Heart Failure: Scope of the Problem

“Final common pathway” of most heart disease

Prevalence: 5 million patients in USA
15 million patients (51 countries, ESC)

Incidence: 550,000 new cases diagnosed/yr USA
4% population - Europe

Office visits: 12 - 15 MM/yr
Hospitalizations: 6.5 MM days/yr, 20% world
Mortality rate: 75% male, 62% female @ 5yrs
(Framingham)

NYHA Class IV 75% mortality at 2yrs.

Hospitalization: The Predominant Contributor to Heart Failure Costs

60.6% Inpatient care
$23.1 billion

38.6% Outpatient care
$14.7 billion
(3.4 visits/year/patient)

0.7% Transplants
$270 million

Total = $38.1 billion
(5.4% of total healthcare costs)

Epidemiology of Heart Failure

Heart Failure:
Final Common Pathway of All Forms of Heart Disease

- More deaths from heart failure than from all forms of cancer combined
- 4.7 million symptomatic patients; estimated 10 million in 2037
- Incidence: About 550,000 new cases per year
- Prevalence is 1% between the ages of 50 and 59 years; progressively increasing to >10% over age 80

Heart Failure

A clinical syndrome characterized by easy fatigability, decreased exercise capacity, shortness of breath or “breathlessness,” possibly accompanied by peripheral edema and increased urinary frequency

Forward failure vs. Backward failure
Left sided failure vs. Right sided failure
Systolic failure vs. Diastolic failure
Chronic Failure vs. Acute failure

Systolic Heart Failure

**Forward and Backward Problem**

- LV failure
  - Hypotension (BP < 90mmHg), Shock, CI < 2.0
  - Organ Hypoperfusion
  - Reduced Coronary Perfusion Pressure (MAP - PCW)
  - Refractory Pulmonary Edema
- RV Failure
  - Inadequate L sided filling
  - Persistently elevated CVP

Liver
RV → Lungs
LV → Kidney
Diastolic Heart Failure

Largely Backward Problem

LV failure
- Decreased LV Relaxation
- Increased stiffness
- Reduced Unstwist/suction
- Reduced filling.

RV Failure
- ? Above
- Persistently elevated CVP

Increased Pressure!!

Liver
RV
Lungs
LV
Kidney

Heart Failure Continuum

Diastolic Heart Failure
DHF

Systolic Heart Failure

Classification of HF: Comparison Between ACC/AHA HF Stage and NYHA Functional Class

<table>
<thead>
<tr>
<th>ACC/AHA HF Stage</th>
<th>NYHA Functional Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>A At high risk for heart failure but without structural heart disease or symptoms of heart failure (eg, patients with hypertension or coronary artery disease)</td>
<td>None</td>
</tr>
<tr>
<td>B Structural heart disease but without symptoms of heart failure</td>
<td>I Asymptomatic</td>
</tr>
<tr>
<td>C Structural heart disease with prior or current symptoms of heart failure</td>
<td>II Symptomatic with moderate exertion</td>
</tr>
<tr>
<td>D Refractory heart failure requiring specialized interventions</td>
<td>IV Symptomatic with rest</td>
</tr>
</tbody>
</table>

Congestive Heart Failure (CHF): Therapeutic Options

Mild to Moderate CHF (NYHA Class I, II)
- Drug Therapy:
  - ACE inhibitors, AR blockers
  - Diuretics, Spironolactone
  - Digitalis, Nitrates
  - Beta Blockers

Severe and End Stage (NYHA Class III, IV)
- BiV Pacing, ICD
- Drugs + IV inotropes
- Cardiac transplantation
- Devices - IABP, VADs, TAH
Advanced/End-Stage CHF: Patient groups

- Advanced ischemic cardiomyopathy
- Advanced dilated cardiomyopathy
- Cardiogenic shock
  - Chronic CHF with critical low output
  - Post-MI
  - Postcardiotomy

- Chronic CHF - IV inotrope dependent
- Chronic CHF, Class IV po Tx, low Na, hi BUN/Cr
- CHF with refractory Ventricular arrhythmias
- Post-transplant graft dysfunction

**Accelerated Mortality: Advanced CHF**

NYHA Class IV 75% mortality at 2yrs.

**PROFILE-LEVEL # Pts**

<table>
<thead>
<tr>
<th>LEVEL</th>
<th>Year</th>
<th>Official Shorthand</th>
<th>General time frame for support</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERMACS LEVEL 1</td>
<td>82</td>
<td>&quot;Crash and burn&quot;</td>
<td>Hours</td>
</tr>
<tr>
<td>INTERMACS LEVEL 2</td>
<td>81</td>
<td>&quot;Sliding fast&quot;</td>
<td>Days to week</td>
</tr>
<tr>
<td>INTERMACS LEVEL 3</td>
<td>18</td>
<td>&quot;Stable but Dependent&quot;</td>
<td>Weeks</td>
</tr>
<tr>
<td>INTERMACS LEVEL 4</td>
<td>9</td>
<td>&quot;Frequent flyer&quot;</td>
<td>Weeks to few months, if baseline restored</td>
</tr>
<tr>
<td>INTERMACS LEVEL 5</td>
<td>4</td>
<td>&quot;Housebound&quot;</td>
<td>Weeks to months</td>
</tr>
<tr>
<td>INTERMACS LEVEL 6</td>
<td>3</td>
<td>&quot;Walking wounded&quot;</td>
<td>Months, if nutrition and activity maintained</td>
</tr>
<tr>
<td>INTERMACS LEVEL 7</td>
<td>4</td>
<td>Advanced Class III</td>
<td></td>
</tr>
</tbody>
</table>

**Heart Transplantation**

- 125 US centers (75 in the rest of the world)
- 2500 heart transplants performed in the US/yr
- 1500 in the rest of the world
- 1 year survival rate approaching 85%, 5 year 70%
- 8000 pts/yr listed

A chronic shortage of donors exists/ timing issue

Many transplant-eligible patients die waiting on the UNOS transplant list
UNOS Waiting List:
Deaths/Patient Year

2007  14.7%

1000 - 1200 patients/yr

The Total Artificial Heart: Pumping Our Way Into the Future - Marvin J. Slepian, M.D.
End-Stage CHF: Mechanical Therapies

- Intra-aortic balloon pumps
- ECMO (Extracorporeal Membrane Oxygenation)
- Ventricular assist devices
  - LVAD - surgical, percutaneous
  - BiVAD
- Ventricular replacement devices
- Total Artificial Heart

Ventricular Support: Concepts

LVAD Supports the left ventricle only.
TAH Replaces both ventricles.

HeartMate II
Blood-Immersed Bearings

SynCardia™
Total Artificial Heart System

- Implantable
- Full Cardiac Replacement
- Full Normalization of Hemodynamics
- CE Approved - Europe
- FDA approved - USA
Cardiac Surgery: Advanced Heart Disease
Early 1960’s

Advanced Heart Disease → Cardiac Replacement → Artificial Heart (TAH) → Cardiac Transplantation

Advanced Heart Disease: Replacement Tx

2 Camps
- Cardiac Transplantation
  - Barnard
  - Kantrowitz
  - Shumway
- Bioprosthetic Artificial Organ (TAH)
  - DeBakey
  - Cooley

Heart Transplantation

First Heart Transplant - December 3, 1967 (18d survival)
Groote Schuur Hospital, Cape Town, South Africa
2nd Heart TX, Philip Blaiberg (563 d survival)

Dr Christian Barnard Louis Washkansky (55)

December 15, 1967
Cardiac Transplantation: 1970

170 Transplants - multiple medical centers
146 Deaths
17% survival rate

September 17, 1971
Willem Kollf MD PhD
Univ of Groningen (Holland)
Cleveland Clinic
Univ of Utah
February 11, 2009
Philadelphia
Age 97

1969 Domingo Liotta
47 yo M, failed post-MI ventriculoplasty
3d support
Am J Cardiol 24:723, 1969

Theft, unethical, betrayal
“childish act”
December 2, 1982:
Barney Clark, a 61-year-old retired dentist, becomes the first person to receive a permanent artificial heart. In an operation at the University of Utah Medical Center in Salt Lake City, doctors replace Clark's dying heart with an artificial heart made of plastic named the Jarvik-7 after its creator, Dr. Robert Jarvik. The artificial heart is slightly larger than a human heart, but weighs about half the same. It is connected by hoses to its power supply - a 375-pound external air compressor carried in a large cart.
**Phoenix Heart: Thomas Creighton**

March 3, 1985

33 yo Auto mechanic
MI x 2
Tx - failed acutely
CPR
CPB 7h 41min
Called for TAH
Phoenix implanted
11h
2nd HTX
Shock Lung

---

**Phoenix Heart: March 1985**

Outlet Conduits

To PA
To AO

Inlet Valves

Left Ventricle

Right Ventricle

Air Inflow Port

---

**Trends in Heart Transplants**

UNOS: 1970–2005

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td>'70</td>
<td>10</td>
</tr>
<tr>
<td>'75</td>
<td>27</td>
</tr>
<tr>
<td>'80</td>
<td>57</td>
</tr>
<tr>
<td>'85</td>
<td>719</td>
</tr>
<tr>
<td>'90</td>
<td>2,107</td>
</tr>
<tr>
<td>'95</td>
<td>2,363</td>
</tr>
<tr>
<td>'00</td>
<td>2,199</td>
</tr>
<tr>
<td>'05</td>
<td>2,125</td>
</tr>
</tbody>
</table>

*Source: United Network for Organ Sharing (UNOS), scientific registry data.*
After the Phoenix Heart

Utah (Jarvik) 7-70 TAH

First Successful Bridge to Transplantation With TAH (SYMBION Jarvik 7)

1985
MICHEAL DRUMMOND
9 DAYS

August 29, 1985
Mark Levinson, Jack Copeland, Michael Drummond, Richard Smith, August, 1985 (Time Magazine)

First Bridge to Transplantation in the World: 1985 (going home)

All national television networks present at University Medical Center, Tucson, Arizona
**1987 FDA Shut-Down of Symbion**

Jarvik - CEO  
Credibility gap with the FDA (submissions, conduct)  
“Lack of planning and control”  
“many false starts”  
“lack of management depth”  
“lack of focus”  
“poor documentation”  

“Lack of planning and control”  
“many false starts”  
“lack of management depth”  
“lack of focus”  
“poor documentation”

---

**End-Stage CHF: Cardiac Replacement**

<table>
<thead>
<tr>
<th>TX</th>
<th>Initial Human Experience</th>
<th>Moratorium Stanford/MCV</th>
<th>Immunospression Cyclosporin</th>
<th>1st Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>POP Human 1 Cooley '69</td>
<td>POP Human 1 Cooley '81</td>
<td>Initial Destination Tx TAH (Devries)</td>
<td>1st Successful BTT TAH '85 (Copeland)</td>
<td>1st Tx BTT BIVF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>POP</td>
<td>POP</td>
<td>Initial</td>
<td>Successful</td>
<td>1st</td>
<td>Tx</td>
</tr>
<tr>
<td>TAH</td>
<td>Human 1</td>
<td>Destination</td>
<td>BTT</td>
<td>Tx</td>
<td>BTT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1959</td>
<td>Akutusu TAH</td>
</tr>
<tr>
<td>1960</td>
<td>Initial Human Experience</td>
</tr>
<tr>
<td>1970</td>
<td>POP Human 1 Cooley '69</td>
</tr>
<tr>
<td>1979</td>
<td>Jarvik TAH</td>
</tr>
<tr>
<td>1980</td>
<td>Initial Destination Tx TAH (Devries)</td>
</tr>
<tr>
<td>1990</td>
<td>Successful BTT TAH '85 (Copeland)</td>
</tr>
<tr>
<td>1993</td>
<td>1st Tx BTT BIVF</td>
</tr>
<tr>
<td>1999</td>
<td>CardioWest TAH</td>
</tr>
<tr>
<td>2000</td>
<td>Univ of Arizona</td>
</tr>
</tbody>
</table>

---

**For Jarvik Heart Pioneer, Drug Ads Raise Profile and Questions**

Pfizer to End Lipitor Ads by Jarvik  

---

26th Annual Roland D. Pinkham, M.D. Basic Science Lectureship  
11/16/2012  

The Total Artificial Heart: Pumping Our Way Into the Future - Marvin J. Slepian, M.D.  
14
**Spectrum of Mechanical Support**

- **IABP**
- **Ventricular Assist Device**
- **Bi-Ventricular Failure**
- **GAP**
- **Bi-Ventricular Replacement/Total Heart**

**Initial presentation of CHF is frequently LV failure**

**RV failure (bi-ventricular) progresses with time**

Eventually all LV failure pts develop varying degrees of RV failure

> 50% of Class IV CHF pts have RV failure

RV failure often occurs/declared once pt is on an LVAD

---

**SynCardia™ TAH: History**

- Evolved from Univ. Utah / Jarvik
- Significant early clinical experience
  - J7-100 TAH: 44 patients / 6 patient years
  - J7-70 TAH: 159 patients / 11 patient years
- 1991: Tech transfer to Univ. of Arizona
- Developed under CardioWest Technologies Inc.
- 1993-2002: IDE trial
- 1998: European CE approval
- **2001: SynCardia founded**

---

**2001 SynCardia**

Mission: To complete the development and obtain regulatory approval for the CardioWest TAH. “To complete the job.”

Focus
- Quality system
- Technical
- Trial completion
- PMA submission
- FDA approval
- CMS
Innovation Issues: TAH

Technology - Material, Valves, Driveline
Medical - Patient Selection, Antithrombotic Tx
Corporate - Quality system, documentation
Regulatory – FDA violations
Reimbursement – Non coverage decision
Financing – unplanned
Management – stewardship, credibility

Different skill set
Alignment of all the stakeholders issue

SynCardia™
Total Artificial Heart System

Implantable
Full Cardiac Replacement
Full Normalization of Hemodynamics
CE Approved - Europe
FDA approved - USA

SynCardia™
Total Artificial Heart System

Implantable TAH

External Console
Drivelines

Implantable TAH

SynCardia™
Total Artificial Heart

Stroke volume 70 milliliters
Inflow valve 27 millimeter Medtronic-Hall
Outflow valve 25 millimeter Medtronic-Hall
Seamless blood diaphragm
Four(4) flexible polyurethane diaphragms
Maximum output >9 liters per minute
Weight 180 grams
**SynCardia™ TAH:**

**Advantages over LVAD**

Complete biventricular replacement/performance

TAH **obviates the following native heart issues** that could affect a patient on a LVAD

1) Arrhythmias
2) Right ventricle function
3) Prosthetic Aortic Valve
4) Thrombus in ventricle
5) Septal defects

**SynCardia™**

_Total Artificial Heart System_

**Fill phase**

**Eject phase**

**TAH Advantages**

1) Decreased CVP
2) Overcome PA
3) Cardiac output
4) Organ Recovery

**SynCardia CardioWest™ vs Abiocor™ TAH**
SynCardia™
Total Artificial Heart

- Stroke volume 70 milliliters
- Inflow valve 27 millimeter Medtronic-Hall
- Outflow valve 25 millimeter Medtronic-Hall
- Seamless blood diaphragm
- Four (4) flexible polyurethane diaphragms
- Maximum output >9 liters per minute
- Weight 180 grams

SynCardia TAH: Characteristics

- Implantable components - chest only
- Shortest blood path and exposure to artificial surfaces
- Full circulatory support
- No dependence on native heart
- Highest level of cardiac output
- Normalizes hemodynamics
- Effective on the sickest of patients
- Implantable components simple and reliable
The Clinical Need: When Medical Therapy Fails

- Bi-Ventricular Failure
- End-Organ Decompensation
- Hemodynamic Stabilization
- Organ Recovery
- Heart Available
- Cardiac Transplantation
- TAH
- Death

SynCardia CardioWest TAH: U.S. Pivotal Trial

AIMS:
To examine the:
1. Efficacy
2. Safety

of cardiac replacement with the CardioWest TAH in bridge to transplantation
**Hypothesis**

Patients with irreversible biventricular failure, could be saved utilizing the CardioWest TAH as a bridge to transplantation.

**Study Design**

- Prospective, Non-randomized
- Multi-center
- Critically ill patients
- Irreversible End-Stage CHF, NYHA Class IV
- Transplant-eligible

**Historical Controls:**
Patients meeting identical entry criteria

**Study End Point Variables**

**Primary Efficacy Endpoint**
Treatment Success (at 30 days post-transplant)
- Alive, NYHA Class I or II, Ambulatory
- Not on ventilator or dialysis

**Secondary Efficacy Endpoints**
- Survival
- Hemodynamics
- End-Organ Function and Ambulation

**Safety Parameters**
- Adverse Events
**Study Sites:**

**5 Centers 12 Surgeons**

- **University Medical Center, Tucson, AZ**
  - Jack Copeland, Francisco Arabia
- **Loyola University Medical Center, Chicago, IL**
  - Bryan Foy, Henry Sullivan, Alvaro Montoya
- **LDS Hospital, Salt Lake City, UT**
  - James Long, Donald Doty
- **St. Luke’s Medical Center, Milwaukee, WI**
  - Alfred Tector, Terence Schmahl, David Kress
- **U of Pittsburgh Medical Center, Pittsburgh, PA**
  - Bartley Griffith, Robert Kormos

**Study Patients**

- **All Patients**
  - n=130
  - **Control**
    - n=35
  - **Implant**
    - n=95
  - **Core**
    - n=81
  - **Out of Protocol**
    - n=14

**Study Inclusion Criteria**

- Eligible for transplant
- NYHA Class IV
- BSA > 1.7 m² or T10 ≥ 10 cm
- Hemodynamic insufficiency

**Hemodynamic Insufficiency Demonstrated by A or B below**

**Criteria A**

- Cardiac index ≤2.0 L/min/m² + one of the following:
  - Systolic arterial pressure ≤90 mm Hg
  - Central venous pressure ≥18 mm Hg

**Criteria B**

- Two of the following:
  - Dopamine ≥ 10 μg/kg/min
  - Dobutamine ≥ 10 μg/kg/min
  - Other drugs at maximum levels
  - Intra-aortic balloon pump (IAPB)
  - Cardiopulmonary bypass (CPB)
**Study Exclusion Criteria**

- Use of any VAD
- Pulmonary vascular resistance ≥ 8 Wood units (640 Dynes-sec/cm²)
- Dialysis in previous 7 days
- Serum creatinine ≥ 5 mg/dl
- Total bilirubin ≥ 5 mg/dl
- Cytotoxic antibodies ≥ 10%

**Chosen for TAH rather than LVAD Because:**

<table>
<thead>
<tr>
<th>Core</th>
<th>81</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>66</td>
</tr>
<tr>
<td>15</td>
<td>11</td>
</tr>
</tbody>
</table>

On HL machine, CPS/ECMO

- CVP >18 mmHg
- RVEF <20%

*All on IABP, max inotropes, and failing hemodynamics. Two with V-tach, one with mechanical aortic valve, and one with RV injury at sternotomy

**Representative Resected Heart**

**Control Group**

UNOS Status 1 Patients Screened 635
Eliminated as too small (BSA <1.7) (47)
Eliminated by medical history (70)
Eliminated as not sick enough (324)
Eliminated for use of other VAD (159)

**Total meeting study criteria** 35

*No ethical option for randomization*
Hierarchy of Support at Baseline

<table>
<thead>
<tr>
<th>Support</th>
<th>Cores</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPS</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>IABP, 5 Drugs</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5 Drugs</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>IABP, 4 Drugs</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>4 Drugs</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>IABP, 3 Drugs</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>3 Drugs</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>IABP, 2 drugs</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>2 Drugs</td>
<td>20</td>
<td>37</td>
</tr>
<tr>
<td>IABP, 1 Drug</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

Primary End Point: Treatment Success

- ≥ 3 Drugs or CPS
  - 66% Cores
  - 20% Controls

- ≤ 2 Drugs
  - 34% Cores
  - 80% Controls

Survival

- Survival to transplant: 79.1% 68.5%-87.3%
- Survival to 30d post-transplant: 71.6% 60.5%-81.1%
- 1 year survival from study entry: 70.4% 63.3%-77.4%
- 1 year survival from transplant: 85.9% 79.9%-92.0%

Survival to Transplantation

- Control
- Core TAH

Compares favorably with published survival data

Copeland….Slepian NEJM 361:859, 2004
### Time to Transplant (Mean)
- **Cores**: Mean = 8.5 Days
- **Controls**: Mean = 79.1 Days

**Median**: Cores = 6 days, Controls = 47 days (longest 414 days)

**Total Study Days**: 6,411 Cores, 299 Controls

### Overall Duration of Survival
- Control vs Core TAH
- Proportion Alive vs Time (years)

### Survival from Transplantation
- Control vs Core TAH vs UNOS
- Proportion Alive vs Time (years)

### Post-Transplant Survival of Cardiac Recipients
<table>
<thead>
<tr>
<th>Indicator</th>
<th>Core Patients</th>
<th>UNOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number transplanted</td>
<td>81</td>
<td>4481</td>
</tr>
<tr>
<td>Survival rate at 1 year</td>
<td>85.9%</td>
<td>84.7%</td>
</tr>
<tr>
<td>Survival rate at 3 years</td>
<td>80.7%</td>
<td>77.6%</td>
</tr>
<tr>
<td>Survival rate at 5 years</td>
<td>63.8%</td>
<td>69.8%</td>
</tr>
</tbody>
</table>
## Secondary Efficacy Endpoints: Hemodynamic Recovery

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Day 1</th>
<th>$\Delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac index</strong> (L/min/m²)</td>
<td>1.9</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td><strong>Systolic arterial pressure</strong> (mm Hg)</td>
<td>92.8</td>
<td>121.7</td>
<td></td>
</tr>
<tr>
<td><strong>Central venous pressure</strong> (mm Hg)</td>
<td>19.7</td>
<td>13.6</td>
<td></td>
</tr>
<tr>
<td><strong>Organ perfusion pressure</strong> (mm Hg)</td>
<td>48.6</td>
<td>67.5</td>
<td></td>
</tr>
</tbody>
</table>

### Cardiac Index

Cardiac Index (Mean ± 2SE) (Core TAH)

![Cardiac Index Graph](chart1)

### Renal Function

Creatinine (Mean ± 2SE) (Core TAH)

![Creatinine Graph](chart2)

### Hepatic Function

Total Bilirubin (Mean ± 2SE) (Core TAH)

![Total Bilirubin Graph](chart3)
Ambulation (Core TAH)

<table>
<thead>
<tr>
<th>Days on Study</th>
<th>Able to Get-out-of-Bed (% of Patients)</th>
<th>Able to Walk &gt;100 Ft (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>7</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>14</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>21</td>
<td>80%</td>
<td>80%</td>
</tr>
</tbody>
</table>

From Kaplan Meier Estimates

Complications During Support

- Takeback for bleeding: 23/81 (28%)
- Device malfunction: 3/81 (4%)
- Fit complications: 2/81 (2%)
- Mediastinal infections: 3/81 (4%)
- Visceral embolus: 1/81 (1%)
- Dialysis: 12/81 (15%)
- Stroke: 4/81 (5%)

linearized rate 0.068 strokes/pt-yr

Causes of Death Prior to Transplantation

<table>
<thead>
<tr>
<th>Core Patients (17/81 = 21%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Organ Failure</td>
</tr>
<tr>
<td>Procedural / Technical</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Pre-implantation Cardiac Arrest</td>
</tr>
<tr>
<td>Pulmonary Edema</td>
</tr>
</tbody>
</table>

*2 coagulopathy after FIEBA administration, 2 due to central line wedging in TAH tricuspid valve
**SynCardia CardioWest TAH: Indication for Use**

As an in-hospital bridge to transplantation in cardiac transplant candidates at imminent risk of death due to irreversible biventricular failure

---

**Clinical Perspective**

**Right Ventricular Failure: Caveats**

- RVF incidence 11-26% of pts on LVADs…..
- 1/3 to 1/2 of pts with RVF require an RVAD, i.e. biventricular support
- More likely to occur in “sicker” patient, “emergent vs elective or urgent”
- Affects outcomes… decreasing the successful bridge to transplant rate
- Prospective ability to predict…..inaccurate in many situations

---

**2005 American Heart Association Top 10 Advances for 2004**

1. First Implantable Artificial Heart Approved.
2. Drug improves heart failure survival among blacks.
3. One-two punch open blocked brain vessels faster.
4. Less invasive technique for stroke prevention.
5. Artificial blood vessels work like the real thing.
6. Public defibrillators a lifesaver.
7. Preventing birth defects-in the womb.
8. Genetic screening for heart disease.
10. One drug tackles two harmful habits.
Biventricular Support

- Hybrid systems.....poor outcomes.... only 1/3 of patients bridged*
- Paracorporeal Systems....flow limited, require competent aortic valve, limited by liability of the native heart pathology
- Total Artificial Heart...high flows, not limited by native heart pathology


LVAD Mortality Risk Factor Profile vs TAH Cohort Baseline

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>Death (%)</th>
<th>TAH Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine output &lt; 30 ml/h</td>
<td>3.9</td>
<td>67%</td>
<td>36 ± 19</td>
</tr>
<tr>
<td>BUN &gt; 40</td>
<td>3.1</td>
<td>54%</td>
<td>20 ± 7</td>
</tr>
<tr>
<td>CVP &gt; 16 mmHg</td>
<td>3.0</td>
<td>35%</td>
<td>42 %</td>
</tr>
<tr>
<td>Mechanical Vent</td>
<td>2.4</td>
<td>50%</td>
<td>16 ± 4</td>
</tr>
<tr>
<td>Reoperation</td>
<td>1.8</td>
<td>33%</td>
<td>38 %</td>
</tr>
</tbody>
</table>


Risk Factor Analysis for Bridge to Transplantation
With the CardioWest Total Artificial Heart

<table>
<thead>
<tr>
<th>End Point</th>
<th>Variable</th>
<th>Odds Ratio for Death</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival to transplant</td>
<td>History of smoking</td>
<td>0.55</td>
<td>0.34 to 0.90</td>
<td>0.01</td>
</tr>
<tr>
<td>Survival to 30 days after transplant</td>
<td>History of smoking</td>
<td>0.70</td>
<td>0.42 to 1.14</td>
<td>0.02</td>
</tr>
<tr>
<td>Survival to 30 days after transplant</td>
<td>Prothrombin time ≥ 16 seconds</td>
<td>4.74</td>
<td>1.60 to 13.92</td>
<td>0.04</td>
</tr>
<tr>
<td>Survival to 1 year after transplant</td>
<td>Prothrombin time ≥ 18 seconds</td>
<td>3.80</td>
<td>1.01 to 14.33</td>
<td>0.05</td>
</tr>
</tbody>
</table>

52 risk factors
5 centers


The Total Artificial Heart: Pumping Our Way Into the Future - Marvin J. Slepian, M.D.
MCS Device Selection:  
**Bi-Ventricular Support**

- Acuity of Presentation
- Myocardial Substrate – AMI, Defects, AVR/MVR
- Length of Support anticipated/ ?Recovery
- Tx Eligible/Device eligible
- Co-Morbidities
- Flow Demand
- VAD Risk factors
- Scoring Systems

---

**BiVAD vs TAH in BTT: Penn + Arizona Experience**

n = 151 pts Class IV CHF with Biventricular CHF
90 pts Penn (BiVAD), 61 pts Arizona (TAH)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BiVAD (1 choice)</th>
<th>TAH (2 choices)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTT</td>
<td>46%</td>
<td>77%</td>
</tr>
<tr>
<td>Discharge</td>
<td>38%</td>
<td>68%</td>
</tr>
<tr>
<td>Reoperation</td>
<td>70%</td>
<td>21%</td>
</tr>
<tr>
<td>RF/ Dialysis</td>
<td>34%</td>
<td>20%</td>
</tr>
<tr>
<td>MOF Death</td>
<td>20%</td>
<td>11%</td>
</tr>
<tr>
<td>Stroke</td>
<td>29%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Leshnower, Acker, Slepián et al  Presentation at ISHLT 2007

---

BIVAD/TAH: Flow vs BSA

Flow L/M

CI=2.0
CI=2.5
CI=3.0
CI=3.5

BiVAD vs TAH in BTT: Penn + Arizona Experience

Implant Dates: Jun 23, 2006 – Dec
Implant Dates: June 23, 2006 – March 31, 2009

Leshnower, Acker, Slepián et al  Presentation at ISHLT 2007
Results:
PMA Trial vs AMI Subset

<table>
<thead>
<tr>
<th>BTT Treatment Success</th>
<th>PMA</th>
<th>AMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>79.0%</td>
<td>78.0%</td>
<td></td>
</tr>
<tr>
<td>69.0%</td>
<td>78.0%</td>
<td></td>
</tr>
</tbody>
</table>

VADs vs.TAH in Shock - Acute MI: Survival

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVAD</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>BiVAD</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>FFBP (ECMO)</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>FFP + LVAD or BiVAD</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>9 (35%)</td>
</tr>
<tr>
<td>TAH</td>
<td>9</td>
<td>6 (66%)</td>
</tr>
</tbody>
</table>

El Banayosy et al  HZ NRW

**Unique Uses for TAH**
- Severe Biventricular failure
- Massive LV Infarct
- Ventricular Thrombus
- Ventricular Septal Defects
- Ventricular rupture
- Refractory Arrhythmias
- Prosthetic Aortic Valves
- Failed Cardiac transplant/ VAD
- Adult Congenital Heart disease
- Cardiac Malignancies
- Complex Reoperative
- Infiltrative/Restrictive CM - Amyloid

---

Friday February 1, 2008

**MEDICARE PROPOSES COVERAGE WITH EVIDENCE DEVELOPMENT FOR ARTIFICIAL HEART DEVICES**

The Centers for Medicare & Medicaid Services (CMS) today proposed coverage with evidence development of artificial heart devices. CMS proposes to cover artificial heart devices in Medicare beneficiaries who are enrolled in Food and Drug Administration (FDA)-approved studies.

“Our proposal relaxes a long-standing non-coverage policy, gives access to our beneficiaries and promotes evidence development through FDA approved studies of this advanced technology,” said CMS Acting Administrator Kerry Weems.

Offical as of May 1, 2008
### Active Centers: TAH Implants

#### North American Centers (selected)
- Arizona: 129
- Barnes: 20
- Cleveland: 39
- Loyola: 4
- Maryland: 4
- Mayo-Phx: 50
- MCV: 64
- Michigan: 6
- Milwaukee: 15
- Montreal: 10
- Ohio St: 4
- Ottawa: 32
- Penn State: 5
- Sharp: 7
- Salt Lake City/IMC: 12
- U Penn: 7
- Integr: 10
- Methodist: 4

Total = 97

#### European Centers (selected)
- Bad Oyenhausen: 145
- Berlin: 49
- Cologna: 2
- Erlangen: 1
- Fribourg: 8
- Hannover: 2
- La Pléile: 226
- Leipzig: 3
- Muenster: 2
- Nantes: 64
- Padua: 4
- Bern: 1
- Goteborg: 2
- Innsbruck: 1
- Naples: 3
- Rome: 3
- Sydney: 3
- Vienna: 1
- Moscow: 1
- Ismir: 4

Total = 10/12

N = 50

N = 47

**Total = 97 > 1100 implants**

### U.S. Post Market Surveillance Study

#### Hypothesis

The outcomes achieved in the original US Pivot Trial of the TAH will be translatable in the hands of multiple surgeons across varying implanting medical centers in the United States.

Slepian MJ et al ISHLT 2012

### U.S. Post Market Surveillance Study

- 2007 – 2011
- 110 patients
- 15 Medical centers

% Implants
- 1 center – 43%
- 3 centers – 8 – 14%
- 11 centers < 8%

Slepian MJ et al ISHLT 2012

### U.S. Post Market Surveillance Study

#### Results

<table>
<thead>
<tr>
<th></th>
<th>PMSS</th>
<th>PMA (in + out protocol)</th>
<th>PMA (in protocol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age</td>
<td>49</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>Male (%)</td>
<td>89</td>
<td>87</td>
<td>86</td>
</tr>
<tr>
<td>BSA (m2)</td>
<td>2.1</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Ischemic CM (%)</td>
<td>37</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Transplanted (%)</td>
<td>75.5</td>
<td>74.7</td>
<td>79.9</td>
</tr>
<tr>
<td>Died (%)</td>
<td>24.5</td>
<td>25.3</td>
<td>20.1</td>
</tr>
<tr>
<td>Alive at 30d f/u (%)</td>
<td>90.1</td>
<td>88.7</td>
<td>90.9</td>
</tr>
<tr>
<td>Alive at 1yr f/u (%)</td>
<td>82.5</td>
<td>76.1</td>
<td>86</td>
</tr>
</tbody>
</table>

Slepian MJ et al ISHLT 2012
The Future:

TAH Discharge Experience

Largely Germany, > 35 pts
78 yrs of outpatient experience
56% of Total TAH experience
At home de facto DT

Have more data at home than in hospital!

TAH(Excor) D/C Study: Results

22/22 pts successfully d/c home
Maintained in Hosp 18 ± 7 d prior to d/c
Maintained Home 179 ± 140d (2 – 598d)
Total OOH Days = 3938

15/22 Successfully Tx (68%)
7/22 Died

El Banayosy and Slepian Submitted JHLT 2012

TAH (Excor) D/C Study: Results

PE: Pts generally felt well,
No increase in fatigue
All with Mean BP > 90,
All NYHA Class I or II

6/22 Driving Car
3/22 Resumed Work
8/22 Resumed Sexual activity

87% of time of support Out of Hospital
Evolution of SynCardia “Mobility” Drivers

Freedom™ Portable Driver
- European CE Approval: March 1, 2010
- FDA Conditional Approval of IDE Study: March 26, 2010

The 13.5 lb Freedom™ driver system and the SynCardia temporary Total Artificial Heart

CAUTION - The Freedom™ driver system is an investigational device, limited by United States law to investigational use.
Freedom™ Driver System Receives Conditional Approval from the FDA to Undergo IDE Clinical Study

The U.S. Food and Drug Administration (FDA) has given SynCardia conditional approval to begin its Freedom™ driver system study in the United States under an investigational device exemption (IDE). This approval is conditional upon the Company's submission of additional information to the FDA in 45 days. The 13.5 lb Freedom driver is the first U.S. portable driver designed to power the SynCardia temporary Total Artificial Heart inside and outside the hospital.

SynCardia may begin the clinical study immediately, following Institutional Review Board (IRB) approval at each hospital participating in the study. The clinical study may enroll 60 patients at up to 30 institutions.

CAUTION – The Freedom™ driver system is an investigational device, limited by United States law to investigational use.

Freedom Driver: Clinical Experience

102 pts

10/18/12

Need 30 discharged

U.S.

52 pts enrolled

35 discharged

17 In Hospital

8 pts in que

OUS

46 pts Europe

4 pts Australia

Avg days support 105

10/18/12

SynCardia™ TAH-t-50

Current Typical MCS Design Strategy

Geometry/CFD Evaluation

In Vivo Animal Studies

Human Clinical Trials

Many Repetitive Cycles
Device Thrombogenicity Emulation (DTE)

Numerical Modeling
CFD (Fine Mesh) + Particles
Plot distribution of stress accumulation (PDF)
Identify “Hot spot” trajectories

In Vitro “Wet” Emulation
Hemodynamic shearing device
Program Hot Spot flight paths
Gel filtered platelets (PAS)

Strategy for Improved MCS Designs
With Enhanced Thrombresistance

Device Thrombogenicity
Emulation (DTE)

In Vitro Device Closed
Loop Studies (PAS)

Hemodynamic Shearing
Device (HSD)
(Platelet/thrombin Studies)

Numerical
Simulations (PDF)

Stress
Accumulation
Hx

Stress Loading
Waveform
“Hot spot” trajectories

Direct
Enhanced
Strategy

Design Modifications:
Debakey VAD vs Heart Assist V

"Inflow Hub"
3 Blade flow straightener
Ball in cup bearing
Streamlined inlet hub & bearing taper

Impeller
Blade leading edge angle
Pitch angle
Tip – shroud clearance

“Outflow Hub”
Ball in cup bearing
Impeller – diffuser interface

Gaurav Girdhar1, Michalis Xenos2, Yared Alemu1, Wei-Chu Chiu1, Bryan E. Lynch3, Jolyon Jesty2, Shmuel Eliazer1, Marvin J. Slepian3, Danny Bluestein4

March 2, 2012
Probability Distribution Function (PDF): Origin vs Optimized Design

The PDF is the Thrombogenic Footprint of the device

Original (Debakey) vs Optimized (HeartAssist 5)

Platelet Activity State

PAS = rate of platelet activation over time for whole device

Correlation of numerical simulations with “wet/real” platelet data

Improved design has markedly reduced platelet activation (order of magnitude lower)

Mechanical Heart Valves: TAH Alternatives

On-x

ATS

St Jude

Regent

Sorin

Syncardia Total Artificial Heart (TAH) Design iterations

Syncardia Cardiowest TAH with Medtronic-Hall monoleaflet MHV

Medtronic ATS bileaflet MHV

Stony Brook University

Arizona College of Medicine

NIBIB Quantum Grantee Meeting 4/4/2011

26th Annual Roland D. Pinkham, M.D. Basic Science Lectureship 11/16/2012

The Total Artificial Heart: Pumping Our Way Into the Future - Marvin J. Slepian, M.D. 37
Freedom 2

- Smaller
- Lighter 6-8 lbs
- Quieter
- Increased ruggedness
- Simpler driveline connector
- Longer battery life
- Greater pneumatic power

Platelet Activity State (PAS): Mechanical Circulatory Support Systems

Polymeric Endoluminal Paving and Sealing

Endoluminal Polymer Layer

Polymeric Endoluminal Paving and Sealing
Endoluminal Hydrogels: Mechanical Thromboprotection

Hill-West, Slepian PNAS 1994

Endoluminal Hydrogels Limit Stented Artery Thrombosis


Endoluminal Hydrogels: Temporary Tissue Barriers

Hill-West, Slepian. PNAS 1994
Endoluminal Hydrogels Limit Late Intra-Stent Neointimal Thickening

Stent alone  Stent + Gel Paving
Slepian, MJ et al *Circulation* 92: No. 8, I-382, 1995

Surface Nano-texturing: Nano “Ensemble”
Nanowell distribution on p-doped silicon substrata and cell adhesion model

Tran et al *Adv Healthcare Mat* – Accepted for pub 2012

Nano Ensemble – EC Adhesive Synergy
Progression of feature addition to build pro-adhesive surface (steps from left to right)

Tran et al *Adv Healthcare Mat* – Accepted for pub 2012

Stretchable Electronics
High performance electronics that are ultra-thin, stretchable, and conformal

The Total Artificial Heart: Pumping Our Way Into the Future - Marvin J. Slepian, M.D.
Core Building Block 1: Stretchable Electrode Arrays
(Islands and interconnects fabricated together and transferred to PDMS)

Balloon Angioplasty/EP Smart Catheters

µLEDs (On-off switching of each cell)

Wavelengths: 600-900 nm (near UV)

LEDs on balloon catheter enable:
- Highly localized delivery of photoactivated pharmaceuticals

Materials for multifunctional balloon catheters with capabilities in cardiac electrophysiological mapping and ablation therapy

Nature Materials March 7, 2011
Transient/Biodegradable Electronics
Electronics = Magnesium, Thin Iron, Ultra-thin Silicon
Substrate = Biodegradable polymers – Natural, Synthetic

Take Home Lessons: TAH
Clarity of Mission and Vision
Adequate capitalization
Quality manpower and leadership
Engage the FDA upfront, Pre-IDE mtg, speak to and check in often, build relationship with reviewer(s)

Risk reduction

Scientific Rigor in framing the PMA:
Hypothesis, Trial design, Controls (Performance standards), Statistical analysis
Clear proposed labeling – Indication for Use
Defined training and certification plan
Pre-defined proposal for Post-market surveillance
Stay on top of CAPAs
Thorough failure analysis (root cause)
Communication for improvements & substitutions
All = Risk reduction

CMS (not =) FDA
Agency pride and independence of mission
Meet with CMS early to determine standard of necessary and reasonable, identify uniqueness
Cost effective to plan studies to satisfy both as much as possible
Bring CMS along early, invite them to the FDA, keep them informed
Business strategy + Risk reduction
Lessons Learned: Rheology

Mathematical modeling is a valuable tool for medical device development. Development of correlative, validated in vitro assays will enhance the value of modeling. Combination of in silico, in vitro and in vivo methods can enhance the safety and effectiveness of design and compress the time and cost of development.

Changing Landscape

Bridge to Recovery
Bridge to Decision
Bridge to Bridge

Bridge to Transplant
Destination Tx
Blurring

Short term support
Long term support

Time vs Dictated Outcome

Summary

TAH
- Immediate hemodynamic recovery for irreversible bi-ventricular failure
- Lower morbidity/mortality than BiVADs
- End-Organ Recovery
- Saves lives
- Higher BTT rate than any VAD/BiVAD
- QOL/ Patients Out of Bed, Walking
- Portable driver technology affords ambulatory freedom and hospital discharge