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
HEART FAILURE
Diffuse LVH on MRI in Fabry disease

Data source: General University Hospital, Prague
Cardiac symptoms in AFD

- LV hypertrophy absent
- LV hypertrophy present

Proportion of patients (%)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>LV Hypertrophy Absent</th>
<th>LV Hypertrophy Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cardiac symptom</td>
<td>50.8</td>
<td>89.9</td>
</tr>
<tr>
<td>Dyspnoea/heart failure</td>
<td>19.9</td>
<td>58.8</td>
</tr>
<tr>
<td>Angina/chest pain</td>
<td>24.9</td>
<td>49.6</td>
</tr>
<tr>
<td>Arrhythmia/palpitations</td>
<td>26.0</td>
<td>52.9</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>18.2</td>
<td>30.3</td>
</tr>
</tbody>
</table>
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%
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
3. Reduced LVEF

The diagnosis of HF-PEF requires four conditions to be satisfied:
1. Symptoms typical of HF
2. Signs typical of HF
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
<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIG-PEF</td>
<td>Digoxin</td>
<td>Trend to ↓ hospitalizations ↑ UAP</td>
</tr>
<tr>
<td>CHARM-PRESERVED</td>
<td>Candesartan</td>
<td>Trend ↓ hospitalizations</td>
</tr>
<tr>
<td>I-PRESERVE</td>
<td>Irbesartan</td>
<td>No effect</td>
</tr>
<tr>
<td>PEP-CHF</td>
<td>Perindopril</td>
<td>↓ hospitalizations</td>
</tr>
<tr>
<td>SENIORS HF-PEF</td>
<td>Nebivolol</td>
<td>Trend to ↓ Clinical complications</td>
</tr>
<tr>
<td>subgroup</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOP-CAT</td>
<td>Spironolactone</td>
<td>Effective in subjects recruited in USA and LATAM</td>
</tr>
</tbody>
</table>
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

LRI = low renal involvement; HRI = high renal involvement

Mean LPWT slopes (mm/year)    Mean IVST slopes (mm/year)

 KDIGO Controversies Conference on Fabry Disease | October 15-17, 2015 | Dublin, Ireland

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”

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 + M1 stenosis
LAD occlusion
LAD stenosis

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
Alcohol septal ablation

Mage et al., Echocardiography. 2005;22:333-9
Alcohol septal ablation

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

AUG 59.7 mmHg
AVA 0.00 cm²
81/67 (69)
190/37 (74)

POST

AUG 6.6 mmHg
AVA 0.00 cm²
121/71 (90)
125/20 (55)

Mabbage et al., Echocardiography. 2005;22:333-9
Alcohol septal ablation
LVOT gradient
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

### Recommendations

| 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 |

<table>
<thead>
<tr>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ila</td>
<td>C</td>
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### ESC 2014 HCM guidelines
#### Recommendations for Afib / flutter

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKA (INR 2.0-3.0) unless contraindicated</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Flutter should be treated the same as AFib</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>HAS-BLED score should be considered</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>If VKA cannot be used, consider NOAC</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Lifelong anticoagulation</td>
<td>I</td>
<td>C</td>
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### ESC 2014 HCM guidelines

#### Recommendations for Afib / flutter

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<tr>
<td>Restoration of sinus rhythm, by DC or pharmacological cardioversion with intravenous amiodarone, should be considered in patients presenting with recent-onset AF.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Amiodarone should be considered for achieving rhythm control and to maintain sinus rhythm after DC cardioversion.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>β-Blockers, verapamil and diltiazem are recommended for controlling ventricular rate in patients with permanent or persistent AF.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>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.</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

Cornea verticillata

General University Hospital, Prague CZ

Amiodarone – development of lysosomal phospholipidosis

- Rat model
- Amiodarone – 150 mg / kg
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

- **Atrial flutter / fibrillation….6%**
  - 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

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%

Reduction in peak heart rate (HR) <1 SD below average impacts survival during long-term follow-up among asymptomatic women.
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

- Atrial flutter / fibrillation….6%²
  - Severely impairs LV filling, worsens HF symptoms
  - Risk of embolic stroke - anticoagulate!

- Ventricular arrhythmias (PVCs, NSVTs, SVTs-SCD)

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- Conduction impairment
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Potentially malignant arrhythmias in AFD are associated with advanced disease

Arrhythmias in men

- 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.

Implantable defibrillators in hypertrophic cardiomyopathy

Secondary prevention

Primary prevention

Log-Rank P<.001

Time Elapsed After Implant, y

Cumulative Rate of First Appropriate Intervention, %

No. at risk

Primary prevention 123 95 85 70 51 39 28 18 16

Secondary prevention 383 332 256 205 148 95 70 43 28

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).“

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?