Heart Failure Therapies
State of the Art: 2018

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DISCLOSURES
Consulting and Speaking For:
Abbott
Medtronic
Boston Scientific
Novartis

HEART FAILURE PREVENTION, IS MOST IMPORTANT:
OBJECTIVES

1. Understand HF Classification and Guideline Based Treatment Strategies for HF Stages C and D
   a. Reduced EF
   b. Preserved EF
   c. Hospitalized patients

2. Understand Novel Medical Therapy
   a. Neprilysin inhibitor / Angiotensin receptor blocker

3. Understand Novel Device Therapy
   a. Ambulatory Pulmonary Artery Pressure monitoring

4. Updates on Left Ventricular Assist Device and Transplantation
   a. When to refer to LVAD or transplant center

DEFINITIONS

• “Heart Failure” is a clinical syndrome!
  - Collection of symptoms: dyspnea, fatigue, exercise intolerance, etc
  - Collection of signs: edema, rales, gallops, etc
  - Similarities of clinical expression (see above), do NOT indicate the underlying mechanisms of disease are the same, OR that treatment will be similar……
STAGES AND FUNCTIONAL CLASSES OF HF

- Do not separate HFpEF from HFrEF
- Represent a continuum, but don’t imply that progression is inevitable.
- You can “move” between functional classes in response to treatment.
- Compliment each other
- Useful in everyday communication among all of us...

HOW TO SPEAK “HEART FAILURE”

- “This patient has HF” Decide the following:
  - ACUTE (uncompensated) or CHRONIC (compensated) or both?
  - Involvement of LEFT or RIGHT ventricle or BOTH?
  - SYSTOLIC or DIASTOLIC, or both?
  - Functional and stage classification?
  - Mr. Green has acute on chronic, biventricular, systolic and diastolic, Class III-C heart failure……!
DEFINITIONS OF HFrEF AND HFpEF

- Heart failure with preserved ejection fraction (HFpEF), heart failure with normal ejection fraction (HFNEF), or diastolic heart failure EF >40-50%

*Don’t confuse with diastolic dysfunction – abnormal mechanical property (in absence of clinical syndrome)*

- Heart Failure with reduced ejection fraction (HFrEF): (“systolic heart failure”) EF < 40%

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HF STAGES AND TREATMENTS

GUIDELINE BASED HF THERAPIES

HFrEF - STAGE C
PHARMACOLOGIC TREATMENT FOR STAGE C and HFrEF

2017: Class I, LOE B recommendation: ARNI

MAGNITUDE OF BENEFIT OF PHARMACOLOGIC THERAPY FOR STAGE C HFrEF

Table 13. Medical Therapy for Stage C HFrEF: Magnitude of Benefit Demonstrated in RCTs

<table>
<thead>
<tr>
<th>LVEF</th>
<th>RR Reduction in Mortality (%)</th>
<th>RR for Mortality Reduction (Graded in 30 nmol/L)</th>
<th>RR Reduction in Hospitalizations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>17</td>
<td>26</td>
<td>39</td>
</tr>
<tr>
<td>ARNI</td>
<td>24</td>
<td>9</td>
<td>41</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>20</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>Nitrates/Dihydropyridines</td>
<td>43</td>
<td>2</td>
<td>50</td>
</tr>
</tbody>
</table>

CUMULATIVE INCREMENTAL REDUCTION IN ODDS OF DEATH AT 24 MONTHS

DON'T FORGET ICD AND CRT THERAPIES

- ICD is recommended for primary prevention of SCD in patients with HFrEF (at least 40 d post-MI) with LVEF ≤ 35% and NYHA class II-III symptoms who are on chronic GDMT and who are expected to live > 1 year.

- ICD is recommended for primary prevention of SCD in patients with HFrEF (at least 40 d post-MI) with LVEF ≤ 30% and NYHA class I symptoms who are on chronic GDMT and who are expected to live > 1 year.

- CRT is indicated for patients who have LVEF ≤ 35%, sinus rhythm and LBBB with a QRS > 150 ms, NYHA class II, III, or ambulatory class IV symptoms and on GDMT.

GUIDELINE BASED HF THERAPIES

HFpEF - STAGE C

WHAT ABOUT HFpEF!?
PATIENT CHARACTERISTICS

HFpEF TRENDS

Owan TE et al. NEJM 2006

HFpEF TRENDS
RESPONSE TO TREATMENT HFpEF AND HFrEF

Borlaug BA et al. Circulation 2011

Hospitalized HF patients

EVALUATION OF THE HOSPITALIZED HF PATIENT

Congestion at rest? (e.g. orthopnea, elevated jugular venous pressure, pulmonary rales, 2+ edema, edema)

Do nothing go get a cup of coffee! No IV Diuretics

Yes IV Diuretics

Warm and Dry Cold and Dry

Yes Cold and Dry Cold and Wet

Inotropes

Inotropes and IV Diuretics
THERAPY RECOMMENDATIONS FOR THE HOSPITALIZED PATIENT

- **Recommended**
  - LVAD patients requiring mechanical ventricular assistance should receive anti-thrombotic therapy
  - LVAD patients requiring mechanical anticoagulation therapy should receive an HRT monitored dose greater than 400 mg daily
  - LVAD patients requiring mechanical anticoagulation therapy should receive a warfarin dose greater than 400 mg daily
  - LVAD patients requiring mechanical anticoagulation therapy should receive a warfarin dose greater than 400 mg daily

- **Medications**
  - Intolerance or dose reduction
  - Increasing diuretic dose

- **Laboratory / Other**
  - Worsening renal / hepatic function
  - Pulmonary hypertension
  - Right ventricular dysfunction
  - Poor / no response to CRT

THINK ABOUT THE FUTURE – LVAD AND TRANSPLANT REFERRAL

**Symptoms:**
- Recurrent admissions
- Refractory to meds

**Medications:**
- Intolerance or dose reduction
- Increasing diuretic dose

**Laboratory / Other:**
- Worsening renal / hepatic function
- Pulmonary hypertension
- Right ventricular dysfunction
- Poor / no response to CRT

“NOVEL” HF THERAPIES
Neprilysin Inhibition: Sacubatril-Valsartan (ENTRESTO)

- Neprilysin is a natural enzyme that degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin.
- Inhibition of Neprilysin increases the levels of these substances, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive cardiac and vascular remodeling.

8442 patients with class II (71%) and III (23%) heart failure
- EF < 40%, HF symptoms, BNP >150pg/ml
- Compared to 'Standard of Care' Enalapril (10 mg BID)
- Primary outcome: Composite of death from CV causes or hospitalization from HF

RESULTS OF PARADIGM-HF
**RESULTS AND CONCLUSION OF PARADIGM-HF**

- Angiotensin receptor–neprilysin inhibition was superior to ACE-I alone in reducing the risks of death and of hospitalization for heart failure.

**Inclusion Criteria:**
- NYHA III symptoms for at least 3 months
- Irrespective of LVEF
- HF hospitalization in last 12 months
- Reduced EF patients had to be on stable medical therapy
RESULTS OF CHAMPION TRIAL

- Treatment group had 3X's the changes to medical regimen vs. control group
- LOS for HF related hospitalizations was shorter in treatment group
- 37% reduction in overall HF related hospitalizations!
- NNT to prevent one HF related hospitalization = 4

PRE-SPECIFIED SUB-GROUP ANALYSIS:
Rate of HF hospitalizations by baseline EF

STAGE D HEART FAILURE
STAGE D HF = HIGH MORTALITY

- Rose EA et al. NEJM 2001; Rogers et al. JACC 2007; Hershberger et al. JACC 2003; Gorodeski et al. Circ Heart Fail 2009

HEART FAILURE CONTINUUM

OPTIONS

- Optimal Medical Therapy / Palliative Care
- Mechanical Circulatory support
- Cardiac Transplantation
EPIDEMIOLOGY - REMINDER

- 5.7-6.0 million Americans live with heart failure.
- 550,000 new cases are diagnosed each year.
- 100,000 Americans ages 35-74 have NYHA IIIb/IV or Stage D heart failure


LVAD VOLUME

Lund LH et al. JHLT 2017

“Proposing heart transplantation to cure heart failure is analogous to proposing the lottery to cure poverty”

Lund LH et al. JHLT 2017
**GENERAL INDICATIONS FOR LVAD / TRANSPLANT**

- Class IIIb / IV NYHA heart failure
- Failed OMT for at least 45 of 60 days, or has been IABP dependent for 7 d or IV inotrope dependent for 14 d
- LVEF < 25%
- Functional limitation with peak VO2 max < 14 ml/kg/min unless IABP or inotrope dependent or physically unable to perform testing

Slaughter MS et al JHLT 2010

**EVOLUTION OF MECHANICAL CIRCULATORY SUPPORT**

1st Generation
- Pulsatile Pumps

2nd Generation
- Axial Flow

3rd Generation
- Centrifugal Flow

Continuous Flow

**DURABLE LEFT VENTRICULAR ASSIST DEVICES**

HeartMate II LVAD

HeartWare
LVAD SURVIVAL – THE GOOD

LVAD SURVIVAL: ALL COMERS

Jorde UP et al. Presented at the ISHLT annual meeting, April 25, 2013

Kirklin JK et al. JHLT 2017
LVAD FUNCTIONAL STATUS – THE GOOD

Park S et al. Circulation 2012

LVAD – THE NOT SO GOOD

Kirklin JK et al. JHLT 2015

LVAD SURVIVAL: LEVEL OF ILLNESS MATTERS!

Kirklin JK et al. JHLT 2017
MECHANICAL CIRCULATORY SUPPORT AS BRIDGE TO TRANSPLANTATION

[Bar chart showing the percentage of patients over years from 2005 to 2015]

JHLT. 2017 Oct; 36(10): 1037-1079

Additional Imaging studies required for KUMC OHT evaluation:
- Abd US
- ABI's
- Carotid US
- Panorex
- Chest / Abd / Pelvis CT

Additional Consultations required for KUMC OHT evaluation:
- Renal
- Psychiatry
- Palliative Care
- Financial
- Social
- Pulmonary
- Hepatology

Box 2: Evaluation protocol for cardiac transplantation

- General:
  - Complete history and physical
  - Blood chemistries
  - Blood crossmatch
  - Blood type and screen
  - Inotropic profile
  - Serum electrolytes
  - Urinalysis and 24-hour urine collection
  - Pulmonary function testing
  - Dental evaluation

- Cardiovascular:
  - Electrocardiogram
  - Exercise treadmill testing
  - Right-sided heart catheterization with hemodynamics evaluation
  - Exercise treadmill testing with oxygen consumption determination

- Infectious:
  - Serologic testing for Hepatitis A, B, C
  - HIV
  - Varicella-zoster
  - CMV
  - Varicella-zoster
  - Leptospira
  - Angiotensin-converting enzyme
  - Tuberculosis
  - Peripherally derived skin test
  - Graft versus host disease
  - CMV

- Genetic:
  - Blood type and screen
  - Leukocyte antigen antibodies screen
  - Pancytopenia
  - Social evaluation
  - Psychiatric evaluation
  - Additional tests as indicated
**SELECTION PROCESS**

- Multidisciplinary group composed of
  - Surgeons
  - Cardiologists
  - Social workers
  - Financial workers
  - Transplant coordinators
  - Nutrition
  - Pharmacy
  - Palliative Care

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**SURGICAL APPROACH**

[Davies RR et al. JTCVS 2010]

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**IMMUNOSUPPRESSION**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ADVERSE EFFECTS</th>
</tr>
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<tbody>
<tr>
<td>FK506 - (Prograf®/Tacrolimus)</td>
<td>Nephritis, neuropathy, diabetes mellitus, hypertension, hyperlipidemia</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Nephritis, hypertension, gingival hyperplasia, hyperlipidemia</td>
</tr>
<tr>
<td>Mycophenolate Mofetil (CellCept®)</td>
<td>Nausea, diarrhea, leukopenia</td>
</tr>
<tr>
<td>Azathioprine - (Imuran®)</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td>Steroids</td>
<td>Diabetes, cushingoid features, cataracts, weight gain, osteopenia</td>
</tr>
</tbody>
</table>

SUMMARY

- Heart Failure classification is important for communication and as a guide to medical and device therapies
- Stage D Heart failure has a very high 1 year mortality
- There are many benefits and complications of LVAD therapy
- Cardiac transplant is a scarce resource, however remains the gold standard treatment for end-stage heart failure
- Everyone in this room will be exposed to end stage heart failure patients regardless of your chosen area of practice
THANK YOU FOR YOUR TIME!!