Advanced Heart Failure:
The Nuts & Bolts of Therapies Beyond Medications

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Disclosures

• I will not be speaking about off-label use of products.

• I have no financial or consulting relationships with any of the therapies I am discussing today.

• No conflict of interest for my discussion today.
Topics

• Burden of Advanced Heart Failure
• Cardiac Transplantation
• Mechanical Circulatory Support (MCS)
Heart Failure Prevalence

• Heart failure affects over 6.4M patients in the United States.

• 300,000-800,000 Americans have advanced heart failure.

• Over 250,000 patients die of heart failure each year.

Heart Failure Prevalence Increases With Age


AHA. Heart Disease and Stroke Statistics—2005 Update:
A Report From the American Heart Association Statistics Committee

*Note: Figures are US only
Heart Failure is an Epidemic

- Heart failure prevalence is expected to double over the next 30 years

**Status within 5 years of Diagnosis**

- Survival 50%
- Mortality 50%
# New York Heart Association Classification of Heart Failure

<table>
<thead>
<tr>
<th>Class</th>
<th>Patient Symptoms</th>
</tr>
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</table>
| Mild  | No limitation of physical activity  
|       | No undue fatigue, palpitation or dyspnea |
| Mild  | Slight limitation of physical activity  
|       | Comfortable at rest  
|       | Less than ordinary activity results in fatigue, palpitation, or dyspnea |
| Moderate | Marked limitation of physical activity  
|       | Comfortable at rest  
|       | Less than ordinary activity results in fatigue, palpitation, or dyspnea |
| Severe | Unable to carry out any physical activity without discomfort  
|       | Symptoms of cardiac insufficiency at rest  
|       | Physical activity causes increased discomfort |

Criteria Committee of the New York Heart Association, 1964.
CHF Population by NYHA Class

Class I
1.68 M (35%)

Class II
1.68 M (35%)

Class III
1.20 M (25%)

Class IV
240 K (5%)
Projected Mortality for Advanced Heart Failure Exceeds Other Terminal Diseases

Data on file, Thoratec Corporation.

Cardiac Transplantation
Cardiac Transplantation

Indications

“Medically Refractory Heart Failure”

• Accepted Indications
  – Refractory cardiogenic shock (inotropes, MCS, IABP)
  – Persistent NYHA IV HF (peak VO2 < 10 cc/kg/min, RER > 1.0)
  – Intractable angina
  – Intractable ventricular arrhythmias

• Probable Indications
  – Peak VO2 < 14 cc/kg/min and advanced symptoms

• Inadequate Indications
  – EF < 20%
  – History of NYHA III/IV
  – Peak VO2 > 14 cc/kg/min without other indications
Cardiac Transplantation
Contraindications-”absolute”

- Systemic illness (Less 2 year survival)
  - Active or recent (<5yrs) malignancy
  - AIDS
  - Lupus, sarcoid, amyloid
  - Irreversible renal or hepatic dysfunction
  - Severe COPD (FEV1 <1L)

- Fixed Pulmonary Hypertension
  - MCS and re-evaluate
### Most Contraindications are Relative

<table>
<thead>
<tr>
<th>Relative Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco abuse</td>
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<tr>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>PVD if limits rehab</td>
</tr>
<tr>
<td>Optimal</td>
</tr>
<tr>
<td>Carefully selected patients &gt;70 yr</td>
</tr>
<tr>
<td>Noncompliance</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Renal failure eGFR&lt;40 cc/min</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>significant end organ damage</td>
</tr>
<tr>
<td>Psychosocial</td>
</tr>
</tbody>
</table>

- EGFRI<40 cc/min
- BMI<30 kg/m2
- Patients >70 yr
Cardiac Transplantation
The evaluation

Conditions which limits post transplant survival or quality of life

• History, physical, follow-up visits
• Immunocompatibility and ABO, HLA typing, PRA
• Assessment of HF severity
  • EKG, Echo, CPX, Echo
• Multiorgan function
  • Labs, GFR, CXR, PFTs, Vascular, Abdominal US
• Infection
  • Hep B/C, HIV, RPR, HSV, CMV, Toxo, EBV, Varicella, PPD, vaccines (flu, pneumovax, Hep B)
• Malignancy
  • Colonoscopy, Mammography, Gyn/Pap, PSA
• Psychosocial
  • SW, Psych, Financial, Neurocognitive testing
• Appropriate consultations
  • Cardiac surgery
Accepted for Transplant

Inotropic Dependent

YES
PA catheter

List 1B

List 1A

NO
List Status 2

Re-eval every 1-3 months

Evaluate for MCS

Bridge to Transplant
Cardiac Transplantation

Status

• Status 1A
  • High dose intropes or multiple with SWG
  • Continuous mechanical ventilation
  • MCS: VAD (30 dys), IABP, ECMO, TAH
  • MCS with objective evidence of device-related complications

• Status 1B
  • At least one of the following
    – Ventricular assist device implanted
    – Continuous infusion of IV intropes

• Status 2
  • Does not meet criteria for status 1A or 1B

• Status 7
  • Temporarily unsuitable to receive a transplant
NUMBER OF HEART TRANSPLANTS REPORTED BY YEAR

90% of US transplants in 2009 were on Status 1A or 1B patients

Almost 1500 pts. Have died waiting for Tx between 2006-2009

ScandiaTransplant - Denmark, Finland, Norway, Sweden, Iceland

Eurotransplant - Austria, Belgium, Croatia, Germany, Luxembourg, The Netherlands, Slovenia
Cardiac Transplantation

- Remains the most effective Tx for end-stage heart disease, although donor shortage limits its use
- 1-year survival: 86% (2002)
- 5-year survival: 71%
- 10-year survival: 46%

Major Limitations of Transplantation

- **2,200 Heart Donations**
  - On the decline
  - 240,000 Class IV Heart Failure Patients

- **Multiple co-morbidities**
  - May not be a candidate

- **Time**
  - Too sick to wait.
  - Not clear if they are or will be candidate

- **Labor intense patient management**
  - Biopsies
  - Immunosuppression
Mechanical Circulatory Support (MCS)
VAD: Ventricular Assist Device

- A VAD is a mechanical circulatory device that is used to partially or completely replace the function of a failing heart

- Goal of device: to shunt blood away from the failing ventricle (Left or Right) and provide flow to the circulation (Systemic or Pulmonary)
VAD: Ventricular Assist Device

- Bridge to transplantation (BTT)
  - Typically referred for transplant but too ill to survive until transplantation

- Destination therapy (DT)
  - Advancing heart failure despite maximum medical and device therapy
  - Does not qualify and/or desire transplantation

We will focus our discussion on destination therapy
**VAD system: basic features**

- **Pump**
  - Internal

- **Wearable or portable control system**

- **Power source**
  - Battery power that is outside of the body
LONG-TERM USE OF A LEFT VENTRICULAR ASSIST DEVICE FOR END-STAGE HEART FAILURE

ERIC A. ROSE, M.D., ANNETINE C. GELUNS, PH.D., ALAN J. MOSKOWITZ, M.D., DANIEL F. HEITJAN, PH.D., LYNNE W. STEVENSON, M.D., WALTER DEMBITSKY, M.D., JAMES W. LONG, M.D., PH.D., DEBORAH D. ASCHEIM, M.D., ANITA R. TIERNEY, M.P.H., RONALD G. LEVITAN, M.SC., JOHN T. WATSON, PH.D., AND PAUL MEIER, PH.D., FOR THE RANDOMIZED EVALUATION OF MECHANICAL ASSISTANCE FOR THE TREATMENT OF CONGESTIVE HEART FAILURE (REMATCH) STUDY GROUP

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History of DT – REMATCH Trial

- Randomized clinical trial
  - optimal medical therapy vs. pulsatile flow LVAD
- Non-transplant candidates (n=129)
  - EF ≤ 25%,
  - peak VO2 < 12 ml/kg/min,
  - or continuous infusion inotropes
- FDA approval for HM I (XVE) as destination therapy

Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device

Mark S. Slaughter, M.D., Joseph G. Rogers, M.D., Carmelo A. Milano, M.D., Stuart D. Russell, M.D., John V. Conte, M.D., David Feldman, M.D., Ph.D., Benjamin Sun, M.D., Antone J. Tatooles, M.D., Reynolds M. Delgado, III, M.D., James W. Long, M.D., Ph.D., Thomas C. Wozniak, M.D., Waqas Ghumman, M.D., David J. Farrar, Ph.D., and O. Howard Frazier, M.D., for the HeartMate II Investigators*

NEJM 2009;361(23):2241-51.
Comparison of HM I (XVE) and HM II

<table>
<thead>
<tr>
<th></th>
<th>HM I</th>
<th>HM II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (gm)</td>
<td>1250</td>
<td>280</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>450</td>
<td>63</td>
</tr>
<tr>
<td>Noise</td>
<td>Audible</td>
<td>Silent</td>
</tr>
<tr>
<td>Moving parts</td>
<td>Many</td>
<td>One</td>
</tr>
<tr>
<td>Maximal flow (l/min)*</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Clinical Durability (yr)</td>
<td>1.5</td>
<td>Est. &gt; 5</td>
</tr>
</tbody>
</table>

* at mean pressure=100 mm Hg

HM II with controller and batteries
Primary Endpoint

Survival at 24 months, free from disabling stroke or re-operation for device replacement (intention-to-treat)

Primary Composite Endpoint (% of Patients)

- 62/134 (46%) for CF LVAD
- 7/66 (11%) for PF LVAD

Hazard Ratios [95% CI]

- Primary Endpoint: P<0.001
- Reoperation to Replace Device: P<0.001
- Death < 2 years: P=0.048
- Disabling Stroke: P=0.56

P<0.001

NEJM 2009;361(23):2241-51.
Actuarial Survival vs REMATCH

When Should the MCS Discussion Begin?

Stage A
High risk with no symptoms

Stage B
Structural heart disease, no symptoms

Stage C
Structural disease, previous or current symptoms

Stage D
Refractory symptoms requiring special intervention

Hospice
VAD, transplantation
Inotropes
Aldosterone antagonist, nesiritide
Consider multidisciplinary team
Revascularization, mitral-valve surgery
Cardiac resynchronization if bundle-branch block present
Dietary sodium restriction, diuretics, and digoxin
ACE inhibitors and beta-blockers in all patients
ACE inhibitors or ARBs in all patients; beta-blockers in selected patients
Treat hypertension, diabetes, dyslipidemia; ACE inhibitors or ARBs in some patients
Risk-factor reduction, patient and family education

Early Evaluation is Critical

- Timely referral for advanced treatment evaluation and intervention is critical before disease progresses \(^1\)
- Repeated readmissions of HF patient to hospital is a warning sign for intervention \(^1,2\)

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1 Russell, SD, Miller L, Pagani F. Advanced Heart Failure: A Call to Action. *Circulation* 2008. Publication Pending

When do you pull the Trigger to Refer?

It is never too early
Clinical Criteria for LVAD

- Unacceptable symptoms despite maximum medical or device therapy.
- Peak VO2 < 14 ml/kg/min or < 50% age-gender predicted on treadmill.
- Recurrent pulmonary edema within 6 mos.
- Weight loss due to cardiac cachexia.
- Recurrent ventricular arrhythmias +/- defibrillation.
- Progressive cardio-renal syndrome and hyponatremia
Worrisome signals: Need to consider MCS

- Hypotension
- Laboratory
  - Renal insufficiency
  - Hepatic dysfunction
  - Hyponatremia
- Pulmonary Hypertension
- RV dysfunction
- Unresponsiveness to CRT
- Need for Inotropes

- Symptoms
  - Refractory
  - At rest
- Recurrent admissions

- Medications
  - Intolerance or lower doses
    - ACE-I/ARBs
    - Beta blockers
  - Increasing diuretic doses
Ideal time for referral

• NYHA III or IV plus one of the following:
  • Inability to walk < 1 block without dyspnea (shortness of breath)
  • Serum sodium < 136 mmol/L
  • BUN > 40mg/dL
  • Intolerant or refractory to ACE-I / ARB / BB
  • Diuretic dose > 1.5mg/kg
  • One or more CHF related hospital admissions within 6 months
  • CRT nonresponder
  • Hematocrit < 35%

MCS Evaluation:

Neurologic, Psychosocial, and Psychiatric Considerations

- Assess candidates’ ability to:
  - Care for equipment
  - Exercise
- Patients with PAD, Stroke, >60 yo., Diabetes should have CT and MRI
- Consider history of psychiatric disorders, drug abuse and compliance issues
  - May need commitment contract
- Should have support from others
- Address advanced directives

MCS Evaluation: Other Issues

• Gastrointestinal Bleeding
  • Must be assessed and treated pre-implant
  • Consider effects of anticoagulation therapy during support

• CT chest – without contrast
  • With all redo sternotomy patients

• Peripheral Vascular Disease
  • Evaluate severity pre-LVAD
  • Abdominal ultrasound
  • Ankle-brachial index
**Functional Status**

% NYHA Class I or II

- **Percent of patients**
  - Baseline
  - 3 mo: 75%
  - 68%
  - 12 mo: 76%
  - 61%
  - 24 mo: 80%
  - 100%

6 Minute Walk Distance

- **Meters**
  - Baseline
  - 3 mo: 319 m
  - 291 m
  - 12 mo: 318 m
  - 306 m
  - 24 mo: 372 m
  - 277 m

**LVAD Duration**

- **CF LVAD**
- **PF LVAD**

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NEJM 2009;361(23):2241-51.
Quality of Life

MLWHF

<table>
<thead>
<tr>
<th>LVAD Duration</th>
<th>Baseline</th>
<th>3 mo</th>
<th>12 mo</th>
<th>24 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF LVAD</td>
<td>75.4</td>
<td>37.4</td>
<td>34.1</td>
<td>29.6</td>
</tr>
<tr>
<td>PF LVAD</td>
<td>76.1</td>
<td>42.1</td>
<td>44.4*</td>
<td>61.0</td>
</tr>
</tbody>
</table>

KCCQ

<table>
<thead>
<tr>
<th>LVAD Duration</th>
<th>Baseline</th>
<th>3 mo</th>
<th>12 mo</th>
<th>24 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF LVAD</td>
<td>27</td>
<td>63</td>
<td>66</td>
<td>70</td>
</tr>
<tr>
<td>PF LVAD</td>
<td>27</td>
<td>57</td>
<td>59</td>
<td>33</td>
</tr>
</tbody>
</table>

* p<0.05 between treatments at 12 mo
† over time for both treatments

NEJM 2009;361(23):2241-51.
Summary and Conclusions

• Heart failure population is continuing to increase
• Mortality remains high despite advance medical and device therapy
• Advanced heart failure patients failing optimal therapies have a poor prognosis
• Transplantation has very good long term outcomes
• Organ availability is the major limitation for transplantation
Summary and Conclusions

• Continuous flow LVAD patients experienced early and sustained improvement in survival, exercise capacity, functional class and quality of life

• Results support the use of continuous flow LVAD therapy for long term support in advanced heart failure patients

• LVADs are a good options for patients who may not want or qualify for transplantation

• VADS and Total Artificial Hearts are evolving quickly to become one of the primary therapies of advance heart failure
Thank You

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