Destination LVADs -2013-2014 Advances
A rapidly evolving alternative to heart transplantation

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Columbia University
ACC/AHA Stages:

- A Risk
- B Asx Structural dx
- C Sx ever
- D= IV sx Refractory to Optimal Med Rx

NYHA Symptom Class: Back and forth

NYHA IV

INTERMACS Profiles

INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support

NYHA I II III

D= IV sx Refractory to Optimal Med Rx

e.g. Tx, VAD, Continuous Inotropes only indicated for Stage D
Stage D CHF

Screen for Heart Transplant
Exclude significant co-morbidities

Screen for Destination LVAD

Investigational Drug Trials
Chronic Infusion Therapy
Hospice

Yes
Approved Device
Device Trials

No
List

No
Population Estimate of Potential LVAD/Tx Patients

300 Million US Population

45-50% Preserved Systolic Function 3.0-3.5 M

HF = 2.6% Population or 7 Million Total

50-55% Systolic HF 3.0-3.5 Million

35% Class I
35% Class II
25% Class III (5-10% IIIIB)
2-5% Class IV

Class III B 100-150,000
Class IV 75-150,000

Theoretical Candidates for Mech Circ Support
Class IIIb+IV < 75 yrs
150-250,000 Pts

Figure 2: Current Estimate of the Number of Advanced HF Patients (3)

This represents approximate number of potential VAD candidates.
Adult Heart Transplants
Kaplan-Meier Survival by Era and Transplant Type
(Transplants: January 1982 – June 2012)

All pair-wise comparisons within each era were significant at p < 0.0001.

Median survival (years):
Adult Heart Transplants
Donor and Recipient Age by Transplant Type
(Transplants: January 2006 – June 2013)

Recipient Age:
- 18-39
- 40-59
- 60-69
- 70+

Donor age:
- 0-10
- 11-17
- 18-39
- 40-59
- 60+

% of transplants
2011 U.S. Donor Heart Utilization
Source: OPTN & SRTR Data Report

<table>
<thead>
<tr>
<th>Reason For Un-utilization</th>
<th>Hearts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor Organ Function</td>
<td>1,413</td>
</tr>
<tr>
<td>Donor Medical Hx.</td>
<td>572</td>
</tr>
<tr>
<td>Other</td>
<td>571</td>
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<tr>
<td>No Recipient Located</td>
<td>144</td>
</tr>
<tr>
<td>Organ Refused National</td>
<td>143</td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td>137</td>
</tr>
<tr>
<td>Organ Refused Region</td>
<td>72</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>3,052</strong></td>
</tr>
</tbody>
</table>
Cold Ischemia Limitations

- Ischemic Injury
- No Resuscitative Capabilities
- No Assessment Capabilities
- Time and Distance Limitation
- Limits Utilization of Donor Hearts
Warm Preservation
Transmedics

- Physiologic Preservation
- Resuscitative Capabilities
- Metabolic Assessment
- Expand Time & Distance
- Improve Utilization
OCS Heart Overview
EXPAND Heart Focus On Low & Medium Risk Donor Hearts

**Low Risk**
- Donor Age 40-45
- Long X-Clamp Time
- LVH 12-14 mm
- Down Time <20 min
- Ischemic Time <4 hrs
- IDDM
- EF 40-45%
- Dopamine dose <5

**Medium Risk**
- Donor Age 45-55+
- LVH 14-16 mm
- Downtime >20 min
- Ischemic Time >4 hrs
- Single Vessel CAD
- Dopamine Dose >5
- NE >5

**High Risk**
Adult Heart Transplants

% of Patients Bridged with Mechanical Circulatory Support* (Transplants: January 2000 – December 2012)

% of patients

Year


* LVAD, RVAD, TAH, ECMO
Adult Heart Transplants

% Bridged with MCS by Year and Device Type

Year

- ECMO
- VAD+ECMO
- TAH
- LVAD+RVAD
- RVAD
- LVAD

% of patients

2005 2006 2007 2008 2009 2010 2011 2012
<table>
<thead>
<tr>
<th>Medical Device</th>
<th>2007 N</th>
<th>2007 %</th>
<th>2012 N</th>
<th>2012 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any life support</td>
<td>929</td>
<td>48.6</td>
<td>1276</td>
<td>62.7</td>
</tr>
<tr>
<td>Intravenous inotropes</td>
<td>829</td>
<td>43.4</td>
<td>736</td>
<td>36.2</td>
</tr>
<tr>
<td>Left ventricular assist device</td>
<td>421</td>
<td>22.0</td>
<td>724</td>
<td>35.6</td>
</tr>
<tr>
<td>Intra aortic balloon pump</td>
<td>136</td>
<td>7.1</td>
<td>120</td>
<td>5.9</td>
</tr>
<tr>
<td>Right ventricular assist device</td>
<td>88</td>
<td>4.6</td>
<td>53</td>
<td>2.6</td>
</tr>
<tr>
<td>Ventilator</td>
<td>49</td>
<td>2.6</td>
<td>20</td>
<td>1.0</td>
</tr>
<tr>
<td>Extra corporeal membrane oxygenation</td>
<td>15</td>
<td>0.8</td>
<td>18</td>
<td>0.9</td>
</tr>
<tr>
<td>Inhaled NO</td>
<td>7</td>
<td>0.4</td>
<td>5</td>
<td>0.2</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>1</td>
<td>0.1</td>
<td>1</td>
<td>0.0</td>
</tr>
</tbody>
</table>
REMATCH
Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure

- 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 XVE as destination therapy

CMS Patient Criteria--DT

- Refractory NYHA Class IV Heart Failure
- Life Expectancy <2 years
- Non-candidate for heart transplantation
- LVEF< 25%
- Failed optimal medical management for 60 of previous 90 days
- VO2<12 mL/kg/min or need for inotropes
  - Hypotension, renal dysfunction, pulmonary congestion
- BSA>1.5 m2
- Absence of comorbidities limiting survival
- Dependence on inotropes for 2 weeks

http://www.cms.hhs.gov/
Destination Therapy Trials

Survival Rates in Two Trials of Left Ventricular Assist Devices (LVADs) as Destination Therapy

- Continuous-flow LVAD (2009): P=0.008
- Pulsatile-flow LVAD (2009): P=0.09
- Medical Therapy (2001)

Fang JC NEJM 2009
INTERMACS Hospital Activation and Patient Enrollment
Primary Prospective Implants: June 23, 2006 to June 30, 2014

- **2006**: 97 new patients
- **2007**: 337 new patients
- **2008**: 741 new patients
- **2009**: 1009 new patients
- **2010**: 1651 new patients
- **2011**: 1919 new patients
- **2012**: 2282 new patients
- **2013**: 2660 new patients
- **2014**: 1100 new patients

**Key Events**
- **Protocol Amendment 2.2** (07/2007)
- **Protocol Amendment 2.3** (05/2007)
- **Heartmate II DT approval** (01/2010)
- **Heartmate II BTT approval** (04/2008)
- **Launch Date** (06/2006)

**Graph Details**
- **Activated Hospitals**
- **Patient Accrual**

**Graph Notes**
- The graph shows the number of activated hospitals and patient accrual from June 2006 to June 2014, with key milestones highlighted.

**Sources**
- American College of Cardiology
INTERMACS - Kaplan-Meier Survival for Continuous Flow LVADs (with or without RVAD implant at time of LVAD operation) by Pre-Implant Device Strategy
Primary Prospective Implants: June 23, 2006 to June 30, 2014

Pre-Implant Device Strategy
- Bridge to Transplant (n = 2843, Deaths = 496)
- Bridge to Candidacy (n = 3687, Deaths = 902)
- Destination Therapy (n = 3931, Deaths = 1255)

Shaded areas indicate 70% confidence limits
p (log-rank) = <.0001
Event: Death (censored at transplant or recovery)
Heart Replacement Therapy in Patients > 65 Yrs

- Evaluated all patients undergoing DT LVAD, BTT LVAD, or OHT alone at CPMC between 2005-2012
- Included all patients aged 65-72 years who underwent LVAD or isolated OHT
- Stratified patients according to treatment strategy
  - Group DT: Destination therapy LVAD
  - Group BTT: Bridge to Transplant LVAD
  - Group HTx: isolated heart transplant without mechanical support
- Time zero was on day of implant for patients receiving an LVAD and day of transplant for patients receiving heart transplant
- Primary outcome of interest was 2 year overall survival
Baseline Group Characteristics

<table>
<thead>
<tr>
<th></th>
<th>DT</th>
<th>BTT</th>
<th>HTx</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n</td>
<td>24</td>
<td>43</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>69.7 ± 2.2</td>
<td>67.2 ± 2.1</td>
<td>67.1 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>20 (83.3)</td>
<td>38 (88.4)</td>
<td>46 (97.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>Ischemic etiology, n (%)</td>
<td>21 (87.5)</td>
<td>24 (55.8)</td>
<td>29 (61.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.5 ± 0.5</td>
<td>3.5 ± 0.7</td>
<td>3.47 ± 0.5</td>
<td>0.99</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>19.5 ± 5.2</td>
<td>20.4 ± 4.4</td>
<td>21.9 ± 9.1</td>
<td>0.33</td>
</tr>
<tr>
<td>LVEDD, cm</td>
<td>6.4 ± 0.9</td>
<td>6.8 ± 0.8</td>
<td>6.2 ± 1.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean PAP, mmHg</td>
<td>41.5 ± 7.5</td>
<td>35.5 ± 9.7</td>
<td>30.3 ± 9.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>27.5 ± 7.4</td>
<td>25.3 ± 9.0</td>
<td>20.2 ± 7.2</td>
<td>0.001</td>
</tr>
<tr>
<td>PVR, dyn*s/cm(^5)</td>
<td>445.5 ± 165.5</td>
<td>284.1 ± 136.7</td>
<td>288.3 ± 184.4</td>
<td>0.005</td>
</tr>
<tr>
<td>Inotrope dependence, n (%)</td>
<td>18 (75.0)</td>
<td>41 (95.3)</td>
<td>39 (83.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Pre-op MCS</td>
<td>7 (29.2)</td>
<td>16 (37.2)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
### Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DT</th>
<th>BTT</th>
<th>HTx</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival to discharge, n (%)</td>
<td>21 (87.5)</td>
<td>36 (83.7)</td>
<td>41 (87.2)</td>
<td>0.87</td>
</tr>
<tr>
<td>Reoperation for bleed, n (%)</td>
<td>3 (12.5)</td>
<td>8 (18.6)</td>
<td>11 (23.4)</td>
<td>0.54</td>
</tr>
<tr>
<td>Need for CRRT, n (%)</td>
<td>3 (12.5)</td>
<td>7 (16.3)</td>
<td>7 (14.9)</td>
<td>0.92</td>
</tr>
<tr>
<td>Respiratory failure, n (%)</td>
<td>3 (12.5)</td>
<td>6 (14.0)</td>
<td>8 (17.0)</td>
<td>0.86</td>
</tr>
<tr>
<td>Any infection, n (%)</td>
<td>6 (25.0)</td>
<td>14 (32.6)</td>
<td>12 (25.5)</td>
<td>0.71</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>2 (8.3)</td>
<td>2 (4.7)</td>
<td>2 (4.3)</td>
<td>0.75</td>
</tr>
<tr>
<td>Post-op MCS, n (%)</td>
<td>1 (4.2)</td>
<td>4 (9.3)</td>
<td>4 (8.5)</td>
<td>0.74</td>
</tr>
<tr>
<td>Follow-up time, years</td>
<td>1.7 ± 1.1</td>
<td>2.5 ± 2.0</td>
<td>4.2 ± 2.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
2 Year Survival

log-rank p = 0.47

# at risk

DT: 21 19 13 9
BTT: 35 33 27 20
HTx: 41 40 35 33
Conclusions

• No difference in survival to discharge or 2-year survival between DT, BTT, or HTx groups
• No difference in rates of major complications
• There is a need for a multi-center trial in elderly ESHF patients to determine optimal heart replacement therapy
Long Term Complications

• Infection (driveline, pump)
• CVAs
• Device Thrombosis
• Bleeding Acquired von Willebrand’s disease
• Aortic Insufficiency
• Right Heart Failure
• Line fractures/mechanical failure
Overall Occurrence of Confirmed Pump Thrombosis at 3 Months after HeartMate II Implantation.


Delayed Post operative anticoagulation-no heparin
Lower INR due to aVWD
Frequent GI bleeds
Usually dimers; High Molecular Weight >15
Next Generation VADs
Heartmate III

- Fully Magnetically Levitated
  - Large pump gaps designed to reduce blood trauma
  - Artificial pulse
- Textured blood contacting surfaces
- Wide range of operation
  - Full support (2 – 10 L/min)
- Advanced Design for Surgical Ease
HeartMate III

- HeartMate III secondary flow paths are \( \sim 0.5 \text{ mm} \) along the side, and \( \sim 1.0 \text{ mm} \) pump above and below the rotor.
- HeartMate III pump surfaces are flat and flow is undisturbed, wedging surfaces required for hydrodynamic bearings are not needed.
HeartMate III: Full MagLev Technology

Key Design Benefits: Fluid Dynamics

- The HeartMate III rotor and volute have been designed to minimize shear and avoid stasis over the entire range of operation (2 to 10 L/min).
- The relatively large secondary flow paths facilitate smooth flow transitions, generous washing, and low shear.
- Impressively low hemolysis has been demonstrated in both in vitro and in vivo (plasma-free hemoglobin always <10 mg/dL) studies.

*In development. Not approved for sale.*
HeartMate III: Artificial Pulse

Key Potential Benefits

- **Artificial Pulse**
  - Full Magnetic Bearing permits sharp speed changes and ability to implement an artificial pulse
  - Potential clinical advantages / reduced adverse events\(^1-^4\)
    - Aortic insufficiency
    - Bleeding
    - Thrombosis & stroke

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2. Letsou G, et.al. *Improved left ventricular unloading and circulatory support with synchronized pulsatile left ventricular assistance compared with continuous-flow left ventricular assistance in an acute porcine left ventricular failure model.* J Card Surg 2010;140:1181-8.

*In development. Not approved for sale.*
HM III Clinical Study Protocol

• 5 US centers; 10 patients/center
• 1:1 Randomization between HMII vs HMIII
• No distinction between BTT or DT patients
• Inclusion Criteria
  – Age > 18 yrs; BSA > 1.2 m$^2$
  – NYHA Class IIIIB or 4; LVEF ≤ 25%
  – Inotrope dependent or CI < 2.2 L/min/m$^2$ on OMM or IABP for 7 days
Jarvik 2000 Heart as Destination Therapy

The Jarvik 2000 heart includes:

• the blood pump inside the heart,
• the internal cable (blue arrow),
• the behind-the-ear connector (green arrow),
• the belt worn controller, battery, and external cables.
HeartWare HVAD® System

- Miniaturized implantable blood pump
- Pericardial placement – no pump pocket
- Provides full support
- Centrifugal design, continuous flow
- Hybrid magnetic / hydrodynamic impeller suspension
- Optimizes flow, pump surface washing and hemocompatibility
- Thin, flexible driveline with fatigue resistant cables
Outcomes for HVAD (n=140) by competing outcomes methodology

HVAD patients (Safety Population): N = 140; Each Patient to Day 360

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVAD</td>
<td>140 126 105 87 71 65 58</td>
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</table>
## HVAD and MVAD Comparison

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HVAD</th>
<th>MVAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>160 g</td>
<td>85 g</td>
</tr>
<tr>
<td>Pericardial Volume</td>
<td>50 cc</td>
<td>15 cc</td>
</tr>
<tr>
<td>Priming Volume</td>
<td>15 cc</td>
<td>5 cc</td>
</tr>
<tr>
<td>Inflow Outer Diameter</td>
<td>21mm</td>
<td>21mm</td>
</tr>
<tr>
<td>Base Height</td>
<td>21.6mm</td>
<td>12.7mm</td>
</tr>
<tr>
<td>Base Width</td>
<td>50mm</td>
<td>30mm</td>
</tr>
</tbody>
</table>
MVAD® Pump Overview

- Pericardial placement
- Axial design, continuous flow
- Miniaturized single piece wide-blade impeller
- 10mm “quick connect” outflow graft
- Thin (3.5mm diameter) driveline

MVAD® Pump Impeller Design

In development. Not approved for clinical use.
MVAD® Pump is a next-generation platform designed to enable:

- Support for a wider range of patients
- Left and right ventricular support (LVAD, RVAD)
- Partial and full flow (turn-down capability)
- Less invasive implant technique (e.g. thoracotomy)

Randomized Evaluation of VAD Intervention before Inotropic Therapy (REVIVE-IT)

– 2 yr study in patients w Class III CHF randomized to HMII or medical therapy

– Composite endpoint: survival without disabling stroke +6min walk distance > 75 m over baseline

– Rehab protocol built into protocol

– Pt not a transplant candidate

– Peak VO2 < 14 ml/kg/min

– 6 min walk test < 300 m
Energy Transmission and Power Sources for MCSD to Achieve Total Implantability
Conclusion

- Device technology continues to evolve
- Patient Survival is improving
- Many Device Complications remain
- Future clinical trials will identify those patients who benefit more from device therapy than transplant