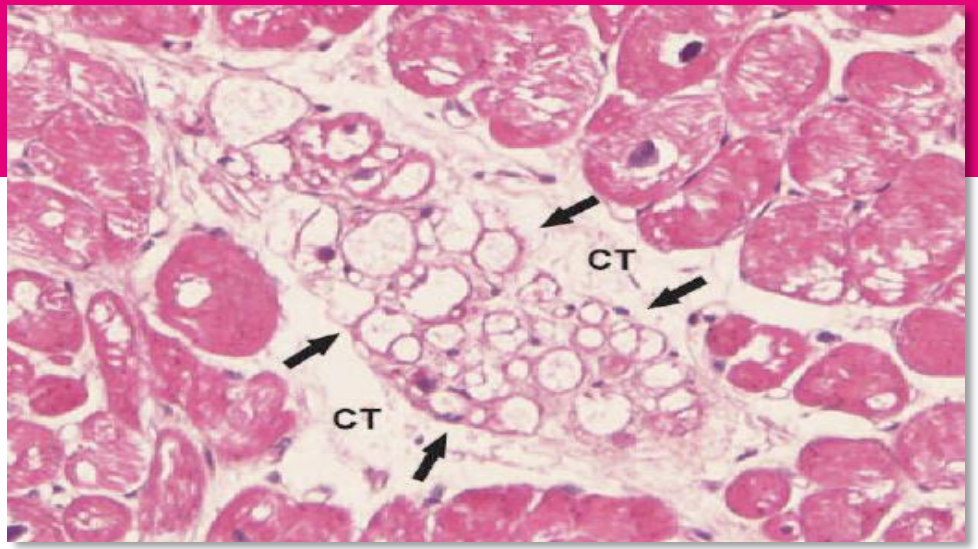

EKG Webcast Fabry

Mehdi Namdar, MD, PhD, PD, Médecin Adjoint Agrégé, chargé de cours – Leitender Arzt
Service de Cardiologie – Hôpitaux Universitaires de Genève

27.05.2020 – Webcast

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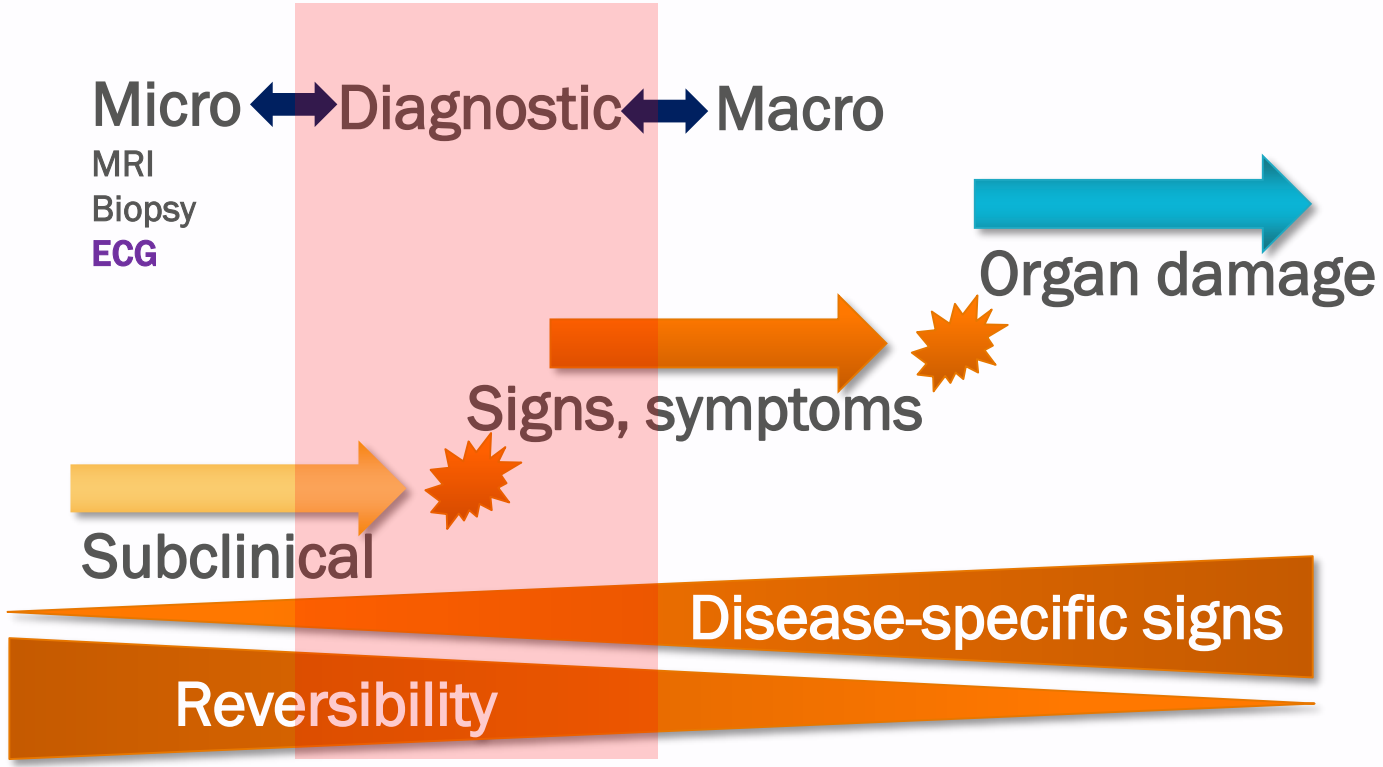
FACULTÉ DE MÉDECINE
UNIVERSITÉ DE GENÈVE

DISCLOSURES

- Speaker Fees/Honoraria/Travel Grants
  - Bayer, Biosense Webster, Biotronik, Boston Scientific, Daiichi Sankyo, Medtronic, Sanofi Genzyme, Shire (now part of Takeda)
- Advisory Boards
  - Amicus, Bayer, Biotronik, Boston Scientific, Daiichi Sankyo, GBc, Sanofi Genzyme, Shire (now part of Takeda)
- Investigatorships
  - Biotronik, Daiichi Sankyo, Biosense Webster, Boston-Scientific, Sanofi Genzyme
- Research/Fellowship Grants
  - Abbott, Biotronik, Biosense Webster, Sanofi Genzyme, Shire (now part of Takeda)
- Presidency
  - CHAR (Swiss Arrhythmia Foundation)

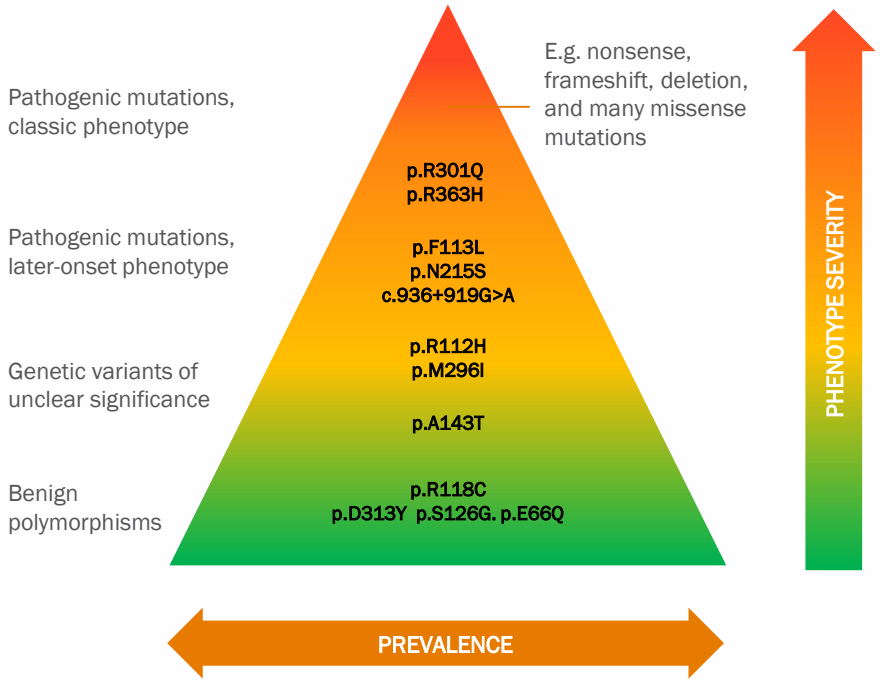
Dynamic disease course



ECG, electrocardiogram; MRI, magnetic resonance imaging.

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

Fabry disease genotype–phenotype correlations



- > 900 *GLA* variants have been reported to date[1]
  - Due to the large number of de novo variants, there is often not enough evidence across enough individuals for full phenotypic characterization[2]
  - This accounts for extensive heterogeneity of Fabry disease manifestations[3]

GLA, galactosidase alpha.

Figure from Ortiz A, et al. Mol Genet Metab. 2018;123:416-27.
1. The Human Gene Mutation Database. Available from: http://www.hgmd.cf.ac.uk/ac/gene.php?gene=GLA. Accessed August 2019.
2. Curiati MA, et al. J Inborn Errors Metab Screen. 2017;5:1-7.
3. Germain DP. Orphanet J Rare Dis. 2010;5:30.

Two major phenotypes: classic and later-onset Fabry disease

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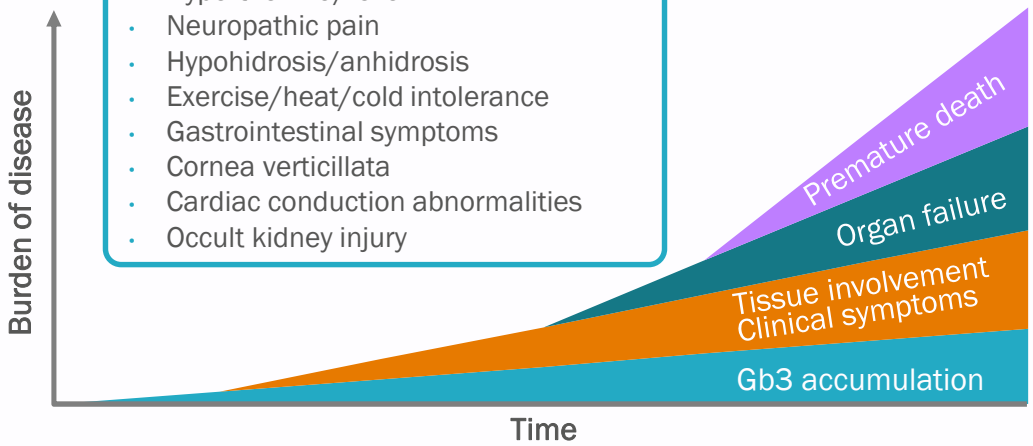
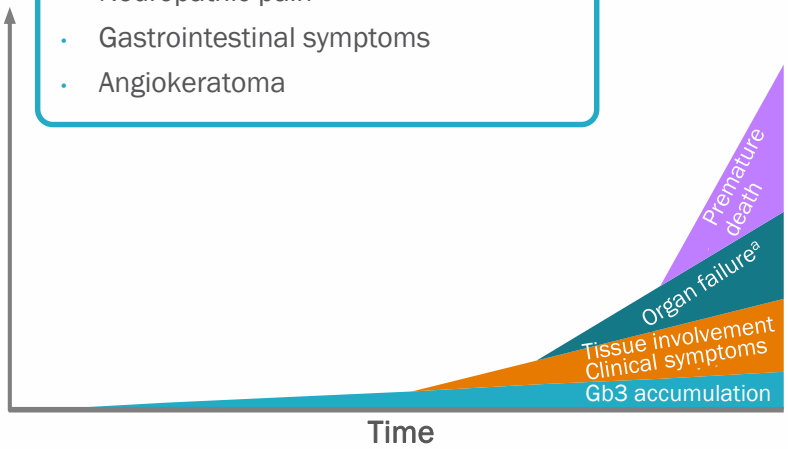
Classic disease – early manifestations[1–4]

- Angiokeratoma
- Hyperthermia/fever
- Neuropathic pain
- Hypohidrosis/anhidrosis
- Exercise/heat/cold intolerance
- Gastrointestinal symptoms
- Cornea verticillata
- Cardiac conduction abnormalities
- Occult kidney injury



Later-onset disease – general lack of early manifestations, such as[5]

- Neuropathic pain
- Gastrointestinal symptoms
- Angiokeratoma

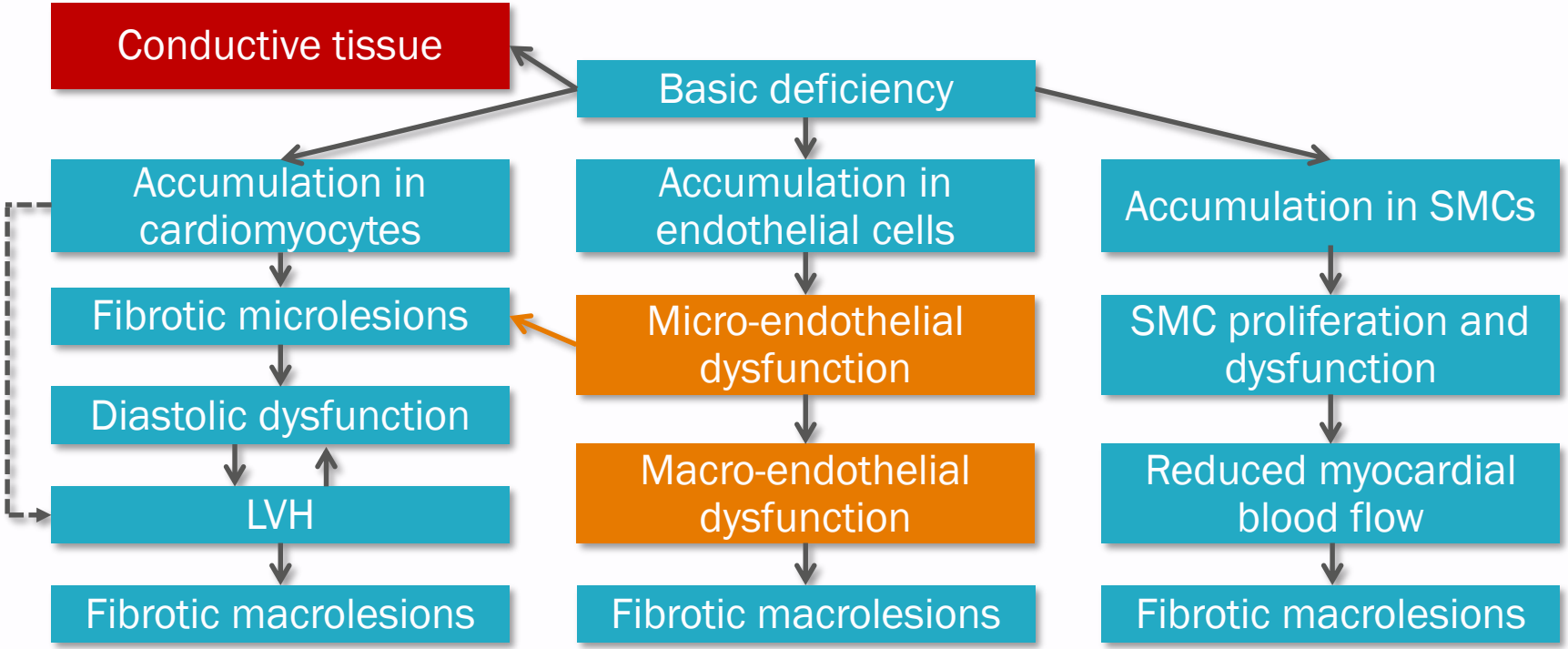


Male and female manifestations can differ significantly within these phenotypes[1]

[a] Organ failure is not common in later-onset disease.
Gb3, globotriaosylceramide.

Figures adapted from Eng CM, et al. J Inherit Metab Dis. 2007;30:184-92.
1. Ortiz A, et al. Mol Genet Metab. 2018;123:416-27.
2. Verrecchia E, et al. Eur J Intern Med. 2016;32:26-30. 3. Ries M, et al. Eur J Pediatr. 2003;162:767-72.
4. Fernandez A, Politei J. J Inborn Errors Metab Screen. 2016;4:1-9. 5. Germain DP, et al. Mol Genet Genomic Med. 2018;6:492-503.

Simplified course of disease pathogenesis in Fabry disease



LVH, left ventricular hypertrophy; SMC, smooth muscle cell.

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

THE ELECTROCARDIOGRAM IS…

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a highly sensitive *electro-anatomical* tool, i.e. whatever happens in the myocardium → electrical signature with a considerable temporal and spatial resolution

highly reproducible & not expensive at all

…old & beautiful…

…REGARDER N'EST PAS VOIR…
WHAT DO WE SEE AND WHY DO WE SEE WHAT WE SEE?

ELECTRO-ANATOMICAL PRELUDE...
...WHY DO WE SEE WHAT WE SEE...

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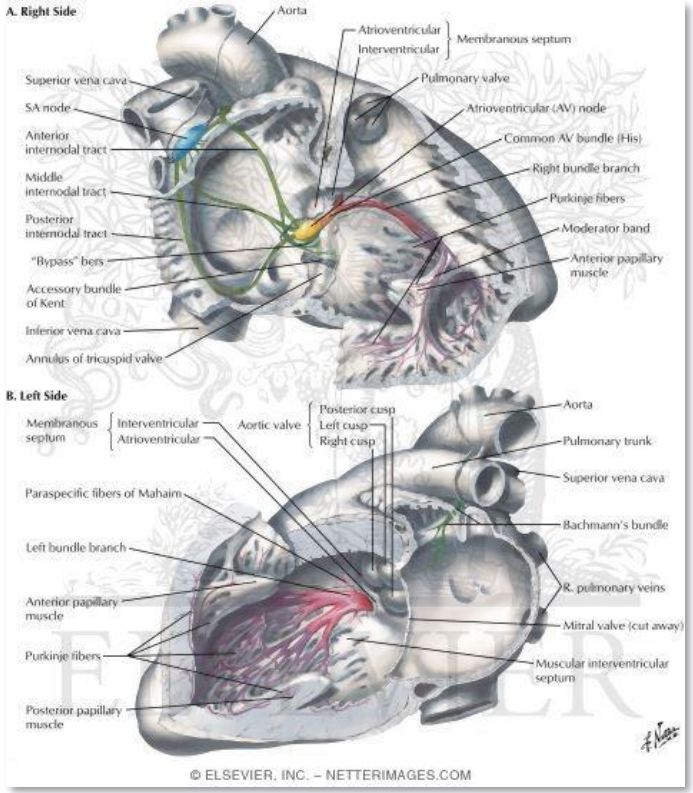
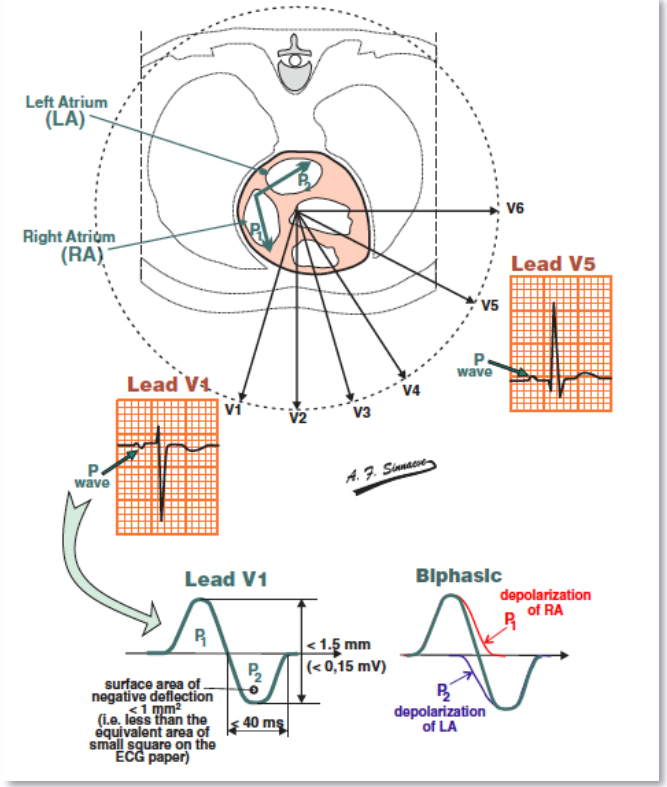
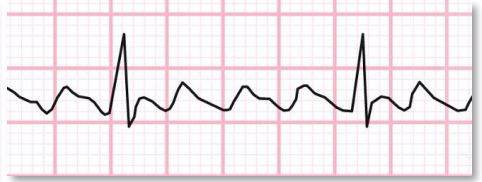
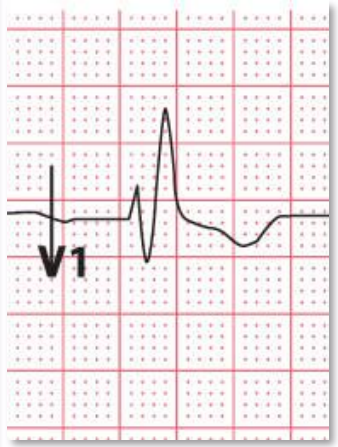
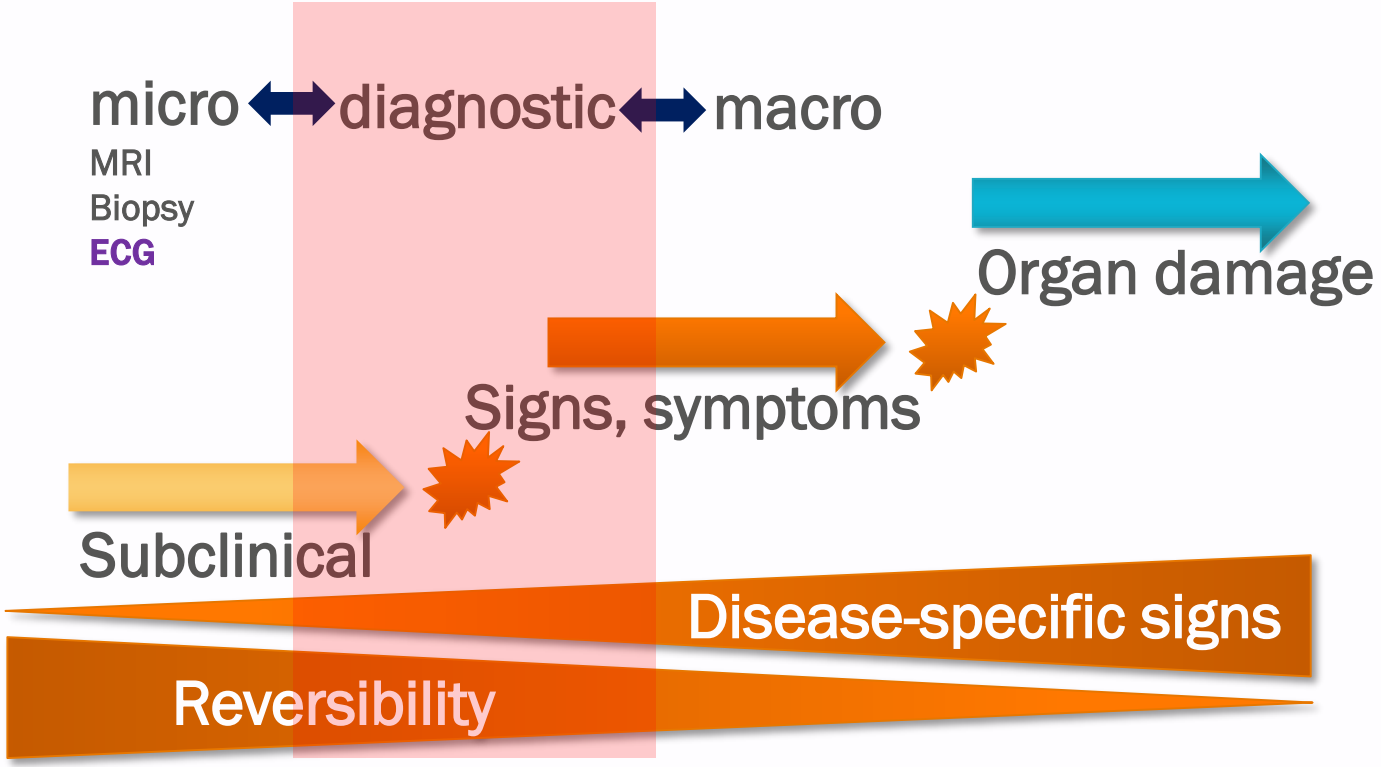






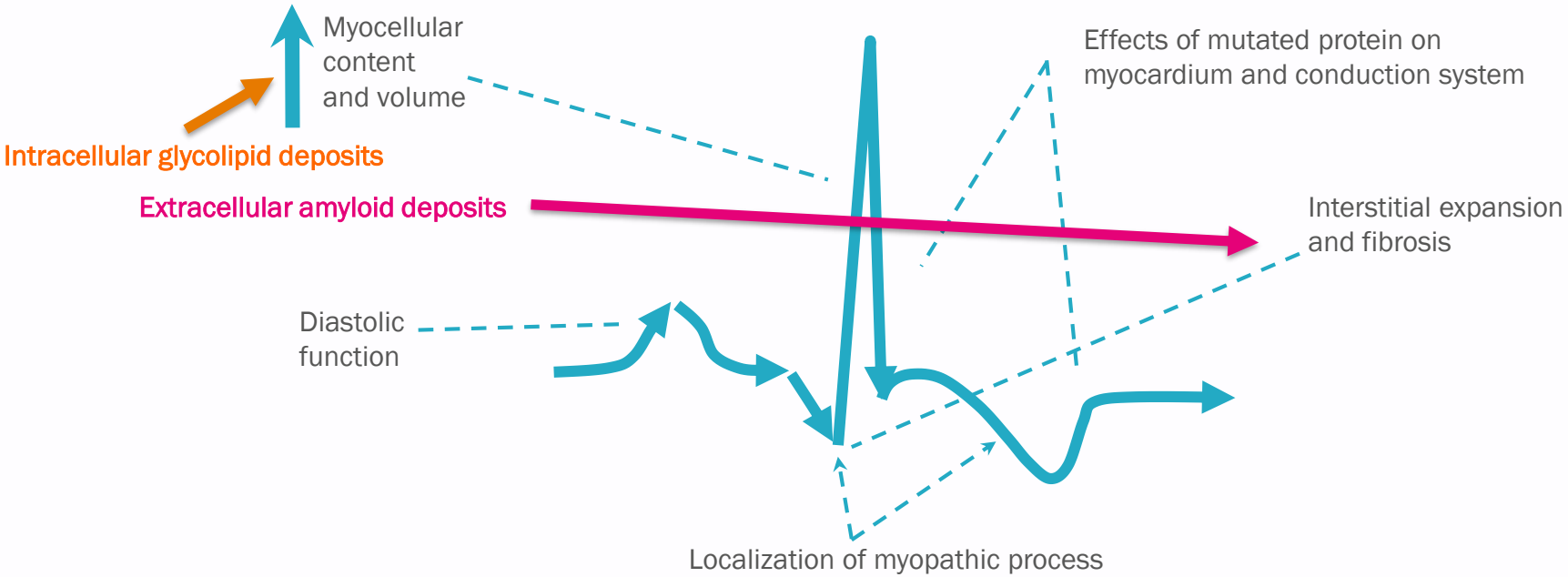


DYNAMIC DISEASE COURSE



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

ECG ABNORMALITIES IN CARDIOMYOPATHIES



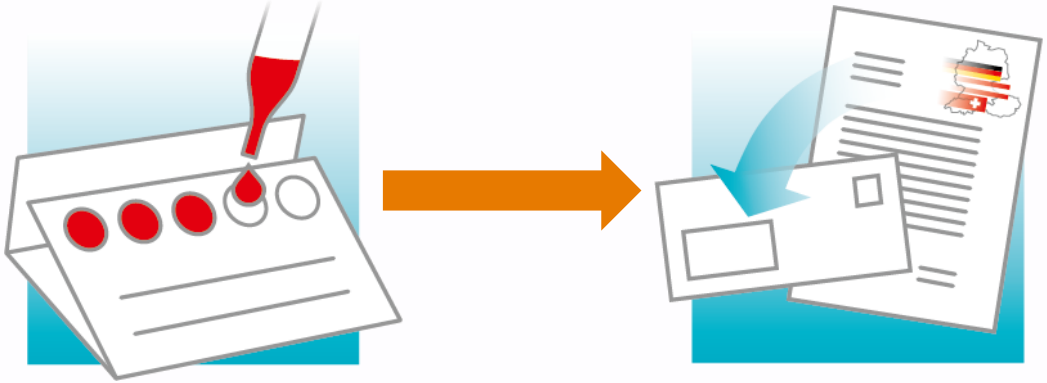
ECG, electrocardiogram.

Courtesy of Dr. M. Pieroni

Was mache ich bei einem Morbus Fabry Verdachtsfall?

Mittels **Trockenblutkarte (DBS)** zur Messung von

- Enzymaktivität von α-Galaktosidase A
- Krankheitsmarker lyso-GL3 (= lyso-Gb3)
- Gen-Analyse



Erhältlich z.B. von:
Archimed Life Science GmbH
unter der Service-Hotline
0800 / 1115200 (kostenfrei)
oder per eMail
Archimed-Diagnostikinitiative@viluacare.de

Sanofi-Aventis Deutschland GmbH unterstützt die Diagnostik-Initiative für lysosomale Speicherkrankheiten von Archimed Life Sciene GmbH. Daher kann Archimed Ärzten die Trockenblut-Testung kostenfrei anbieten.

ERT can improve regional myocardial function

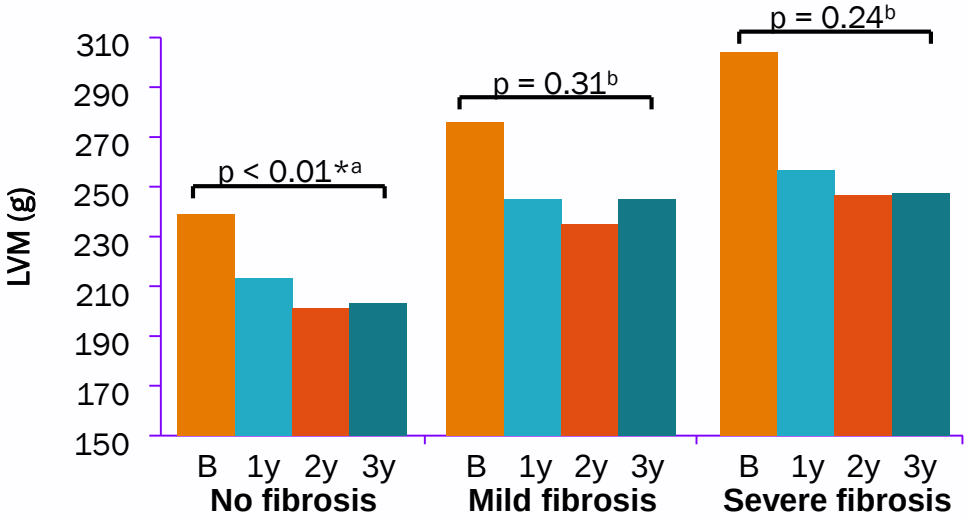
LV radial function before and after 6 and 12 months of ERT treatment

- 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

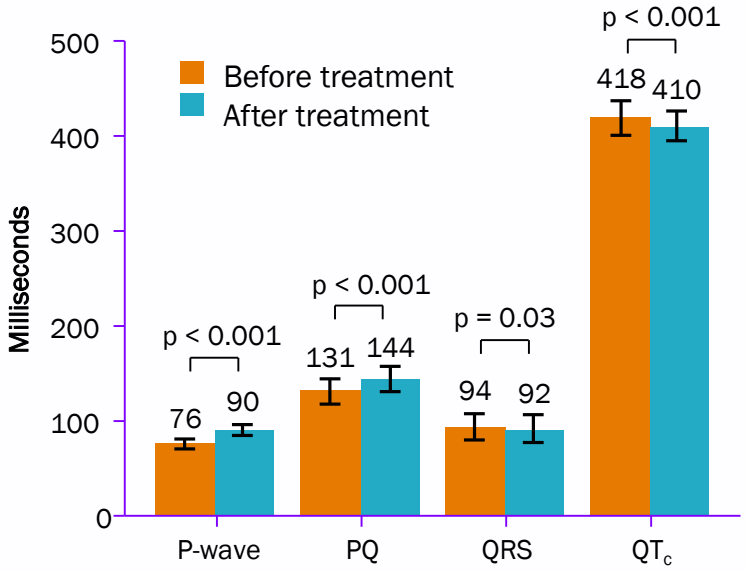


[a] Effect of ERT over time
[b] Comparison of fibrosis groups
- no fibrosis vs mild fibrosis
- no fibrosis vs severe fibrosis

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

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

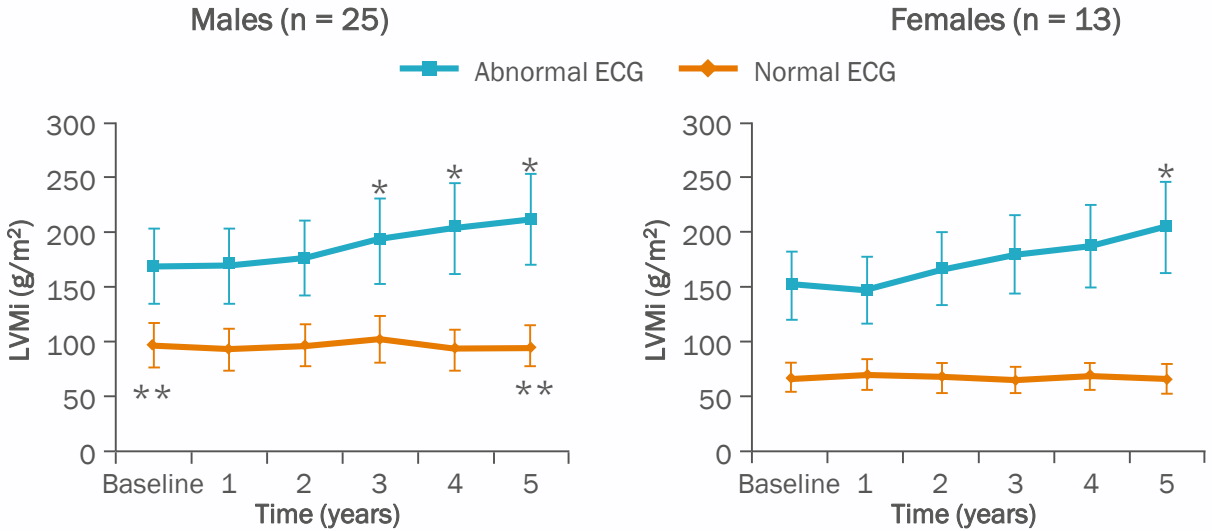
ERT has a consistent and positive effect on ECG parameters



- 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



- Retrospective analysis of data from 38 patients with Fabry disease receiving ERT
- Median follow-up duration: 6.4 ± 1.2 years

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

ERT, enzyme replacement therapy.

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

Patients with an abnormal baseline ECG are s associated with disease progression

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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.

Time dependence of risk factors for clinical events

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Cox proportional hazards regression analysis assessing the time dependence of risk factors for clinical events[a]

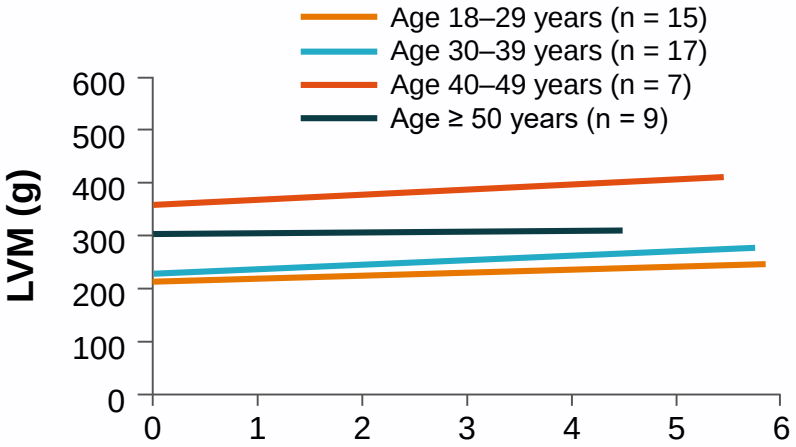
	Years on agalsidase beta 1mg/kg EOW								
	Model 1: 0–0.5 years			Model 2: > 0.5–5 years			Model 3: > 0–5 years		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Pre-ERT event: yes (vs no)	1.1	0.6–2.0	0.81	1.8	1.2–2.7	< 0.01	1.5	1.1–2.1	0.02
Age ≥ 40 years at first ERT (vs age < 40 years)	4.4	2.2–8.7	< 0.01	2.5	1.7–3.8	< 0.01	2.9	2.1–4.2	< 0.01
Male (vs female)	1.9	1.1–3.4	0.03	1.5	1.0–2.1	0.06	1.6	1.1–2.2	< 0.01

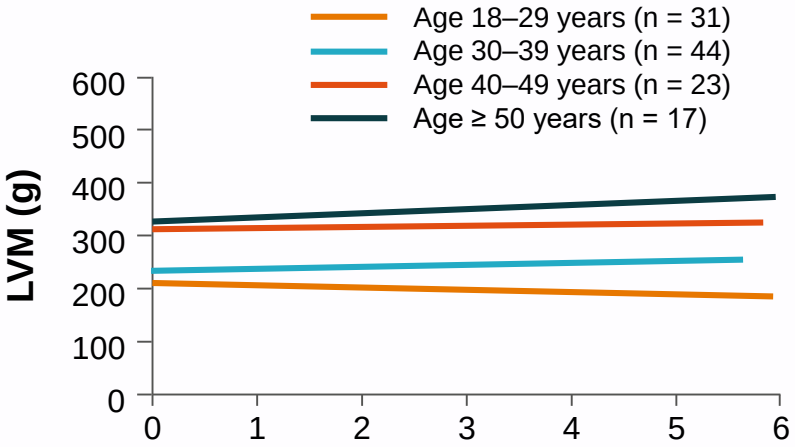
Registry analysis
Clinical events defined as renal failure, cardiac events, stroke, and death.
[a] Three models were run to assess if the incidence of events according to the above factors was time-dependent: Model 1 examined risk factors within the first 6 months; Model 2 examined risk factors within 6 months to 5 years; Model 3 examined risk factors for the entire analysis period of up to 5 years.

CI, confidence interval; EOW, every other week;
ERT, enzyme replacement therapy; HR, hazard ratio.

Ortiz A, et al. J Med Genet. 2016;53:495-502.

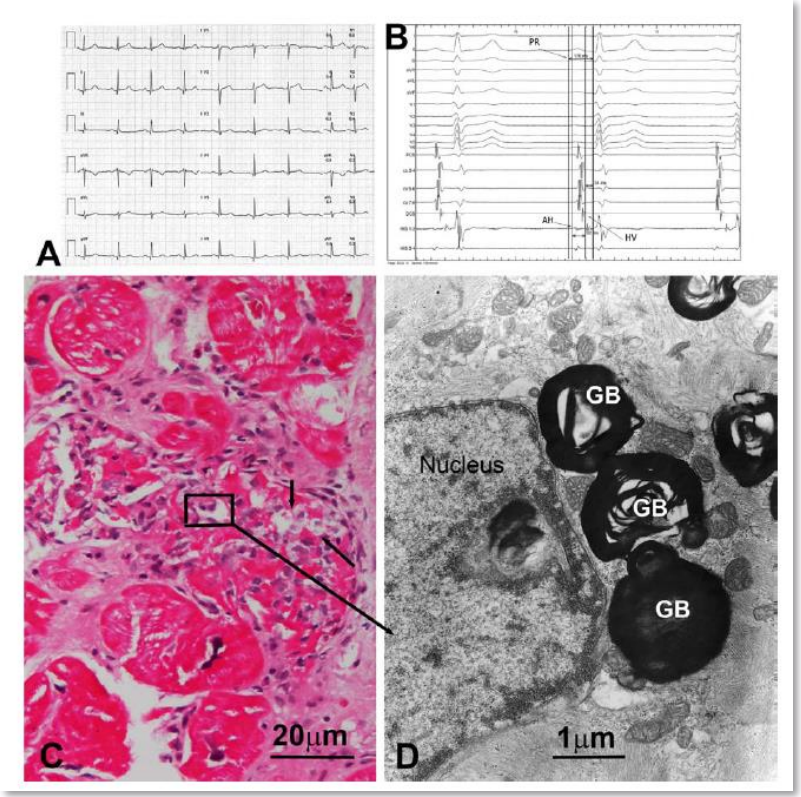
Agalsidase beta 1mg/kg EOW significantly reduced LVM in patients aged < 30 years (vs untreated)





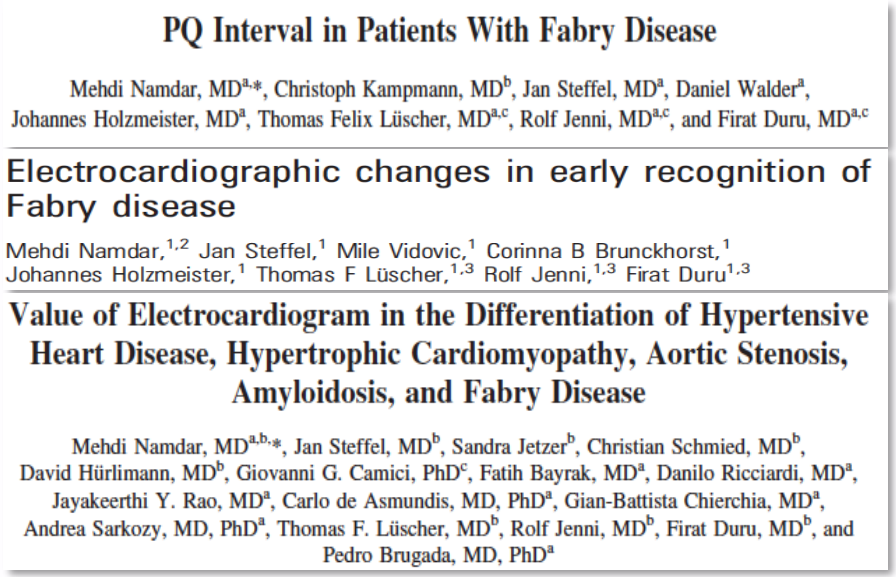
Germain DP, et al. Genet Med. 2013:15:958-65.

CORRELATION OF EARLY INFILTRATION WITH MICROFIBROSIS WITH ECG/EGM



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

ECG CHANGES IN FARBY - PREHISTORIC



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]

→ Typical ECG signs[1]

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

→ Differentiation vs other LVH and prognosis
novel index[3]

1. Namdar M, et al. Am J Cardiol 2010;105:753–756; 2. Namdar M, et al. Heart 2011;97:485–490; 3. Namdar M, et al. Am J Cardiol 2012;109:587–593

Detectable Pre-hypertrophic Phenotype in Fabry Disease: Low Native T1 and Structural, Functional, and ECG Changes

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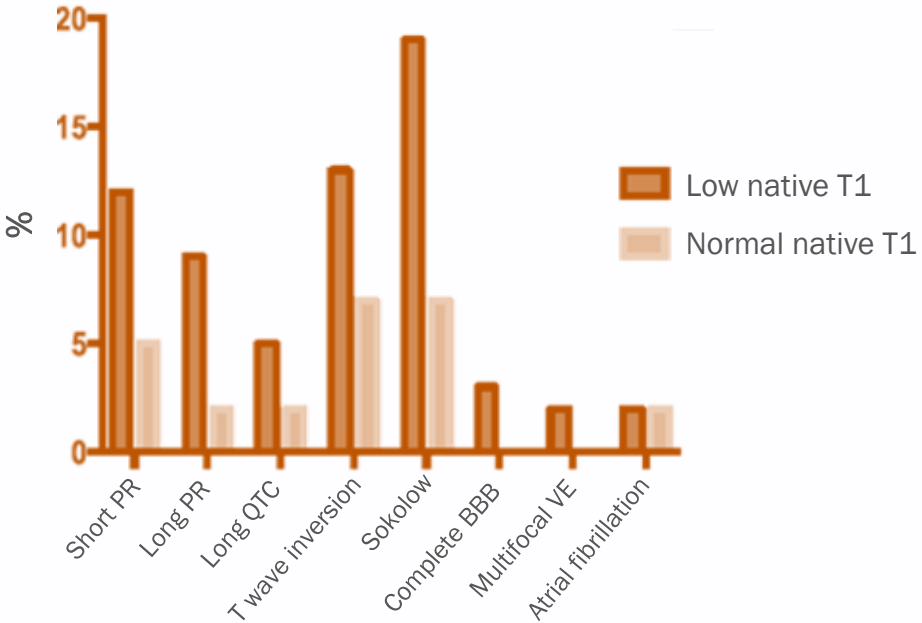
Comparison of ECG Abnormalities Between Low Native T1 and Normal Native T1 Fabry Disease Subgroups



Comparison Between Low 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/m^2	63±10	58±9	<0.05
LVEF, %	73±8	69±7	<0.01

BBB, bundle branch block; ECG, electrocardiogram; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MWT, maximal wall thickness; NT-proBNP, N-terminal pro B-type natriuretic peptide; VE ventricular ectopics.

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

Predictors of Clinical Evolution in Pre-Hypertrophic Fabry Disease

Parameters	Fabry Disease Global Cohort (n=44)	Normal T1 (n=18)	Low T1 (n=26)	Normal T1 vs Low T1 p value
Left ventricular mass, g/m^2	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 left ventricular wall thickness, 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
Late gadolinium enhancement, n (%)	4 (9.1)	0 (0)	4 (15.4)	0.12
Mainz Severity Score Index	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
Enzyme replacement therapy, n (%)	18 (40.9)	5 (27.8)	13 (50.0)	0.15
Classic 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
Sokolow-Lyon Index	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

Data presented as mean±SD (median, interquartile range) or n (%).

Camporeale A, et al. Circ Cardiovasc Imaging 2019;12:e008424.

ECG ABNORMALITIES IN FABRY

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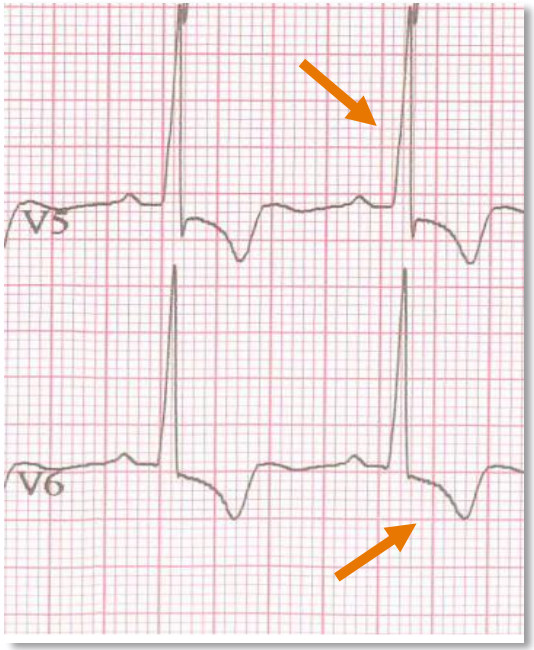
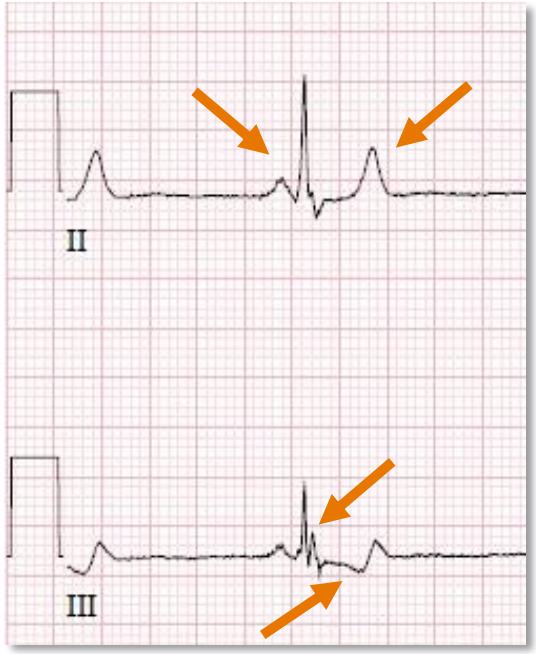
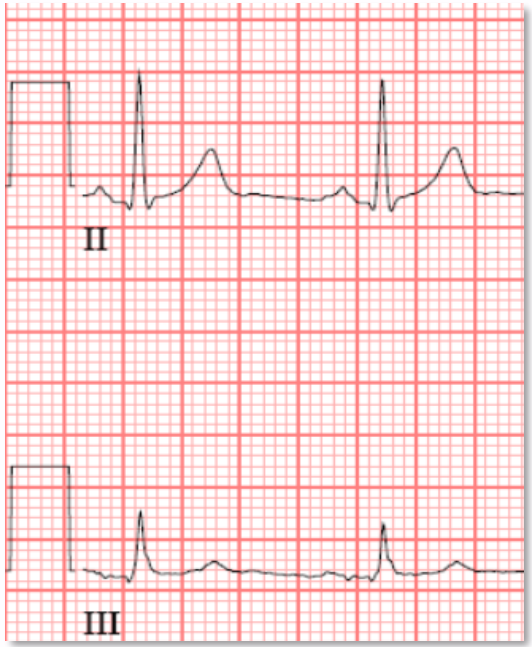
FABRY

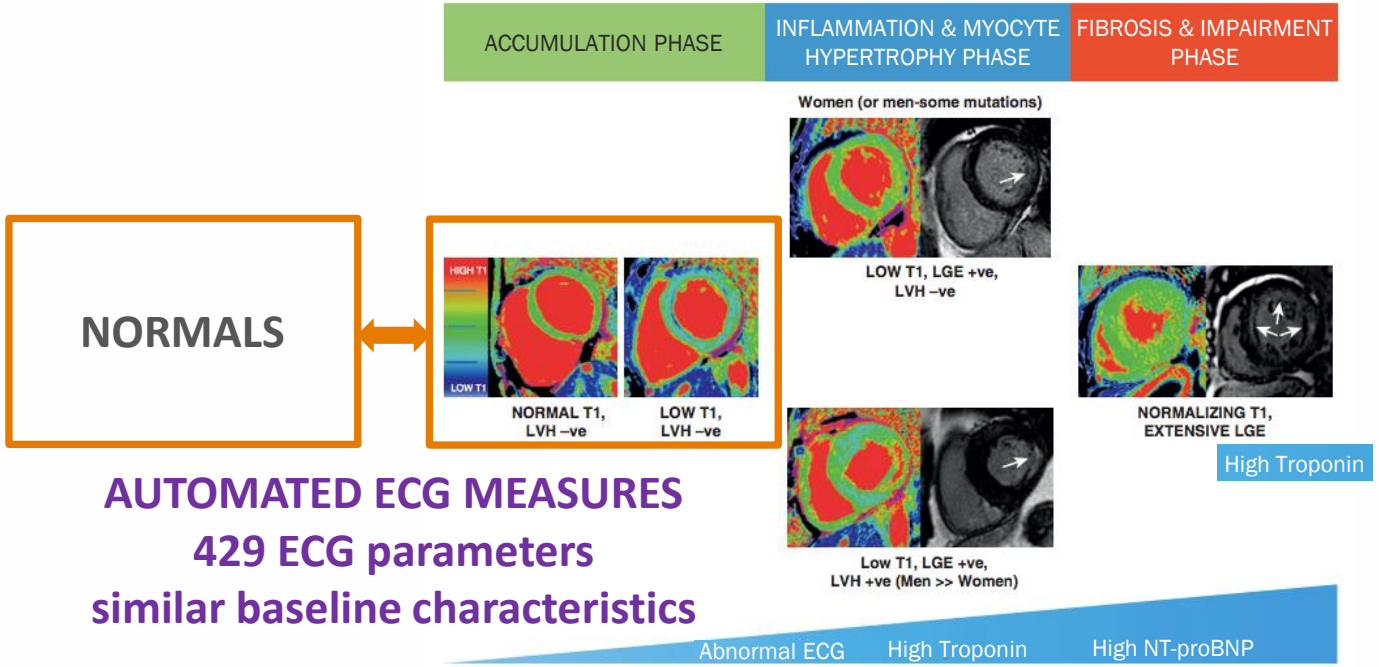




NORMAL



RECOGNITION OF EARLY CHANGES



ECG, electrocardiogram; LGE, late gadolinium enhancement;
LVH, left ventricular hypertrophy; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Nordin S, et al. JACC Cardiovasc Imaging 2019;12:1673–1683

PRE-HYPERTROPHIC ECG CHANGES

HUG
Hôpitaux Universitaires de Genève

429 AUTOMATED MEASURES

↓

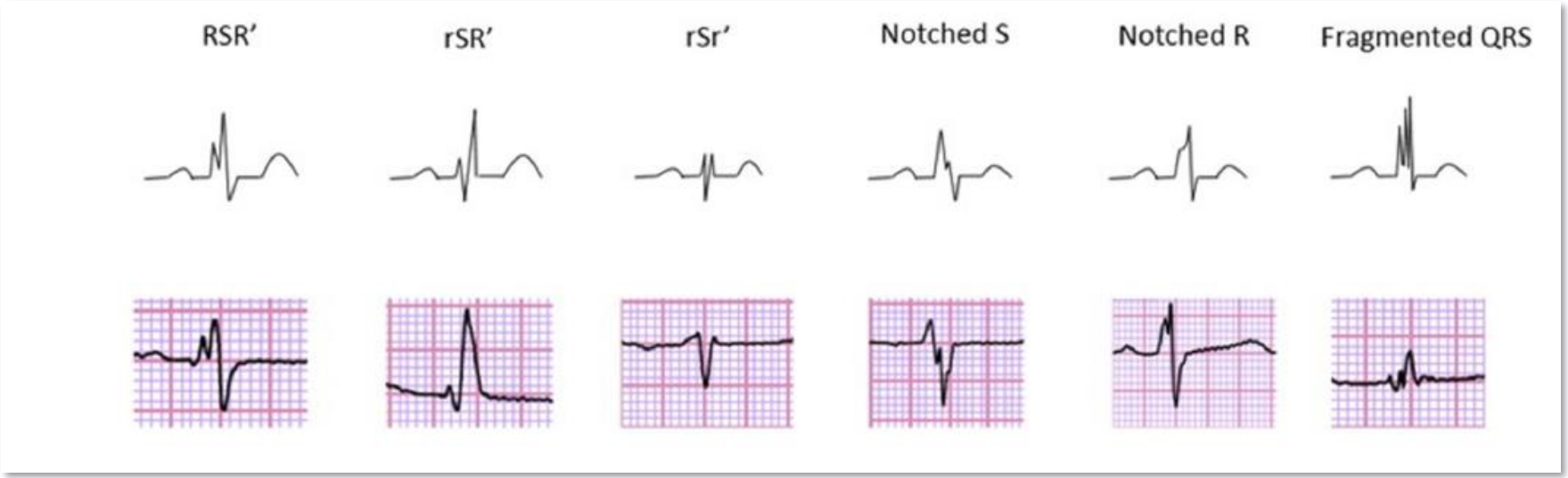
43 SIGNIFICANT ONES

↓

SELECTION OF MOST DISCRIMINANT ONES

COMBINED SCORE

FRAGMENTED QRS AS INDICATOR FOR EARLY PATHOLOGICAL CONDUCTION

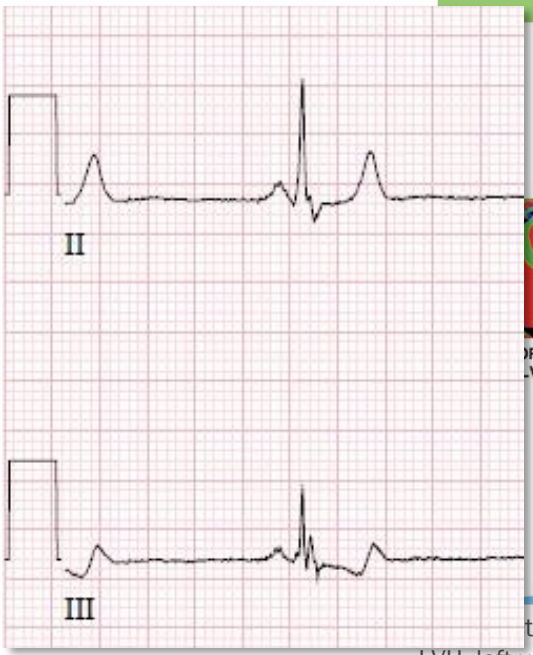


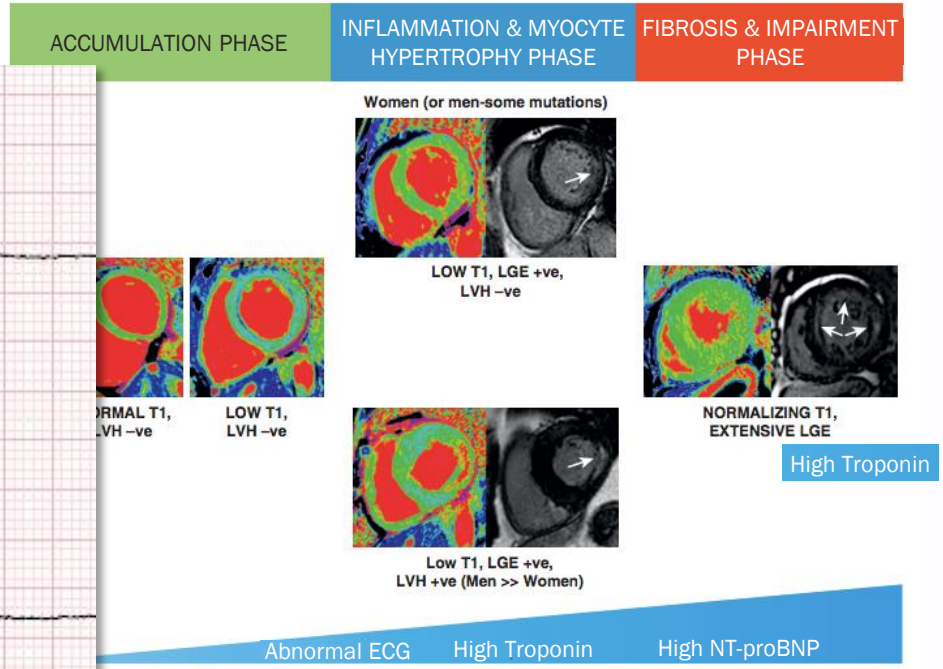
→ **Associated with adverse cardiac events (blocks/VT/SCD)**

Haukilahti MAE, et al. Front. Physiol. 7:653.


Mmmm, Tastes
like a combination
of Who Cares?
&
So What?
someecards
user card

MRI vs. ECG…OR: HOW EARLY BECOMES LATE…





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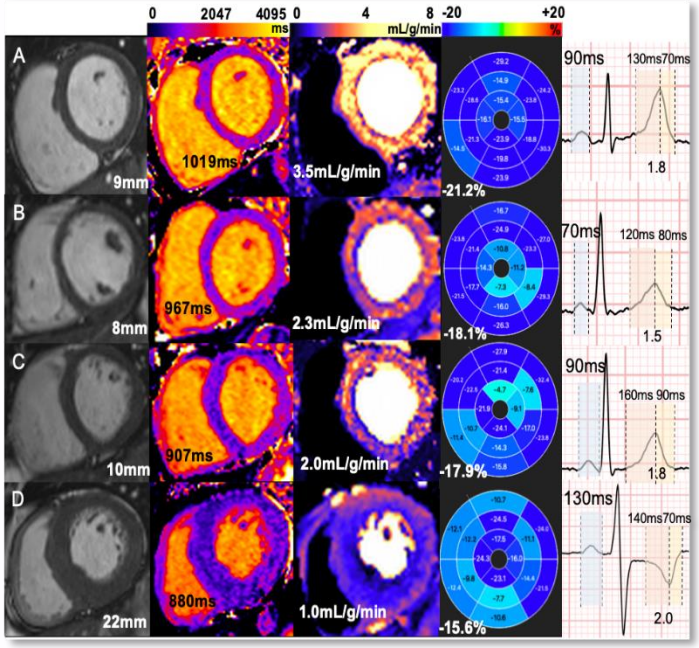
Nordin S, et al. JACC Cardiovasc Imaging 2019;12:1673–1683

Stages of Cardiac Involvement in Fabry Disease: Electrocardiographic changes in Fabry disease precede left ventricular hypertrophy and sphingolipid storage in cardiovascular magnetic resonance!!



A – healthy control, no left ventricular hypertrophy (LVH), normal T1, MBF (stress myocardial blood flow), GLS (global longitudinal strain), P wave time and T wave ratio.

B – FD with normal T1 and without LVH; MBF and GLS are mildly reduced, P wave is short and T wave ratio reduced.

C – FD with low T1 and without LVH, low MBF and GLS, P wave duration and T wave ratio are no different from control.

D – FD with LVH; T1 is low, MBF and GLS are significantly impaired, P wave is long and T wave ratio increased

Augusto J. et al. Manuscript in press EHJ CVI

THUS, IT SEEMS REASONABLE TO STATE THAT…

…ECG changes not only precede LVH, but also detect very early atrial and ventricular remodeling processes when imaging seems normal…even normal T1…change of paradigms?

…the ECG changes we see make sense and are in line with MRI findings…

…a really normal ECG is quite reassuring…excellent negative predictive value…

…automated ECG measures and combination thereof may be helpful for detection of very early cardiac involvement…

…one day perhaps we screen based on ECG and combined indices…

…it is worth investing in more ECG studies…we don't know enough…probably never will…

Presenter's own opinion

THANKS TO...

HUG
Hôpitaux Universitaires de Genève

- Automated ECG core-lab in Glasgow Peter MacFarlane
- Iacopo Olivotto, Peter Nordbeck, Philippe Richardot
- Stephan Rohr Cellular EP Bern
- Christian Lovis Medical IT, Campus Biotech Geneva
- James Moon and his group in London...

- ...and many others who will send us thousands of ECGs to feed the machine...