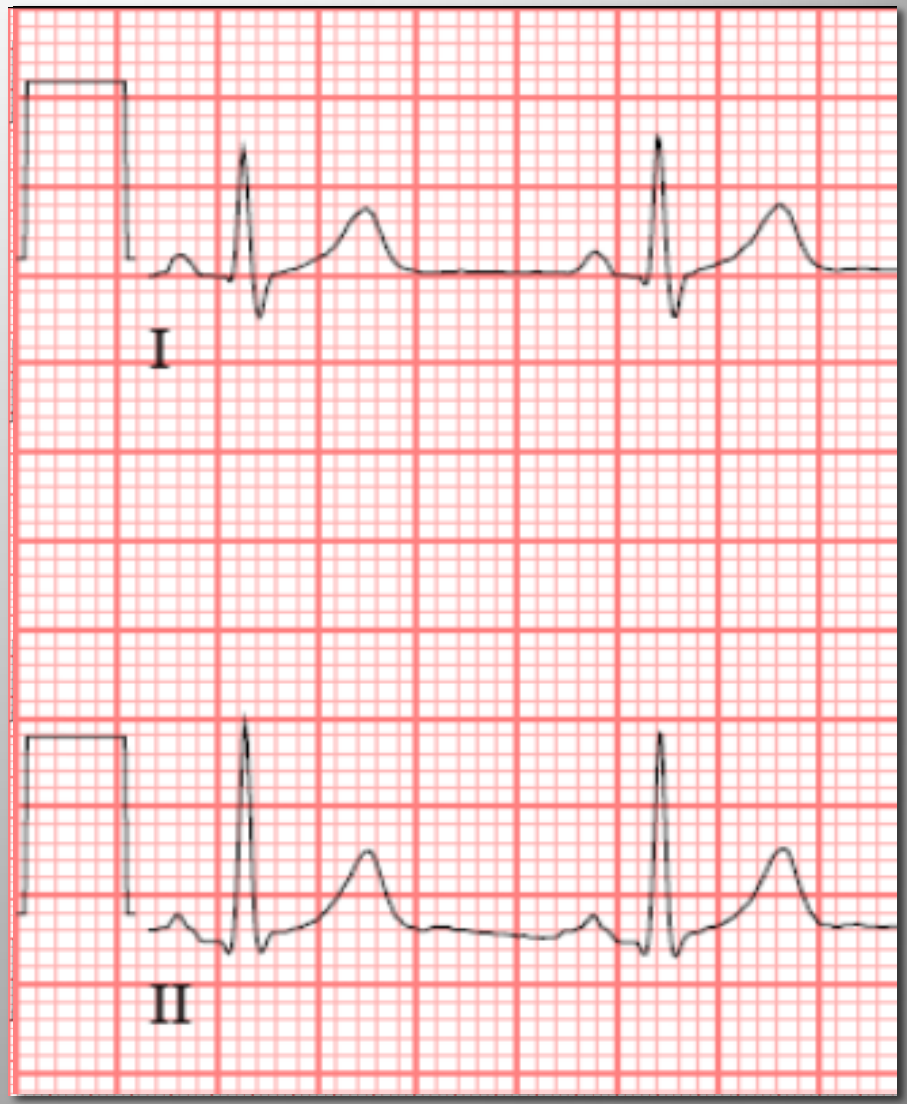

Namdar M personal data

Source: yorkcardiology.uk

# FABRY

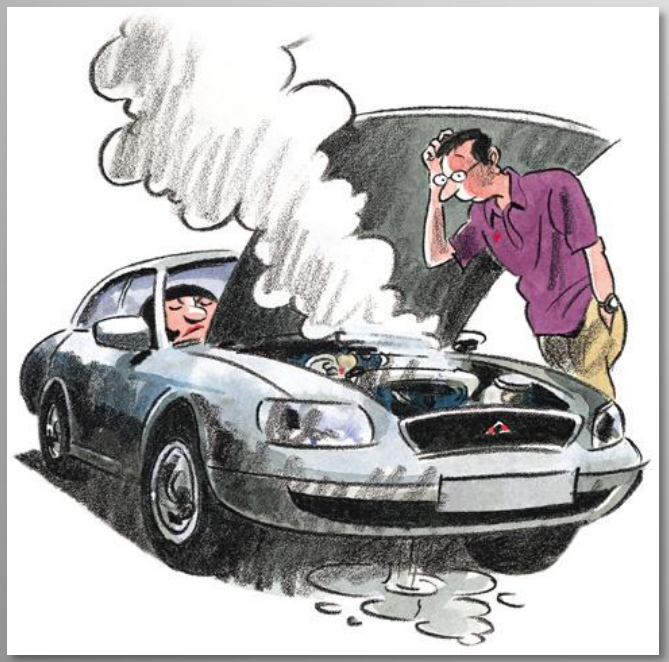



# NORMAL

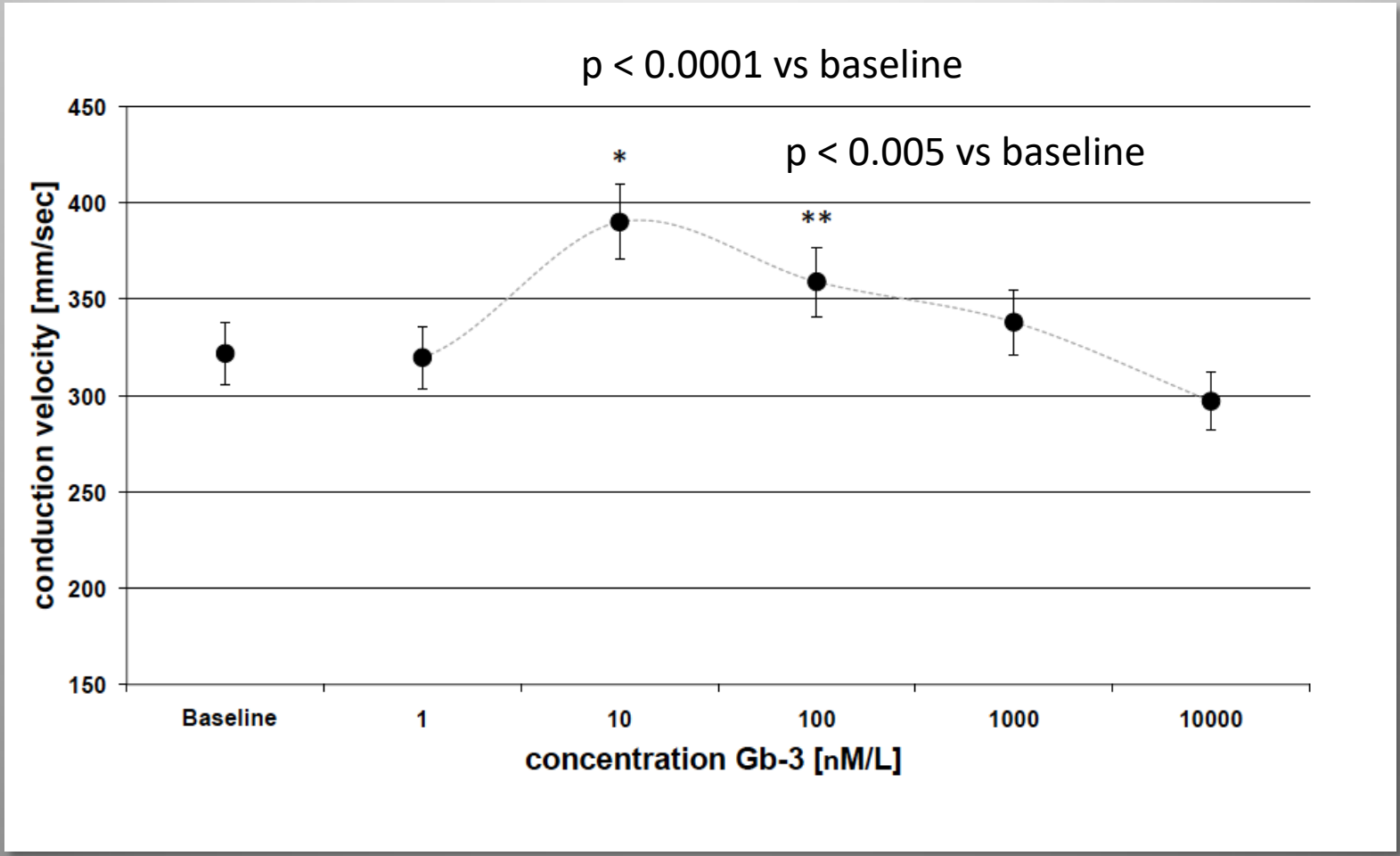



Namdar M personal data

# Almost inexistent and exquisite phenomenon - completely counterintuitive if not paradoxical in the context of any cardiac disease !!!

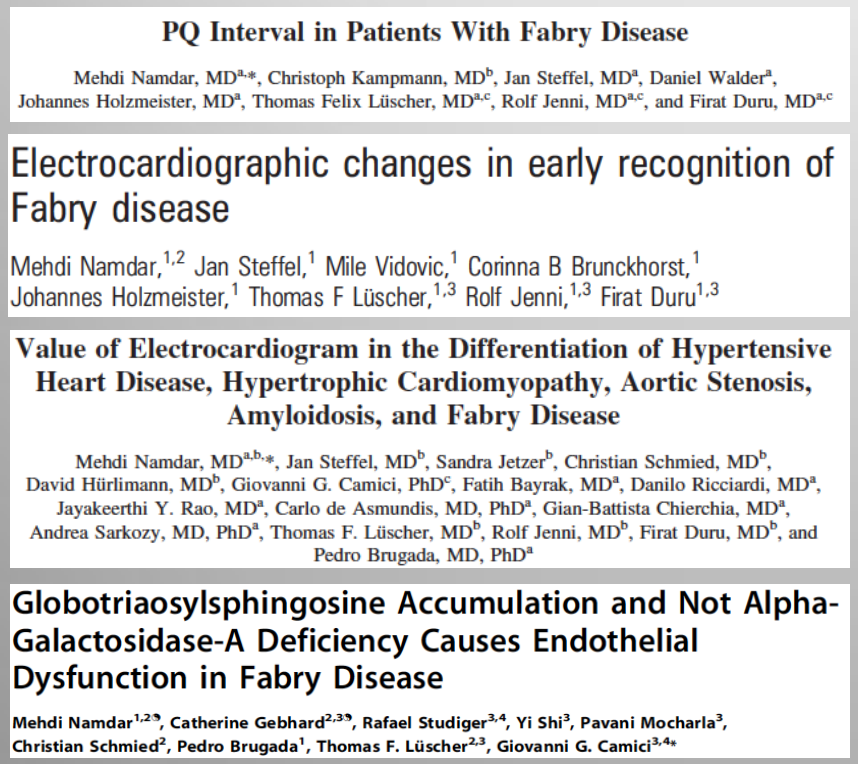


# Increased conduction velocity!!




Namdar M et al. Ms in preparation

# ECG changes and GL-3-related endothelial dysfunction in Fabry disease



**PQ Interval in Patients With Fabry Disease**

Mehdi Namdar, MD[a,*], Christoph Kampmann, MD[b], Jan Steffel, MD[a], Daniel Walder[a], Johannes Holzmeister, MD[a], Thomas Felix Lüscher, MD[a,c], Rolf Jenni, MD[a,c], and Firat Duru, MD[a,c]

**Electrocardiographic changes in early recognition of Fabry disease**

Mehdi Namdar,[1,2] Jan Steffel,[1] Mile Vidovic,[1] Corinna B Brunckhorst,[1] Johannes Holzmeister,[1] Thomas F Lüscher,[1,3] Rolf Jenni,[1,3] Firat Duru[1,3]

**Value of Electrocardiogram in the Differentiation of Hypertensive Heart Disease, Hypertrophic Cardiomyopathy, Aortic Stenosis, Amyloidosis, and Fabry Disease**

Mehdi Namdar, MD[a,b,*], Jan Steffel, MD[b], Sandra Jetzer[b], Christian Schmied, MD[b], David Hürlimann, MD[b], Giovanni G. Camici, PhD[c], Fatih Bayrak, MD[a], Danilo Ricciardi, MD[a], Jayakeerthi Y. Rao, MD[a], Carlo de Asmundis, MD, PhD[a], Gian-Battista Chierchia, MD[a], Andrea Sarkozy, MD, PhD[a], Thomas F. Lüscher, MD[b], Rolf Jenni, MD[b], Firat Duru, MD[b], and Pedro Brugada, MD, PhD[a]

**Globotriaosylsphingosine Accumulation and Not Alpha-Galactosidase-A Deficiency Causes Endothelial Dysfunction in Fabry Disease**

Mehdi Namdar[1,2*], Catherine Gebhard[2,3*], Rafael Studiger[3,4], Yi Shi[3], Pavani Mocharla[3], Christian Schmied[2], Pedro Brugada[1], Thomas F. Lüscher[2,3], Giovanni G. Camici[3,4*]

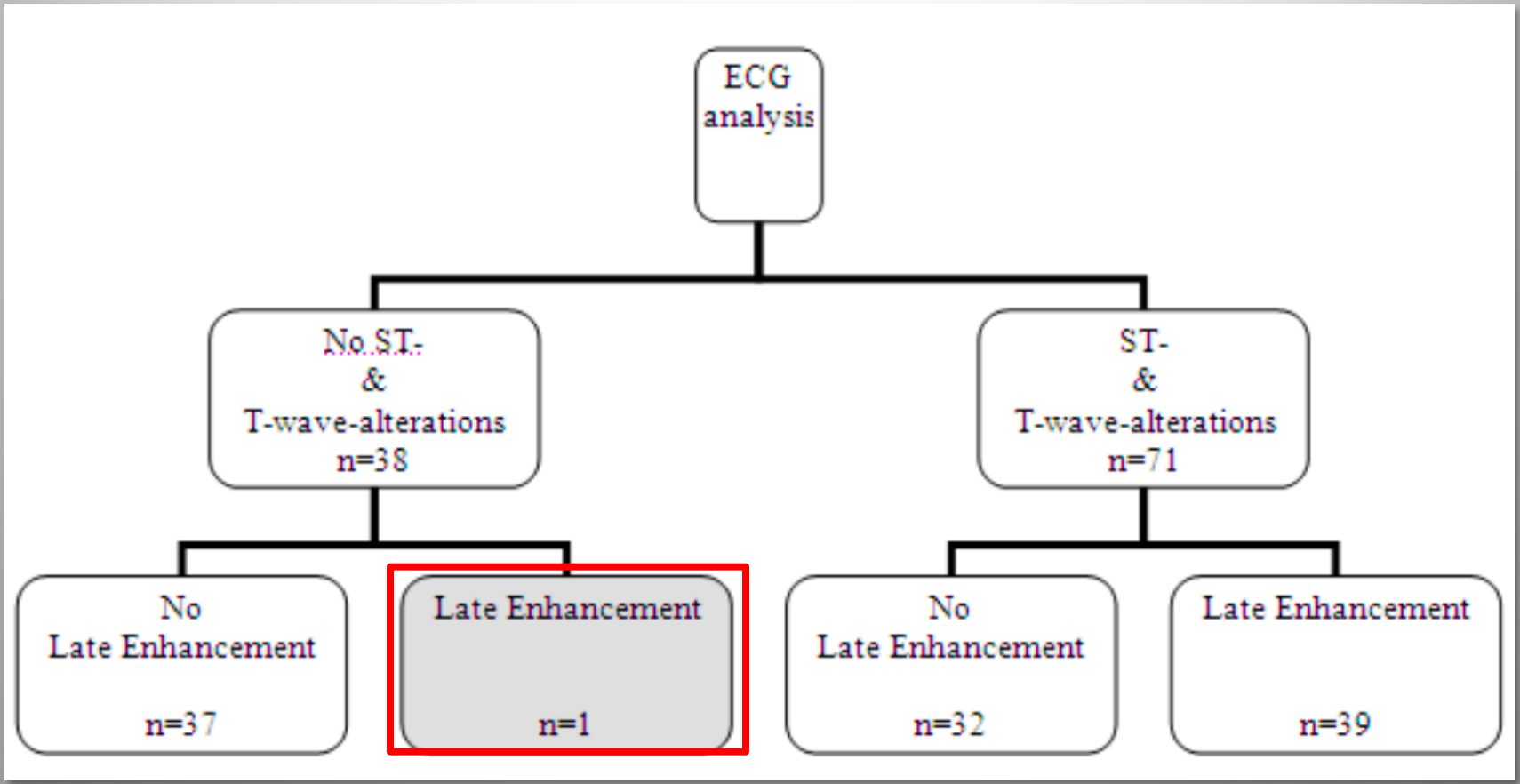
→ **Typical ECG signs[1]**

→ **Early diagnosis before LVH develops**
**P wave very sensitive[2]**

→ **Differentiation vs other LVH and prognosis**
**Novel index[3]**

→ **Endothelial dysfunction and extralysosomal GL-3[4]**

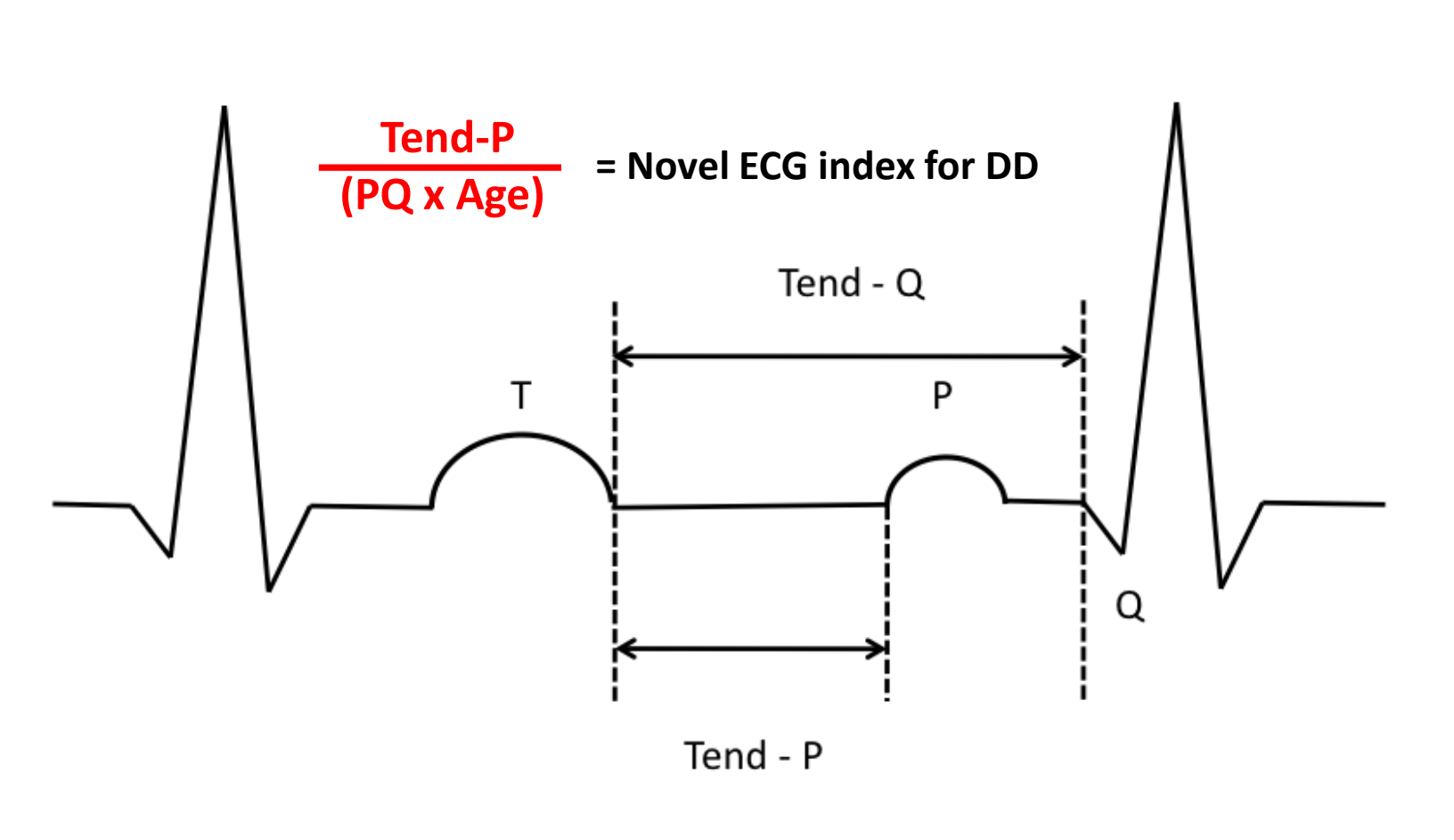
1. Namdar M, et al. Am J Cardiol. 2010;105:753-6. 2. Namdar M, et al. Heart. 2011;97:485-90.
3. Namdar M, et al. Am J Cardiol. 2012;109:587-93. 4. Namdar M, et al. PLoS One. 2012;7:e36373.




**Fibrosis unlikely when repolarization normal**

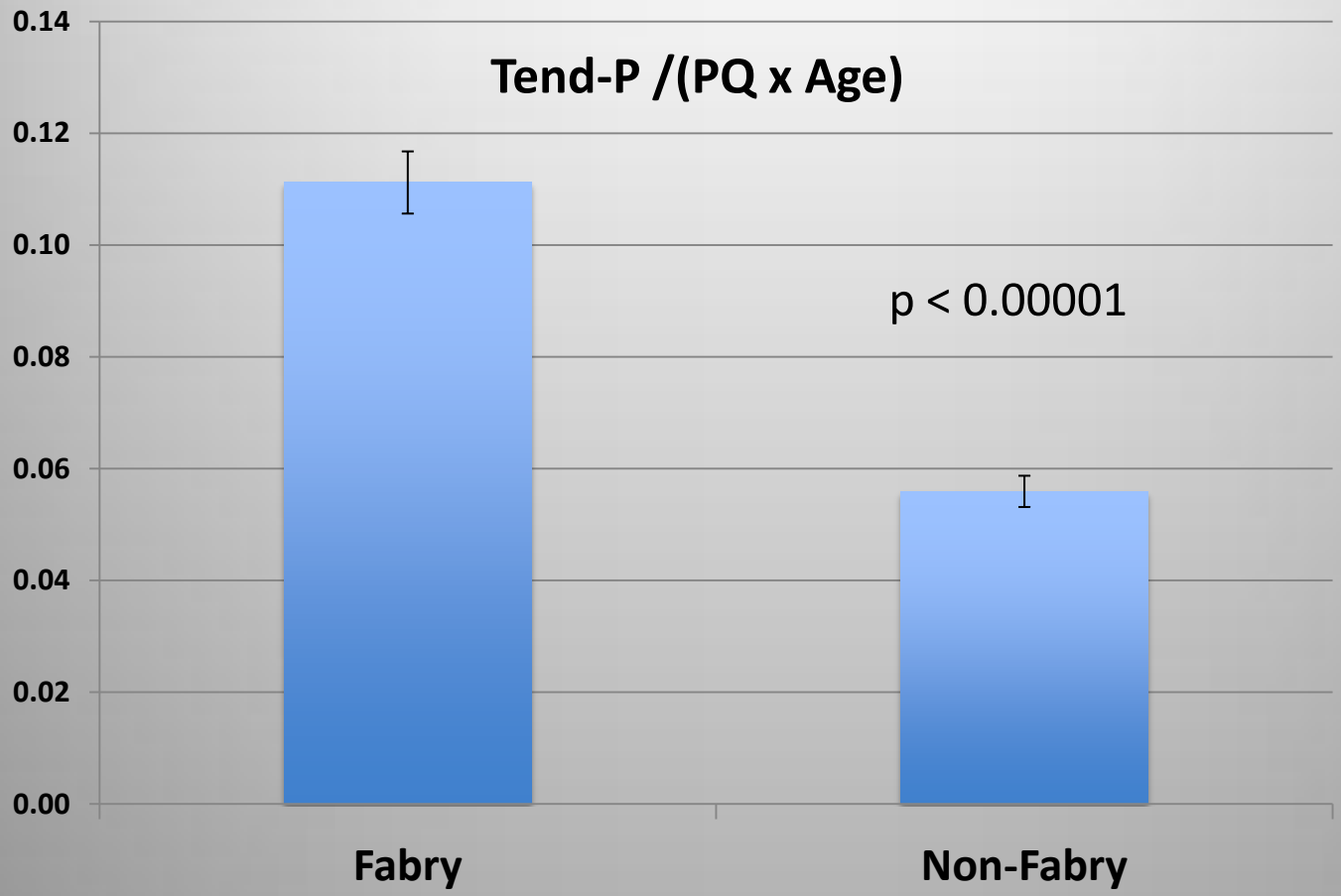
Niemann M, Namdar M et al. J Inherit Metab Dis. 2012 Oct 11.

# Diastolic dysfunction as detected by a novel ECG index




Namdar M, personal data

# Diastolic dysfunction as detected by a novel ECG index




**Diastolic Dysfunction**

Namdar et al. Manuscript under review

Namdar et al. PLoS One. 2013 Nov 5;8(11):e79152

# IS THERE ANY LINK BETWEEN ONE AND THE OTHER "MICROSCOPIC” TOOL?

# Detectable prehypertrophic phenotype in Fabry disease - low native T1 & structural, functional, and ECG changes

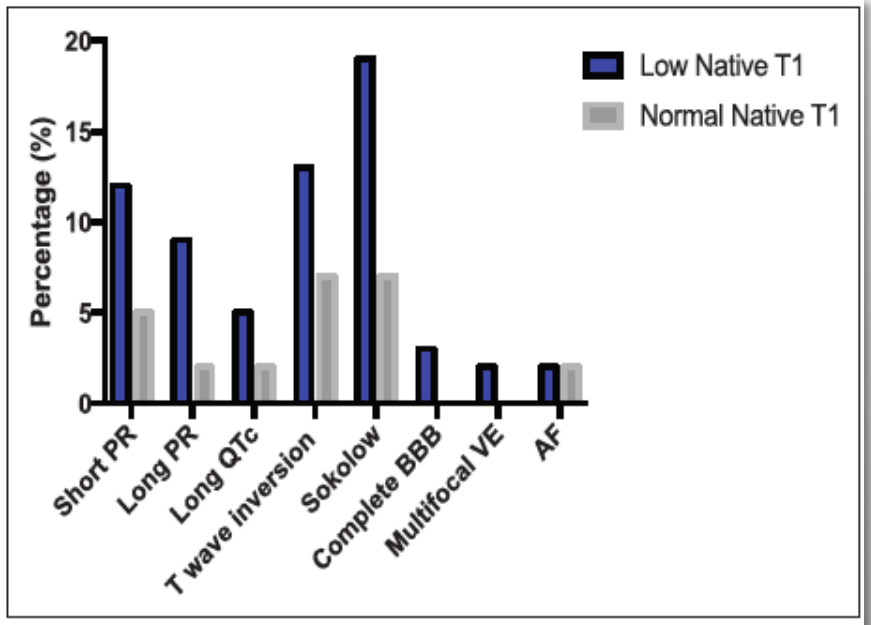



**Figure 3. Comparison of ECG abnormalities between low native T1 and normal native T1 Fabry disease subgroups.**
AF indicates atrial fibrillation; BBB, bundle branch block; and VE, ventricular ectopics.

**Table 3. Comparison Between Low Native T1 and Normal Native T1 Fabry Disease With ECG, LGE, Troponin, NT-proBNP, MWT, LVMi, and LVEF**

| | Low Native T1 | Normal Native T1 | *P* Value |
|---|---|---|---|
| ECG (n=100) | | | 0.005 |
| Abnormal | 31 | 10 | |
| Normal | 28 | 31 | |
| LGE (n=88) | | | 0.01 |
| Positive | 14 | 2 | |
| Negative | 38 | 34 | |
| Troponin (n=73) | | | 0.45 |
| Raised | 5 | 2 | |
| Normal | 35 | 31 | |
| NT-proBNP (n=76) | | | 0.89 |
| Raised | 7 | 5 | |
| Normal | 36 | 28 | |
| Structure and function (n=100) | | | |
| MWT, mm | 9±1.5 | 8±1.4 | <0.005 |
| LVMi, g/m² | 63±10 | 58±9 | <0.05 |
| LVEF, % | 73±8 | 69±7 | <0.01 |

BSA indicates body surface area; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass indexed to BSA; MWT, maximum wall thickness; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Nordin et al. Circ Cardiovasc Imaging. 2018;11:e007168.

Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

# Predictors of Clinical Evolution in Prehypertrophic Fabry Disease

| | | | | |
|---|---|---|---|---|
| LV mass, g/m² | 75.5±16.5 (75.5, 60.0 to 89.0) | 63.2±12.9 (59.0, 55.0 to 73.0) | 84.8±12.8 (87.0, 75.0 to 95.0) | <0.0001 |
| Maximum LVWT, mm | 9.2±2.0 (9.0, 7.0 to 11.0) | 7.6±1.7 (7.0, 7.0 to 8.0) | 10.3±1.3 (11.0, 9.0 to 11.0) | <0.0001 |
| Native septal T1, ms | 906±68 (922, 842 to 967) | 970±22 (972, 948 to 986) | 857±48 (852, 821 to 892) | <0.0001 |
| Septal T2, ms | 40±3 (41.0, 38.0 to 43.0) | 40.8±3.4 (41.0, 39.0 to 43.0) | 39.7±3.2 (40.0, 37.0 to 43.0) | 0.30 |
| LGE, n (%) | 4 (9.1) | 0 (0) | 4 (15.4) | 0.12 |
| MSSI | 15.0±8.7 (12.0, 9.0 to 21.5) | 11.6±7.1 (10.0, 8.0 to 13.0) | 17.5±9.0 (19.0, 9.0 to 25.0) | 0.01 |
| ERT, n (%) | 18 (40.9) | 5 (27.8) | 13 (50.0) | 0.15 |
| Classical mutation, n (%) | 30 (68.2) | 9 (50.0) | 21 (80.8) | 0.03 |
| PR interval, ms | 144.8±23.1 (141.0, 131.0 to 157.0) | 140.5±15.9 (140.5, 131.0 to 147.0) | 147.9±27.0 (141.0, 131.0 to 161.0) | 0.57 |
| QRS interval, ms | 96.2±11.2 (95.0, 89.0 to 100.0) | 95.2±10.0 (96.5, 88.0 to 100.0) | 96.2±11.8 (94.0, 92.0 to 100.0) | 0.71 |
| SLI | 29.1±8.2 (28.0, 21.0 to 36.0) | 24.9±7.7 (23.5, 21.0 to 26.0) | 32.1±7.2 (33.0, 27.0 to 38.0) | 0.0001 |
| Repolarization abnormalities, n (%) | 17 (38.6) | 2 (11.1) | 15 (57.7) | 0.0001 |

Circ Cardiovasc Imaging. 2019;12:e008424.

**EXTRALYSOSOMAL/CIRCULATING PLASMATIC GL3/LYSO-GL3**

**INTERACTION WITH MEMBRANE CHANNELS/TOXICITY…**

# FUTURE DIRECTIONS & ONGOING STUDIES

## DIGITALIZED ECGs
## &
## MACHINE LEARNING FOR RECOGNITION OF ECG ABNORMALITIES AND PREDICTION OF ASSOCIATED DISORDERS BASED ON ELECTRONIC MEDICAL RECORDS

**Many of the ECG indices/parameters lack sufficient Sensitivity and Specificity**

**→ To detect novel ECG indices derived from digitized ECGs of patients with FD with and without cardiac involvement via comparison with ECGs from apparently healthy individuals.**

# Digitalized ECG parameters (N=384!!)

| | I | II | III | aVR | aVL | aVF | V1 | V2 | V3 | V4 | V5 | V6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P onset | 270 | 270 | 270 | 270 | 270 | 270 | 270 | 270 | 270 | 270 | 270 | 270 |
| P+ ampl | 47 | 118 | 74 | 0 | 31 | 96 | 35 | 39 | 48 | 97 | 72 | 35 |
| P− ampl | 0 | 0 | −28 | −80 | −15 | 0 | 0 | 0 | 0 | 0 | 0 | −11 |
| P+ dur | 72 | 72 | 60 | 0 | 22 | 72 | 72 | 72 | 72 | 72 | 72 | 62 |
| P dur | 72 | 72 | 72 | 72 | 72 | 72 | 72 | 72 | 72 | 72 | 72 | 72 |
| Q ampl | 0 | 0 | 0 | −714 | −170 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Q dur | 0 | 0 | 0 | 68 | 36 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Delta wave | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| R ampl | 449 | 1,007 | 601 | 0 | 223 | 797 | 457 | 480 | 660 | 1,838 | 1,373 | 891 |
| R′ ampl | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| R dur | 58 | 64 | 45 | 0 | 26 | 56 | 23 | 36 | 43 | 64 | 64 | 56 |
| R′ dur | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| R notch | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| S ampl | 0 | 0 | −97 | 0 | 0 | 0 | −1,082 | −629 | −412 | 0 | 0 | 0 |
| S′ ampl | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| S dur | 0 | 0 | 24 | 0 | 0 | 0 | 48 | 33 | 22 | 0 | 0 | 0 |
| S′ dur | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| QRS onset | 446 | 440 | 440 | 440 | 440 | 440 | 438 | 438 | 438 | 438 | 438 | 440 |
| p-p QRS ampl | 449 | 1,007 | 698 | 714 | 393 | 797 | 1,539 | 1,109 | 1,072 | 1,838 | 1,373 | 891 |
| QRS dur | 58 | 64 | 70 | 68 | 62 | 56 | 72 | 70 | 66 | 64 | 64 | 56 |
| QRS area | 748 | 1,523 | 776 | −1,133 | −13 | 1,150 | −748 | 229 | 725 | 2,714 | 2,038 | 1,295 |
| QRS def | 28 | 30 | 28 | 0 | 44 | 28 | 8 | 14 | 28 | 32 | 32 | 28 |
| ST ampl | 15 | −4 | −20 | −5 | 18 | −12 | −6 | −4 | −7 | −14 | −4 | −10 |
| 2/8 ST ampl | 14 | 53 | 39 | −33 | 7 | 46 | 0 | 6 | 20 | 43 | 31 | 14 |
| 3/8 ST ampl | 67 | 204 | 137 | −135 | −9 | 171 | −4 | 39 | 66 | 174 | 114 | 55 |
| ST slope | 13 | 43 | 35 | −30 | −11 | 39 | 0 | 11 | 18 | 40 | 28 | 16 |
| T+ ampl | 129 | 286 | 170 | 0 | 0 | 227 | 0 | 58 | 98 | 248 | 170 | 85 |
| T− ampl | 0 | 0 | 0 | −206 | −34 | 0 | −17 | 0 | 0 | 0 | 0 | 0 |
| T morph | 1 | 1 | 1 | −1 | −1 | 1 | −1 | 1 | 1 | 1 | 1 | 1 |
| ST60 (Medtron) | 2 | −3 | −5 | 0 | 4 | −4 | −3 | 0 | −1 | −10 | −5 | −3 |
| ST80 | 33 | 93 | 60 | −63 | −12 | 76 | −2 | 12 | 30 | 93 | 66 | 33 |
| STM (Medtron) | 3 | −7 | −10 | 2 | 7 | −9 | −1 | 0 | −4 | −12 | −7 | −7 |

Namdar M, et al. Eur Heart J. 2018;39 (Suppl 1): ehy565.2357.

**Parameters (9 selected)**

LV strain

P+ amp V2

Heart rate

Q dur V1

ST60 amp V2

QT dispersion

SpQRS-tang

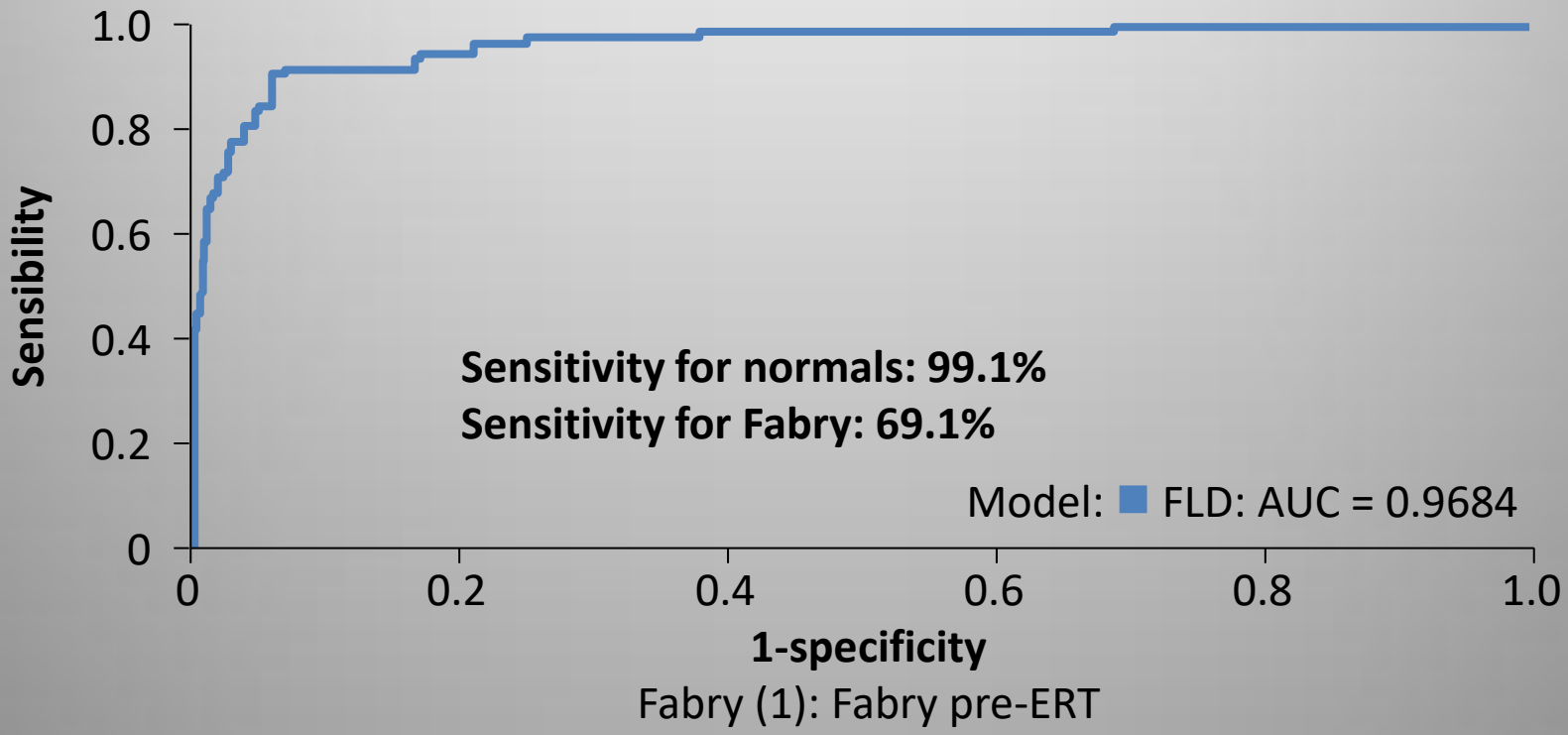
LVH score

QRS area V2

| | Investigational centers | | | Total (n = 2,941) |
|---|---|---|---|---|
| | Glasgow, UK (n = 1,496) | Florence, Italy (n = 562) | Würzburg, Germany (n = 883) | |
| Diagnosis | | | | |
| Normal (apparently healthy), n (%) | 1,496 (100) | 0 (0.0) | 0 (0.0) | 1,496 (50.9) |
| Fabry (pre ERT), n (%) | 0 (0.0) | 42 (7.5) | 70 (7.9) | 112 (3.8) |
| **Mean age, years** | **37** | | **48** | |
| **Median age, years** | **36** | | **50** | |
| **SD, years** | **13** | | **15** | |
| **Males, %** | **57** | | **38** | |

Namdar M, et al. Eur Heart J. 2018;39 (Suppl 1): ehy565.2357.

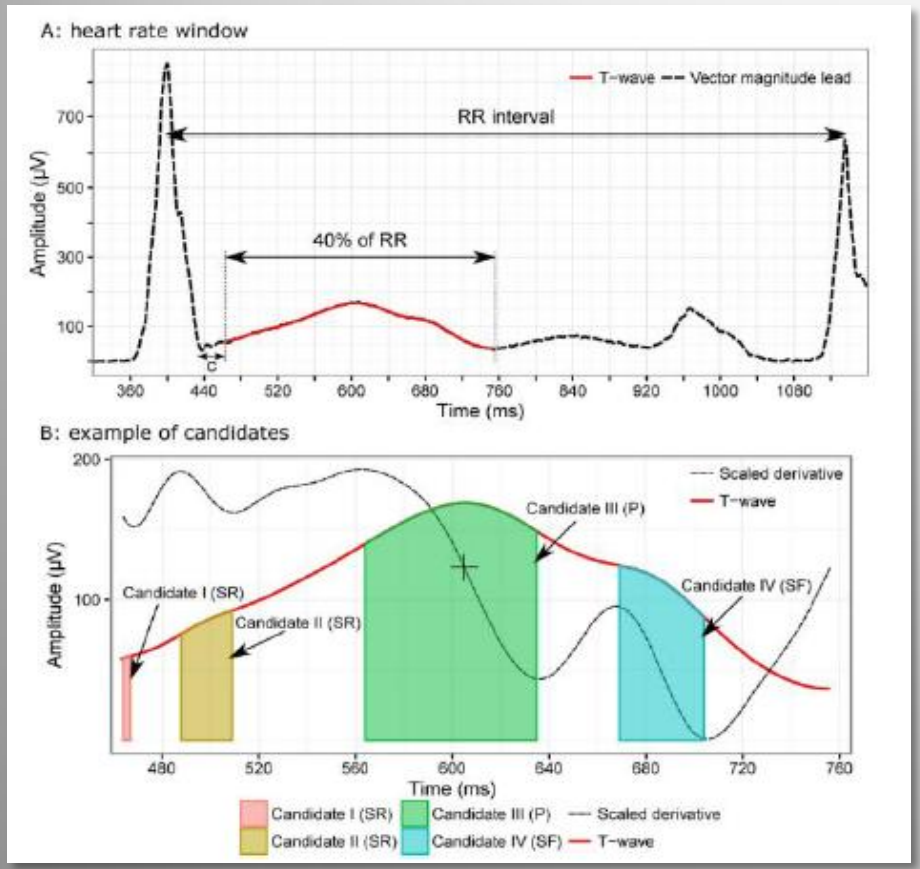
# ROC curve

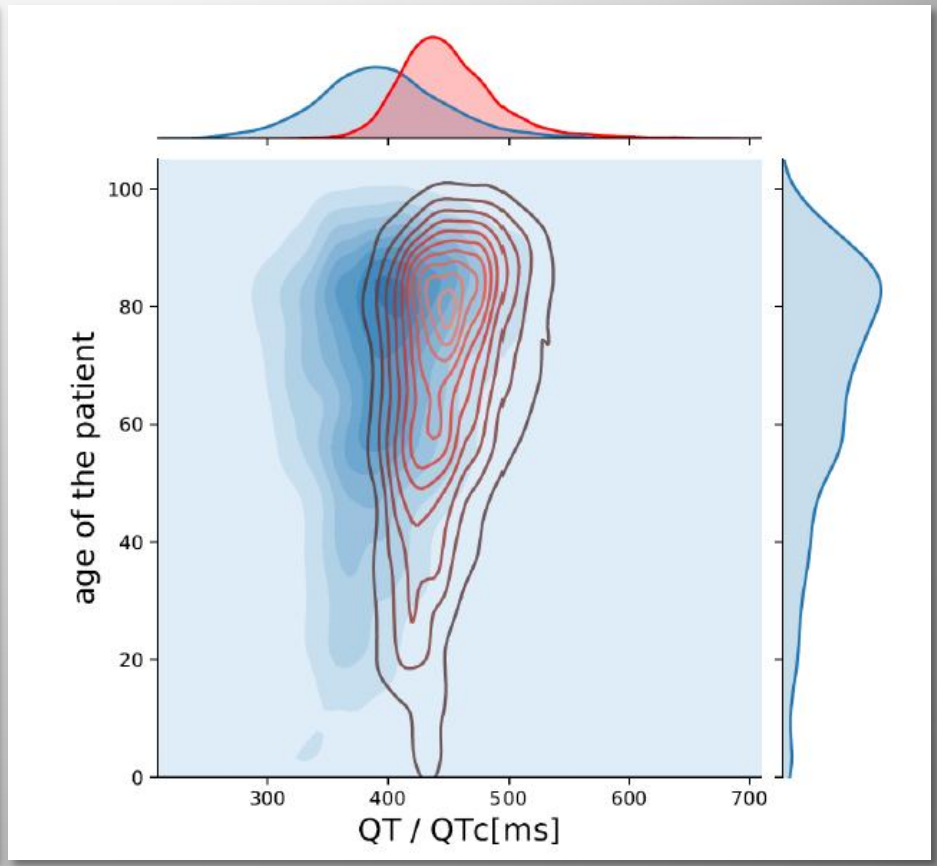



Namdar M, et al. Eur Heart J. 2018;39 (Suppl 1): ehy565.2357.

AUC, area under the curve; ROC, receiver operating characteristic.

# MACHINE LEARNING APPROACH



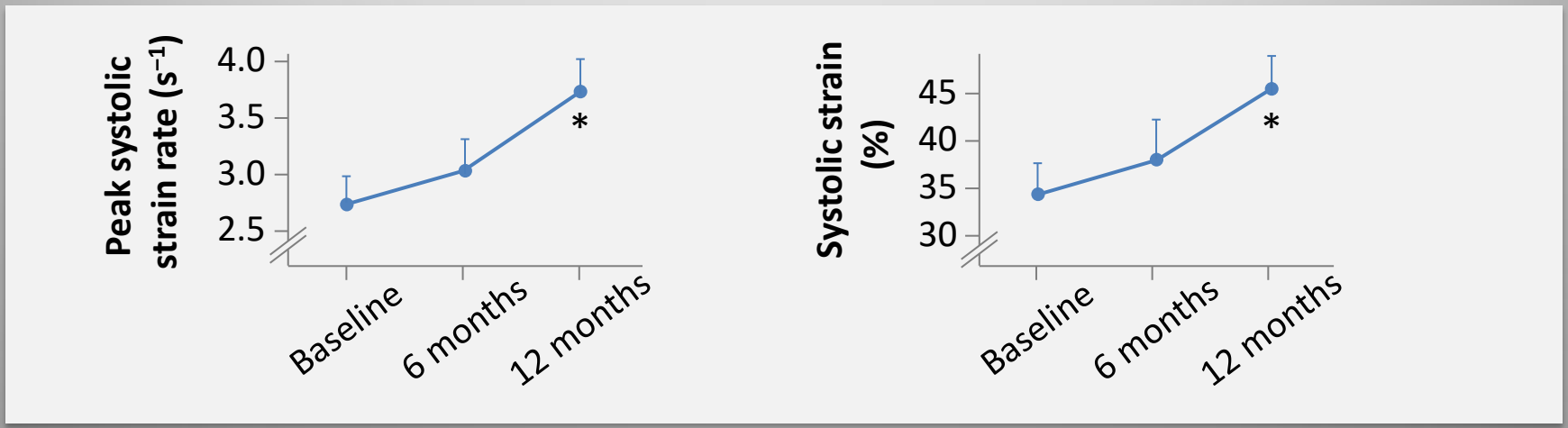

ML-based techniques is expected to support clinicians in two ways: 1. more accurate detection of abnormalities that would be missed using traditional diagnostic criteria (QT duration, axis, visual T-wave morphology). 2. raises the dimensionality of patient-specific information by integrating narrative and textual data to foster personalized therapeutics and precision medicine.

PLOS ONE 2016 Dec 30;11(12):e0166925.
Girardin F, Namdar M et al. study ongoing

# ENZYME REPLACEMENT THERAPY AND ECG

# ERT can improve regional myocardial function

**LV radial function before and after 6 and 12 months of ERT treatment**

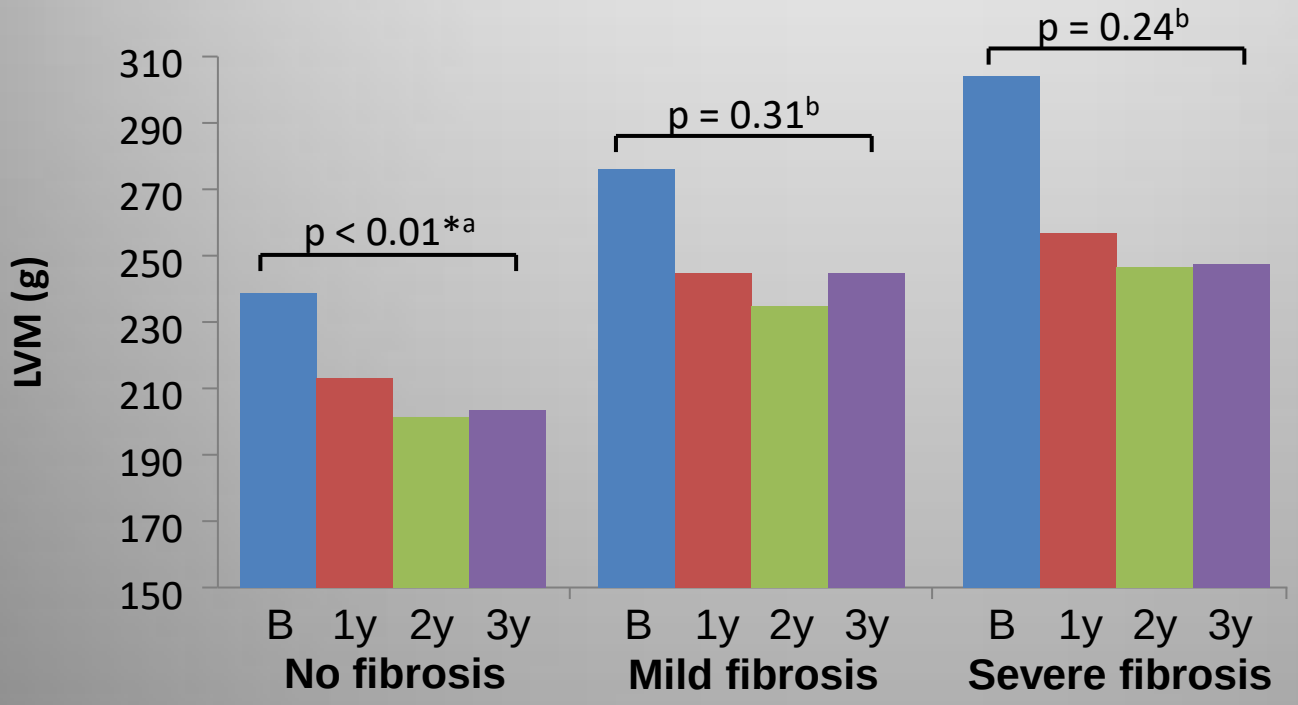



- Radial function was assessed by peak systolic strain rate (left) and systolic strain (right)

*$p < 0.05$ vs baseline. LV, left ventricle.

Weidemann F, et al. Circulation. 2003;108:1299-301.

# Treatment based reduction of LVM is dependent on level of fibrosis at initiation

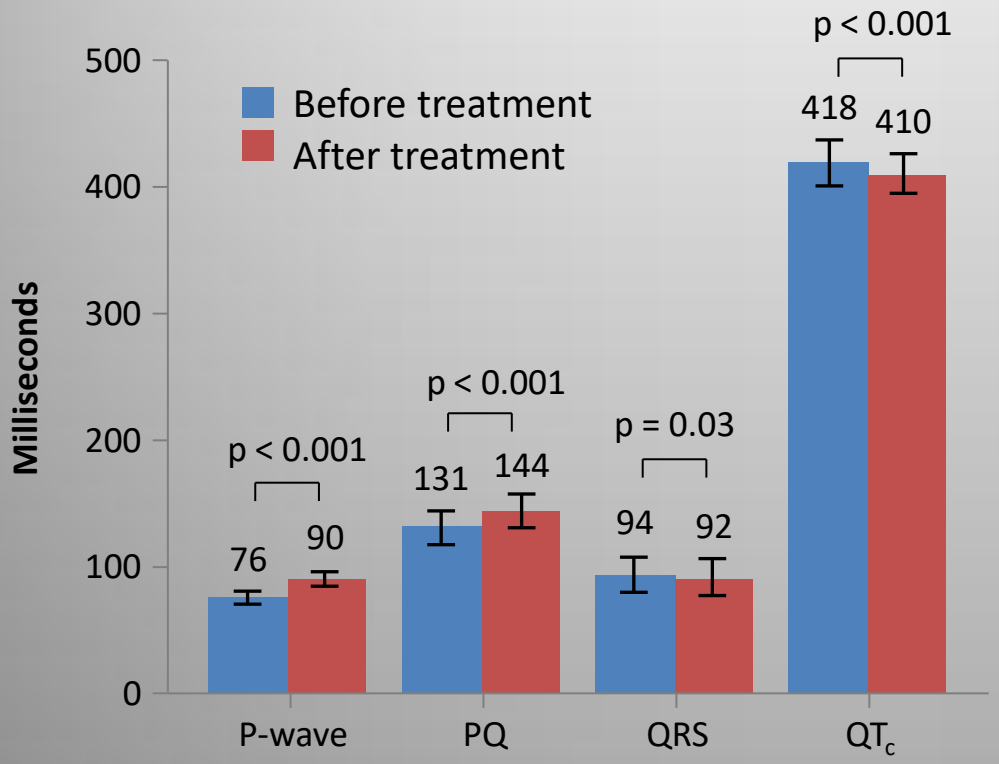



[a] Effect of ERT over time
[b] Comparison of fibrosis groups
- no fibrosis vs mild fibrosis
- no fibrosis vs severe fibrosis

B, baseline; LVM, left ventricular mass; y, year.

Weidemann F, et al. Circulation. 2009;119:524-9.

# ERT has a consistent and positive effect on ECG parameters

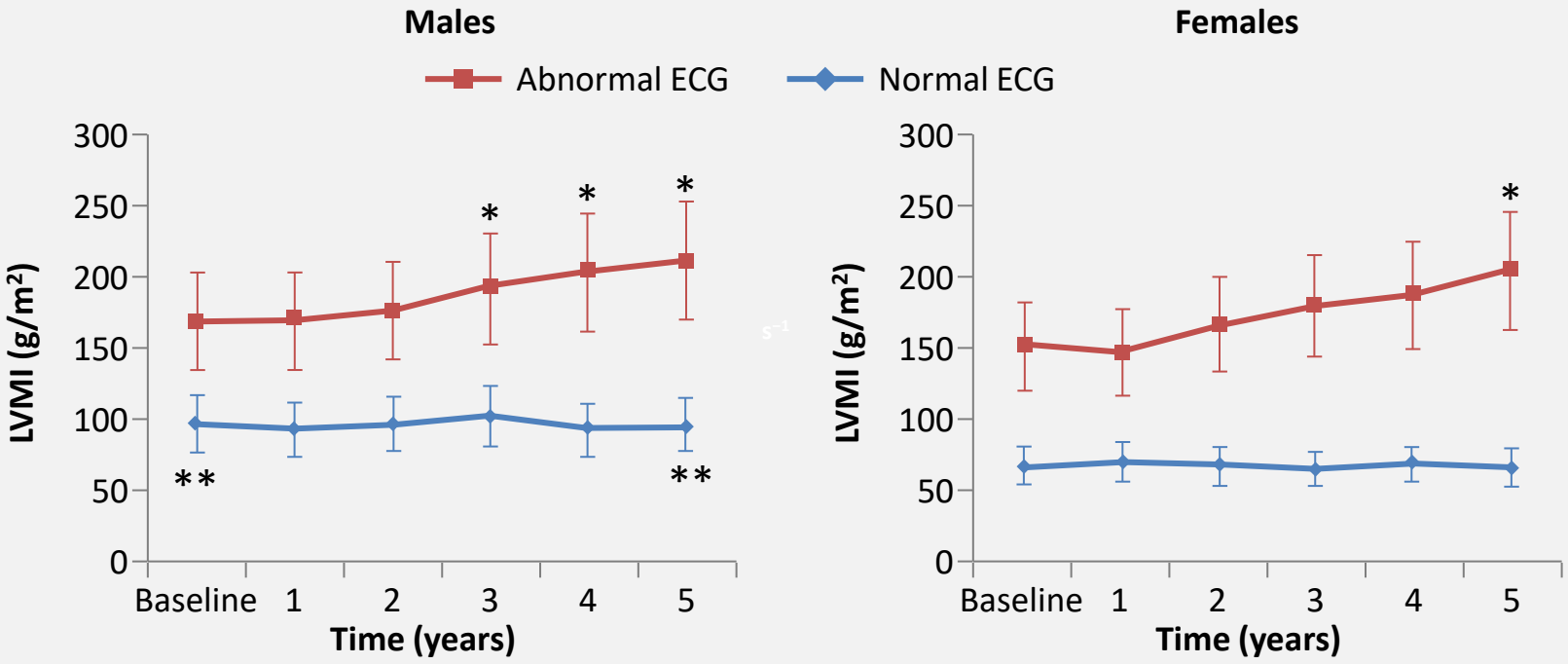



- Effect of ERT on ECG parameters consistent regardless of:
  - sex (male/female)
  - baseline LVH (yes/no)
  - disease burden (MSSI)

Motwani M, et al. Mol Genet Metab. 2012;107:197-202.

# The value of ECG parameters as markers of treatment response in Fabry cardiomyopathy

Christian Schmied,[1] Albina Nowak,[2] Christiane Gruner,[1] Eric Olinger,[3] Huguette Debaix,[3] Andreas Brauchlin,[1] Michelle Frank,[1] Saskia Reidt,[1] Pierre Monney,[4] Frédéric Barbey,[5] Dipen Shah,[6] Mehdi Namdar[6]




* $p < 0.05$ compared with previous follow-up.
**$p < 0.005$ for males vs females.

Schmied C, et al. Heart. 2016;102:1309-14.

# Patients with an abnormal baseline ECG are strongly associated with disease progression

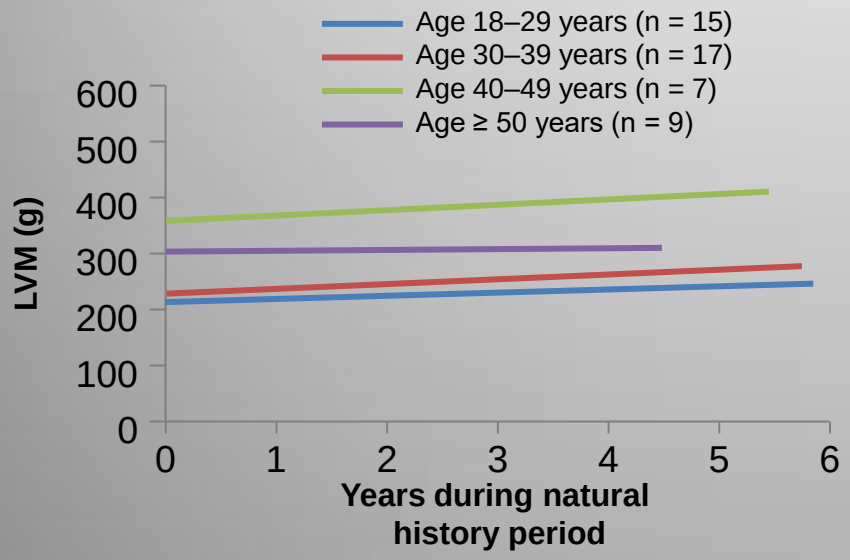
**Criterion values and coordinates of the ROC curve for age at treatment initiation/diagnostic performance of an abnormal baseline ECG for disease progression**

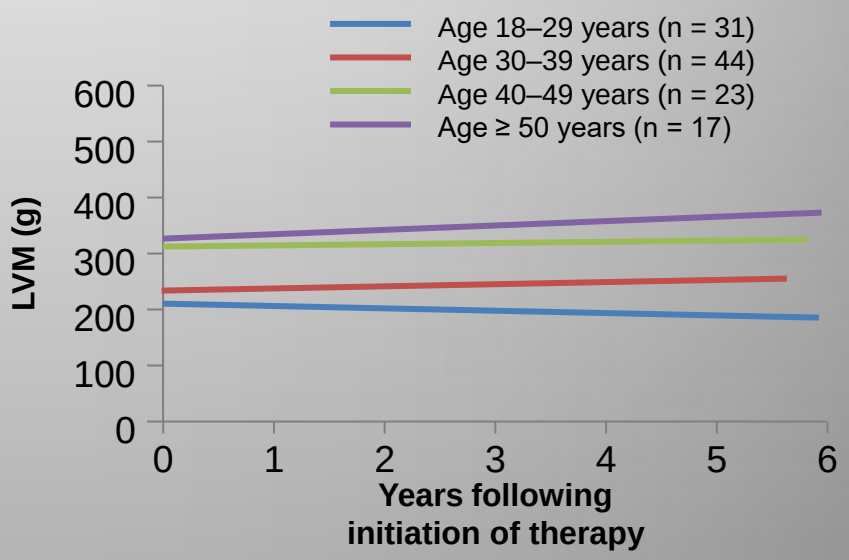
| Age at treatment initiation (years) | Sensitivity (%) | Specificity (%) | +LR | 95% CI | −LR | 95% CI |
|---|---|---|---|---|---|---|
| > 27 | 100 | 61.1 | 2.57 | 1.4–4.6 | – | – |
| > 28 | 100 | 66.7 | 3.0 | 1.6–5.8 | – | – |
| > 29 | 94.4 | 72.2 | 3.4 | 1.6–7.2 | 0.08 | 0.01–0.5 |
| > 30 | 94.4 | 77.8 | 4.25 | 1.8–10.2 | 0.07 | 0.01–0.5 |
| > 31 | 94.4 | 83.3 | 5.67 | 2.0–16.0 | 0.07 | 0.01–0.5 |
| > 35 | 94.4 | 88.9 | 8.5 | 2.3–31.5 | 0.06 | 0.009–0.4 |
| > 36 | 94.4 | 94.4 | 17 | 2.4–114.6 | 0.06 | 0.009–0.4 |
| > 37 | 94.4 | 100 | – | – | 0.06 | 0.008–0.4 |
| > 38 | 83.3 | 100 | – | – | 0.17 | 0.06–0.5 |
| Abnormal baseline ECG | 94.1 | 88.9 | 8.47 | 2.28–31.46 | 0.07 | 0.01–0.45 |

CI, confidence interval; +LR, positive likelihood ratio;
−LR, negative likelihood ratio; ROC, receiver operating characteristic

Schmied C, et al. Heart. 2016;102:1309-14.

# Agalsidase beta 1mg/kg EOW significantly reduced LVM in patients aged <30 years (vs untreated)




LVM, left ventricular mass.

Germain DP, et al. Gen Med. 2013:15:958-65

## Conduction abnormalities

**Morbidity**  **Mortality**

## Arrhythmia

**Table 3** Annual incidence (per 100 person-years) and CI of study end-points

| | Total (classical/cardiac variants) events | All patients | |
|---|---|---|---|
| | | Incidence | CI |
| Cardiac death | 7 (5/2) | 0.52 | 0.21 to 1.06 |
| AF* | 13 (11/2) = 6% (vs. 1-2% normal) | 1 | 0.53 to 1.71 |
| NYHA III/IV | 21 (15/6) | 1.62 | 1.00 to 2.48 |
| Device† | 13 (9/4) | 1.07 | 0.57 to 1.84 |
| Primary | 30 (24/6) | 2.64 | 1.78 to 3.77 |

**no sign difference classical vs. cardiac variants**

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

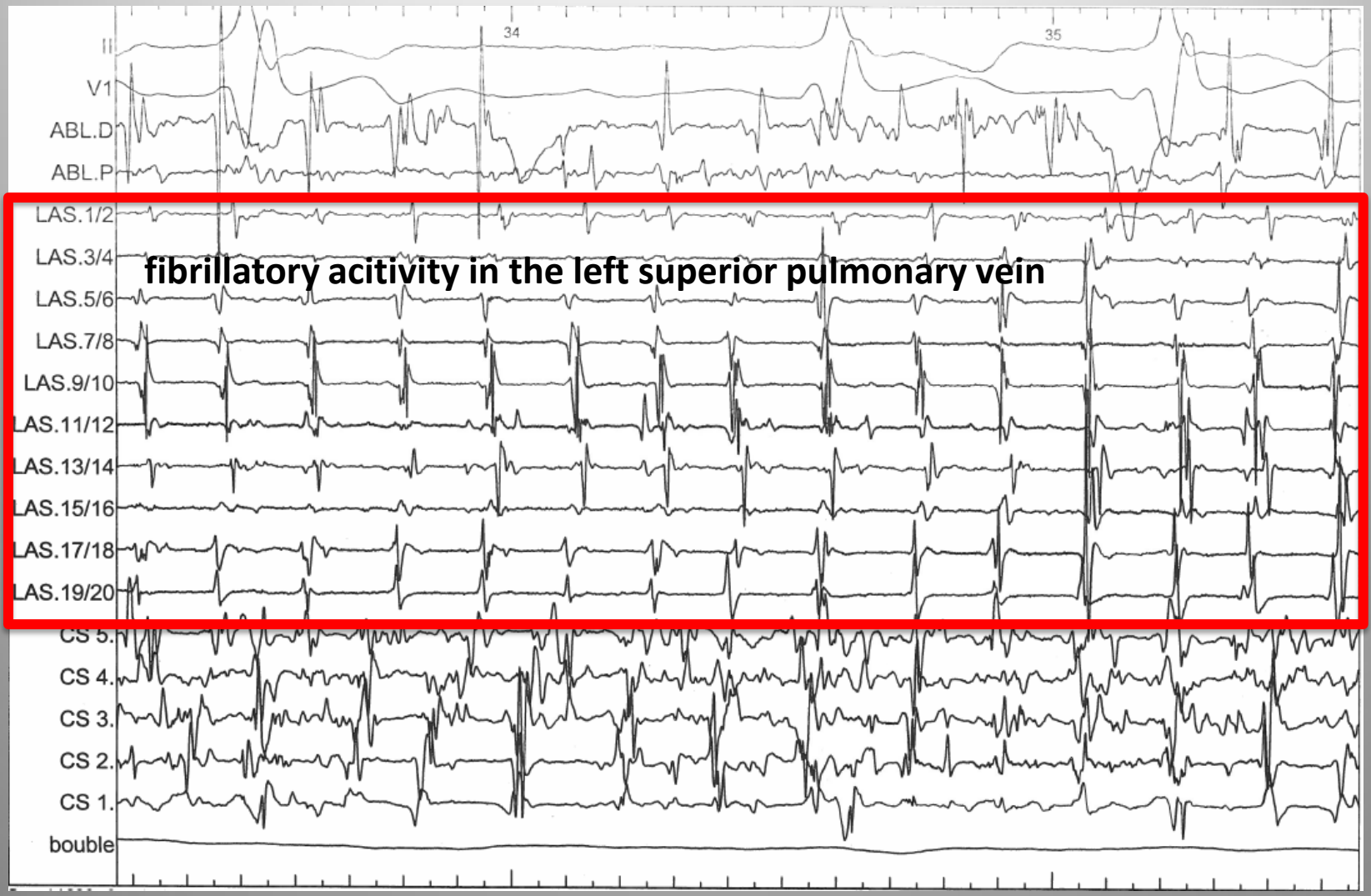
**Table 4** The relation of baseline clinical characteristics to cardiac outcomes (Cox regression with Firth's penalised likelihood estimation. Multivariate analysis)

| End points (dependent variables) | Predictors (indpendent variables) | HR | CIs | p Value |
|---|---|---|---|---|
| Composite | Age | 1.04 | (1.01 to 1.08) | 0.004 |
| | MSSI | 1.05 | (1.01 to 1.09) | 0.012 |
| | QRS duration (ms) | 1.03 | (1.00 to 1.05) | 0.020 |
| NYHA III/IV | Age | 1.05 | (1.01 to 1.09) | 0.003 |
| | MSSI | 1.06 | (1.02 to 1.10) | 0.003 |
| Atrial fibrillation | Age | 1.05 | (1.00 to 1.10) | 0.04 |
| | LA | 1.11 | (0.99 to 1.24) | 0.053 |
| | LVMI | 1.02 | (1.01 to 1.03) | 0.02 |
| Device | Age | 1.05 | (1.00 to 1.09) | 0.033 |
| | QRS duration (ms) | 1.05 | (1.02 to 1.08) | 0.002 |
| Death | LA | 0.83 | (0.58 to 1.07) | 0.081 |
| | LVMI | 1.05 | (1.02 to 1.09) | 0.000 |

LA, left atrial diameter (mm); LVMI, indexed LV mass ($g/m^2$); MSSI, Mainz Severity Score Index; NYHA, New York Heart Association.

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

**52-yrs old male, under ERT, 14mm, symptomatic PAF, refractory / contraindication to AAD – underwent PVI by means of RF**
**→ 18 months FU in SR off AAD & non-Vit-K antagonist**



**Pulmonary vein isolation successful in restoring and maintaining sinus rhythm**

**Pulmonary veins remain the source of critical triggers necessary for AF initiation despite apparent diffuse myocardial involvement**

**No evidence of „Fabry-AF“**

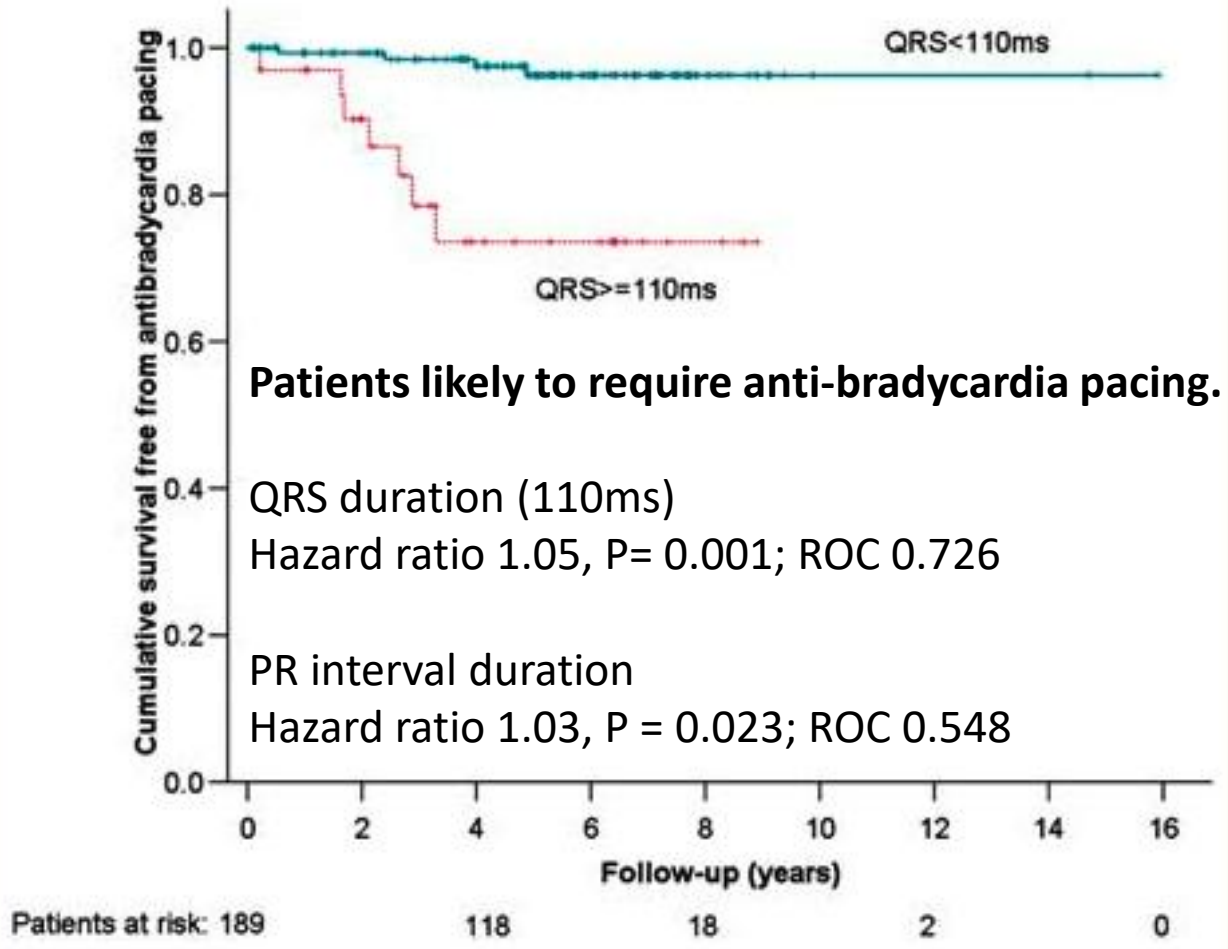
**Amiodarone cationic amphiphilic drug inhibiting lysosomal degradation of phospholipids and corneal verticillata similar to FD → not recommended**

**Beta blockers → sinus bradycardia, limiting tolerability**

**The choice of other AAD classes therapy limited in Fabry cardiomyopathy.**

**Oral anticoagulation (role of non-Vit-K antagonists to be evaluated)**

# Blocks




**Patients likely to require anti-bradycardia pacing.**

QRS duration (110ms)
Hazard ratio 1.05, P= 0.001; ROC 0.726

PR interval duration
Hazard ratio 1.03, P = 0.023; ROC 0.548

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

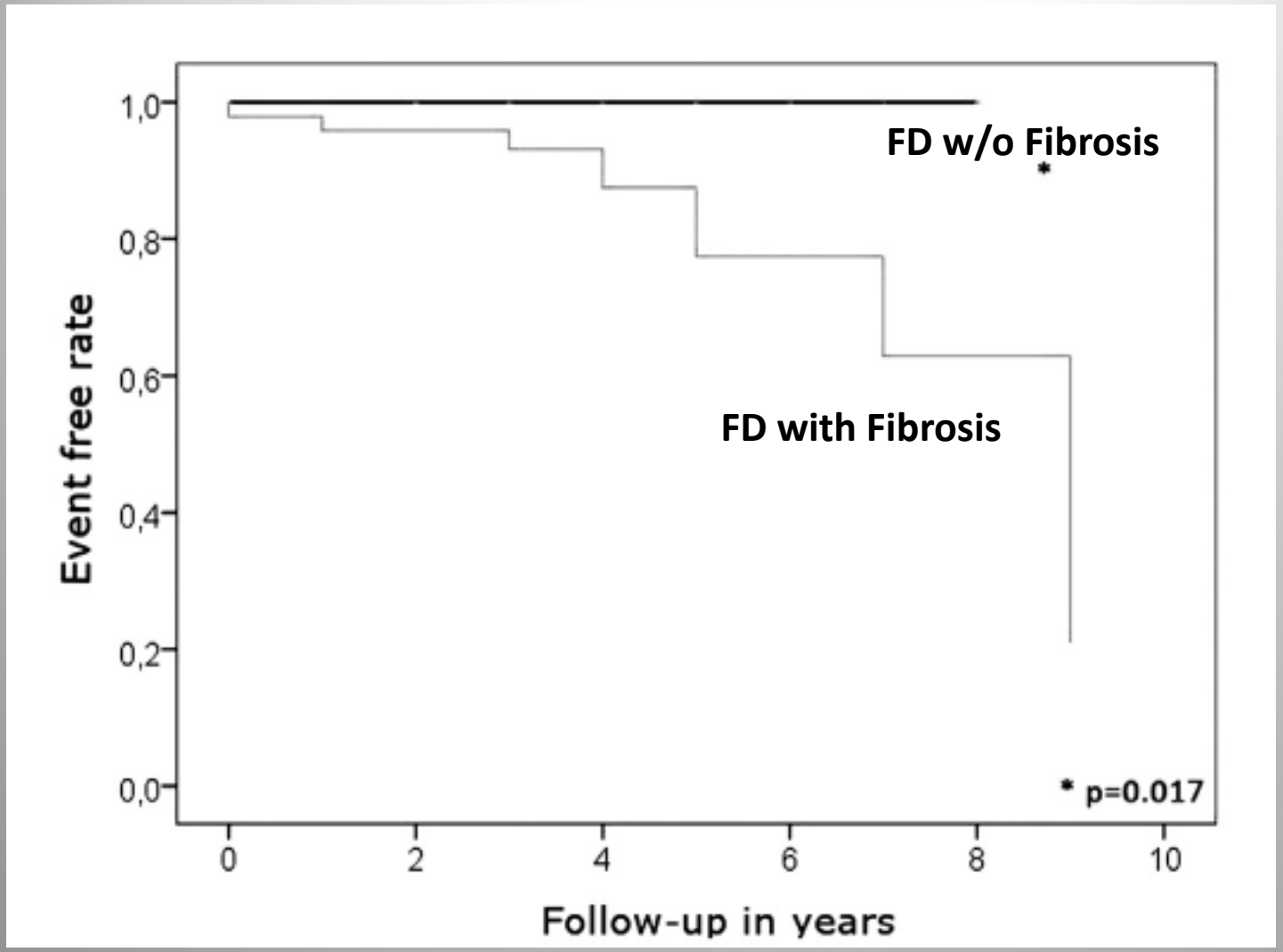
**Table 4** The relation of baseline clinical characteristics to cardiac outcomes (Cox regression with Firth's penalised likelihood estimation. Multivariate analysis)

| End points (dependent variables) | Predictors (indpendent variables) | HR | CIs | p Value |
|---|---|---|---|---|
| Composite | Age | 1.04 | (1.01 to 1.08) | 0.004 |
| | MSSI | 1.05 | (1.01 to 1.09) | 0.012 |
| | QRS duration (ms) | 1.03 | (1.00 to 1.05) | 0.020 |
| NYHA III/IV | Age | 1.05 | (1.01 to 1.09) | 0.003 |
| | MSSI | 1.06 | (1.02 to 1.10) | 0.003 |
| Atrial fibrillation | Age | 1.05 | (1.00 to 1.10) | 0.04 |
| | LA | 1.11 | (0.99 to 1.24) | 0.053 |
| | LVMI | 1.02 | (1.01 to 1.03) | 0.02 |
| Device | Age | 1.05 | (1.00 to 1.09) | 0.033 |
| | QRS duration (ms) | 1.05 | (1.02 to 1.08) | 0.002 |
| Death | LA | 0.83 | (0.58 to 1.07) | 0.081 |
| | LVMI | 1.05 | (1.02 to 1.09) | 0.000 |

LA, left atrial diameter (mm); LVMI, indexed LV mass ($g/m^2$); MSSI, Mainz Severity Score Index; NYHA, New York Heart Association.

Patel V, et al. Heart 2015;0:1–6.

# Ventricular arrhythmias




Krämer et al. AJC 2014 Sep 15;114(6):895-900

# CONCLUSIONS

**Cardiac involvement is present early in life but is not detected clinically until the third or fourth decade**

**Age (ca. > 35 yrs) seems to play an important role as an epi-parameter for the development of diastolic dysfunction, LVH, Fibrosis and ECG alterations**

**ERT to start before signs of manifest cardiomyopathy – for the time being = LVH and/or ECG abnormalities**

**T1 – MRI – Mapping of utmost importance for early recognition of myocardial involvement**

**ECG changes/arrhythmia may precede LVH (not just villain bystanders) – preclincal ECG changes/trends important precursors of clinical events**

**Arrhythmia major driver for morbidity & mortality**

**AAD choice in AF limited → consider pulmonary vein isolation**

# SEARCH & TREAT ARRHYTHMIA IN FABRY DISEASE!

- **ERT is well tolerated**
- **ERT is of proven benefit: no progression rather than regression**
- **Start ERT as early as possible, for optimal outcomes**
- **There is a missing link between GL-3 accumulation, clearing, and ERT effect, toxicity of circulating GL3, lyso-GL3?**
- **The ERT effect is related to baseline characteristics**

- **→ stage of cardiomyopathy and age are important factors**