Medical therapy is superior to surgical therapy for restrictive cardiomyopathy

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If there was medical therapy...it would be superior to surgical therapy for restrictive cardiomyopathy
No disclosures
Thank God for Diastolic Dysfunction…

- HFpEF treatment
  - Where do we stand?
  - What’s on the horizon?
## Treatment of HFpEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic and diastolic <strong>blood pressure</strong> should be controlled according to published clinical practice guidelines</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Diuretics should be used for relief of symptoms due to <strong>volume overload</strong></td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Coronary revascularization for patients with CAD in whom angina or demonstrable <strong>myocardial ischemia</strong> is present despite GDMT</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Management of <strong>AF</strong> according to published clinical practice guidelines for HFpEF to improve symptomatic HF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Use of beta-blocking agents, ACE inhibitors, and ARBs for <strong>hypertension</strong> in HFpEF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>ARBs might be considered to decrease hospitalizations in HFpEF</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Nutritional supplementation is not recommended in HFpEF</td>
<td>III: No Benefit</td>
<td>C</td>
</tr>
</tbody>
</table>
### Updates since 2013

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<tr>
<td>Aldosterone receptor antagonists might be considered to decrease hospitalizations in HFpEF</td>
<td>IIb</td>
<td>B-R</td>
</tr>
<tr>
<td>Routine use of nitrate or PDE5 inhibitors to increase activity or QOL in HFpEF is ineffective</td>
<td>III – No benefit</td>
<td>B-R</td>
</tr>
</tbody>
</table>

2017 ACC/AHA/HFSA Focused update of the 2013 ACCF/AHA Guideline for the Management of heart Failure
HFpEF Rx: What \textit{doesn't} work

- Irbesartan (I-PRESERVE)
- Perindopril (PEP-CHF)
- Nevibolol (SENIORS)
- Candesartan (CHARM-Preserved)
- Imdur (NEJM 2015)
- Digoxin (DIG trial)
- Ivabradine (EDIFY)
- Sildenafil (RELAX)
- Irbesartan (I-PRESERVE)
- Statins (GISSI-HF)
HFpEF Rx: What *could* possibly work

**THERE IS**

still hope
TOPCAT

- The TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial investigated the effects of spironolactone on a combined endpoint of death, aborted cardiac death, and HF hospitalization in patients with HFP EF.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Spironolactone (N = 1722)</th>
<th>Placebo (N = 1723)</th>
<th>Hazard Ratio with Spironolactone (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with Event</td>
<td>no. (%)</td>
<td>no./100 person-yr</td>
<td>Participants with Event</td>
<td>no. (%)</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>320 (18.6)</td>
<td>5.9</td>
<td>351 (20.4)</td>
<td>6.6</td>
</tr>
<tr>
<td>Components of the primary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>160 (9.3)</td>
<td>2.8</td>
<td>176 (10.2)</td>
<td>3.1</td>
</tr>
<tr>
<td>Aborted cardiac arrest</td>
<td>3 (0.2)</td>
<td>0.05</td>
<td>5 (0.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>206 (12.0)</td>
<td>3.8</td>
<td>245 (14.2)</td>
<td>4.6</td>
</tr>
<tr>
<td>Additional secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>252 (14.6)</td>
<td>4.2</td>
<td>274 (15.9)</td>
<td>4.6</td>
</tr>
<tr>
<td>Hospitalization for any reason</td>
<td>766 (44.5)</td>
<td>18.8</td>
<td>792 (46.0)</td>
<td>20.0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>65 (3.8)</td>
<td>1.2</td>
<td>64 (3.7)</td>
<td>1.1</td>
</tr>
<tr>
<td>Stroke</td>
<td>57 (3.3)</td>
<td>1.0</td>
<td>60 (3.5)</td>
<td>1.1</td>
</tr>
</tbody>
</table>

* Some participants had more than one component of the primary outcome and are included once for the primary outcome and once for each component they had.
† Shown are unadjusted hazard ratios calculated with the use of Cox proportional-hazards models.
Cardiomems

Champion trial SUB-analysis:

- HFpEF or diastolic HF patients represent ~50% of all HF patients.
- The effect in HFpEF patients demonstrates an estimated NNT = 2.

HF Hospitalization Reduction
(18 mo follow-up)

n=115, p=0.0004

50% Reduction
p<0.0001 vs. control

Relative Risk Reduction

70%
60%
50%
40%
30%
20%
10%
0%

HFpEF

PA pressure-guided therapy

SIGNIFICANTLY REDUCED HF HOSPITALIZATIONS
in HFpEF patients in the treatment group, demonstrating that the CardioMEMS™ HF System is the first effective treatment strategy to manage 50% of patients hospitalized with HF.

REDUCE LAP HF Trial
InterAtrial Shunt Device - Mode of Action

Elevated LV/LA pressure

Pulmonary Venous hypertension

Pulmonary Congestion & Dyspnea

Transcatheter interatrial shunt device

NYHA Class

Baseline 6M 12M

0 50 100%

*** ***

Baseline 6M 12M

0 20 40 60 80

ML WHF Score

*** ***

Baseline 6M 12M

200 300 400 500

metres

6MWD

** **

***p<0.001 vs baseline
Paragon-HF Trial

Phase II Trial (ARNI vs. Valsartan)
Reduced NT-proBNP
Reduced LA size
Improved NYHA functional class

Relax-AHF

Serelaxin

Restrictive Cardiomyopathy

- Least common form of heart muscle disease
- Becoming more and more recognized
- Typically non-dilated ventricles
- Wall thickness normal or increased (infiltrative)
- Dilated atria
- Diastolic dysfunction $\rightarrow$ systolic dysfunction
Restrictive Cardiomyopathy

- Pressure

- Volume

- Restriction

- Normal

Diastolic ventricular pressure → Venous congestion → Jugular vein distension, Hepatomegaly & ascites, Peripheral edema

Rigid Myocardium → Ventricular filling → CO → Weakness, Fatigue

EKG

- LV

- RV

PRESSURE (mmHg)

E = 1.2 m/sec

A = 0.5 m/sec

DT = 128 msec
Causes of Restrictive Cardiomyopathies

- **Myocardial**
  - Noninfiltrative
    - Idiopathic
    - Familial
    - HCM
    - Scleroderma
    - Diabetes
    - Pseudoxanthoma elasticum
  - Infiltrative
    - Amyloidosis
    - Sarcoidosis
    - Gaucher’s Dz
    - Hurler’s Syndrome
    - Fatty Infiltration
  - Storage Disorders
    - Hemochromatosis
    - Fabry’s Dz
    - Glycogen Storage Dz

- **Endomyocardial**
  - Endomyocardial Fibroelastosis
  - Hypereosinophilic (Loeffler’s) syndrome
  - Carcinoid syndrome
  - Metastatic cancer
  - Radiation
  - Toxins
  - Drugs
    - Anthracyclines
    - Methysergide
    - Ergotamine
    - Mercurial agents
    - Busulfan

- *Important to distinguish from constrictive pericarditis*
Idiopathic RCM

- Sporadic, AD, or AR
- May be associated with distal skeletal myopathy, occasionally heart block
- A-fib present in 74%
- Diagnosis of exclusion
- 5 yr survival 64%
- Survival adversely related to:
  - Male gender
  - Age > 70
  - NYHA Class
  - Dilated LA > 60

- Treatment:
  - Largely supportive
  - Loop diuretics
  - OHT or TAH

Lysosomal Storage Diseases (Fabry’s, Danon, PRKAG2)

- **Anderson-Fabry’s Disease**
  - Reduced or absent activity of $\alpha$-galactosidase A
  - Intracellular accumulation GL-3 in heart, skin (angiokeratomas), kidneys (CKD), nerves (neuropathy)
  - Unlike Amyloid, QRS voltage correlates with LVH
    - LV mass correlates with disease severity
    - CMR: mid-myocardial LGE of basal inf wall with sparing of subendocardium
  - Treatment: Fabrazyme (algalsidase-beta)

  [Graphs and images showing data on LV mass and LGE over time, as well as incidence of events over years on agalsidase beta therapy.]


Endomyocardial Diseases

- Endomyocardial fibroelastosis (EMF)
  - Most common form of RCM (12 million worldwide)
  - Equatorial countries (Uganda, Nigeria, Brazil) – impoverished young adults (malnutrition, parasitic infection, genetics, autoantibodies, diet)
  - 2 phases: Active (inflammation/eosinophilia) $\rightarrow$ chronic (restrictive)
    - Biventricular and RHF
    - A-fib 30% and embolic complications common
EMF - Treatment

• Med tx – Na/fluid restriction, loop diuretics, ASA or anticoagulation

• Hypereosinophilic Syndrome (Loeffler’s)
  ➢ Corticosteroids +/- cytolytic Tx (hydroxyurea, IFN-alpha)

• Surgical Tx – endocardectomy and valve repair/replacement
  ➢ Technically challenging and not available in most endemic areas
  ➢ Survival rates as high as 70% at 10 yrs
Iron Overload Cardiomyopathy

- Hereditary Hemochromatosis or secondary
- Iron deposition in multiple organs (heart, liver, skin, pancreas, pituitary, joints)
- Dx: ferritin level >300 ng/mL (200 in women), % transferrin saturation > 45-55%
- Restrictive → dilated CMY (normal wall thickness
  - Systolic dysfunction indicates a poor prognosis
- Conduction disturbances and arrhythmias
  - Increased risk of SCD
- MRI: T2* relaxation time (severe < 10msec)
- Bx: Orange deposits, prussian blue

Treatment

- Phlebotomy – improves cardiac function and decreases arrhythmias
- Minimize alcohol intake (increases iron absorption)
- Chelation therapy
  - Oral Deferiprone and Deferasirox
  - IV Deferoxamine
  - Guided by CMR T2* imaging
  - Convincingly shown to improve systolic and diastolic function, prevent VT, reduce mortality in patients with secondary forms of iron overload

Potential therapies

- Antioxidants, CCB, hepcidin
Cardiac Sarcoidosis

- Noncaseating granulomas in lungs, spleen, lymph nodes, skin, liver, parotid glands, heart
- **Autopsy**: Cardiac involvement in 25%, Clinically: 5%
- **Cardiac**:
  - RCM → DCM
  - high-grade AV block, VT → syncope, SCD (17% with extensive granulomas)
- **CMR**: patchy, sparing endocardium
- FDG PET – distinguish active inflam from scar
  - Patchy distribution
    - Biopsy sensitivity of 20-30%
    - Electroanatomic mapping, ECG or image guided increase Bx yield

- **Treatment**
  - **Immunosuppression (steroids)**
    - No RCTs
    - Improves arrhythmias and can resolve heart block
    - Mixed results as to affect on EF once < 30%
    - Shown to preserve EF with active sarcoid if EF normal at initiation of Rx
  - PPM/ICD
  - MTX and MMF are also being used 2nd line (among others)
  - **ESHD → OHT** has good outcomes with rare recurrence of sarcoid in the new heart or progression of extracardiac sarcoid

Radiation Induced Heart Disease

- Can occur even substantially < 20 Gray
- Can manifest 10-15 yrs (even decades) after tx
- Can involve many cardiac structures
  - Coronary arteries: ostial stenoses
  - Valves: stenosis
  - Pericardium: constrictive pericarditis
  - Myocardium, endocardium: Interstitial fibrosis of RV > LV, RCM
- RCM more likely to occur with concomitant tx with anthracycline chemoTx or very high radiation doses

Treatment
- Diuretics
- TAH?
Surgical challenge

How am I supposed to get…

Into…
Conclusions

• RCM comprises a heterogeneous group of diseases, often manifesting in heart failure which can be very difficult to treat with standard medical therapy.

• Higher index of suspicion, better imaging techniques can expedite diagnosis and treatment for those RCM which do have specific therapy.

• In most cases, no true surgical “treatment”, only replacement therapy with OHT or TAH