Management of Patients with Cardiac Manifestations

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Disclosure of Interests

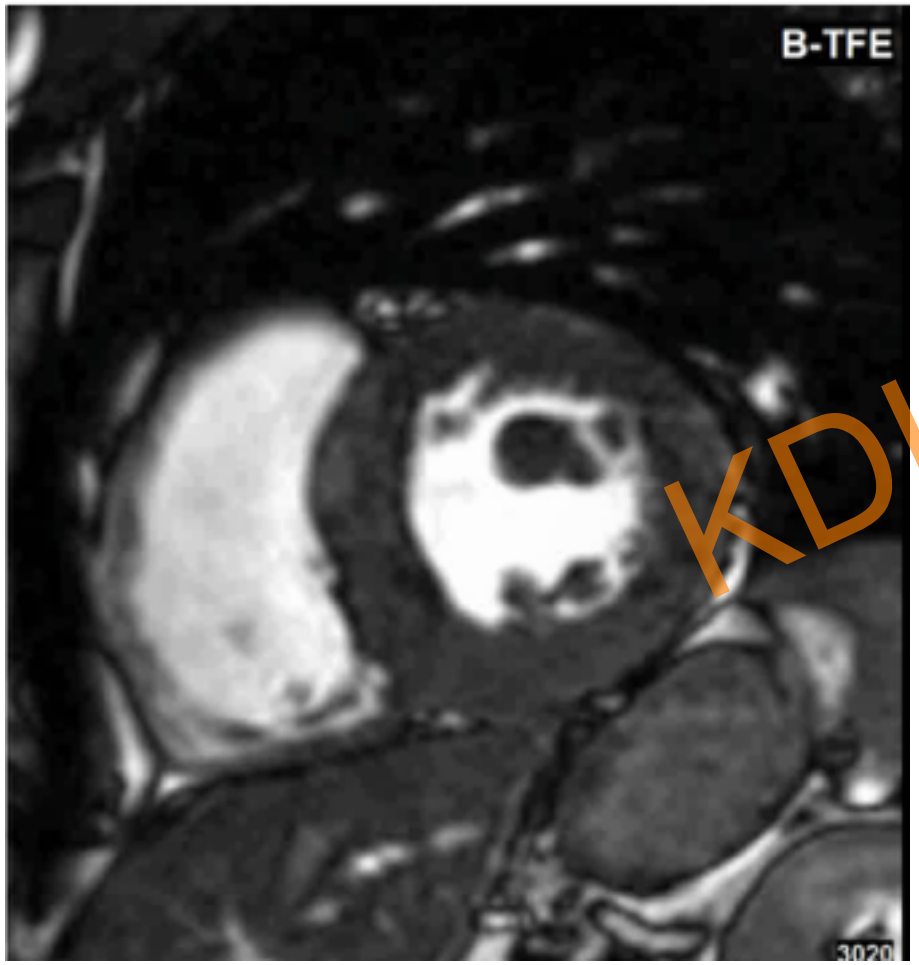
Speaker´s honoraria, travel reimbursements and consultancy honoraria from:

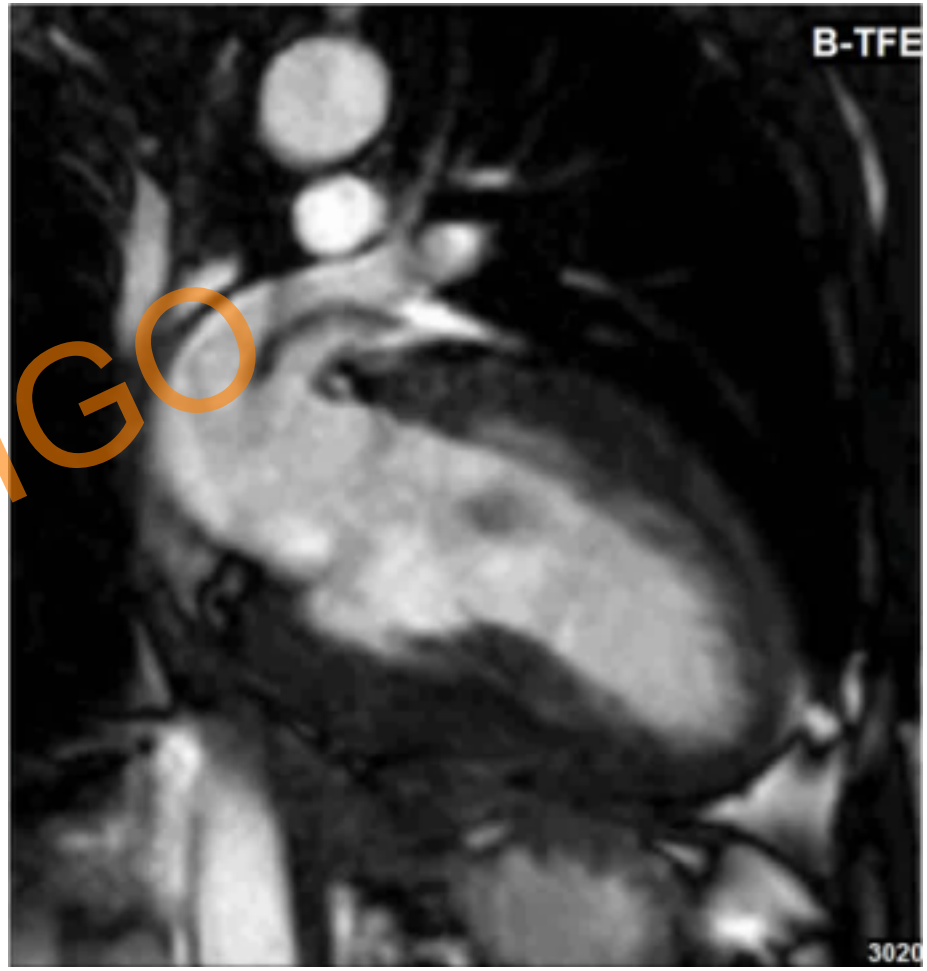
- Genzyme
- Shire HGT
- Amicus Therapeutics
- Actelion

KDIGO

HEART FAILURE

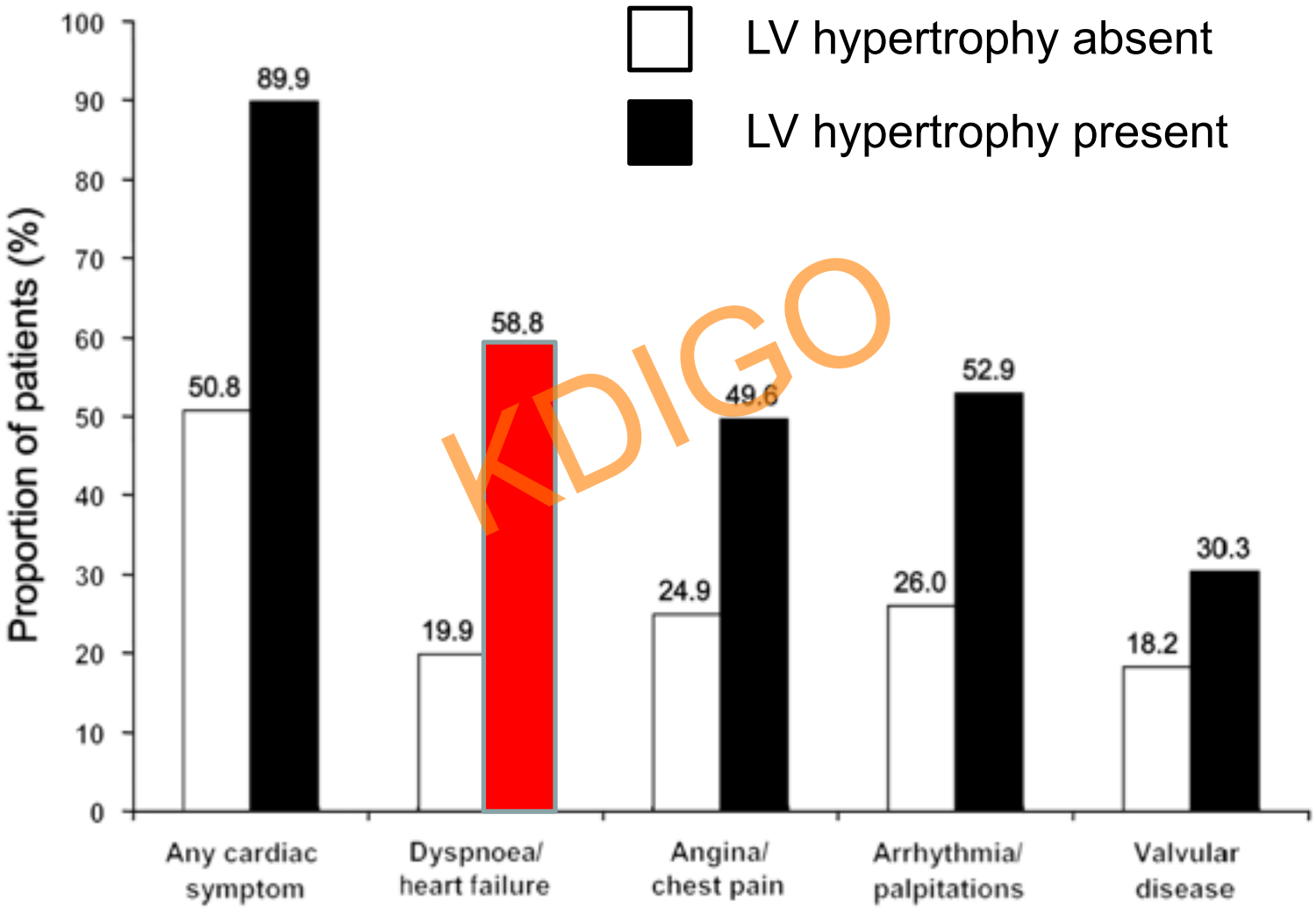
Diffuse LVH on MRI in Fabry disease





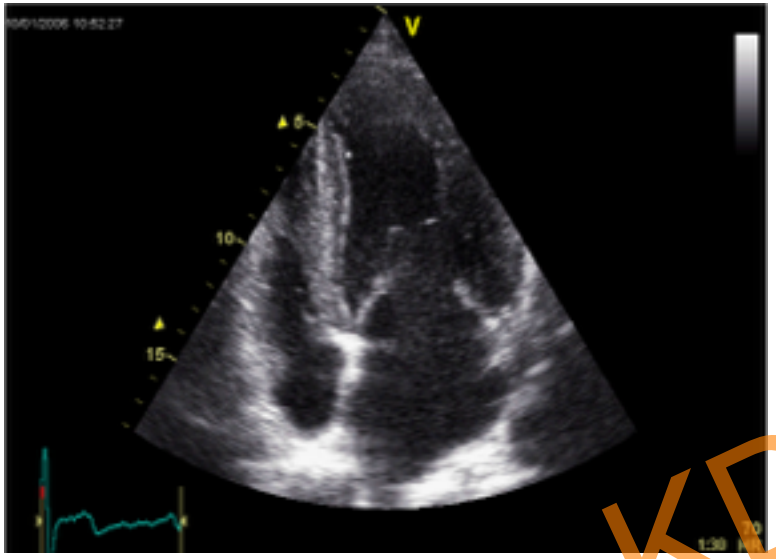
Data source: General University Hospital, Prague

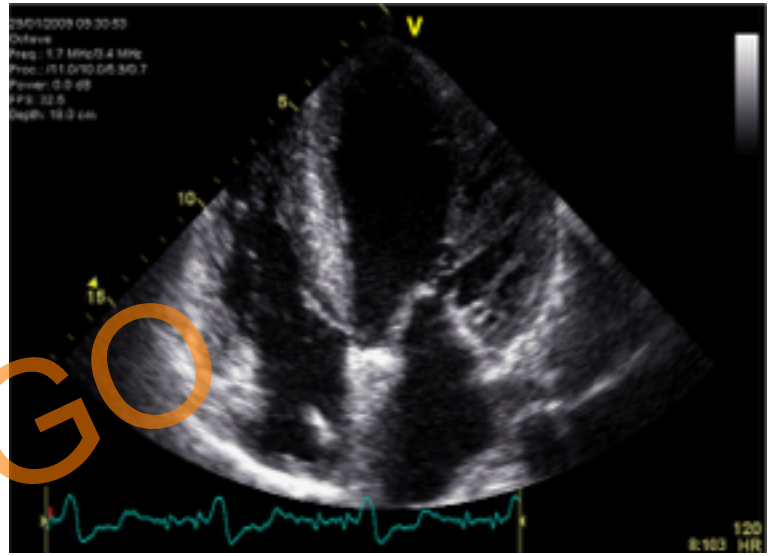
Cardiac symptoms in AFD

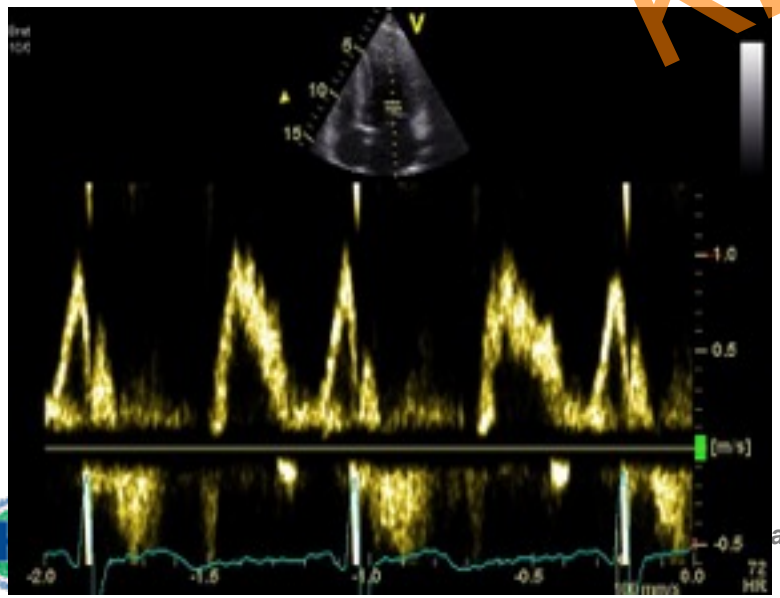


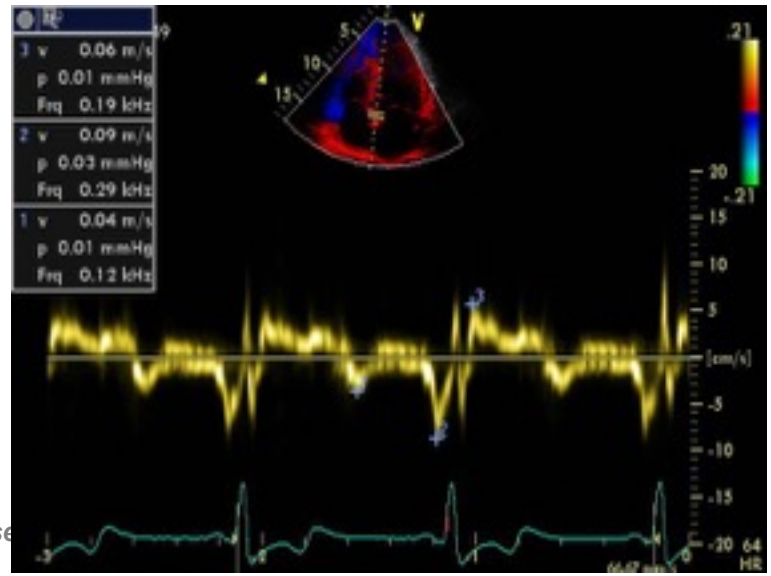
Linhart et al., European Heart Journal 2007 28(10):1228-1235

Fabry left ventricular function



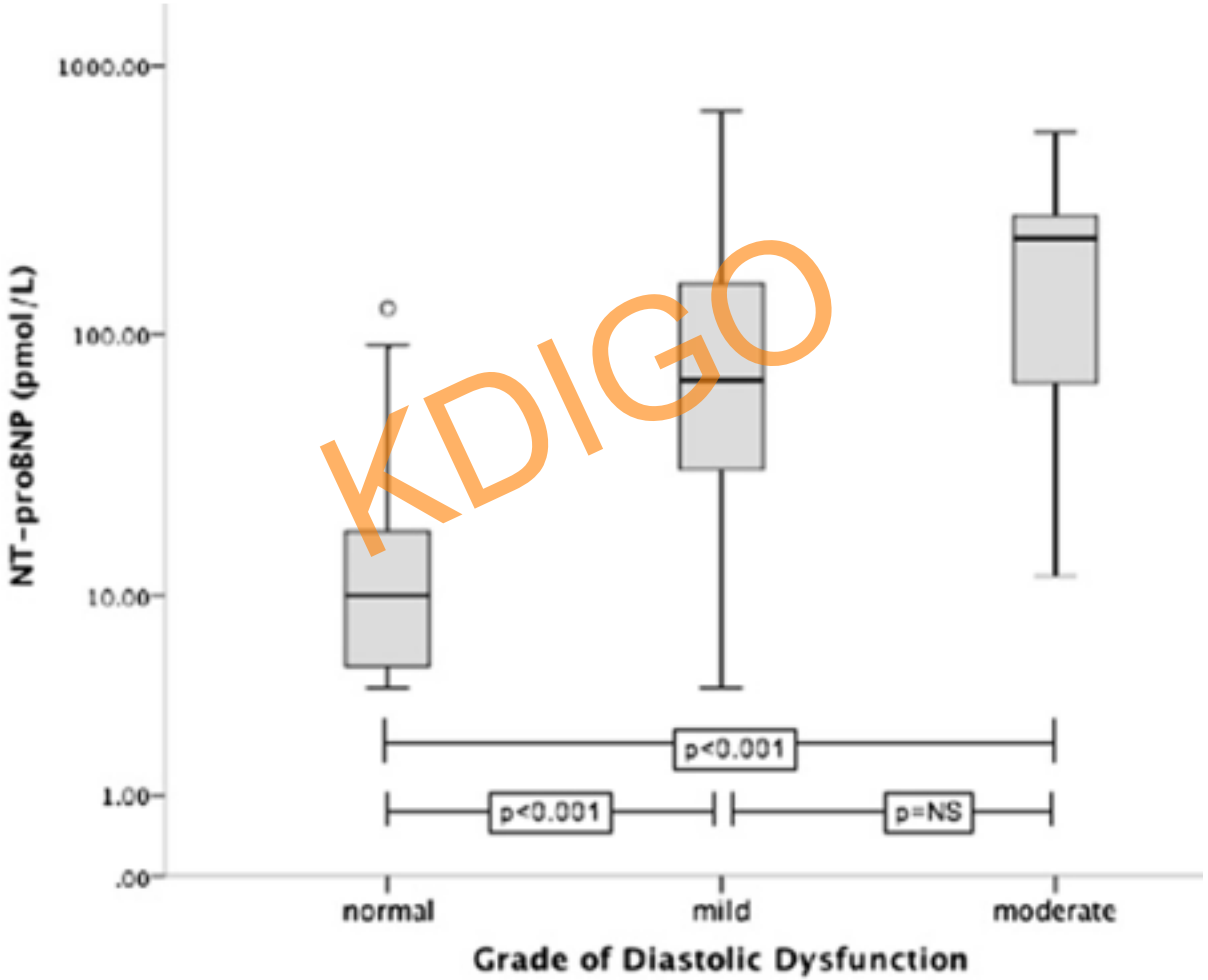






N-Terminal Pro-BNP in Diagnosis of Cardiac Involvement in AFD Patients

117 patients, (age 48 ± 15 years, 46.2% men) - BNP elevated in 57%



Coats et al., Am J Cardiol. 2013;111:111-7.

Diagnosis of heart failure

The diagnosis of HF-REF requires three conditions to be satisfied:
1. Symptoms typical of HF
2. Signs typical of HF[a]
3. Reduced LVEF
The diagnosis of HF-PEF requires four conditions to be satisfied:
1. Symptoms typical of HF
2. Signs typical of HF[a]
3. Normal or only mildly reduced LVEF and LV not dilated
4. Relevant structural heart disease (LV hypertrophy/LA enlargement) and/or diastolic dysfunction (see Section 4.1.2)

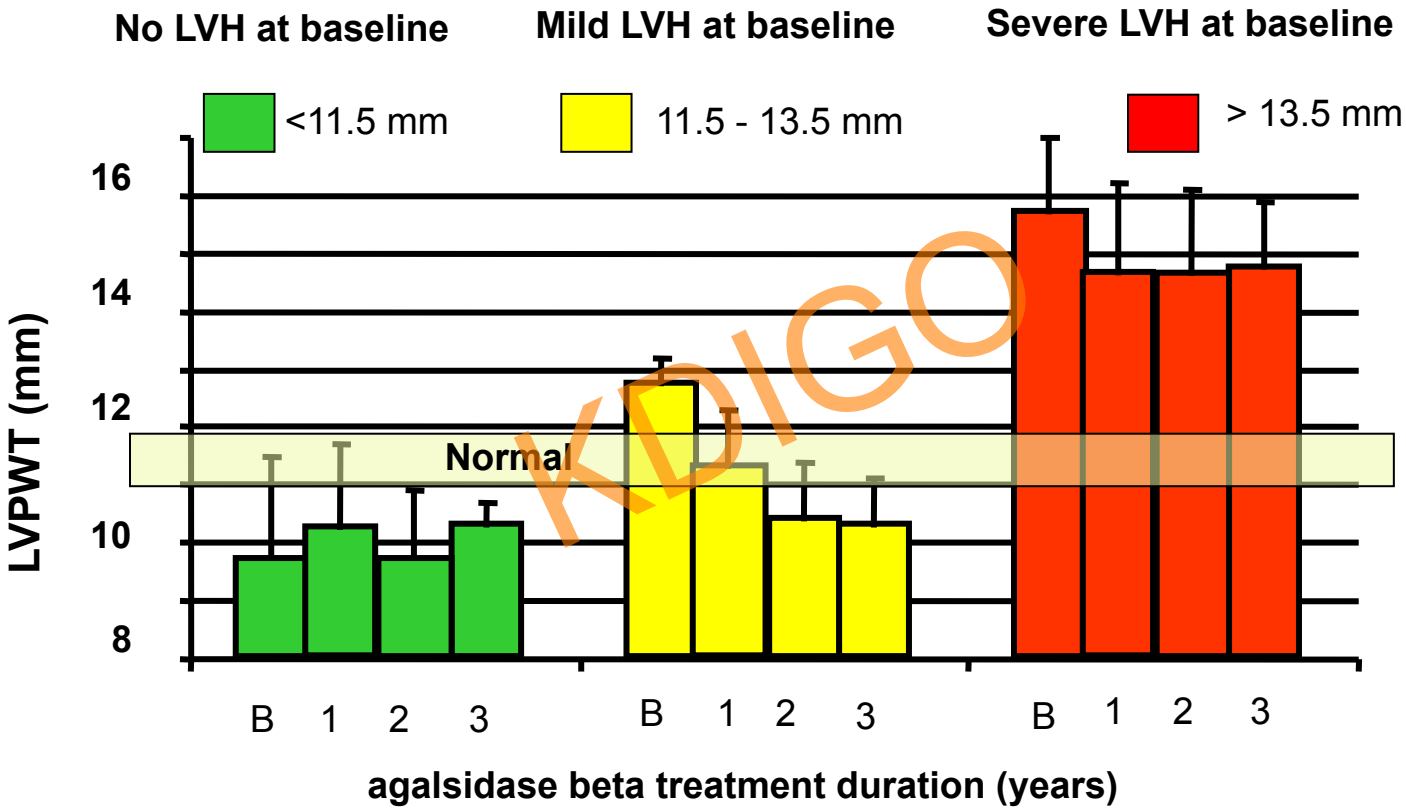
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. European Heart Journal 2012; 33: 1787–1847

Trials in heart failure with preserved ejection fraction

DIG-PEF	Digoxin	Trend to ↓ hospitalizations ↑ UAP
CHARM-PRESERVED	Candesartan	Trend ↓ hospitalizations
I-PRESERVE	Irbesartan	No effect
PEP-CHF	Perindopril	↓ hospitalizations
SENIORS HF-PEF subgroup	Nebivolol	Trend to ↓ Clinical complications
TOP-CAT	Spironolactone	Effective in subjects recruited in USA and LATAM

J Am Coll Cardiol. 2015;65:1668-1682.

Effect of enzyme replacement therapy on cardiac structure



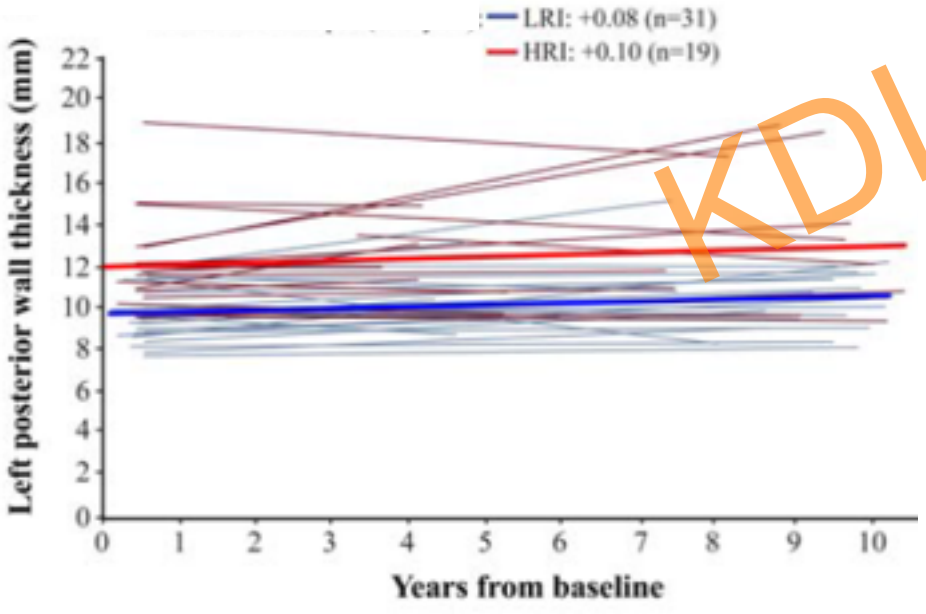
LVPWT = left ventricular posterior wall thickness
LVH = left ventricular hypertrophy

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

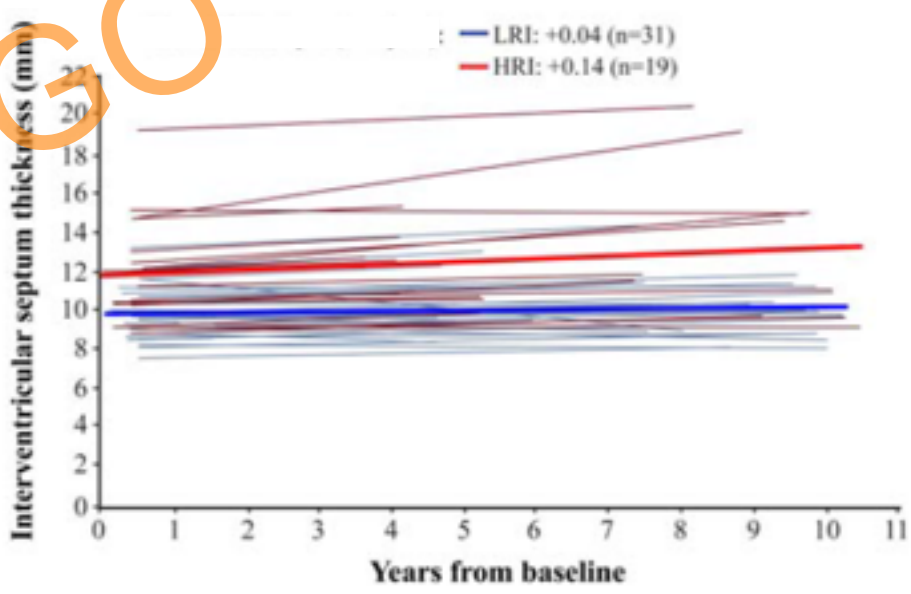
Ten-year outcome of enzyme replacement therapy with agalsidase beta

- 52/58 patients with classic Fabry disease from the phase 3 clinical trial and extension study, and the Fabry Registry
- 81% of patients (42/52) no severe clinical event during the treatment interval
- 94% (49/52) were alive at the end of the study

Mean LPWT slopes (mm/year)



Mean IVST slopes (mm/year)



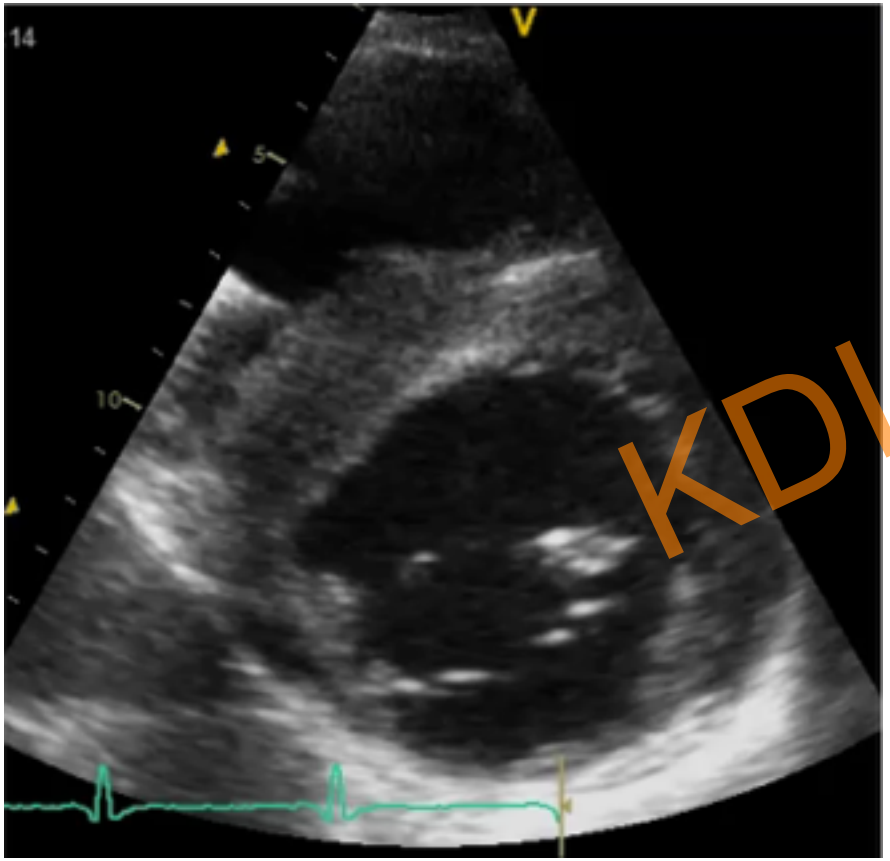
LRI = low renal involvement; HRI = high renal involvement

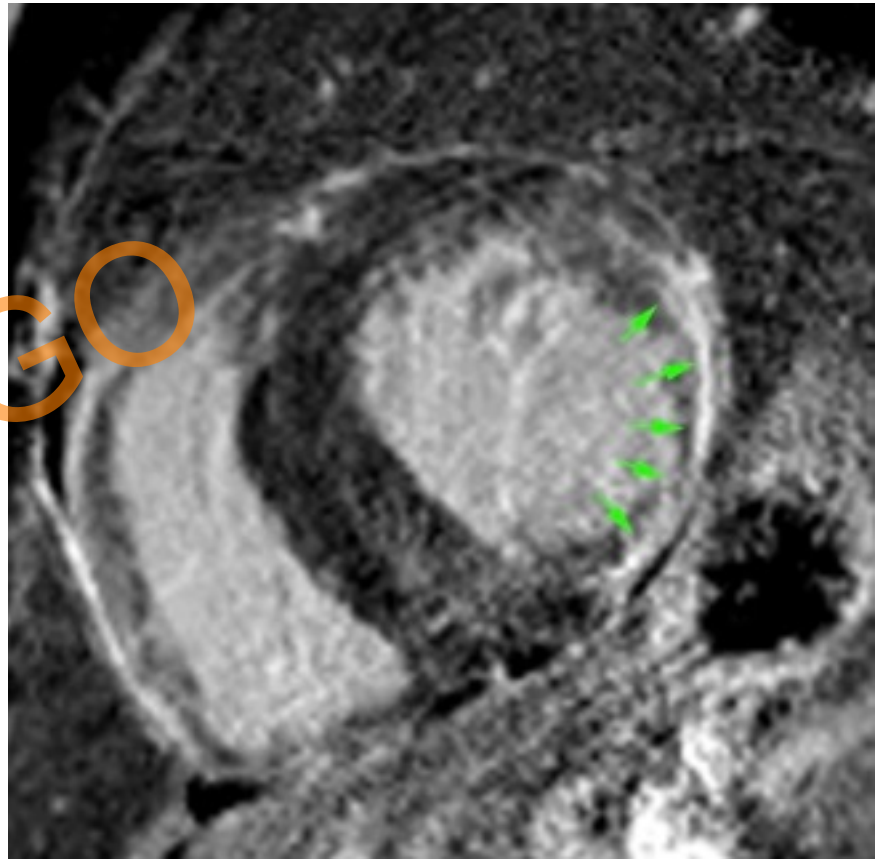
Germain DP, et al. J Med Genet 2015;52:353–8.

Unsolved questions

- Is there any role of ACEi / ARBs /MRAs in prevention of LVH / HF symptoms in Fabry?
- Are betablockers safe?
- By preventing LV mass growth – do we prevent heart failure development?

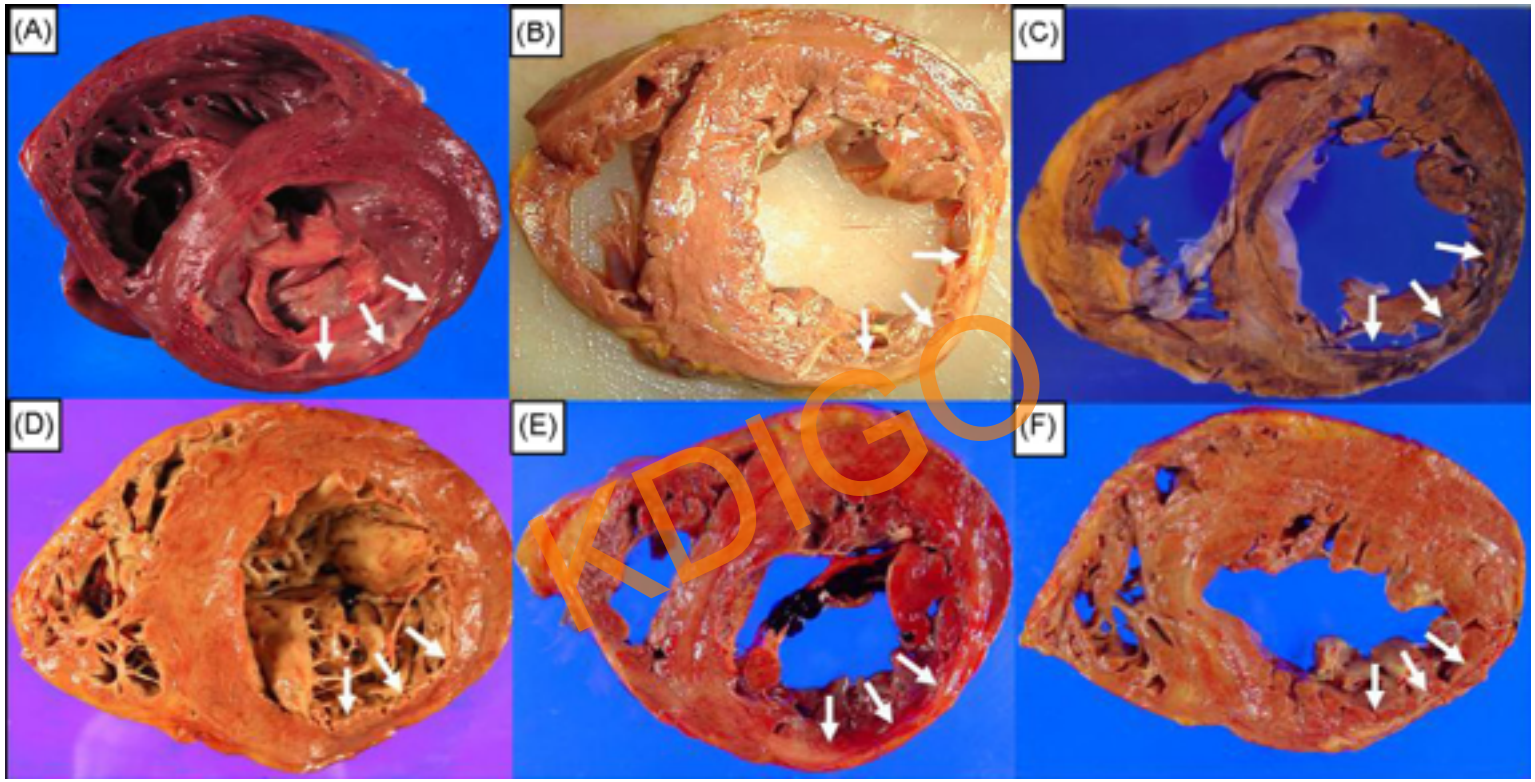
Extensive fibrosis and akinesia of the posterolateral wall





Cases and imaging source: General University Hospital, Prague, CZ

Terminal stage of cardiac variant patients

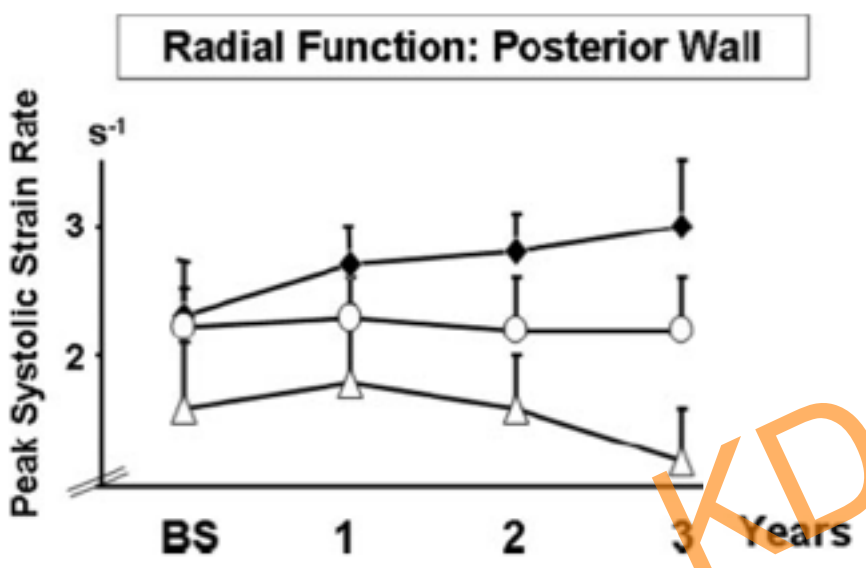


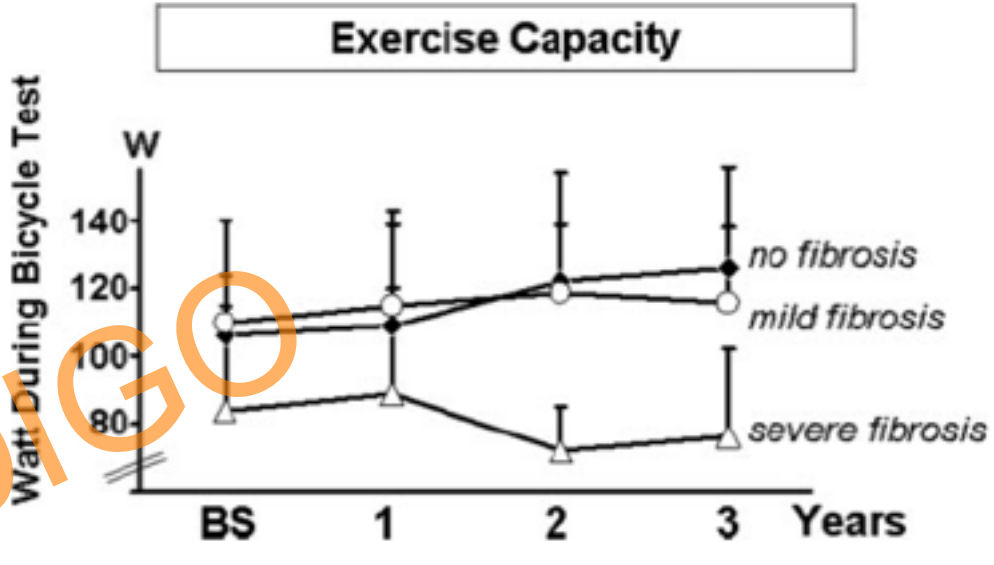
- 7 pts with autopsy – 6 died of terminal heart failure + 1 of VF
- Left ventricular hypertrophy in all patients
- all patients non-sustained VT on Holter monitoring

VF = ventricular fibrillation, VT = ventricular tachycardia

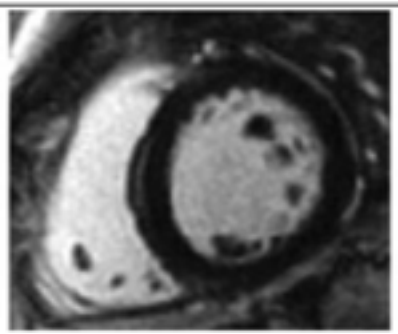
Takenaka et al. Journal of Cardiology 2008;51:50–59

Fibrosis extent predicts functional improvement induced by agalsidase beta

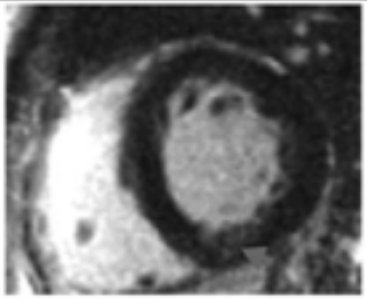




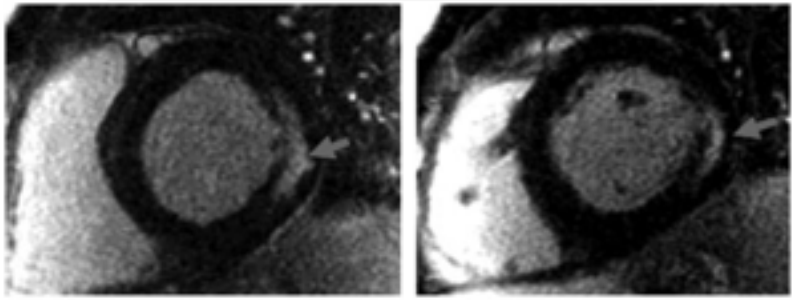
Patient: "*No Fibrosis*"



Patient: "*Mild Fibrosis*"



Patient: "*Severe Fibrosis*"



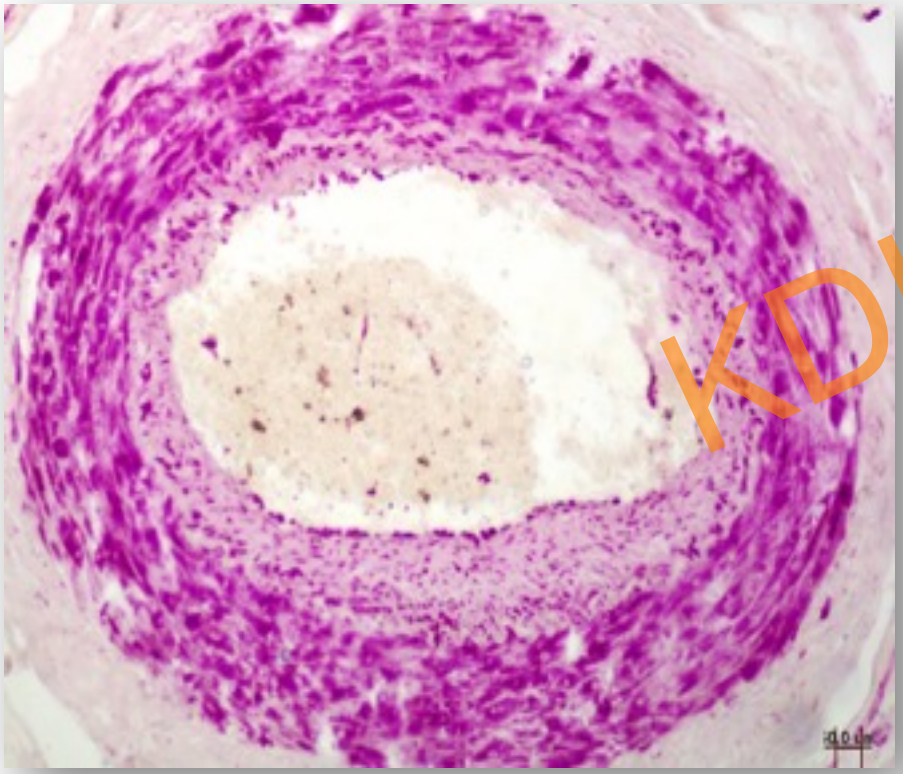
Weidemann F. et al. *Circulation*. 2009;119:524-529.

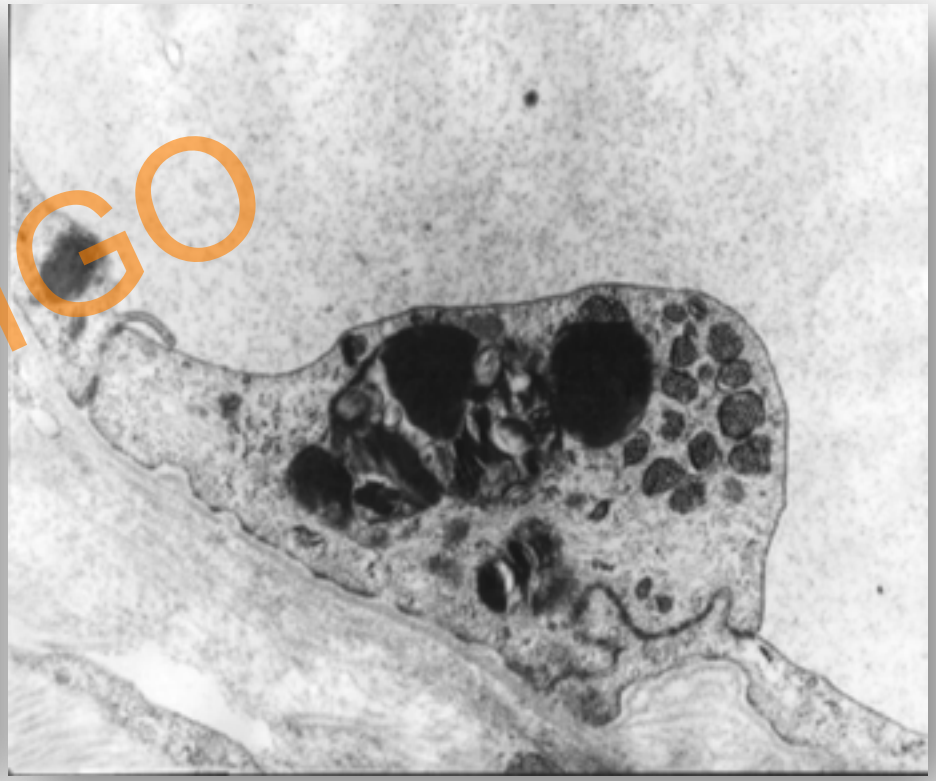
Unsolved questions

- Will early ERT stop fibrosis formation
- Posterolateral „replacement fibrosis“ vs. diffuse „interstitial fibrosis“
- Will T1 mapping replace the LGE visualization?

CORONARY HEART DISEASE

Fabry disease – a vascular pathology ?

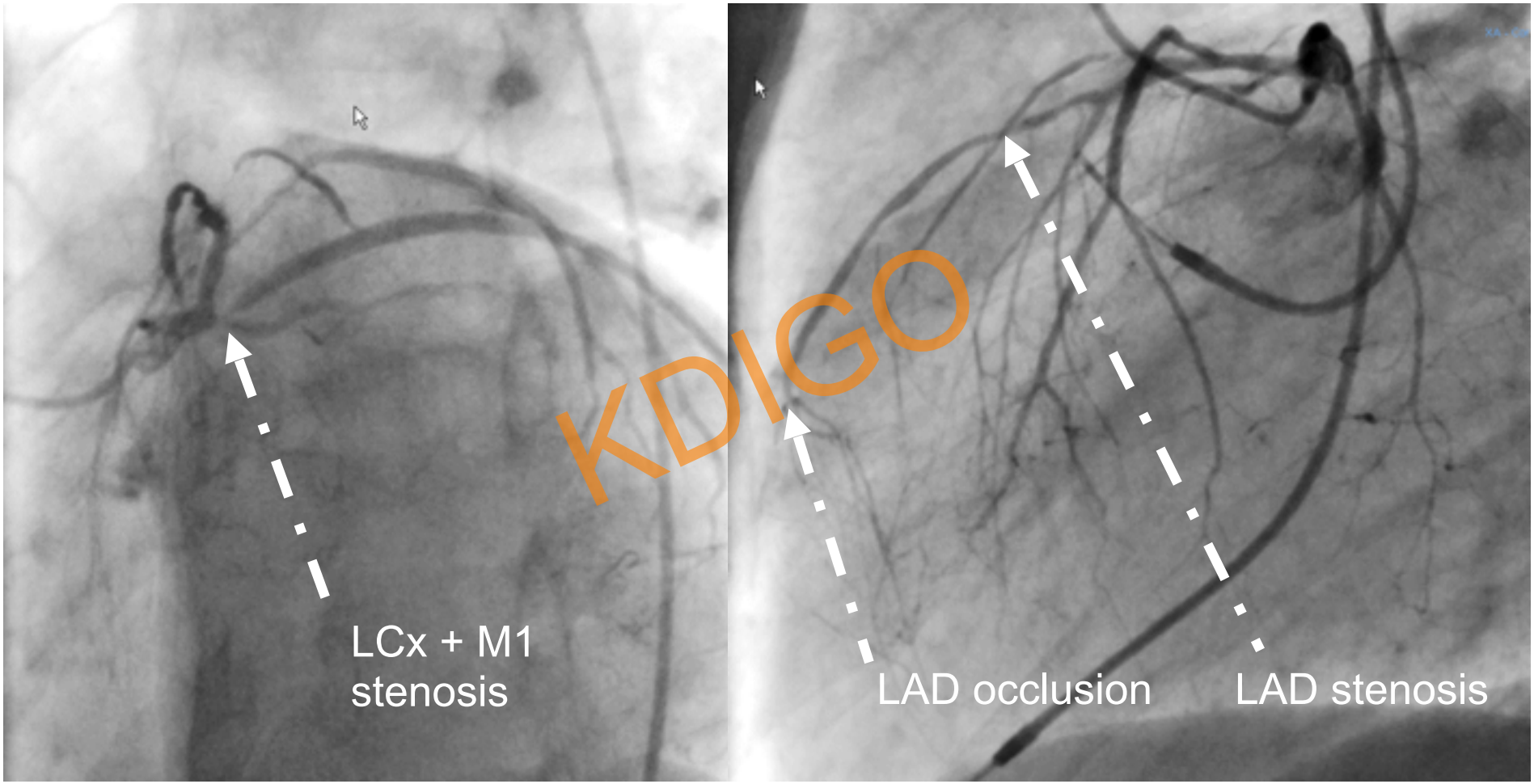




Courtesy M. Elleder, Charles University, Prague

Coronary heart disease

Male, 52 years, classically affected, on hemodialysis, ERT start at age 42 years



LCx – left circumflex coronary artery
M1 – first left marginal artery
LAD – left anterior descending coronary artery

Cases and imaging source:
General University Hospital, Prague, CZ

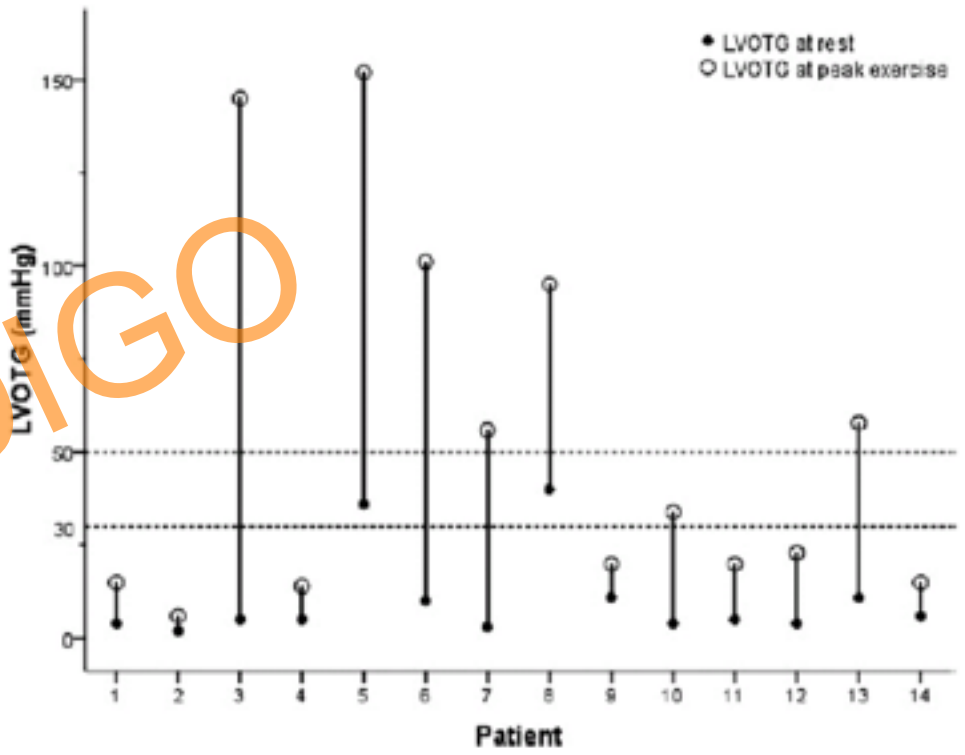
Unsolved questions

- Revascularization strategies and outcomes
- Optimal diagnostic methods for detection of asymptomatic CAD
- Optimal medical treatment specific to Fabry disease (betablockers?)

OBSTRUCTIVE CARDIOMYOPATHY

Obstructive gradient inducible by exercise in Fabry cardiomyopathy

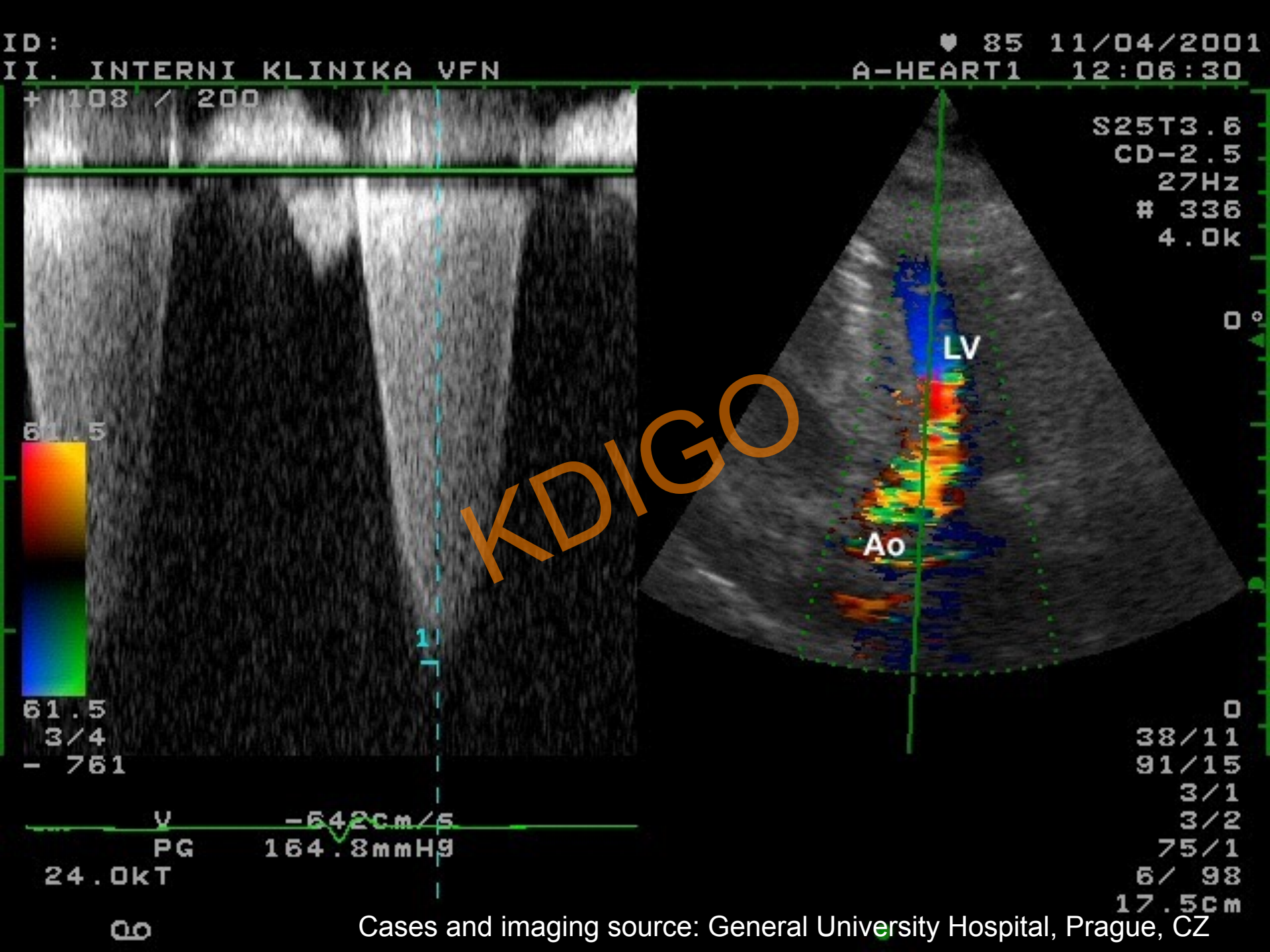
- 14 patients (6 male [43%])
- mean age 54.3 ± 10 years, (38 -74 years)
- moderate to severe cardiac symptoms
- without resting LVOTO (<30 mm Hg)
- LVH in 93%



Latent LVOTO in 6 / 14 patients. In 5 cases caused by SAM

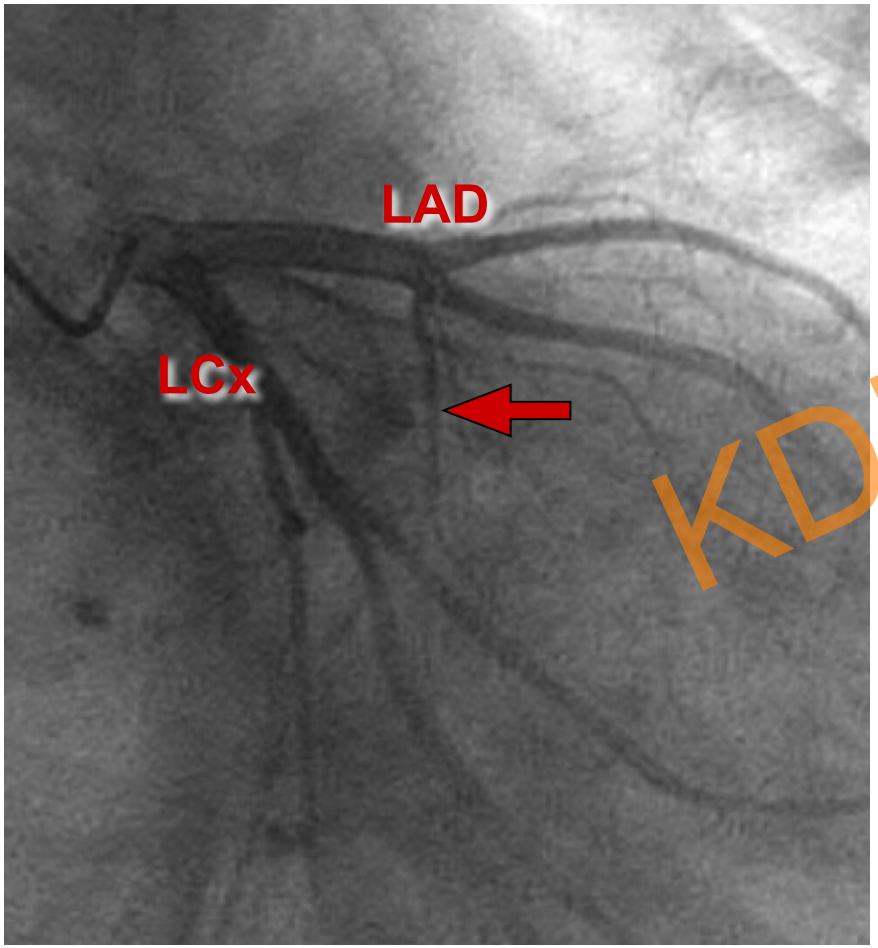
LVOTO = left ventricular outflow obstruction
SAM = systolic anterior motion of the mitral valve
LVH = left ventricular hypertrophy

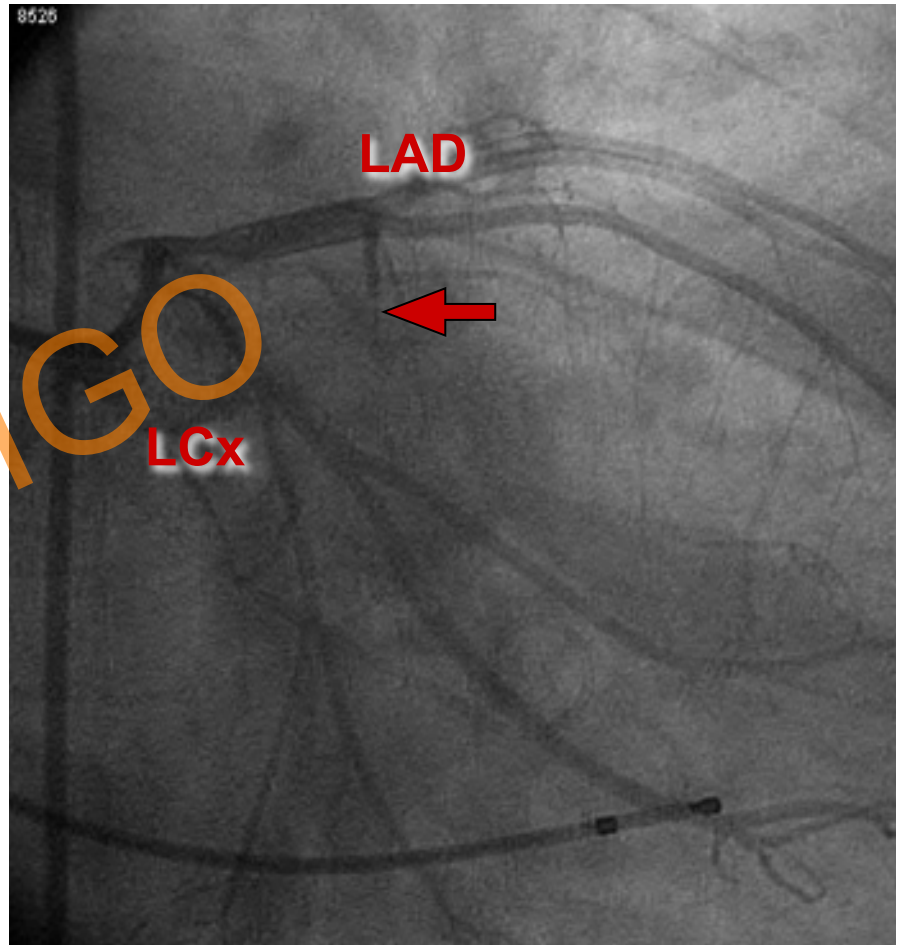
Calcagnino M. et al. JACC 2011;58, 88-9



Cases and imaging source: General University Hospital, Prague, CZ

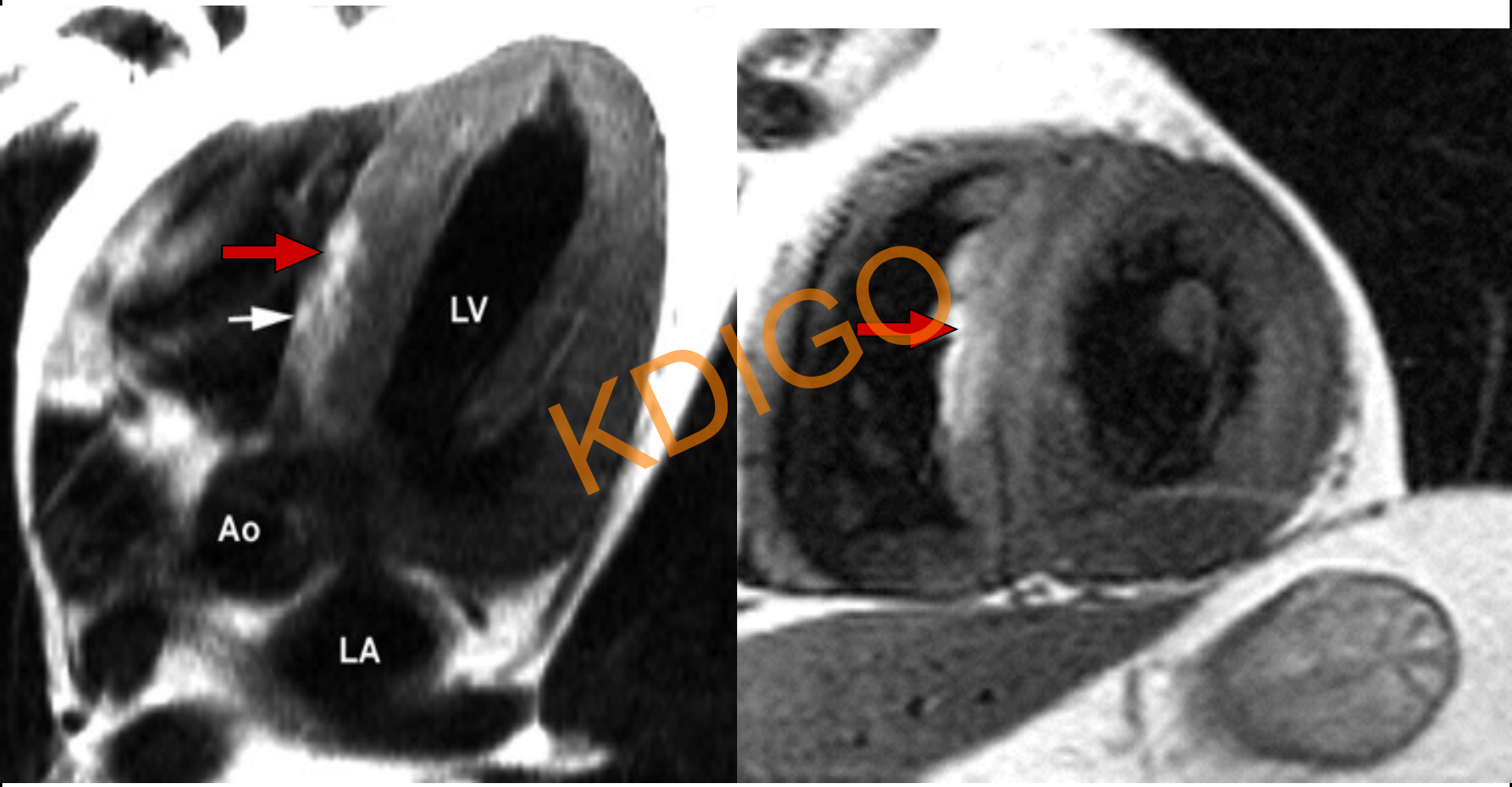
Alcohol septal ablation



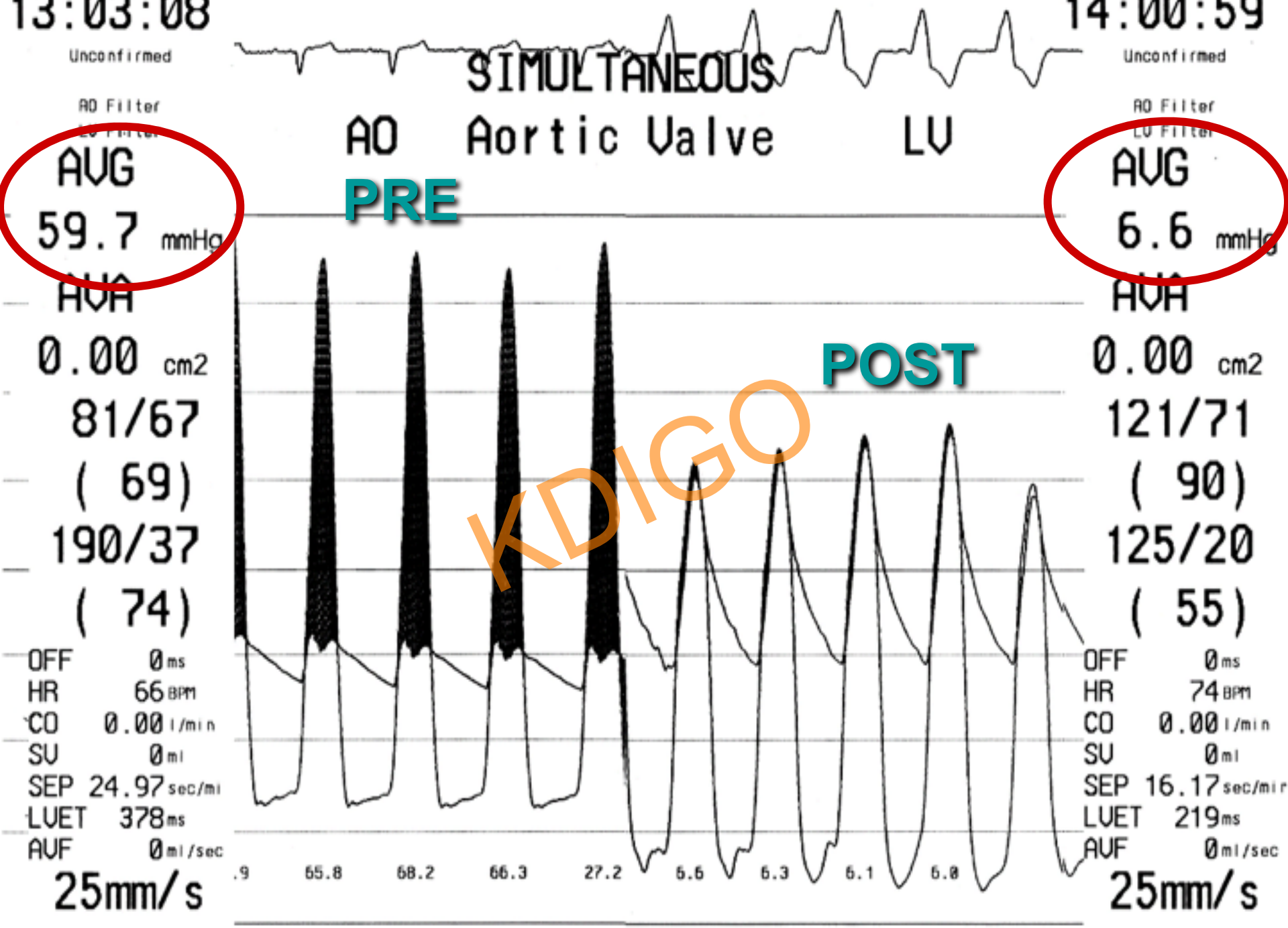


Magage et al., Echocardiography. 2005;22:333-9

Alcohol septal ablation



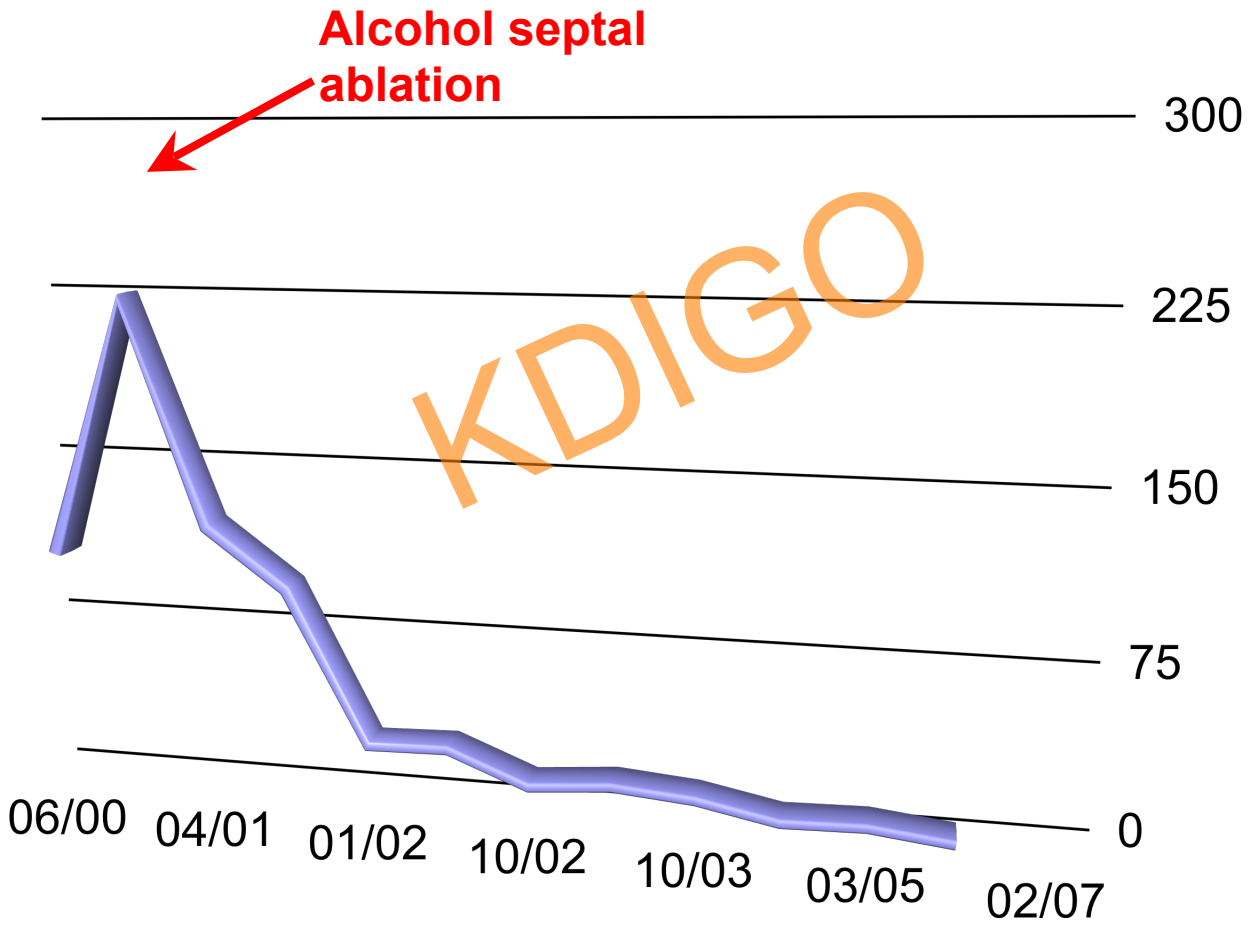
Magage et al., Echocardiography. 2005;22:333-9



Magage et al., Echocardiography. 2005;22:333-9

Alcohol septal ablation

LVOT gradient



Cases and imaging source: General University Hospital, Prague, CZ

Unsolved questions

- Should we seek LVOTO in all symptomatic patients by stress echocardiography
- Optimal LVOTO treatment (feasibility and durability of alcohol ablation)
- Optimal medical treatment specific to Fabry disease (betablockers?)

ARRHYTHMIAS

Arrhythmias

- Atrial flutter / fibrillation….6%[2]
  - Severely impairs LV filling, worsens HF symptoms
  - Risk of embolic stroke - anticoagulate!
- Ventricular arrhythmias (PVCs, NSVTs, SVTs-SCD)
- Chronotropic incompetence
  - Worsens symptoms - pacing → risk of dyssynchrony
- Conduction impairment
  - Short PR
  - AV conduction impairment → pacing → dyssynchrony

1) Shah et al. Am J Cardiol 2005;96:842– 846
2) Patel et al. Heart. 2015 ;101:961-6.

How to detect the paroxysmal atrial fibrillation

Recommendations	Class	Level
48-Hour ambulatory ECG monitoring **every 6–12 months** to detect AF should be considered in patients who are in sinus rhythm and have an **LA diameter of ≥45 mm**	IIa	C

Elliott et al. Eur Heart J. 2014 14;35:2733-79.

ESC 2014 HCM guidelines
Recommendations for Afib / flutter

Recommendations	Class	Level
VKA (INR 2.0-3.0) unless contraindicated	I	B
Flutter should be treated the same as AFib	I	C
HAS-BLED score should be considered	IIa	B
If VKA cannot be used, consider NOAC	I	B
Lifelong anticoagulation	I	C

Elliott et al. Eur Heart J. 2014 14;35:2733-79.

ESC 2014 HCM guidelines
Recommendations for Afib / flutter

Recommendations	Class[a]	Level[b]
Restoration of sinus rhythm, by DC or pharmacological cardioversion with intravenous amiodarone, should be considered in patients presenting with recent-onset AF.	IIa	C
Amiodarone should be considered for achieving rhythm control and to maintain sinus rhythm after DC cardioversion.	IIa	B
ß-Blockers, verapamil and diltiazem are recommended for controlling ventricular rate in patients with permanent or persistent AF.	I	C
Catheter ablation for atrial fibrillation should be considered in patients without severe left atrial enlargement, who have drug refractory symptoms or are unable to take anti-arrhythmic drugs.	IIa	B

??

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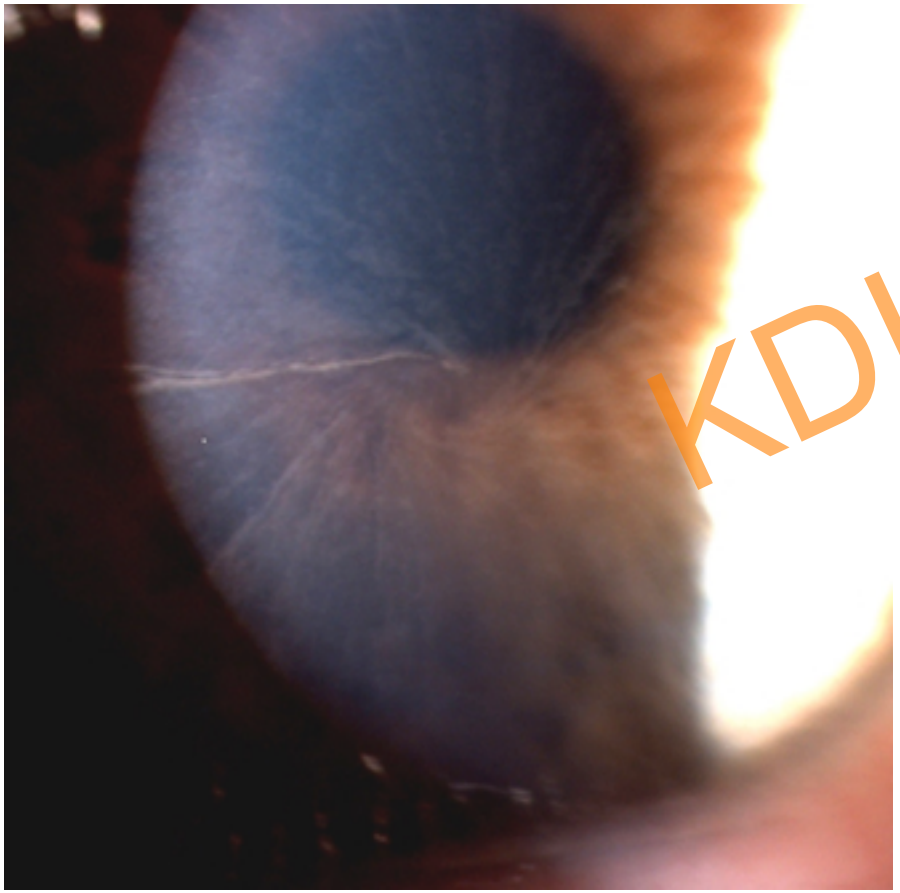
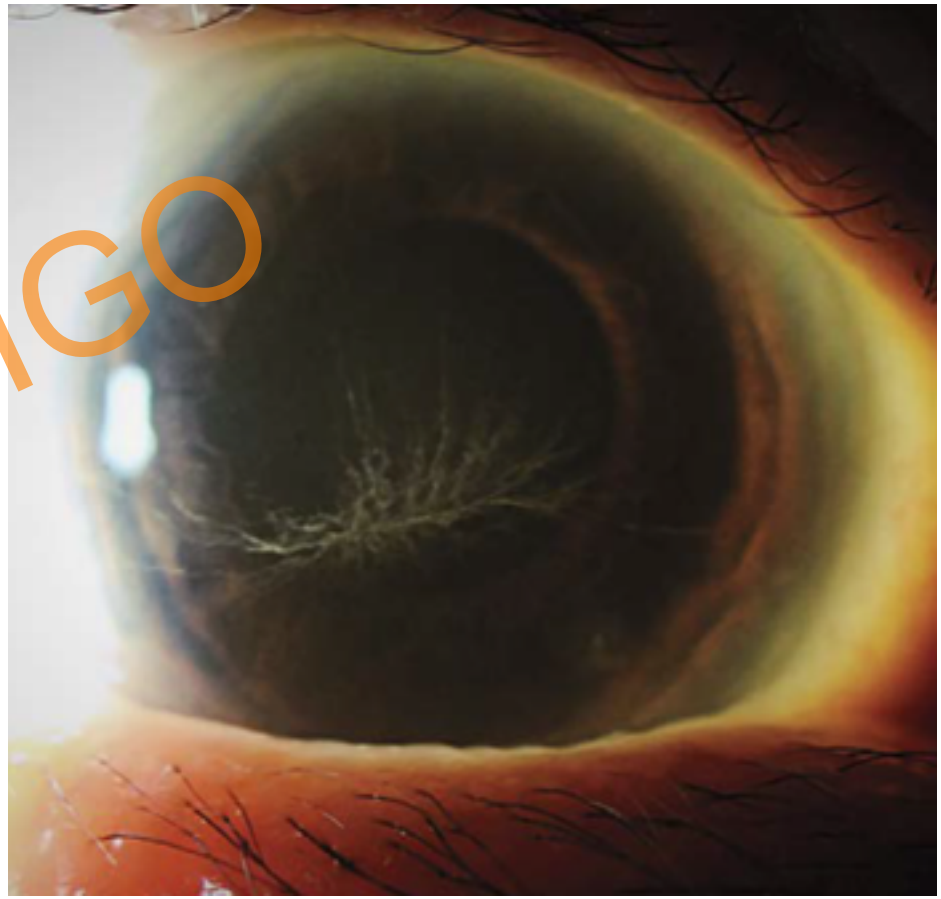
Elliott et al. Eur Heart J. 2014 14;35:2733-79.

Cornea verticillata

General University Hospital, Prague CZ

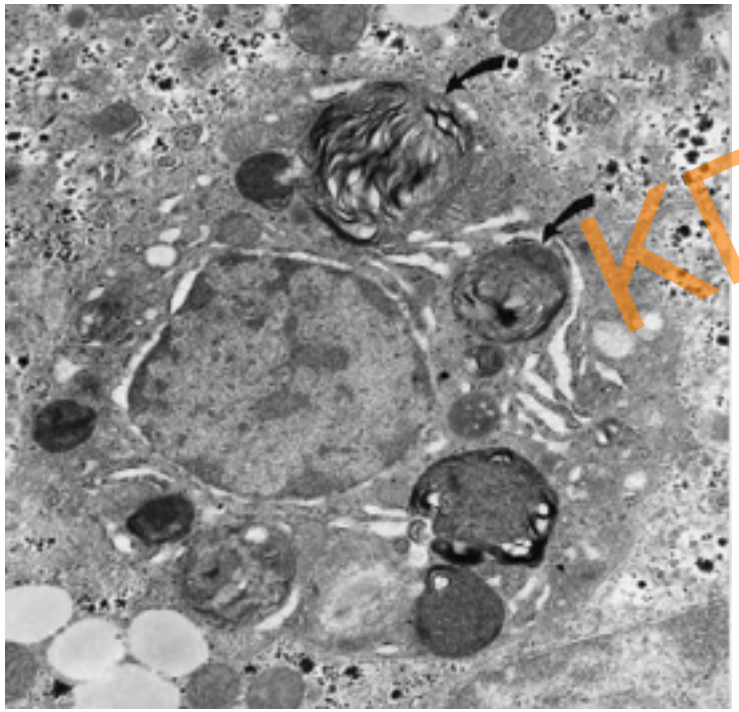
N Engl J Med. 2015 Apr 23;372(17):1656.

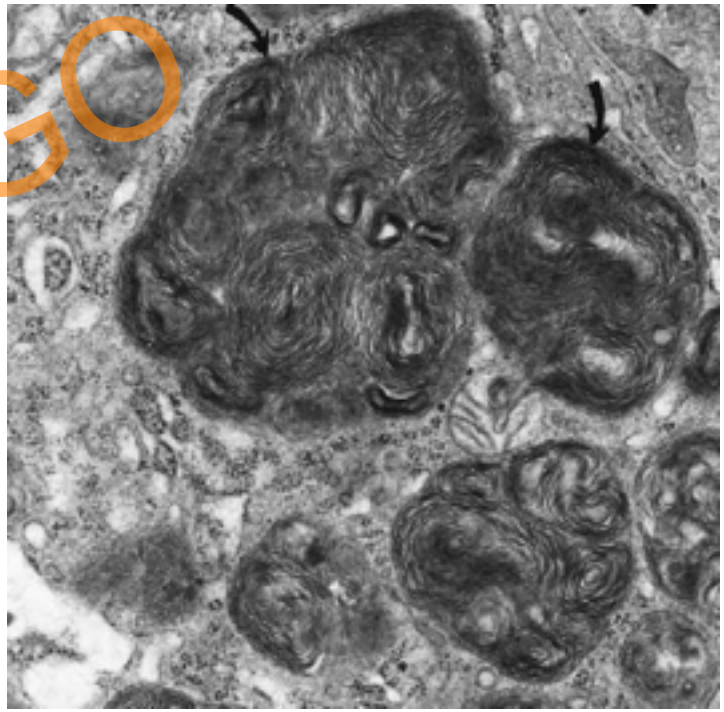




Amiodarone – development of lysosomal phospholipidosis

- Rat model
- Amiodarone – 150 mg / kg





Ágoston M., Toxicology 2003;190:231-241

Unsolved questions

- Should we replace warfarin with NOACs due to lower intracranial bleeding risk?
- What is the real risk of amiodarone use?
- What is the effectiveness and durability of catheter ablation in Fabry disease?

Arrhythmias

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- Chronotropic incompetence
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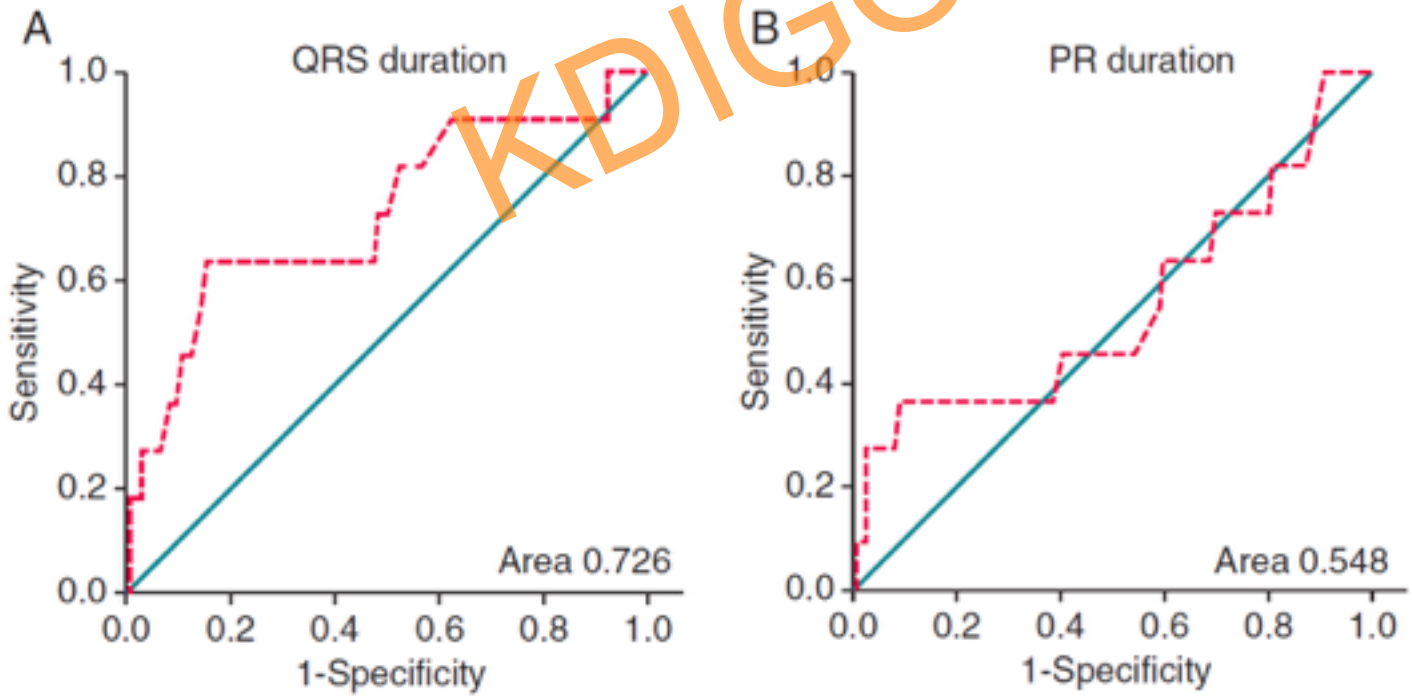
1) Shah et al. Am J Cardiol 2005;96:842– 846
2) Patel et al. Heart. 2015 ;101:961-6.

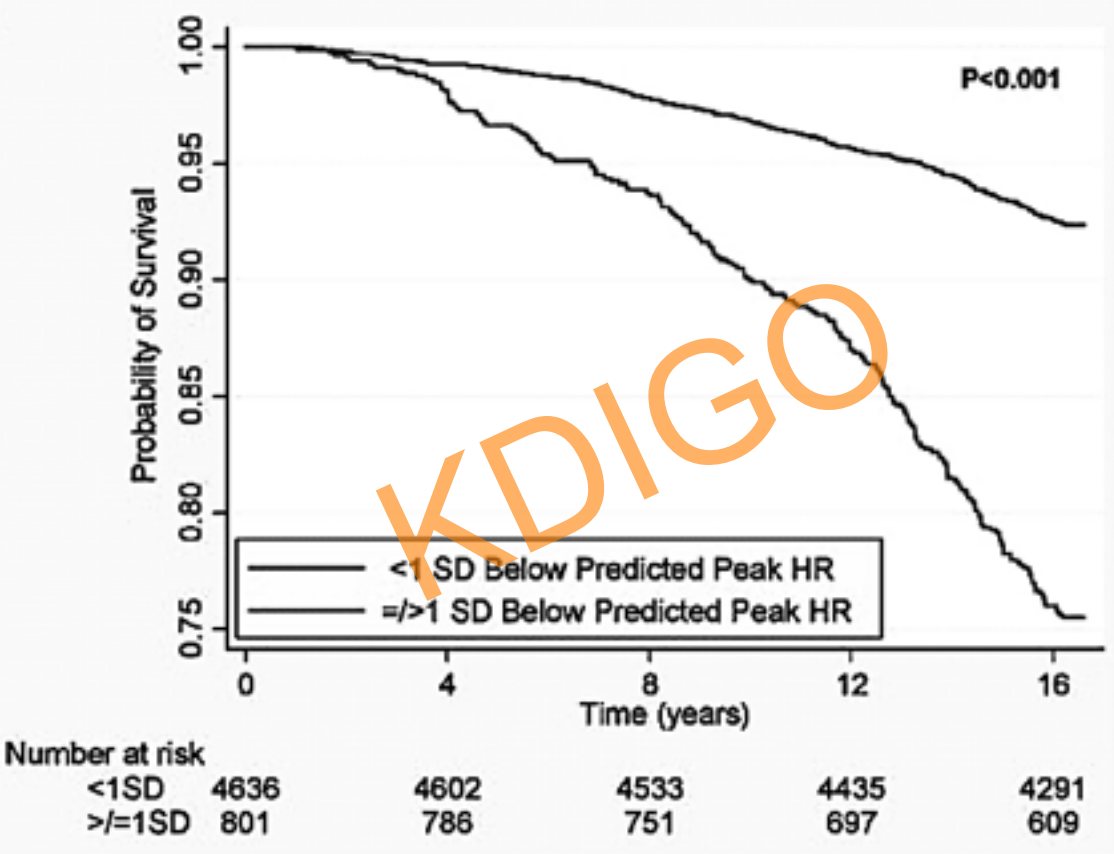
Antibradycardia pacing

- 204 patients (49% males), 5 had pacemaker at baseline
- **6.3 % needed pacemaker implantation**
- 42% for AV conduction, **58% for sinus node dysfunction**
- Annual implant rate 2.3%, 5 years incidence 12%



O´Mahoney et al. Europace 2011;13:1781–1788

Chronotropic incompetence impacts



Reduced survival during long-term follow-up among asymptomatic women with peak heart rate (HR) <1 SD below average

Gulati et al. Circulation. 2010;122:130 –137

Unsolved questions

- Should we test patients for chronotropic incompetence by stress tests
- Optimal pacing for Fabry cardiomyopathy (biventricular pacemakers?)
- Optimal medical treatment specific to Fabry disease (betablockers?)

Arrhythmias

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1) Shah et al. Am J Cardiol 2005;96:842– 846
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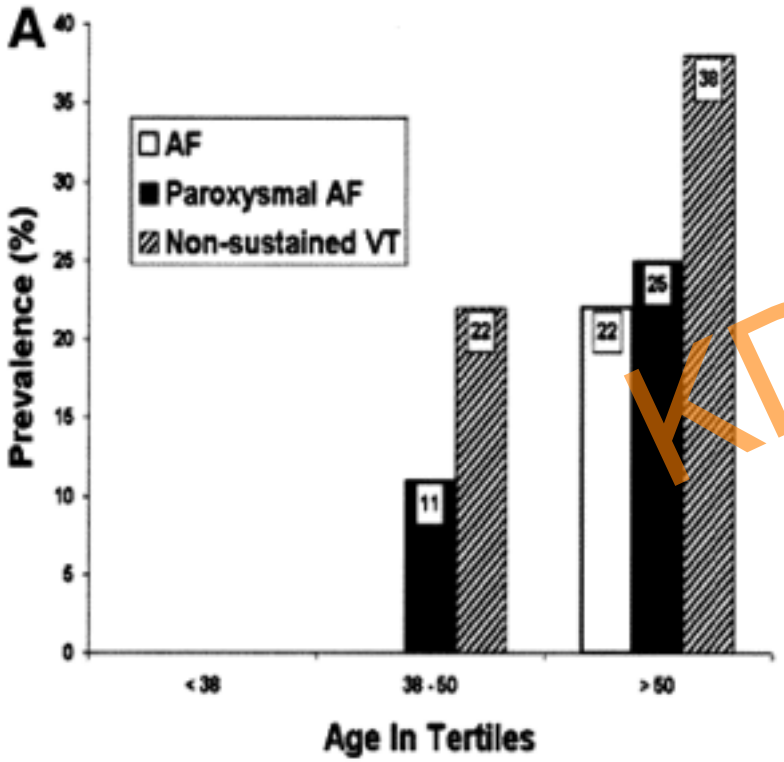
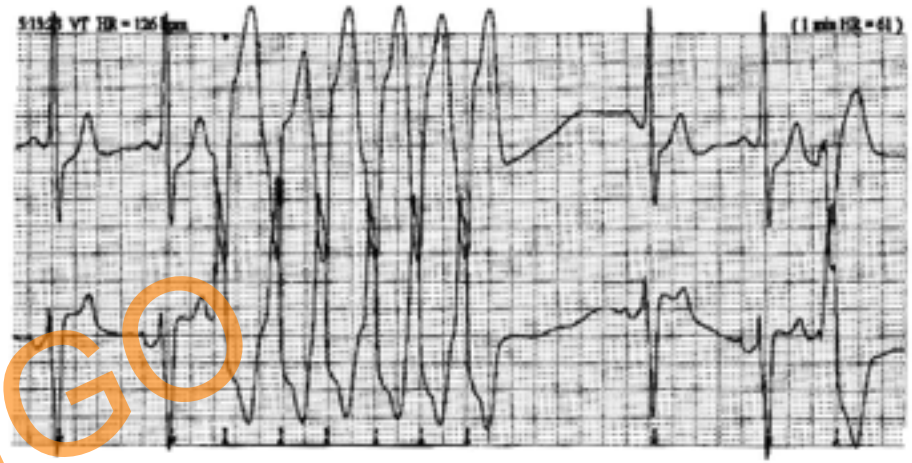
Potentially malignant arrhythmias in AFD are associated with advanced disease

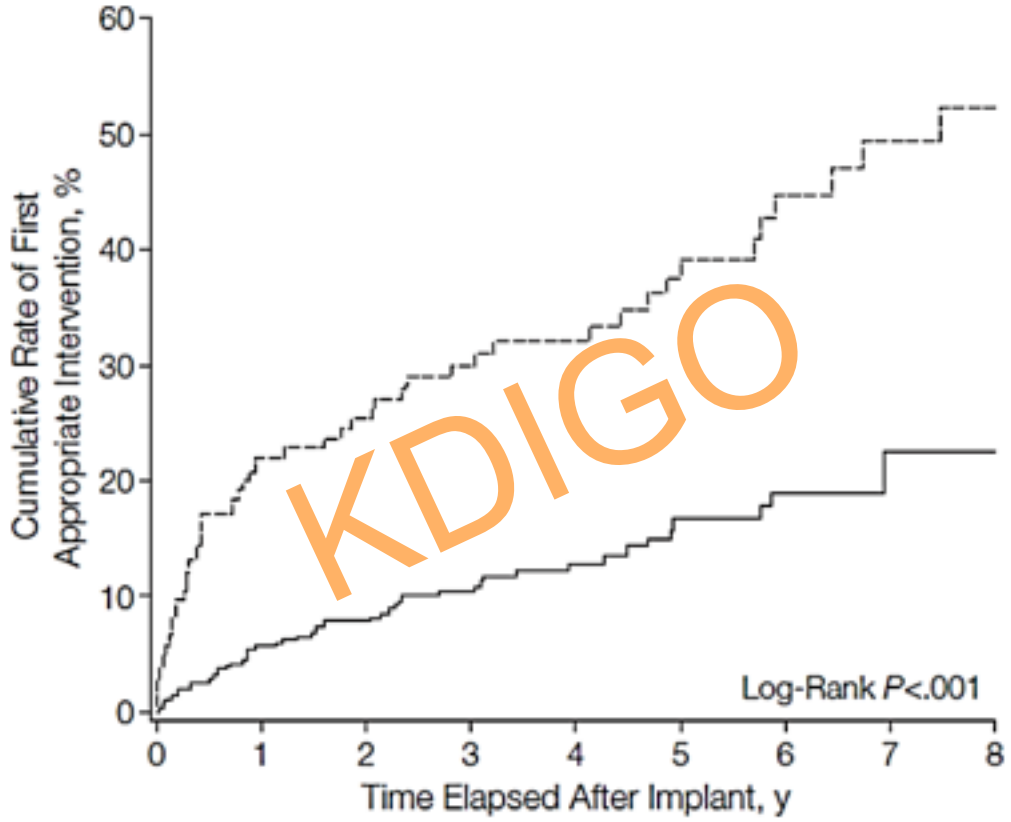




- 5 patients with NSVT
- all men
- age 58.4 ± 15.1 years, 46 - 83
- 3 - history of syncope,
- all 5 - palpitations.
- all 5 LV wall thickness ≥20 mm
- normal coronary arteries.

Shah & Elliott et al. Am J Cardiol 2005;96:842– 846

Implantable defibrillators in hypertrophic cardiomyopathy

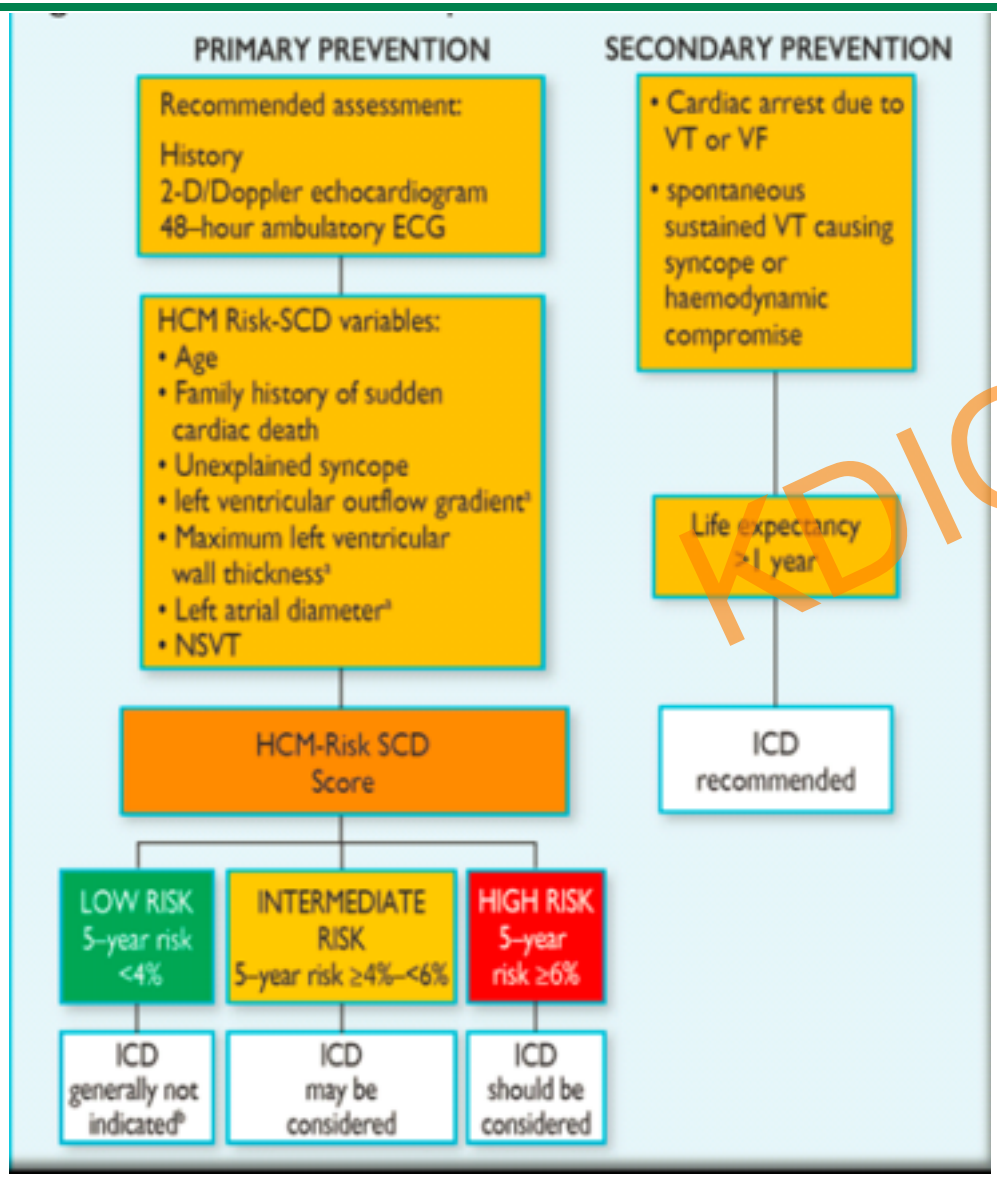


No. at risk

Primary prevention	383	332	256	205	148	95	70	43	28
Secondary prevention	123	95	85	70	51	39	28	18	16

Maron BJ, *JAMA*. 2007;298:405-412

Current guidelines !



„HCM Risk-SCD **should not be used** in patients <16 years of age, elite athletes or in individuals with metabolic / infiltrative diseases (**e.g. Anderson-Fabry disease**) and syndromes (e.g. Noonan syndrome).“

Elliott et al. Eur Heart J. 2014 14;35:2733-79.

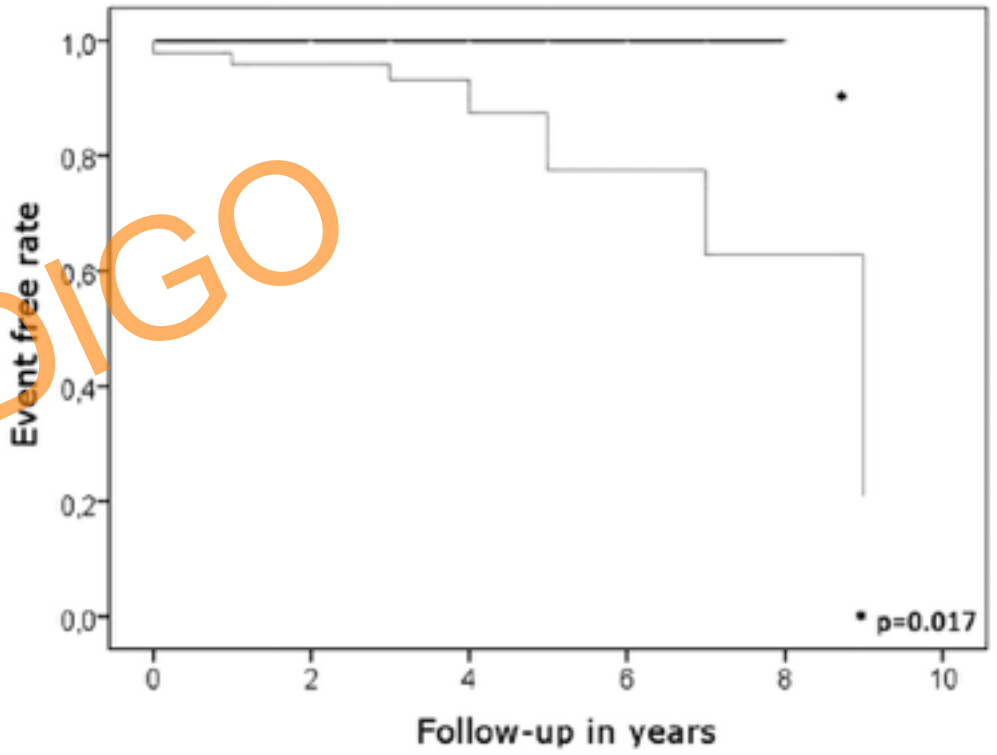
Fibrosis and arrhythmias in Fabry

No fibrosis n= 25
Fibrosis n = 48

Average amount of fibrosis
1.8 ± 1.8% of cardiac mass

Age / gender ?

Malignant arrhythmias
predicted only by annual fibrosis increase



Krämer et al. Am J Cardiol 2014;114:895e900

Unsolved questions

- Sudden death risk stratification
- ICD outcomes (appropriate vs. inappropriate ICD discharges, complication rates)
- Role of RFA ablation of arrhythmic substrates

CONCLUSIONS

Concomitant / adjunctive treatment

- ACEi / ARBs / spironolactone
  - kidney function?
  - HF-PEF?
- Caution:
  - betablockers – bradycardia
  - amiodarone – lysosomal impairment
- Pacing – in AV blocks, excessive bradycardia / chronotropic incompetence
  - Caution: induction of dyssynchrony – biv. pacing?
- ICD – if syncope, severe LVH, NSVT, fibrosis?