Mechanical Circulatory Support for Unstable Heart Failure

Michael A. Acker, MD
William Measey Professor of Surgery
Chief of Cardiovascular Surgery
University of Pennsylvania Health System
After extensive experimental work, the left ventricular bypass pump was employed in a 37 year old woman whose left ventricle was unable to resume adequate function following replacement of aortic and mitral valves.

After ten days of circulatory support her left ventricle recovered enough to resume function and the device was removed. She returned to normal activity for about six years until she was tragically killed in an automobile accident.

Spurred on by this initial success, a variety of devices, such as the intra-aortic balloon, has been created to provide hemodynamic stabilization for gravely ill patients.
TWO-STAGED CARDIAC TRANSPLANTATION

47-YEAR-OLD MALE WITH ADVANCED CORONARY ARTERY OCCLUSIVE DISEASE, LEFT VENTRICULAR ANEURYSM AND COMPLETE HEART BLOCK.

SURGERY PERFORMED APRIL 4, 1969.

RESECTION OF LVA ACCOMPLISHED, BUT PATIENT COULD NOT BE WEANE FROM CARDIOPULMONARY BYPASS.

LIOTTA TAH IMPLANTED FOR CARDIAC SUPPORT.

TAH FUNCTIONED FOR 64 HOURS.

ALLOGRAFT IMPLANTED 64 HOURS AFTER TAH AND PATIENT DIED 32 HOURS LATER OF PSEUDOMONAS PNEUMONIA.
Orthotopic Cardiac Prosthesis for Two-Staged Cardiac Replacement

A. Cooley, M.D., F.A.C.C., Domingo Liotta, M.D., Grady L. Hallman, M.D., Robert D. Bloodwell, M.D., F.A.C.C., Robert D. Leachman, M.D., F.A.C.C. and John D. Milam, M.D.

Houston, Texas

Clinical experience with cardiac transplantation has evidenced the feasibility of cardiac replacement in man but has made apparent the need for a mechanical device that will provide circulation and sustain life in emergency conditions while a suitable allograft is obtained. The cardiac prosthesis used in a 47 year old man consisted of two reciprocating pumps constructed entirely of synthetic materials and activated pneumatically in the orthotopic position by a control console connected by tubes passed through the patient’s chest wall. The device supported the patient’s circulation for 64 hours while a donor for cardiac transplantation was obtained. Death of the recipient from Pseudomonas pneumonia occurred 32 hours after the allografting. The first
Artificial heart gives new purpose to life, Schroeder tells media

LOUISVILLE, Ky. (AP) — A tearful William Schroeder said Sunday night his artificial heart has given him “a real, new purpose in life,” and the device works so well, “I don’t even know it’s there.”

Schroeder, 52, who is beginning his third week with the heart, also wiped tears from his eyes. “I only had 40 days to live. With the new heart, I feel like I have 10 years.”

Schroeder, who remained in satisfactory condition at Humana Hospital Audubon, said he believed his mission would be accomplished if he became healthy again and could help other people.
Artificial heart recipient Schroeder suffers third stroke, now improving

William J. Schroeder, 53, who has lived with an artificial heart longer than anyone else, suffered a third stroke Nov. 10. Three days later (Nov. 13) he was listed in serious condition but improving.

At AMN press time, Schroeder was in a regular room in the Humana Hospital Audubon in Louisville, Ky. A CT scan run Nov. 12 showed no change from a scan taken on Nov. 11, making physicians believe that bleeding on the right side of his brain, in a previously unaffected area, had stopped. There was a possibility that more CT scans would be taken later in the week.

On Nov. 10, Schroeder suffered a stroke in his specially equipped apartment and was taken to the hospital. A CT scan showed some damage on the right side of the brain. The stroke affected his alertness and left-side movements. He was sent back to the apartment and readmitted to the hospital on Nov. 11 when another CT scan was done.

“No prognosis can be made at this time,” said Gary Fox, MD, the neurologist handling Schroeder’s case, at a briefing on Nov. 13.

**DR. FOX** has been seeing Schroeder two or three times per week since last May. Schroeder’s first two strokes — Dec. 13, 1984, and May 5, 1985 — involved the left side of the brain, and left his speech slurred and right-side movement impaired. Subsequently, he was able walk only with assistance.

Since his stroke in May, Schroeder recuperation had been excellent, Dr. said. Dr. Fox said he thought that Schroeder would recover from this stroke equally as well as he did from the last. “Since Nov. 11 he’s made such marked improvement,” he said, adding that Schroeder was “amazing in his recuperative abilities.”

Schroeder received a Jarvik-7 mechanical heart on Nov. 25, 1984. He was leased from the hospital on Aug. 11 to live in a special apartment where he is receiving 24-hour nursing care.
FDA withdraws OK of Jarvik heart device, cites deficiencies

By MALCOLM GLADWELL
Washington Post

WASHINGTON — The Jarvik artificial heart, the medical device that captured the world's attention eight years ago when it was first implanted in a dying Seattle dentist named Barney Clark, has been recalled by the Food and Drug Administration.

An elaborate combination of graphite, polyurethane, Dacron, Velcro and metal, the electrically powered device became a symbol of the technological prowess of American medicine. Since then more than 150 patients received the device, either as a permanent heart replacement or as a temporary measure until a human heart could be found for transplant.

But in a letter this week to the maker of the implant — Symbion Inc. — the FDA withdrew its approval.

The Jarvik heart became a household word in December 1982 when, in one of the most publicized operations in history, it was implanted in Clark's chest by a team of surgeons led by William DeVries.

Clark, who was near death when the seven-hour operation began, lived 112 days on the device. Although short, that period created euphoria among many in the medical community, raising the possibility that a long-term mechanical alternative to the human heart could be found.

The attention vaulted DeVries into international prominence. Soon afterward he was hired by Louisville's Humana Hospital Corporation, which used the glamour of the Jarvik heart and DeVries's surgical skills to bolster its national reputation. DeVries has since left Humana.

But by the end of the decade, much of the euphoria had faded. Three
Indications for VAD Support

• Bridge to transplant
  – Established "Bridge to Decision"
  – Mandatory for any center performing transplantation
• Bridge to recovery
  – Controversial (excluding post-cardiotomy failure, post MI, fulminant acute myocarditis)
• Permanent/destination therapy
  – Represents the future
Short Term VADs

- Biomedicus
- ECMO
- Levotronics
- Impella -2.5/5.0
- Tandem Heart
  - Percutaneous LVAD, RVAD
- Thoratec PVAD
  - Short to long term
- Abiomed
  - BVS
  - AB5000 (short to long term)
  - Impella (percutaneous)

Primary Indications:
- Post - Cardiotomy Shock
- Post HTx Complications
- Post AMI Cardiogenic Shock
- Fulminant Acute Myocarditis

Primary Goal: Bridge to Recovery
Bridge to Decision
Bridge to Bridge
Cardiogenic Shock
BVAD vs LVAD (perc vs open) vs ECMO

- ECMO
  - Neuro status unknown
  - Profound pulmonary failure
  - Recent use of thrombolytics
  - Post cardiotomy—often easiest if lungs/RV questionable
  - Profound Shock

- BVAD
  - Profound shock with MSOF
  - Intractable VT/VF
  - RV infarct
  - Severe RV dysfunction—(high CVP with low PAP)

- LVAD alone if no evidence of MSOF/severe RVF
  - Perc Tandem for acute MI as bridge
  - Impella 5.0 for dilated heart as bridge
PVAD

LVAD/RVAD/BVAD
Short or longterm extracorporeal
Mult cannulations
Mod invasivie
Ambulation/home
CentriMag® Ventricular Assist Technology: First Disposable MagLev VAD

- Controller & Motor
- Blood Pump
Cardiogenic Shock 
(Bridge to Decision)

- Early MCS key-prior to development of MSOF
- Post MI; Fulminant myocarditis
- Is the LV/RV recoverable?
  - Acute MI; Fulminant myocarditis
  - How long is support anticipated?
  - Are adjuvant procedures needed?
    - CAB; repair of valve etc
- Is the pt a potential transplant candidate?
- Intracorporeal vs Extracorporeal?
- Can we get the patient home?
- **Bridge to Bridge**: ECMO:Tandem; Impella
- Acute—pVAD
- Semi elective--intracorporeal
VADS for Cardiogenic Shock
Acute MI

- Change in the treatment paradigm of CS-AMI unresponsive to standard treatment
  - Early LVAD implantation
  - BVADs/ECMO for profound shock; VT;
    - severe RV dysfunction
  - Bridge to Decision
    - Transplant
    - Recovery
    - Destination
- Apical cannulation in CS-AMI is safe and effective
- Percutaneous LVADs RVADs ECMO
  - Tandem Heart acute MI –bridge to bridge
  - Impella 5.0 dilated LV- bridge to bridge
HeartMate II vs HeartMate XVE LVAD

Continuous-flow LVAD (HM II)
- 1/7 size; 1/4 weight
- Quiet
- 40% smaller lead
- One moving part
- Long term

Pulsatile-flow LVAD (HM XVE)
- Large size
- Noisy
- Large percutaneous lead
- Limited durability
**Actuarial Survival vs REMATCH***

- XVE
  - 25% index mortality
  - 45 days index LOS
  - Months for rehab
  - Fails in 15 months!!

- LVAD REMATCH: 23%
- CF LVAD 58%
- PF LVAD 24%
- OMM REMATCH 8%

* N Engl J Med 2001; 345:1435-43
Glass Half Empty: First Generation LVAD Limitations

- By 2 years benefit largely gone
- Large operation with significant Morbidity
  - Infection (30-50%)
  - Stroke
  - Bleeding
- Large footprint requires BSA >1.5; not suitable for many women and children
- Not totally intracorporeal; large percutaneous driveline
- Limited long-term durability (1-3 yrs)
  - Heartmate < Novacor
- Persistent low but significant CVA incidence
  - Novacor > HeartMate
# HeartMate II vs HeartMate XVE LVAD

<table>
<thead>
<tr>
<th>Continuous-flow LVAD (HM II)</th>
<th>Pulsatile-flow LVAD (HM XVE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 1/7 size; 1/4 weight</td>
<td>- Large size</td>
</tr>
<tr>
<td>- Quiet</td>
<td>- Noisy</td>
</tr>
<tr>
<td>- 40% smaller lead</td>
<td>- Large percutaneous lead</td>
</tr>
<tr>
<td>- One moving part</td>
<td>- Limited durability</td>
</tr>
<tr>
<td>- long term</td>
<td></td>
</tr>
</tbody>
</table>
Evolution of Rotary VADs

• **2\(^{nd}\) Generation**
  - Axial flow pump (10,000 rpm)
  - *Mechanical* blood washed bearings

• **3\(^{rd}\) Generation**
  - Centrifugal flow pump (2–3,000 rpm)
  - *Blood film* (generated by spinning rotor) is required to suspend rotor (hydrodynamic bearing), magnetic force for alignment only

• **4\(^{th}\) Generation**
  - Centrifugal flow pump (2–3,000 rpm)
  - *Total magnetic levitation* of rotor (not dependent on contact, blood film, or spinning of the rotor)
Continuous flow pumps

- Afterload sensitive
  - Increased afterload = lower output
  - Lower afterload = higher output
- Preload insensitive
- Flow estimation poor
- Algorithms for automatic adjustment of flow not available
  - Suck down possible
    - rpms adjusted not to maximally unload ventricle
  - Limited adjustment to changes in preload
- If pump fails significant backflow possible
- ?Anticoagulation Needed
Technology Comparison

Rotary Flow
- Valveless
- High reliability

Axial Flow
- Small, quiet
- Flow range: 2-12 L/min
- Linear H-Q relationship
- Hydrodynamic Bearing
- Long life – 5 yrs

Centrifugal
- Small, quiet
- Flow range: 2-12 L/min
- Flat H-Q curve-esp sensitive to pressure changes-with exercise and no change in pressure will pump more vol and have greater pulsatility
- Non-wearing impeller
- Very long life – 10yrs
HeartMate II Initial Results (n=133)

Use of a Continuous-Flow Device in Patients Awaiting Heart Transplantation

Leslie W. Miller, M.D., Francis D. Pagani, M.D., Ph.D., Stuart D. Russell, M.D., Ranjit John, M.D., Andrew J. Boyle, M.D., Keith D. Aaronson, M.D., John V. Conte, M.D., Yoshifumi Naka, M.D., Donna Mancini, M.D., Reynolds M. Delgado, M.D., Thomas E. MacGillivray, M.D., David J. Farrar, Ph.D., and O.H. Frazier, M.D., for the HeartMate II Clinical Investigators*

Increasing Survival with HM II in BTT

Randall C. Starling, J. Am Coll Cardiol. May 2011
Primary Endpoint
HeartMate II Destination Clinical Trial

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%) Favors CF LVAD
- 7/66 (11%) Favors PF LVAD

Hazard Ratios [95% CI]

- Components:
  - Reoperation to Replace Device: 13 (10%) vs 24 (36%), P<0.001
  - Death < 2 years: 44 (33%) vs 27 (41%), P=0.048
  - Disabling Stroke: 15 (11%) vs 8 (12%), P=0.56

Favors CF LVAD
Favors PF LVAD
Actuarial Survival vs REMATCH*
HeartMate II Destination Therapy Trial

Percent Survival

Months

0  6  12  18  24

LVAD
68%
58%
55%

MEDICAL THERAPY
24%
25%

CF LVAD**
OMM REMATCH
23%
25%
52%
58%
8%

• N Engl J Med 2001; 345:1435-43
• N Engl J Med 2009; 361:2241-2251
## Adverse Events
### HeartMate II Destination Therapy Trial

<table>
<thead>
<tr>
<th>Event</th>
<th>CF LVAD (n=133) [211 pt-years]</th>
<th>PF LVAD (n=59) [41 pt-years]</th>
<th>Risk Ratio [95% Confidence Interval]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pump Replacements</td>
<td>0.06</td>
<td>0.51</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.13</td>
<td>0.22</td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>Ischemic</td>
<td>0.06</td>
<td>0.10</td>
<td></td>
<td>0.38</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>0.07</td>
<td>0.12</td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>Device-related infection</td>
<td>0.48</td>
<td>0.90</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Local non-device infection</td>
<td>0.76</td>
<td>1.33</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0.39</td>
<td>1.11</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding requiring PRBC</td>
<td>1.66</td>
<td>2.45</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Bleeding requiring surgery</td>
<td>0.24</td>
<td>0.29</td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>Other Neurological</td>
<td>0.17</td>
<td>0.29</td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>Right Heart Failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extended Inotropes</td>
<td>0.14</td>
<td>0.46</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVAD</td>
<td>0.02</td>
<td>0.07</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Cardiac Arrhythmias</td>
<td>0.69</td>
<td>1.31</td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>Respiratory Failure</td>
<td>0.31</td>
<td>0.80</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>0.10</td>
<td>0.34</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatic Dysfunction</td>
<td>0.01</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device Thrombosis</td>
<td>0.02</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-hospitalizations</td>
<td>2.64</td>
<td>4.25</td>
<td></td>
<td>0.02</td>
</tr>
</tbody>
</table>

Favors CF LVAD     Favors PF LVAD
HeartMate II Clinical Trial
Reduction in Adverse Events

- Nearly 90% reduction in percutaneous lead infection; no pocket infections
- Nearly 40% reduction in bleeding requiring surgery
- More than 50% reduction in stroke
- Nearly 60% reduction in non-stroke neurological event
- No failures of electromechanical pump mechanism
Long-term mechanical circulatory support (destination therapy): On track to compete with heart transplantation? *J Thorac Cardiovasc Surg* 2012;144:584-603
Long-term mechanical circulatory support (destination therapy): On track to compete with heart transplantation? *J Thorac Cardiovasc Surg* 2012;144:584-603
Stable Survival with HM II in DT

Average Support Duration

- Early Trial = 2.1 ± 1.8 years (Longest: 6 years)
- Mid Trial = 1.8 ± 1.2 years (Longest: 4 years)

Survival (%)

- Mid-Trial (N=281): 73 ± 3%
- Early Trial (N=133): 68 ± 4%
- At Risk:
  - 281
  - 215
  - 187
  - 165
  - 146

P (Log-Rank) = 0.209

Time (Months)
LVAD* Destination Therapy, n=1287 (June 2006-Dec 2011)

Event: Death (censored at Transplant and Explant due to Recovery)

Pulsatile Flow: n=127, deaths=66
Continuous Flow: n=1160, deaths=248

<table>
<thead>
<tr>
<th>Months Post implant</th>
<th>% Survival</th>
<th>Pulsatile</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>74%</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>68%</td>
<td>76%</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>45%</td>
<td>67%</td>
<td></td>
</tr>
</tbody>
</table>

P < 0.0001

Survival in Destination Therapy: Data from James Kirklin, J. Thorac Cardiovasc Surg May 2012
Survival Without Device Exchange or Malfunction:

LVAD* Destination Therapy, n=1287 (June 2006-Dec 2011)

<table>
<thead>
<tr>
<th>Months Post Implant</th>
<th>% Freedom from Device Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CFP</td>
</tr>
<tr>
<td>6</td>
<td>99%</td>
</tr>
<tr>
<td>12</td>
<td>96%</td>
</tr>
<tr>
<td>24</td>
<td>94%</td>
</tr>
</tbody>
</table>

Death/Months (Hazard)

Pulsatile Flow Pumps
N=127, device events=25

Continuous Flow Pumps
N=1160, device events=33

Survival Without Device Exchange or Malfunction:
LVAD* Destination Therapy, n=1287 (June 2006-Dec 2011)

*LVAD: Left Ventricular Assist Device

James Kirklin, J. Thorac Cardiovasc Surg May 2012
Clinically Proven Bearing Technology

• > 10,000 HeartMate II implanted since 2004 with no bearing failures or wear-out

• Clinical durability experience:
  – Support ≥ 1 year: 2110
  – Support ≥ 2 years: 728
  – Support ≥ 3 years: 243
  – Support ≥ 4 years: 62
  – Support ≥ 5 years: 17
  – Support ≥ 6 years: 1

• Estimated Bearing life:
  – >17 years w/3x safety margin

4 year implant bearings
Blood Pump Technology

Blood Pumps

Pulsatile
- Thoratec PVAD
- HeartMate XVE
- WorldHeart, Novacor
- Arrow LionHeart
- Thoratec IVAD
- AbioMed, AB5000
- Berlin Heart EXCOR
- Medos HIA
- WorldHeart, HeartSaver

Rotary
- MicroMed DeBakey*
- Berlin Heart INCOR
- Jarvik 2000
- HeartMate II
- Circulite
- Impella

Centrifugal
- VentraCor, VentrAssist
- HeartMate III
- Terumo, DuraHeart
- HeartWare
- WorldHeart/Levacor
- Arrow, CorAide
- Levotronics
- Levotronics
- Tandem Heart

TAH
- Abiomed, AbioCor
- CardioWest

White font = FDA/CE
Orange font = CE Mark(* US clinical trial)
Black font = in clinical trials
Yellow font = R or D phase
Red font - No longer available
Survival with HVAD in BTT

HVAD ADVANCE BTT Trial

% Survival

<table>
<thead>
<tr>
<th>Days Post Implant</th>
<th>% Survival HVAD</th>
<th>% Survival Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>99%</td>
<td>97%</td>
</tr>
<tr>
<td>60</td>
<td>96%</td>
<td>95%</td>
</tr>
<tr>
<td>180</td>
<td>94%</td>
<td>90%</td>
</tr>
<tr>
<td>360</td>
<td>86%</td>
<td>85%</td>
</tr>
</tbody>
</table>

Event: Death (censored at transplant or recovery)

Days Post Implant

Group | Patients at Risk |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>499 439 370 304 260 217 186</td>
</tr>
<tr>
<td>HVAD</td>
<td>140 128 108 92 76 71 63</td>
</tr>
</tbody>
</table>

Pericardial Placement Advances Therapy

CAUTION: Investigational device. Limited by United States law to investigational use.
Pericardial Placement – a Key Advantage

- No abdominal surgery
- No pump pocket
- 3 step implant technique
- Low blood loss
- Potential for short CPB time

CAUTION: Investigational device. Limited by United States law to investigational use.
LVADs for BTT/DT

- Continuous flow devices—smaller; safer; less complications; less morbid; longer freedom for device failure; increase QOL
  - HMII approved for DT and BT
  - 30-40% of tx pts BTT
  - Heartware approved for BTT
- DT trial underway
  - Jarvik/DuraHeart/EvaHeart//Circulite- clinical trial
MCS for Destination Therapy
CMS Patient Selection Criteria
(REMATCH Criteria)

Not a Tx candidate

Class IV Heart Failure on maximal medical therapy > 60/90 days;

EF < 25%

Peak VO2<12
Contraindications for DT

- Expected non cardiac survival < 2 yrs
- Debilitating stroke
- Irreversible end organ failure
- Severe COPD
- Cardiac cachexia
Other considerations for DT

- Psychiatric disorders
- Drug abuse
- Lack of sound social support that affects ability to care for LVAD at home
VAD Patient Selection: Targeting a Viable Population for DT
The Right Time for LVAD Implantation

“Perfect Window”

Operative Risk

Clinical severity
- heart failure

Too early

Right heart failure
- End-organ dysfunction
- Worsening nutrition

Too late
# Destination Therapy Risk Score

**For In-Hospital Death**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLT ≤ 148 × 10³/µL</td>
<td>7</td>
</tr>
<tr>
<td>Albumin ≤ 3.3 g/dL</td>
<td>5</td>
</tr>
<tr>
<td>INR &gt; 1.1</td>
<td>4</td>
</tr>
<tr>
<td>Vasodilator therapy</td>
<td>4</td>
</tr>
<tr>
<td>MPAP ≤ 25 mmHg</td>
<td>3</td>
</tr>
<tr>
<td>AST &gt; 45 U/mL</td>
<td>2</td>
</tr>
<tr>
<td>HCT ≤ 34 %</td>
<td>2</td>
</tr>
<tr>
<td>BUN &gt; 51 U/dL</td>
<td>2</td>
</tr>
<tr>
<td>No intravenous inotropes</td>
<td>2</td>
</tr>
</tbody>
</table>

Risk Score =
DT Risk Score – HMII Survival

Destination Therapy: Survival Stratified By Risk Category

<table>
<thead>
<tr>
<th>DT Risk Category</th>
<th>90D In-Hospital Mortality</th>
<th>1 Year Survival</th>
<th>Hazard Ratio vs. Low Risk (95% C.I.)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (n=262)</td>
<td>9%</td>
<td>77 ± 3%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Medium (n=297)</td>
<td>12%</td>
<td>69 ± 3%</td>
<td>1.24 (0.94 - 1.64)</td>
<td>0.127</td>
</tr>
<tr>
<td>High (n=79)</td>
<td>19%</td>
<td>62 ± 6%</td>
<td>1.72 (1.19 - 2.49)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

P (log rank) = 0.016
<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Critical cardiogenic shock</td>
</tr>
<tr>
<td>2</td>
<td>Progressive decline</td>
</tr>
<tr>
<td>3</td>
<td>Stable but inotrope dependent</td>
</tr>
<tr>
<td>4</td>
<td>“recurrent” decompensation</td>
</tr>
<tr>
<td>5</td>
<td>comfortable at rest but are exercise intolerant for most activity</td>
</tr>
<tr>
<td>6</td>
<td>able to do some mild activity, but fatigue results within minutes with meaningful physical exertion.</td>
</tr>
<tr>
<td>7</td>
<td>NYHA Class IIIB</td>
</tr>
</tbody>
</table>
### Change in DT Patient Profile Over Time

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Critical cardiogenic shock</td>
<td>29 (18.6)</td>
<td>110 (9.7)</td>
</tr>
<tr>
<td>2. Progressive decline</td>
<td>64 (41.0)</td>
<td>422 (37.3)</td>
</tr>
<tr>
<td>3. Stable but inotrope-dependent</td>
<td>36 (23.1)</td>
<td>346 (30.6)</td>
</tr>
<tr>
<td>4. Recurrent advanced HF</td>
<td>20 (12.8)</td>
<td>177 (15.6)</td>
</tr>
<tr>
<td>5. Exertion intolerant</td>
<td>2 (1.3)</td>
<td>43 (3.8)</td>
</tr>
<tr>
<td>6. Exertion limited</td>
<td>3 (1.9)</td>
<td>21 (1.9)</td>
</tr>
<tr>
<td>7. Advanced NYHA class III</td>
<td>2 (1.3)</td>
<td>12 (1.1)</td>
</tr>
</tbody>
</table>


Long-term mechanical circulatory support (destination therapy): On track to compete with heart transplantation? *J Thorac Cardiovasc Surg* 2012;144:584-603
Survival to D/C Based on INTERMACS

Group 1: INTERMACS 1: crash and burn
Group 2: INTERMACS 2 and 3: hospitalized and inotrope-dependent
Group 3: INTERMACS 4 – 7: poor functional capacity

Group 3 vs Group 1: p = 0.02
Group 3 vs Group 2: p = 0.59
Group 2 vs Group 1: p < 0.009
Lengths of Stay Based on INTERMACS

Group 1: INTERMACS 1: crash and burn
Group 2: INTERMACS 2 and 3: hospitalized and inotrope-dependent
Group 3: INTERMACS 4 – 7: poor functional capacity

Group 3 vs Group 1: p < 0.001
Group 3 vs Group 2: p < 0.001
Group 2 vs Group 1: p = 0.62
Actuarial Survival on MCS

Survival (%)

0 20 40 60 80 100

Group 3 vs 1: p = 0.011
Group 3 vs 2: p = 0.065
Group 2 vs 1: p = 0.18

Months post-LVAD

Group 1 Group 2 Group 3

Boyle A, et al. JHLT 2011; accepted for publication.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Early hazard</th>
<th></th>
<th>Constant hazard</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>P value</td>
<td></td>
<td>HR</td>
</tr>
<tr>
<td>Age (older)</td>
<td></td>
<td></td>
<td></td>
<td>1.24*</td>
</tr>
<tr>
<td>BMI (higher)</td>
<td></td>
<td></td>
<td></td>
<td>1.04†</td>
</tr>
<tr>
<td>History of cancer</td>
<td>1.89</td>
<td>.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of cardiac surgery</td>
<td>1.69</td>
<td>.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>3.14</td>
<td>.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN</td>
<td></td>
<td></td>
<td></td>
<td>1.08‡</td>
</tr>
<tr>
<td>INTERMACS level 1</td>
<td>4.58</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INTERMACS level 2</td>
<td>2.35</td>
<td>.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of pulsatile LVAD</td>
<td></td>
<td></td>
<td></td>
<td>2.63</td>
</tr>
<tr>
<td>RVAD in same operation</td>
<td></td>
<td></td>
<td></td>
<td>3.22</td>
</tr>
</tbody>
</table>

*INTERMACS, Interagency Registry for Mechanical Circulatory Support; HR, hazard ratio; BMI, body mass index; BUN, blood urea nitrogen; LVAD, left ventricular assist device; RVAD, right ventricular assist device. *The hazard ratio denotes the increased risk from 60 to 70 years. †The hazard ratio denotes the increased risk of a 5-unit increase in body mass index. ‡The hazard ratio denotes the increased risk of a 10-unit increase in blood urea nitrogen.
LVAD* Destination Therapy, n=1287

Event: Death (censored at Transplant and Explant due to Recovery)

<table>
<thead>
<tr>
<th>Months Post Implant</th>
<th>% Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>83%</td>
</tr>
<tr>
<td>12</td>
<td>75%</td>
</tr>
<tr>
<td>24</td>
<td>62%</td>
</tr>
</tbody>
</table>

Levels:
- Level 1: n=112, deaths=32
- Level 2: n=435, deaths=106
- Level 3-7: n=613, deaths=110

P = 0.001

James Kirklin, J. Thorac Cardiovasc Surg May 2012
Current Outcome in DT—6MW and QOL

6MWD

EarlyTrial (N=133)
Mid Trial (N=281)

Distance (meters)

P < 0.001 over time
P = 0.907 between groups
P = 0.044 interaction

NYHA Class I or II

Early Trial
Mid Trial

Baseline 6 Mo 12 Mo 18 mo 24 mo

0 0 80% 82% 77% 77% 76% 85% 78% 81%

Pts Tested: 125 267 85 191 73 161 58 130 59 103

KCCQ

Mid Trial (N=281)
EarlyTrial (N=133)

Overall Summary Score

P < 0.001 over time
P = 0.080 between groups
P = 0.308 interaction

Pts Tested

115 89 86 76 62 56
245 201 187 161 133 114

0 1 3 6 12 18 24

Months

MLWHF

EarlyTrial (N=133)
Mid Trial (N=281)

Total Score

P < 0.001 over time
P = 0.043 between groups
P = 0.416 interaction

Pts Tested

116 89 86 75 62 53
250 195 184 155 126 108

0 1 3 6 12 18 24

Months

Park S J et al. Circ Heart Fail 2012;5:241-248
## Current Outcome in DT—Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Early Trial (n=133; 211 Patient-Years)</th>
<th>Mid Trial (n=281; 498.0 Patient-Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients n (%)</td>
<td>Events n (Event Rate)</td>
</tr>
<tr>
<td>Bleeding (PRBC)</td>
<td>108 (81)</td>
<td>349 (1.66)</td>
</tr>
<tr>
<td>Bleeding (reexploration)</td>
<td>40 (30)</td>
<td>49 (0.23)</td>
</tr>
<tr>
<td>Non–Device related Infx</td>
<td>65 (49)</td>
<td>160 (0.76)</td>
</tr>
<tr>
<td>Device-related Infection</td>
<td>47 (35)</td>
<td>100 (0.47)</td>
</tr>
<tr>
<td>Right heart failure*</td>
<td>31 (23)</td>
<td>34 (0.16)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>11 (8)</td>
<td>12 (0.06)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>15 (11)</td>
<td>15 (0.07)</td>
</tr>
</tbody>
</table>

Adapted from Park S J et al. Circ Heart Fail 2012;5:241-248
ROADMAP

- Thoratec sponsored study with HeartMate II
- Broaden patient selection strategies in underserved but approved populations
- Non-randomized, multicenter observational study of VAD vs medical therapy in ambulatory patients meeting FDA approved indications for use
  - Target population: Ambulatory Class IV without inotropes (Intermacs 4-6)
  - Risk stratification
  - End-points: Mortality, functionality, QoL, cross-over, patient preference, economics
Survival of INTERMACS Profile 4-6 Patients after Left Ventricular Assist Device Implant Is Improved Compared to Seattle Heart Failure Model Estimated Survival

Hazard Ratio at 2 years

HR = 0.38, p = 0.0001
NIH REVIVE-IT Trial (REMATCH II)

PILOT trial of only 100 patients

Class IIIB (Intermacs 4-7)

Randomized 1:1 between OMM vs HeartMate II LVAD

2 yr single primary end point: Survival

Multiple secondary end points

Also include functional capacity, QOL, Cost

Needed to validate mortality estimates for OMM

Trial designed to validate risk in OMM
Risk Factors for Mortality with HF (Class IIIB)

>3 Prompt Referral for Advanced Rx

Hospitalization for HF on oral HF therapy

Na+ < 136

BUN > 45, Creat > 2.5, CrCl < 45 cc/min

BNP > 4 x’s upper limit of normal

Diuretic Dose > 2.0 mg/kg/day

Inability to take ACEI/ARB/BB

LVEDD > 7.0

VO2 < 55% predicted
Median Survival Decreases Progressively after Each Hospitalization

Impact of Chronic Kidney Disease (CKD)

1st hospitalization (n=14,374)
2nd hospitalization (n=3,358)
3rd hospitalization (n=1,123)
4th hospitalization (n=417)

Average age of HF hosp
In community = 74-77 years

Setoguchi et al. AHJ 2007
Is This Acceptable Risk: Where Lies the Equipoise?

Park SJ. AHA Scientific Sessions, November 2010.

Soon J. Park, *Circ Heart Fail*. March 2012
Small Continuous Flow Pumps: Unanswered Questions

• Not pre-load sensitive; afterload sensitive
  • Suck down potential—ventricular arrhythmias
  • LV not fully unloaded
  • RV dysfunction with septal shift
• Automatic control systems unavailable or untested; limit flow in fixed mode
  • Need for frequent echos (additional expense and time)
• ? Anticoagulation
  • Pump thrombosis
• ? Long term affects of decreased pulse on medium size arterioles
  • GI Bleeding-AVMs
  • Hemorrhagic Strokes
• ? Long term AI

• Will Regulatory and Financial Realities allow Field to Reach its Potential
George Weisenthaler: “The reason LVAD results are not better is that the cardiologist is only referring pts after one foot is in the grave”

Donna Mancini: “When LVAD results improve then less sick pts will be referred”
60 y.o w/ LVAD and eventual transplant – walked his daughter down the aisle while on the pump. And then attended MaryLou O’Hara’s wedding as well!
VADs at Hospital of University of Pennsylvania

Treatment of End-Stage Heart Failure
CY 2005-2012

50 DT VADS Projected for 2013
Therapeutic Strategy

Strategic Map of Heart Failure Treatment

- **DRUGS**
- **REPAIR**
- **DEVICES**

### Class I (1.7M)
- Medical Treatment

### Class II (1.6M)
- Surgical Repair

### Class III (1.4M)
- AUGMENTATION
  - CRT; girdling devices
- ASSIST (Partial support)

### Class IV (0.36M)
- REPLACEMENT (Full support)
  - Rotary VADs
  - Pulsatile VADs
  - TAH

- **NYHA Class III**
  - 25% of HF Patients
  - Frequent hospitalizations
  - Worsening symptoms despite drug therapy
  - Significant opportunity for new therapies