Mechanical Circulatory Support: 
Main achievements and Challenges

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Disclosures: Consultant for Abbott, Medtronic, Janssen, Mesoblast, Portola, Fineheart, BICR and NupulseCV, Inc.
A Journey That Began in Earnest in 1962, is still Evolving……..

Ventricular Systems are HERE and NOW………..
Advancing Survival in Advanced Heart Failure

Transplant Survival at 2 years
- HM3: 83%: MOMENTUM 3 LT
- HMII: 76%: MOMENTUM 3 LT
- HMII: 72%: INTERMACS Registry 2013-2016
- HMII: 58%: HMII DT
- HM XVE 24%: HMII DT
- OMM 8%: REMATCH Rose, NEJM 2001


## What Devices Do We Have?

<table>
<thead>
<tr>
<th></th>
<th>HeartMate II</th>
<th>HVAD</th>
<th>Jarvik 2000</th>
<th>HeartMate 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Implant Location</strong></td>
<td>Chest/abdomen</td>
<td>Pericardial</td>
<td>Pericardial/intra-cardiac</td>
<td>Pericardial</td>
</tr>
<tr>
<td><strong>Flow Configuration</strong></td>
<td>Axial</td>
<td>Centrifugal</td>
<td>Axial</td>
<td>Centrifugal</td>
</tr>
<tr>
<td><strong>Impeller suspension</strong></td>
<td>Mechanical bearing</td>
<td>Hybrid Magnetic/hydrodynamic</td>
<td>Ceramic Bearing</td>
<td>Magnetically Levitated</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>281 grams</td>
<td>160 grams</td>
<td>90 grams</td>
<td>220 grams</td>
</tr>
<tr>
<td><strong>Maximum Output</strong></td>
<td>10 L/m</td>
<td>10 L/m</td>
<td>7 L/m</td>
<td>10 L/m</td>
</tr>
<tr>
<td><strong>Artificial Pulsatility</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Typical Speed Range</strong></td>
<td>8,000-10,000 RPM</td>
<td>2,000-4,000 RPM</td>
<td>8,000-12,000 RPM</td>
<td>3,000-9,000 RPM</td>
</tr>
</tbody>
</table>
Hemocompatibility Related Adverse Outcomes

“Outcomes encountered as the host interfaces with the device”

PRE-IMPLANT FACTORS
- Female sex
- Prothrombotic genotype
- Prior History of stroke or vascular disease
- Atrial fibrillation

GASTROINTESTINAL BLEEDING
- Loss of vWF function
- Angiodysplasia
- Antiplatelet therapy

NEUROLOGICAL EVENTS (STROKE)
- Septic emboli
- Aortic or carotid thrombi
- Vascular fragility with hypertension

PUMP THROMBOSIS
- Surgical implant technique
- Systemic inflammation
- Oxidative stress
- Pump flow changes
- Anticoagulation

THE DYNAMIC EQUATION
An Alteration in Hemocompatibility + A Change in Clinical Management

AN INTERWOVEN CLINICAL CASCADE
- During hemolysis the risk for stroke rises
- Therapy for pump thrombosis impacts stroke rates
- Gastrointestinal bleeding forces anticoagulation changes
- Strokes force a change in anticoagulant therapy and blood pressure
- Blood pressure changes impact the pump flow

Reference: Mehra MR, European Heart Journal 2019
Contemporary MCS Trials

**ROADMAP**¹

- INTERMACS 4-6: early HMII DT vs. medical rx
- LVAD superior in lowering “failure of current rx”
- Bottom line: LVADS in INTERMACS 4 reasonable

**ENDURANCE**²

- Noninferiority DT HeartWare HVAD vs. HMII LVAD
- Phase 1 complete: HVAD/HM2 noninferior, more stroke in HVAD, more pump thrombus in HMII
- Endurance supplement to assess BP lowering effect on stroke

**MOMENTUM-3**³

- Pivotal HM3 vs. HM II
- Innovative trial design, does away with BTT/DT distinction in favor of short vs. long term support endpoints

## 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>55%</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>
<tr>
<td>Adverse Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<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 NEJM 2017
Von Willebrand Factor (VWF)

- Multimeric protein that stabilizes FVIII in circulation
- Responds to shear stress
  - Exposes binding domains and cleavage domains
- High molecular weight multimers (HMWM) of vWF are more active to mediate platelet adhesion and aggregation

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


Momentum 3 Trial: Final Results (n=1028)

**Primary Endpoint:** Survival at 2 years free of disabling stroke (>3 mRS) or reoperation to replace or remove a malfunctioning device

**Principal Hemocompatibility Related Adverse Events (HRAEs) at 2 years**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>HM3 n (%)</th>
<th>HM II n (%)</th>
<th>HM3 EPPY</th>
<th>HM II EPPY</th>
<th>Relative Risk (95% CI)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected pump thrombosis</td>
<td>7 (1.4)</td>
<td>70 (13.9)</td>
<td>0.01</td>
<td>0.12</td>
<td>0.08 (0.04 - 0.16)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any stroke</td>
<td>51 (9.9)</td>
<td>88 (16.4)</td>
<td>0.08</td>
<td>0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>25 (4.8)</td>
<td>43 (8.5)</td>
<td>0.03</td>
<td>0.07</td>
<td>0.42 (0.30 - 0.57)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>30 (5.8)</td>
<td>65 (12.9)</td>
<td>0.04</td>
<td>0.11</td>
<td>0.46 (0.31 - 0.76)</td>
<td>0.004</td>
</tr>
<tr>
<td>Disabling stroke</td>
<td>26 (5.0)</td>
<td>38 (7.5)</td>
<td>0.04</td>
<td>0.07</td>
<td>0.37 (0.24 - 0.56)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>225 (43.7)</td>
<td>278 (55.0)</td>
<td>0.81</td>
<td>0.95</td>
<td>0.54 (0.34 - 0.85)</td>
<td>0.006</td>
</tr>
<tr>
<td>Requiring surgery</td>
<td>50 (9.7)</td>
<td>89 (17.6)</td>
<td>0.08</td>
<td>0.14</td>
<td>0.84 (0.57 - 0.72)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Not requiring surgery</td>
<td>197 (38.3)</td>
<td>251 (49.7)</td>
<td>0.53</td>
<td>0.81</td>
<td>0.54 (0.39 - 0.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>126 (24.5)</td>
<td>156 (30.9)</td>
<td>0.31</td>
<td>0.49</td>
<td>0.84 (0.54 - 0.75)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

HM3 superior to HMII with reduction in *pump thrombosis, strokes of any type and severity, all bleeding including GI bleeding, cardiac arrhythmias and hospital readmissions*
Intended Use: Bridge to Transplant or Lifetime Therapy?

Survival at two years free of disabling stroke (>3 mRS) or reoperation to replace or remove a malfunctioning device

BTT/BTC (n=396)

- HeartMate III: 90.7%
- HeartMate II: 86.1%
- HR: 0.62 (95% CI: 0.40-0.94), P = 0.02 by log-rank test

DT (n=624)

- HeartMate III: 86.4%
- HeartMate II: 82.4%
- HR: 0.61 (95% CI: 0.46-0.81), P = 0.0006 by log-rank test

No. at Risk:
- HeartMate III: 198
- HeartMate II: 198

Mehra, et al. NEJM 2019; DOI: 10.1056/NEJMoa1900486
Health Resource and Economics: MOMENTUM 3
Effects of A Fully Magnetically Levitated Centrifugal-Flow or Axial Flow LVAD on vWF: A Prospective Multicenter Trial

PRINCIPAL FINDINGS
• HM3 pump is associated with significantly greater preservation of vWF HMWM than the HMII pump
• Loss of vWF HMWM represents a biomarker for post-LVAD circulation related bleeding complications

INTRIGUING NOVEL FINDINGS
• Advanced HF patients at baseline exhibit degradation of vWF HMWM, which correlates with severity of heart failure
• Degree of loss of vWF HMWM even at baseline correlates with bleeding tendency post LVAD, suggesting that bleeding tendencies are present at implantation and “compounded” with the LVAD circulation

[vWF HMWM = Von Willebrand Factor, High Molecular Weight Multimers]

Bansal A….Mehra MR. Journal of Heart and Lung Transplantation at www.jhltonline.org (Published simultaneously)
Nasal Mucosal Vascular Alterations, Gastrointestinal Arteriovenous Malformations, and Bleeding With LVADs

Patel S et al. JACC Heart Fail. 2016 Dec;4(12):962-970.
Right Heart Failure

“retained molecular memory” for HF

Infection and LVADs: Not Just the Driveline

- T-cells induced to activation-induced cell death and progressive defects in cellular immunity

- Suppressive T-regulatory cells emerge in a LVAD supported circulation and compromise cellular immunity

- Serious infections occur in over half of all patients supported with contemporary LVADs at 24-months, and only a little over a third of these infections involve the driveline of the pump
Cardio wireless Coplanar Energy Transfer (CET) system

- Implant coil ring placed around lung and fixed to chest wall
- Received power from external power transmission belt
- Battery: more than 6 hrs of freedom
- Investigational device only

Pya Y et al. JHLT (published online Feb 5th 2019)
Physiological directional flow
RECOVERY DEVICES?
Facilitated “R”

Mechanical Stretch

Neurohormones, Cytokines and Growth Factors

Valve Repair
CRT
LVAD

Revascularization
Cell Therapy

Drugs
Immune targets

Coronary Blood
Cardiac Fibroblasts
Vascular Smooth Cells
Fibrillar Collagen
REVERSE REMODELING WITH MCS IS IMPERFECT

- Only 5% of dysregulated genes revert to normal after LVAD support.
- ECM does not revert to normal on its own and can actually exhibit increased myocardial fibrosis.
- Pathological signals of failure persist in the unsupported ventricle.

*Implant vs explant fold expression change of microRNAs*
Phasic coronary blood flow pattern during a continuous flow left ventricular assist support


Mimics LAD Stenosis

Contribution of the Cardiac Apex to Mechanical Efficiency

We DESTROY The Apex with MCS
The RESTAGE Trial
(Non-ischemics, <5 Years HF, <60 years; n=40)

The concept of recovery remains alive…in highly selected patients….

Highly enriched population (young, non-ischemics. Short duration of HF)
37.5% (ITT)
Small numbers, selected centers

How representative is this population?

Birks E. ISHLT 2018
“Bolstered” Facilitation Using Cell Therapy Mesenchymal Stem Cells During LVAD

LVEF on full LVAD support

LVEF after 15 min of LVAD weaning (on min. support)

Pagani F et al. AHA 2018
NHLBI Recovery Working Group 2016

Drakos S and Mehra MR JHLT 2016
However bad life may seem
....where there is life there is hope