Heart Transplantation and MCS in Advanced Heart Failure

Igor D Gregoric, MD
Professor of surgery, Dept. of CV Surgery at UT, Houston TX
Chief and Program Director, Center for Advanced Heart Failure,
Memorial/Hermann Hospital, Houston, TX

Univerza v Novi Gorici, October 11, 2017
CVD deaths vs. cancer deaths by age (US)

Deaths in Thousands

<table>
<thead>
<tr>
<th>Ages</th>
<th>CVD</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>45-54</td>
<td>48</td>
<td>50</td>
</tr>
<tr>
<td>55-64</td>
<td>81</td>
<td>101</td>
</tr>
<tr>
<td>65-74</td>
<td>120</td>
<td>138</td>
</tr>
<tr>
<td>75-84</td>
<td>242</td>
<td>165</td>
</tr>
<tr>
<td>85+</td>
<td>315</td>
<td>85</td>
</tr>
<tr>
<td>Total</td>
<td>831</td>
<td>560</td>
</tr>
</tbody>
</table>
Hospital Discharges (in millions) for the 10 Leading diagnostic Groups

- Cardiovascular 390-459: 6.2
- Obstetrical V27: 4.1
- Digestive System 520-579: 3.5
- Respiratory System 460-519: 3.5
- External: Injuries, etc. 800-999: 3.0
- Mental 290-319: 2.4
- Genitourinary System 580-629: 2.0
- Musculoskeletal System 710-739: 2.0
- Endocrine System 240-279: 1.7
- Neoplasms 140-239: 1.6
Heart Failure Facts

- U.S. prevalence 4.8 million
- 550,000 new cases CHF each year
- Survival outlook <5 years
- 287,000 deaths per year
- $45 billion spent on CHF

Source: American Heart Association
Etiologies of heart failure

- Coronary artery disease
- Idiopathic cardiomyopathy
- Peripartum cardiomyopathy
- Dilated cardiomyopathy
- Ischemic cardiomyopathy
- Acute valvular disease
- Arrhythmia (supraventricular or ventricular)
- Myocarditis
- Congenital heart disease
- Drug induced
- Diabetes mellitus
- Hypertension
HF Mortality associated with Continuous Inotropic Infusions

Hershberger RE et al. *J Cardiac Failure* 2003;9:180
End Stage Heart Failure
Heart failure

Stage A
High risk with no symptoms

Stage B
Structural heart disease, no symptoms

Stage C
Structural disease, previous or current symptoms

Stage D
Refractory symptoms requiring special intervention

Inotropes
Aldosterone antagonist, nesiritide
Consider multidisciplinary team
Revascularization, mitral-valve surgery
Cardiac resynchronization if bundle-branch block present
Dietary sodium restriction, diuretics, and digoxin
ACE inhibitors and beta-blockers in all patients
ACE inhibitors or ARBs in all patients; beta-blockers in selected patients
Treat hypertension, diabetes, dyslipidemia; ACE inhibitors or ARBs in some patients
Risk-factor reduction, patient and family education

VAD, transplantation
Hospice
Christian Barnard

- Born in South Africa in 1922
- Studied heart surgery at the University of Minnesota then returned to set up a cardiac unit in Cape Town.
- **December 1967**: transplanted the heart of a road accident victim into a 59 year old patient
- Patient only survived 18 days due to infectious complications
The Star

TRANSPPLANTED HEART IS BEATING

Many problems to be answered

From Our Correspondent

CAPE TOWN, Monday.

THIRTY-TWO HOURS after his historic heart transplant in Groote Schuur Hospital, Mr. Louis Washkansky is maintaining his satisfactory condition.

Dr. J. G. Bourne, Medical Superintendent, said that Mr. Washkansky’s condition was stable and that he was being looked after in the best possible way.

"Mr. Washkansky’s condition is satisfactory," he said. "He is in a stable condition and is being looked after in the best possible way."

Saw smash of girl donor

GIRL WOULD DELIVERY

Helicopters in landing

The first sudden death—Spain wins

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Saw smash of girl donor

GIRL WOULD DELIVERY

Helicopters in landing

The first sudden death—Spain wins
## Summary of Heart Transplants as of March 1, 1971

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of Transplants</td>
<td>170</td>
</tr>
<tr>
<td>- US</td>
<td>108</td>
</tr>
<tr>
<td>- Foreign</td>
<td>62</td>
</tr>
<tr>
<td>Total No. of Recipients</td>
<td>167</td>
</tr>
<tr>
<td>- Total No of Deaths</td>
<td>143</td>
</tr>
<tr>
<td>- No of Survivors</td>
<td>24</td>
</tr>
<tr>
<td>- US</td>
<td>18</td>
</tr>
<tr>
<td>- Foreign</td>
<td>6</td>
</tr>
<tr>
<td>Total No of Countries</td>
<td>20</td>
</tr>
</tbody>
</table>
The interest in cardiac transplantation waned during the 1970s as most recipients died within a few months of the transplant operation from infection or rejection.
1976– Discovery Cyclosporine A

- Severity and acuity of rejections decreased
- Lead to a renewed interest in cardiac transplantation in 1980s
- The need for bridge to transplant devices resurfaced
  - LVAD
  - TAH
Most Common Transplantation
-Blood Transfusion-

<table>
<thead>
<tr>
<th>Recipient</th>
<th>Potential donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Anti-A and anti-B antibodies</td>
<td>Green</td>
</tr>
<tr>
<td>A</td>
<td>Green</td>
</tr>
<tr>
<td>Anti-B antibodies</td>
<td>Green</td>
</tr>
<tr>
<td>B</td>
<td>Green</td>
</tr>
<tr>
<td>Anti-A antibodies</td>
<td>Green</td>
</tr>
<tr>
<td>AB</td>
<td>No antibodies against A or B</td>
</tr>
</tbody>
</table>
Immunologic Analysis

- HLA Tissue Typing
- Cytoscreen
- Cross Match
TECHNIQUE
HEART TRANSPLANTATION

Overall
Adult and Pediatric Heart Transplants
Number of Transplants by Year and Location

NOTE: This figure includes only the heart transplants that are reported to the ISHLT Transplant Registry. As such, the presented data may not mirror the changes in the number of heart transplants performed worldwide.
Adult and Pediatric Heart Transplants
Median Donor Age by Location

- Europe
- North America
- Other

Median donor age (years)


JHLT. 2017 Oct; 36(10): 1037-1079
Analysis is limited to patients who were alive at the time of the follow-up.
Adult Heart Transplants
Maintenance Immunosuppression at Time of 1 Year Follow-up by Year

NOTE: Different patients are analyzed in each timeframe.

Analysis is limited to patients who were alive at the time of the follow-up.
Rejection
Grade 3R, Severe (3B)
Adult Heart Transplants
Kaplan-Meier Survival by Era
(Transplants: January 1982 – June 2015)

Median survival (years):

All pair-wise comparisons were significant at p < 0.05.
Adult Heart Transplants
Kaplan-Meier Survival by Ischemic Time
(Transplants: January 2009 – June 2015)

All pair-wise comparisons were significant at p < 0.05 except 0-<2 vs. 2-<4 hours.
Risk Factors For 20 Year Mortality with 95% Confidence Limits

Recipient age

(p < 0.0001)

(N = 22,629)
Risk Factors For 20 Year Mortality with 95% Confidence Limits

Ischemic time

\( p = 0.0156 \)

(N = 22,629)


JHLT. 2017 Oct; 36(10): 1037-1079
Recipient weight (kg)

N = 22,629

Risk Factors For 20 Year Mortality with 95% Confidence Limits
Risk Factors For 20 Year Mortality with 95% Confidence Limits

Age difference

- Hazard Ratio for 20 Year Mortality
- p < 0.0001

(N = 22,629)
Risk Factors For 20 Year Mortality with 95% Confidence Limits
Transplant center volume

p < 0.0001
(N = 22,629)
MCS in Chronic Heart Failure
First Clinical LVAD

- 1963, Michael E. DeBakey
- 42-year-old patient
- Supported for 4 days
- Pump functioned well
- Pt. died of lung complications
First Clinical LVAD Success

- 1966, Michael E. DeBakey
- 37-year old patient
- Postcardiotomy
- Supported for 10 days
- Long-term survivor
Mid 80’s

- Clinical trials with
  - Pneumatic HM I
  - Novacor
First generation Pulsatile Devices for Long Term Use
HeartMate XVE
Working With HM I
HeartMate XVE® - First FDA Approved Device for Destination Therapy

- NYHA class IV end-stage LV failure
- Received optimal medical therapy for at least 60 of the last 90 days
- Life expectancy of < 2 years
- Not a candidate for cardiac transplantation
- LVEF < 25%
- MVO₂ < 12 ml/kg/min or on inotropes
- BSA > 1.5 m²

Data from HeartMate XVE Left Ventricular Assist System Instructions for Use
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


[Graph showing survival rates for LVAD (n=68) and OMM (n=61) groups over months, with survival rates at 24 months: LVAD 23%, OMM 8%]
Evolution of LVAD Technology

1st Generation
Pulsatile Pump

2nd Generation
Axial Flow Pump

3rd Generation
Rotary Pump

DuraHeart
3rd Generation

Ventrassist
3rd Generation

HeartWare
3rd Generation

Levacor
3rd Generation

Heartmate III
3rd Generation

Heartmate II
2nd Generation

DeBakey VAD
2nd Generation

Jarvik 2000
2nd Generation

Heartmate I
1st Generation

Novacor
1st Generation
Axial flow
second generation
LVAD’s
New Technology
- Axial flow
- Inflow cannula
- Fixed speed
- Integrated flow probe
- Subdiaphramatic
Implantation of the Jarvik 2000

- Left Thoracotomy or Sternotomy
- Non Thoracic
- Partial Cardiopulmonary Bypass or No CPB
- Silastic Cuff on Apex
- Pump Placed in LV
- Outflow Graft Anastamosed to Aorta
Different Surgical Approaches

- Left Thoracotomy
- Descending Ao
- Subcostal
- Supraceliac Ao
- Median Sternotomy
- Ascending Ao
Home Discharge Experience

- **Mean Time on Jarvik 2000**: 316 days
- **Max Time on Jarvik 2000**: 825 days
- **Cumulative Time**: 9.5 years (83%)
HeartMate II™

- Axial flow
- Brushless DC motor
- Inflow cannula
- Textured surfaces
  - excluding impeller
- Small (65cc 260g)
- Power requirements
  - (>14 watts)
HMII Anatomical Placement
Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device

Mark S. Slaughter, M.D., Joseph G. Rogers, M.D., Carmelo A. Milano, M.D., Stuart D. Russell, M.D., John V. Conte, M.D., David Feldman, M.D., Ph.D., Benjamin Sun, M.D., Antone J. Tatooles, M.D., Reynolds M. Delgado, III, M.D., James W. Long, M.D., Ph.D., Thomas C. Wozniak, M.D., Waqas Ghumman, M.D., David J. Farrar, Ph.D., and O. Howard Frazier, M.D., for the HeartMate II Investigators*
Actuarial Survival vs REMATCH*
HeartMate II Destination Therapy Trial

Patient Quality of Life
HeartMate II

Patient DXP

- 14 y/o Caucasian male  BSA=1.87
- Dilated viral cardiomyopathy
- Pre Implant:
  - PCWP=22  CO=2.68
  - EF<10%
- Implanted on 9-24-04
- Pump speed maintained at 8600 rpm for 2 months
- Pump speed currently maintained at 10000 rpm since Nov ‘04
- On 03-08-05 patient fell (skateboarding) damaged device and had pump exchanged
- Device was explanted on 10-25-06
Third Generation Blood Pumps
No Valves or Mechanical Bearings

Magnetically-Suspended Impeller

Centrifugal-Flow
- Durahart
- HeartQuest
- HeartMate III
- CentriMag

Axial-Flow
- Pitt Streamliner
- Berlin VAD INCOR

Hydrodynamically Suspended Impeller

CorAid
- HeartWare
- VentrAssist
DuraHeart LVAD

Protocol #08-02-251-181

“Evaluation of the Safety and Effectiveness of the DuraHeart Left Ventricular Assist System in Patients Awaiting Transplant”
The world’s first commercially available Mag-Lev 3rd Generation implantable LVAS
The pump after more than 16 months implantation (Clear indication of enhanced wash-out and reduced shear)
HeartWare LVAS
Surgical Implant and Inlet Position

Apical

Diaphragmatic
Evaluation of the HeartWare HVAD Left Ventricular Assist System for the Treatment of Advanced Heart Failure: Results of the ADVANCE Bridge to Transplant Trial

Keith Aaronson, Mark Slaughter, Edwin McGee, William Cotts, Michael Acker, Mariell Jessup, Igor Gregoric, Pranav Loyalka, Valluvan Jeevanandam, Allen Anderson, Robert Kormos, Jeffrey Teuteberg, Francis Pagani, Steven Boyce, David Hathaway, Leslie Miller for the HeartWare ADVANCE Investigators

February 2011
ADVANCE Trial Secondary Outcome: Survival

Event: Death (censored at transplant or recovery)

ITT Population

<table>
<thead>
<tr>
<th>Days Post Implant</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>98.6%</td>
<td>96.6%</td>
</tr>
<tr>
<td>90</td>
<td>95.6%</td>
<td>93.6%</td>
</tr>
<tr>
<td>180</td>
<td>93.9%</td>
<td>90.2%</td>
</tr>
<tr>
<td>360</td>
<td>90.6%</td>
<td>85.7%</td>
</tr>
</tbody>
</table>

p = .39

HVAD

Control

Patients at Risk

<table>
<thead>
<tr>
<th>Days Post Implant</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>140</td>
<td>499</td>
</tr>
<tr>
<td>90</td>
<td>128</td>
<td>440</td>
</tr>
<tr>
<td>180</td>
<td>108</td>
<td>370</td>
</tr>
<tr>
<td>360</td>
<td>92</td>
<td>305</td>
</tr>
<tr>
<td>300</td>
<td>63</td>
<td>228</td>
</tr>
<tr>
<td>360</td>
<td>36</td>
<td>176</td>
</tr>
<tr>
<td>360</td>
<td>26</td>
<td>127</td>
</tr>
</tbody>
</table>
MCS Complications
LVAD Complications

Perioperative Bleeding
Pericardial Placement with no pocket – a Key Advantage

- No abdominal surgery
- No pump pocket
- Low blood loss
- Potential for shorter implant time
Table 3. Comparison of blood product transfusion between the off-CPB group and CPB groups.

<table>
<thead>
<tr>
<th>Blood product</th>
<th>Off-CPB</th>
<th>CPB</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cells (units)</td>
<td>1.4 ± 1.8</td>
<td>8.1 ± 8.2</td>
<td>0.007</td>
</tr>
<tr>
<td>Fresh frozen plasma (units)</td>
<td>1.3 ± 2.0</td>
<td>6.0 ± 5.6</td>
<td>0.007</td>
</tr>
<tr>
<td>Platelets (units)</td>
<td>0.4 ± 0.9</td>
<td>2.7 ± 1.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cryoprecipitate (units)</td>
<td>0.0 ± 0.0</td>
<td>0.3 ± 0.6</td>
<td>0.073</td>
</tr>
</tbody>
</table>

Abbreviations: CPB = cardiopulmonary bypass
LVAD Complications

Driveline infection
Infection

- S/S and exam:
  - Leukocytosis, fever, erythema, drainage, tenderness around driveline site, positive cultures, hyperdynamic flows, hypotension

- Etiology: (multifactorial)
  - Poor dressing technique, improper immobilization of driveline, immunosuppression (ANC < 1000), diabetes, low albumin/poor nutritional status

- Tx:
  - Antibiotics (po/IV depending on severity), Possible OR for exploration, fluid resuscitation, dressing changes/Vacs etc.
Importance of Nutrition

- Poor Nutrition
- Infection
- Immunocompromise
- Poor Wound Healing
- Organ Mass Reduction
- Multiple Organ Failure
- Inflammatory Response
TET systems
LVAD Complications

GI Bleeding
GI bleeding/AVMs

**S/S:**
- Abdominal pain, low H/H, blood in stool or emesis

**Dx:**
- Colonoscopy, IR, guiac stool

**Etiology:**
- Continuous flow/high pump speed?, supratherapeutic INR, antiplatelet, HIT pts

**Tx:**
- Decrease coumadin dosing, antiplatelet agents, transfuse if indicated,
Arteriovenous Malformation and Gastrointestinal Bleeding in Patients with the HeartMate II Left Ventricular Assist Device

Zumrut T. Demirozu,
Rajko Radovancevic, Lyone Hochman,
Igor D. Gregoric, George V.Letsou, Biswajit Kar,
Roberta C. Bogaev, O. H. Frazier

Cardiopulmonary Transplantation and Center for Circulatory Support

Texas Heart Institute at St. Luke's Episcopal Hospital, Houston, Texas
Patients and Methods

• Of 184 patients, 31 patients (17%) met the criteria for GI bleeding.
• Duration of LVAD support in the study group: 351 ± 272 days
• Average time from LVAD implantation to 1st bleeding episode: 84 ± 132 days (8-707 days)
LVAD Complications

Pump Thrombosis
LVAD Thrombosis

• Pump Related
• Not Pump related
Non Pump related Thrombosis of LVAD
Dislodgement of outflow cannula
Pump replacement

Before

After
Disconnected Bend relief graft
OBR in place

HeartMate-II Outflow Graft and Bend Relief

K.K. McTeague 01/31/2012
OBR damage to graft during exposure for Heart Transplant
Normal connection...

...Slipped Bend Relief!
Evolution of LVAD Technology

1st Generation
Pulsatile Pump

2nd Generation
Axial Flow Pump

3rd Generation
Rotary Pump

DuraHeart 3rd Generation
Ventrassist 3rd Generation
HeartWare 3rd Generation
Levacor 3rd Generation
Heartmate III 3rd Generation

Heartmate II 2nd Generation
DeBakey – Reliant VAD 2nd Generation
Jarvik 2000 2nd Generation
Heartmate I 1st Generation
Novacor 1st Generation

The University of Texas Medical School at Houston
UT Physicians

Memorial Hermann Heart & Vascular Institute
Texas Medical Center
Pump related Thrombosis of LVAD
Bearings – Potentially heat generated in this area
Blood Damage

Numerical Analysis of Blood Damage Potential of the HeartMate II and HeartWare HVAD Rotary Blood Pumps


Artificial Organs
Volume 39, Issue 8, pages 651–659, August 2015
Hemolysis

Hemolysis is a function of shear stress level and exposure time. For most rotary pumps, the exposure times are very short (ms), which is the secret for low hemolysis!

Shear stress induced blood damage:

Below exposure times of 620 ms and/or shear stresses of 425 Pa, the index of hemolysis is negligible.

Paul et al, Artif Organs 2003, 27(6)
Platelet Trajectories

Fig. 5  Stagnant platelet trajectories and recirculation zones in HMII and HA5- (a) The recirculation zones and stagnant platelet trajectories were observed at the downstream of the flow straightener blades of HMII, with approximately 2 mm of the average eddy diameter. (b) Several entrapped platelet trajectories were observed at the entry of the impeller blades of the HMII, and closely following the rotational motion of impeller. (c) Fewer stagnant trajectories were observed at the rear hub region of the HA5 comparing to the HMII, and no recirculation zone was found. (d) No entrapped platelet trajectory was observed at the entry of the HA5 impeller. These platelet trajectories were represented as a time average of their residence time (184 ms).
Fig. 7 Markedly lower stress accumulation of platelet trajectories flow through impeller-shroud gap of HA5 representative shear stress and exposure time of five platelet trajectories flow through the impeller-shroud gap of (a) HMII and (b) HA5 VADs are shown. The platelet trajectories flowing through the HA5 has lower shear stress magnitude and shorter exposure time comparing to the trajectories flowing through the HMII.
Simulation of centrifugal blood pump

Computational fluid dynamics

University of Ljubljana
Faculty of Mechanical Engineering

Preliminary report R02
Preliminary report R02

Primož Drešar

Mentor: Dr. Jože Dušovnik
Co-Mentor: Dr. Igor Gregorič
Figure 13: Rotational flow encircled in red behind driving blades (vector representation of velocity [m s\(^{-1}\)] on XY plane)
Figure 14: Rotational flow encircled in red behind rotor blades and before diffuser (velocity vector representation on XY plane)
Wall Shear Stress

The representation of WSS is limited to surface projection. For improved shear stress evaluation some other methods were developed.

According to authors [4] shear stress of \( \tau > 150 \, \text{Pa} \) is correlated to hemolysis. Values with \( \tau > 9 \, \text{Pa} \) which may contribute to platelet activation (Figure 20) and finally locations with \( \tau < 0.8 \, \text{Pa} \) may correlate with thrombosis.
Figure 24: Scalar Shear Stress of 150 Pa applied to iso-surfaces closing a volume

Table 4: Volumes for critical Shear Stress Scalar (SSS) magnitudes

<table>
<thead>
<tr>
<th>Shear Stress Magnitude</th>
<th>Volume [m$^3$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8 Pa</td>
<td>1.657E-6</td>
</tr>
<tr>
<td>9 Pa</td>
<td>2.2617E-6</td>
</tr>
<tr>
<td>150 Pa</td>
<td>5.0871E-8</td>
</tr>
</tbody>
</table>

Table 4 show calculated volumes of fluid with critical SSS values (K.H.Fraser et. al, 2012).
Findings

• Distinguished flow is showing detachment behind diffuser blades. In this case improvement in diffuser blade geometry would be suggested.

• Taking into account that the bearing is also located behind guiding blades, it might suggest the reason for thrombosis appearance in the same location.
Clinical studies
H-Vad
Endurance trial
(for NEJM publ. / Presented by F. Pagani last year)

Treatment of Patients with Advanced Heart Failure Ineligible for Cardiac Transplantation with an Intra-pericardial Left Ventricular Assist Device

*Joseph G. Rogers¹, *Francis D. Pagani², Antone J. Tatooles³, Geetha Bhat³, Mark S. Slaughter⁴, Emma J Birks⁴, Steven W. Boyce⁵, Samer S. Najjar⁶, Valluvan Jeevanandam⁶, Allen S Anderson⁷, Igor D. Gregoric⁸, Hari Mallidi⁹, Katrin Leadley¹⁰, Keith D. Aaronson², O.H Frazier⁹, Carmelo A. Milano¹
Table 3: Summary of Adverse Events Occurring Through 2 Years for Subjects Receiving Study or Control Device

<table>
<thead>
<tr>
<th>As treated population</th>
<th>Study Device N=296</th>
<th>Control Device N=149</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with event</td>
<td>No. of events</td>
<td>EPPY (410.0 PY)</td>
</tr>
<tr>
<td>Overall Bleeding events</td>
<td>96 (60.8%)</td>
<td>425</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>45 (15.2%)</td>
<td>52</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>45 (15.2%)</td>
<td>47</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>103 (34.8%)</td>
<td>225</td>
<td>0.56</td>
</tr>
<tr>
<td>Cardiac Arrhythmia</td>
<td>111 (37.5%)</td>
<td>175</td>
<td>0.43</td>
</tr>
<tr>
<td>Hepatic Dysfunction</td>
<td>13 (4.4%)</td>
<td>13</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47 (15.9%)</td>
<td>62</td>
<td>0.15</td>
</tr>
<tr>
<td>Sepsis</td>
<td>69 (23.3%)</td>
<td>63</td>
<td>0.20</td>
</tr>
<tr>
<td>Driveline Exit Site Infection</td>
<td>56 (18.9%)</td>
<td>72</td>
<td>0.18</td>
</tr>
<tr>
<td>Stroke</td>
<td>85 (28.7%)</td>
<td>110</td>
<td>0.27</td>
</tr>
<tr>
<td>Ischemic Cerebrovascular Event</td>
<td>50 (16.9%)</td>
<td>65</td>
<td>0.16</td>
</tr>
<tr>
<td>Hemorrhagic Cerebrovascular Event</td>
<td>42 (14.2%)</td>
<td>45</td>
<td>0.11</td>
</tr>
<tr>
<td>TIA</td>
<td>24 (8.1%)</td>
<td>27</td>
<td>0.07</td>
</tr>
<tr>
<td>Renal Dysfunction</td>
<td>43 (14.5%)</td>
<td>54</td>
<td>0.13</td>
</tr>
<tr>
<td>Respiratory Dysfunction</td>
<td>84 (28.4%)</td>
<td>114</td>
<td>0.28</td>
</tr>
<tr>
<td>Right Heart Failure</td>
<td>110 (37.2%)</td>
<td>129</td>
<td>0.31</td>
</tr>
<tr>
<td>RVAD*</td>
<td>8 (2.7%)</td>
<td>8</td>
<td>0.02</td>
</tr>
<tr>
<td>Pump replacement#</td>
<td>23 (7.8%)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Site-reported event. #Events and EPPY are not applicable for pump replacement since only the first event is counted.

**Abbreviations**: EPPY – events per patient year; PY – patient years; GI - gastrointestinal; RVAD - right ventricular assist device; TIA – transient ischemic attack (<24 hours).

Note: P-values for the comparisons between percent of patients with events determined by the Proportion Method.
Figure 5: Forrest Plot of Risk Factors for: (A) Ischemic Cerebrovascular Accident (ICVA) and (B) Hemorrhagic Cerebrovascular Accident (HCVA) in the As-Treated Population for Subjects Receiving the Study Device.

A. ICVA

- MAP (> 90 mmHg)
- INR (≤ 2)
- ASA (≤ 81 mg)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (&gt; 90 mmHg)</td>
<td>14.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>INR (≤ 2)</td>
<td>3.0</td>
<td>0.002</td>
</tr>
<tr>
<td>ASA (≤ 81 mg)</td>
<td>2.2</td>
<td>0.034</td>
</tr>
</tbody>
</table>

B. HCVA

- MAP (> 90 mmHg)
- ASA (≤ 81 mg)
- INR (> 3)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (&gt; 90 mmHg)</td>
<td>9.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ASA (≤ 81 mg)</td>
<td>4.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>INR (&gt; 3)</td>
<td>5.0</td>
<td>0.001</td>
</tr>
</tbody>
</table>
PREVENtion of HeartMate II Pump Thrombosis Through Clinical Management (PREVENT)
PREVENT

• **PREVENTion** of HeartMate II Pump Thrombosis Through Clinical Management

• Prospective Multi-Center Study (US)
  – Up to 20 sites
  – Up to 300 patients

• Objectives:
  – Assess the incidence of HMII pump thrombosis in the current era when recommended clinical practices are adopted
  – Identify risk factors associated with pump thrombosis events
Algorithm for the Diagnosis and Management of Pump Thrombosis

1. **Power Elevations**
   - Early or Late?
     - Early
       - Consider Echocardiogram (± Pump Speed Changes)
     - Late
       - Isolated LDH Rise

2. **Isolated LDH Rise**
   - Hemolysis?
     - Yes
       - Optimize Anticoagulation
       - Check Serum Indices of Hemolysis
     - No
       - Consider Echocardiogram (± Pump Speed Changes)

3. **Evidence of Hemolysis**
   - New CHF Symptoms
     - Admit to Hospital
     - Consider IV Heparin
     - CXR
     - Echocardiogram (± Pump Speed Changes), Consider RHC
     - Monitor LDH, pfHgb, indirect bilirubin, Haptoglobin, Renal Function
   - LV Unloading?
     - Yes
       - Consider Surgical Correction
     - No
       - Chest CT Angiogram
         - Inflow Cannula Malposition or Outflow Graft Obstruction?
           - Yes
             - ICU – Add Inotropes, Diuresis as Needed
           - No
             - Resolved?
               - Yes
                 - Pump Exchange or Urgent Transplantation or Explant for Recovery
               - No
                 - Surgical Candidate?
                   - Yes
                     - Consider Thrombolytics in Patient with End Organ Dysfunction or Hemodynamic Compromise
                   - No
                     - Resolved?
                       - Yes
                         - Pump Exchange or Urgent Transplantation or Explant for Recovery
                       - No
                         - Close Follow Up

**Definitions:**

1. **Power Elevations:**
   - Sustained (>24hrs) Power > 10W; or
   - Sustained (>24hrs) Power Increase > 2W from Baseline

2. **Isolated LDH Rise:**
   - LDH > 3x Upper Limit of Normal (ULN)

3. **Hemolysis:**
   - Clinical Diagnosis; or
   - LDH > 3x ULN and pfHgb > 40

4. **Resolved:** Normal Powers, Normal LDHs, Sufficient LV Unloading, and No Clinical Evidence of Hemolysis

**Abbreviations:** LV, Left Ventricle; LDH, Lactate Dehydrogenase; pfHgb, Plasma-free Hemoglobin; RHC, Right Heart Cath; CXR, Chest X ray
Results - Primary Endpoint
Confirmed Pump Thrombosis at 90 Days 200 pts

P=0.005 (significant)

P=0.784 (not significant)

P=0.500 (not significant)

2.5% [5 events/200]


Conclusion

• Best to avoid LVAD Thrombosis is to prevent it
• Patient selection
• Better pump designs
• Better Blood – surface interface
• Improved flow dynamics
New LVAD Trials
HeartMate III: Design Goals

- Build upon the highly successful HeartMate II LVAS
- Enhanced AE profile
- Increased surgical ease
- Elevate the patient experience
A Healthy Respect for the Blood

What influences hemocompatibility?

- **Hemocompatibility**¹
  - Minimize shear stress
  - Minimize stasis
  - Minimize flow patterns that minimize activation of blood components
  - Minimize interactions between the blood and the contacting surfaces


133CAUTION: Investigational device. Limited by federal (U.S.) law to investigational use.

1011053 8/26/14
Design Configuration

Inlet Recirculation

Shroud Recirculation

Main Flow
HeartMate III: Full MagLev Technology

Key Design Benefits: Optimized Geometry

—HeartMate III secondary flow paths are ~0.5 mm along the side, and ~1.0 mm pump above and below the rotor.
—HeartMate III pump surfaces are flat and flow is undisturbed.
**How much difference is there?**
From a **Red Blood Cell’s Point of View**

<table>
<thead>
<tr>
<th></th>
<th>Gap Size</th>
<th># of Red Blood Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full MagLev</td>
<td>1,000μm</td>
<td>167</td>
</tr>
<tr>
<td>Hydrodynamic Bearing</td>
<td>50μm</td>
<td>8</td>
</tr>
</tbody>
</table>

6-8 μm

at least 20X larger blood flow paths

Stacked RBCs

---

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1011053 8/26/14
HeartMate III: Artificial Pulse

• Rotary pumps have been used chronically with constant rotor speed in more than seventeen thousand patients, confirming that a pulse is not needed for survival.

• However, we hypothesize that augmenting the pulsatility that is generally diminished in rotary pump patients may have benefit for some patients or in certain circumstances, perhaps in part addressing adverse events such as aortic insufficiency, bleeding, and thrombogenesis.

• The HeartMate III centrifugal blood pump is intrinsically capable of very sharp speed changes. We have produced an “artificial pulse” feature that has so far in pre-clinical studies proved to contribute negligible hemolysis and require low incremental power consumption.
Future

- M - VAD

- A - VAD
MINIATURE VAD Development
- for Adults

Circulite
Future LVADs
IRB approved protocols:
- INTERMACS
- LAPTOP-HF
- PROACT (On-X Valve)
- SynCardia TAH Postmarket Surveillance
- SynCardia Freedom driver
- PARTNER II TRIAL
- ROADMAP
- Amplatzer Cardiac Plug Trail
- ABSORB III Randomized Trial
- TEG monitoring in LVADs
- PARACHUTE IV
- TRIS
- Portico TAVR
- Sepian III PARTNER II Version 4.5
- Transfusions in LVADs and HT
- PREVENT
- Recover Right study (Impella RP)
- RELIANTHEART
- Von Willebrand Syndrome in LVADs
- Pathological assessment of explanted hearts
- Heart Mate III

Protocols in submission:
- Aortic annulus measurement
- Outcomes in AHF patients who require MCS or HT
- Left Atrial Pressure Monitoring - Millar catheter
- Milrinone therapy in advanced heart failure
- Clopidogrel in Cardiogenic Shock
- TandemHeart and ECMO; transfusion threshold
- Advanced ECG to Identify non-ST Elevation

Center for Advanced Heart Failure
The University of Texas Medical School at Houston
UT Physicians
MEMORIAL HERMANN
Heart & Vascular Institute
Texas Medical Center
THANK YOU
END