Advanced Heart Failure
What is it and What Can We Do About It?

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Disclosures: Consultant for Boston Scientific, Medtronic, St. Judes, Abbott Vascular, J and J, Teva
It All Began at “Big Barn” on December 3rd 1967
Mechanical Stretch:
- IP$_3$
- PKC
- MAP Kinase
- All (autocrine)
- ET (autocrine)
- Na$^+$/K$^+$ exchanger (ph)

Fetal gene re-expression associated with Hypertrophy

Neurohormones, Cytokines and Growth Factors:
- All
- NE
- ET
- Aldosterone
- TGF-Beta
- Growth Hormone, IGF
- TNF-alpha
- Cardiotrophin-I
- Beta myosin heavy chain
- Skeletal alpha actin
- ANF
Limits of Pharmacological Therapy in HFrEF

- Placebo
- ACE Inhibitors
- ARNIs
- β-Blockers (except Bucindolol)
- Mineralocorticoid Receptor Antagonists
- (Diuretics and Digoxin)

INEFFECTIVE
- EPO for Anemia
- Warfarin for Thromboembolism
- SSRI for Depression
- Statins for HF

POTENTIALLY EFFECTIVE
- Fish Oil (PUFA)
- Ivabradine

Mortality Reduction

Incremental Benefit

- Moxonidine
- Xamoterol

- Hydralazine-Nitrates
- Omapatrilat
- Etanercept
- Endothelin Antagonists
The illusion of stability in HF

- 20% of ‘stable’ patients (no prior HF hospitalization) had a primary event
- 17% died during the course of the trial
- Of stable patients who experienced a primary event, death preceded heart failure hospitalization in 51%
- 60% of these deaths were sudden cardiac deaths
Advanced Heart Failure

HEART FAILURE SYMPTOMS MARKEDLY LIMITING DAILY ACTIVITIES

Ensure optimal pharmacological, CRT, and ICD therapy as indicated

Does this patient meet criteria for increased one-year mortality?

- ≥2 heart failure hospitalizations in the last year
- Persistent hyponatremia (<135mg/dL)
- Reno-circulatory limitations to use of ACEI, ARB or beta-blockers
- High or increasing diuretic requirement
- High-risk profile on calculated survival scores
- Reduced peak exercise capacity
- Frequent use of inotropes
- Recurrent, refractory ventricular arrhythmias
Laplace Therapy

Stress = \frac{P r}{h} = \frac{\text{Pressure} \times \text{Radius}}{\text{Wall Thickness}}

Shah S and Mehra MR. *Scientific American Medicine* 2016
ADVANCING THERAPY
Ventricular Assist Device Innovation

A to G
Gradual Miniaturization over 3 Decades

The Stutter of Innovation in Technology

Through the years
Biomimicry to An Unnatural Physiology?

Now

Continuous Flow LVAS

Pusher Plate LVAS

Then

- Increased shear stress leads to increased micro-particles
- Micro-particles enhance oxidative stress
- Macrovascular function, corrected for shear stress is also markedly decreased in CF LVAS

Whitman et al. JACC Heart Fail. 2015 Sep;3(9):703-11.
Acquired von Willebrand Disease

Observations from Current RCTs in LVAS

ENDURANCE and ENDURANCE supplemental

MOMENTUM 3
### ENDURANCE HEARTWARE VERSUS HEARTMATE II

<table>
<thead>
<tr>
<th>Reported Metric</th>
<th>HVAD</th>
<th>HM II</th>
<th>Statistically Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients for Primary Endpoint</td>
<td>297</td>
<td>148</td>
<td></td>
</tr>
<tr>
<td>Cohort Characteristics: Age</td>
<td>63.9</td>
<td>66.2</td>
<td>Yes</td>
</tr>
<tr>
<td>Cohort Characteristics: Severe Tricuspid Insufficiency</td>
<td>11.8%</td>
<td>5.4%</td>
<td>Yes</td>
</tr>
<tr>
<td>Primary Endpoint – 2 year event-free rate</td>
<td>55%</td>
<td>57.4%</td>
<td>No</td>
</tr>
<tr>
<td>Reason for Endpoint ‘Failure’: Death</td>
<td>34.7%</td>
<td>26.4%</td>
<td>No</td>
</tr>
<tr>
<td>Reason for Endpoint ‘Failure’: Device malfunction, failure requiring exchange, urgent transplant, explant</td>
<td>8.8%</td>
<td>16.2%</td>
<td>Yes</td>
</tr>
<tr>
<td>Survival at 2 years</td>
<td>60.2%</td>
<td>67.6%</td>
<td>No</td>
</tr>
</tbody>
</table>

### Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>HVAD</th>
<th>HM II</th>
<th>Statistically Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI Bleed</td>
<td>.55 EPPY</td>
<td>.44 EPPY</td>
<td>No</td>
</tr>
<tr>
<td>Driveline Infection</td>
<td>.18 EPPY</td>
<td>.12 EPPY</td>
<td>No</td>
</tr>
<tr>
<td>Stroke</td>
<td>.27 EPPY</td>
<td>.09 EPPY</td>
<td>Yes</td>
</tr>
<tr>
<td>Right Heart Failure</td>
<td>.31 EPPY</td>
<td>.22 EPPY</td>
<td>Yes</td>
</tr>
<tr>
<td>Pump exchange</td>
<td>.06 EPPY</td>
<td>.10 EPPY</td>
<td>No</td>
</tr>
</tbody>
</table>

*Rogers J, Pagani F et al. NEJM 2017*
Endurance Supplemental Trial
Primary Endpoint

Incidence of neurological injury (stroke > MRS 0 or TIA) within 12 months HVAD compared to HMII (control)

\[ \Delta = 2.6\% \]

- HVAD (306)
- Control (157)

Neurologic injury was defined as any stroke with MRS > 0 at 24 weeks post-stroke, or a TIA, or spinal cord injury. Note: this endpoint does not include device exchange

Non-inferiority Margin 6%

10.7% upper confidence bound exceeds pre-specified margin of 6%

Difference in success outcomes

-15% -10% 0% 5% 10% 15% 20%

Point estimate with confidence bounds

Non-Inferiority Margin NOT MET

TIA: transient ischemic attack

Milano C 2017 ISHLT
**HeartMate 3 LVAS**

- **Wide** blood-flow passages to reduce shear stress
- **Frictionless** with absence of mechanical bearings
- **Intrinsic Pulse** designed to reduce stasis and avert thrombosis
Acquired von Willebrand Disease
A Hemocompatibility Biomarker

HeartMate II

HeartMate 3

POD 30  POD 7  NC  POD 2  Base

POD 30  POD 7  NC  POD 2  Base

Triplet #10

HMWMs

Netuka........Mehra  JHLT 2016
MAGNETICALLY LEVITATED CENTRIFUGAL PUMP IMPROVES OUTCOME COMPARED WITH A MECHANICAL BEARING AXIAL FLOW PUMP

Survival at 6 months free of disabling stroke or reoperation to replace or remove the pump (ITT)

Non-inferiority Analysis
Absolute difference +9.4% (95% LCB -2.1%), P<0.0001

Superiority Analysis
HR 0.55, (95% CI 0.32-0.95), P=0.037

<table>
<thead>
<tr>
<th>no. at risk</th>
<th>HeartMate 3</th>
<th>HeartMate II</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>152</td>
<td>142</td>
</tr>
<tr>
<td>1</td>
<td>146</td>
<td>125</td>
</tr>
<tr>
<td>2</td>
<td>138</td>
<td>119</td>
</tr>
<tr>
<td>3 Months</td>
<td>135</td>
<td>116</td>
</tr>
<tr>
<td>4</td>
<td>130</td>
<td>110</td>
</tr>
<tr>
<td>5</td>
<td>128</td>
<td>106</td>
</tr>
<tr>
<td>6</td>
<td>127</td>
<td>103</td>
</tr>
</tbody>
</table>

LCB, lower confidence boundary; HR, hazard ratio; and CI, confidence interval

MEHRA MR, NAKA Y ET AL N ENGL J MED 2017;376:440-50
ADVANCING FUTURE THOUGHT

Novel Pathophysiological Targets
Exo-Organoplasty

LV Restoration with Algisyl- LVR

Placement of Alginate Hydrogel via a Limited Thoracotomy

AHA Scientific Sessions
Chicago 2014

Courtesy, Mann D
Neuro-Cardiac Modulation
The Promise of Gene Therapy: Cellular Therapy

Viral vectors bind to cell surface receptors, are endocytosed, and are internalized, the viral particles avoid degradation in endosomes, traverse the nuclear envelope membrane pores, and enter the cell nucleus.

An increased rate of uptake of Ca^{2+} into the SR, when phosphorylated (P), removes Ca^{2+} from the ryanodine receptor (RyR), removing Ca^{2+} release. Thereby, Ca^{2+} uptake is increased in response to β-adrenergic stimulation, which activates adenylate kinase may be a second messenger of the β-adrenergic system.
The Future in Recovery-Regeneration

- Ageing and Diseased Cells
- Autologous (Quality)
- All Cell Types
- Adverse Effects