INTERMACS: Present and Future

Summary of the Registry – Including Analyses of:
Quality of Life, Infection, Stroke, and Other Adverse Events

James Kirklin, MD
Disclosure

I have no financial relationships to disclose
Between June 23, 2006 and December 31, 2013, 158 hospitals participated in INTERMACS and, of these, 141 hospitals actively contributed information on a total of 10,542 patients. Cumulative patient accrual and the number of participating hospitals over this time period are displayed below.
<table>
<thead>
<tr>
<th>Year</th>
<th>Cont Intra Pump</th>
<th>Puls Intra TAH</th>
<th>Puls Intra Pump</th>
<th>Puls Para Pump</th>
</tr>
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<tbody>
<tr>
<td>2006</td>
<td>1</td>
<td>1</td>
<td>78</td>
<td>18</td>
</tr>
<tr>
<td>2007</td>
<td>0</td>
<td>22</td>
<td>260</td>
<td>56</td>
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<tr>
<td>2008</td>
<td>459</td>
<td>30</td>
<td>180</td>
<td>71</td>
</tr>
<tr>
<td>2009</td>
<td>866</td>
<td>24</td>
<td>54</td>
<td>66</td>
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<tr>
<td>2010</td>
<td>1581</td>
<td>29</td>
<td>13</td>
<td>29</td>
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<tr>
<td>2011</td>
<td>1838</td>
<td>26</td>
<td>2</td>
<td>54</td>
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<tr>
<td>2012</td>
<td>2207</td>
<td>41</td>
<td>0</td>
<td>30</td>
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<tr>
<td>2013</td>
<td>2420</td>
<td>66</td>
<td>0</td>
<td>20</td>
</tr>
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</table>

Figure 4: Implants: June 2006 – December 2013, n=10542
Family of MACS

- PediMACS
- MedaMACS
- U-MACS
- IMACS (non-North American Sites)
Family of MACS

**INTERMACS®** – A North American registry established in 2005 for patients who are receiving mechanical circulatory support device therapy to treat advanced heart failure.

**PediMACS** – The pediatric portion of INTERMACS. While INTERMACS has always included durable devices implanted in pediatric patients, pediMACS has been developed to focus on capturing data elements unique to pediatric patients.

**MedaMACS** – The Medical Arm of Mechanically Assisted Circulatory Support (MedaMACS Registry), a prospective study of medically managed advanced heart failure patients, will report the nature of optimal contemporary medical therapy for heart failure and provide information on medical outcomes in terms of timed endpoints of mechanical support, transplant, or death through two years of follow-up.

**IMACS** – The International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support (IMACS) is an international registry intended to enroll and follow patients who receive durable mechanically assisted circulatory support devices (MCSD) in all countries and hospitals that wish to participate.
# INTERMACS Research

## 2007 – April, 2014

### I. Published Papers
- Total papers: 28
- Unique 1st authors: 14
- Unique co-authors: 88
- Journals: 8

### II. Abstracts/Presentations
- Total abstracts: 55
- Unique 1st authors: 42
- Unique co-authors: 209
- Scientific meetings: 6

### III. Total Citations
- 1,396
Top Cited Papers In JHLT
(top 25 most cited articles published since 2009)

2 Second INTERMACS annual report: More than 1,000 primary left ventricular assist device implants, Kirklin et al. 168

3 The Fourth INTERMACS Annual Report: 4,000 implants and counting, Kirklin et al. 157

4 Third INTERMACS annual report: The evolution of destination therapy in the United States, Kirklin et al. 149

6 INTERMACS Profiles of Advanced Heart Failure: The Current Picture, Stevenson et al. 128

10 Predictors of Death and Transplant in Patients With a Mechanical Circulatory Support Device: A Multi-institutional Study, Holman et al. 87

16 Fifth INTERMACS annual report: Risk factor analysis from more than 6,000 mechanical circulatory support patients, Kirklin et al. 74

Extracted from Scopus
DAAP Requests Per Year

Number of DAAP Requests

Year

2007 2008 2009 2010 2011 2012 2013 2014

Data Requests (245)

Research datasets*:
- Sent out: 2007-2014: 15
- Research projects “to be reviewed by DAAP”: 6

Projected

75

Research analysis done by external statistical groups

* Research analysis done by external statistical groups
<table>
<thead>
<tr>
<th>Francis Pagani, Chair</th>
<th>Mark Slaughter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin Strüber</td>
<td>Carmelo Milano</td>
</tr>
<tr>
<td>Anson Cheung</td>
<td>Eduardo Rame</td>
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<tr>
<td>Aamir Jeewa</td>
<td>Ranjit John</td>
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<tr>
<td>Sean Pinney</td>
<td>Francisco Arabia</td>
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<tr>
<td>Daniel Goldstein</td>
<td>Salpy Pamboukian</td>
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<tr>
<td>Monica Colvin-Adams</td>
<td>David Rosenthal</td>
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<tr>
<td>John Spertus</td>
<td>Joseph Rogers</td>
</tr>
<tr>
<td>Josef Stehlik</td>
<td>Leah Edwards</td>
</tr>
<tr>
<td>Jennifer Cowger</td>
<td>Marissa Miller</td>
</tr>
</tbody>
</table>
Planned Major Research for 2014-2015

1. Analyses of the major outcomes: death, transplant, recovery
   - Risk factors
   - Patient specific predictions (with “calculators”)
   - Competing outcomes
     - Patient specific: sub-setting
     - Patient specific: modeling
2. Adverse event burden, Quality of Life, survival
   - Quantification of weights for each adverse event
   - Simulations with “life satisfaction score” (LSS)
3. Total artificial heart:
   - Complete analysis
4. MCS Resource utilization (cost) and Cost-effectiveness analyses
Major Research Initiative: The Role of MCS Destination Therapy for Ambulatory Heart Failure
Two Emerging Patient Groups For Lifetime Support

- Progression toward higher INTERMACS Levels
- Triage from transplant waiting lists
How can INTERMACS help shape the Future of MCS?

Destination Therapy

Rate of Evolution from “Transplant Ineligible” to “Transplant Alternative”
INTERMACS: Patient Selection

Patient Profile/ Status: INTERMACS Levels

1. Critical cardiogenic shock
2. Progressive decline
3. Stable but inotrope dependent
4. Recurrent advanced HF
5. Exertion intolerant
6. Exertion limited
7. Advanced NYHA III

Degrees of Class IV

AMBULATORY HEART FAILURE PATIENTS
## June 2006 – December 2012

<table>
<thead>
<tr>
<th>PATIENT PROFILE AT TIME OF IMPLANT</th>
<th>IMPLANT DATE PERIOD</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>1 Critical Cardio Shock</td>
<td>652</td>
<td>535</td>
<td>321</td>
<td>29.2 %</td>
<td>14.8 %</td>
<td>15.3 %</td>
<td></td>
</tr>
<tr>
<td>2 Progressive Decline</td>
<td>953</td>
<td>1425</td>
<td>788</td>
<td>42.7 %</td>
<td>39.6 %</td>
<td>37.6 %</td>
<td></td>
</tr>
<tr>
<td>3 Stable but Inotrope dependent</td>
<td>333</td>
<td>952</td>
<td>596</td>
<td>14.9 %</td>
<td>26.4 %</td>
<td>28.4 %</td>
<td></td>
</tr>
<tr>
<td>4 Resting Symptoms</td>
<td>201</td>
<td>480</td>
<td>284</td>
<td>9.0 %</td>
<td>13.3 %</td>
<td>13.5 %</td>
<td></td>
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<tr>
<td>5 Exertion intolerant</td>
<td>42</td>
<td>112</td>
<td>63</td>
<td>1.8 %</td>
<td>3.1 %</td>
<td>3.0 %</td>
<td></td>
</tr>
<tr>
<td>6 Exertion limited</td>
<td>25</td>
<td>65</td>
<td>26</td>
<td>1.1 %</td>
<td>1.8 %</td>
<td>1.2 %</td>
<td></td>
</tr>
<tr>
<td>7 Advanced NYHA Class 3</td>
<td>21</td>
<td>25</td>
<td>15</td>
<td>0.9 %</td>
<td>0.6 %</td>
<td>0.7 %</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>2227</td>
<td>3594</td>
<td>2093</td>
<td>100.0 %</td>
<td>100.0 %</td>
<td>100.0 %</td>
<td></td>
</tr>
</tbody>
</table>
Ambulatory Patients With 2 HF Hospitalizations:
Based on how you feel right now, would you want an LVAD?

Responses not affected by age, demographics, prior knowledge of LVAD, or number of HF hospitalizations
This is a randomized trial of the HMII Ventricular Assist System (VAS) versus the best medical therapy in patients with advanced heart failure and whose illness is not severe enough to qualify for transplant or permanent left ventricular assist device (LVAD) therapy based on current guidelines.
INTERMACS Profiling Stratifies Risk of Death or VAD in Medically Managed Heart Failure – Prelim Data

Estimated Survival with Continuous Flow VAD in Profiles ≥4

INTERMACS 6/7
INTERMACS 5
INTERMACS 4

Stewart et al
ISHLT 2013

*Censored at Transplant
INTERMACS Profiling Stratifies Risk of Death or VAD in Medically Managed Heart Failure – Prelim Data

Estimated Survival with Continuous Flow VAD in Profiles ≥4

80-85%

P<0.001

Survival Free of VAD*

0 3 6 9 12

Months since Enrollment

Stewart et al
ISHLT 2013

*Censored at Transplant
Which Treatment would a patient select if the expected survival with 2 therapies is nearly equivalent?
Evolution of the Decision Algorithm
VADs for Ambulatory Heart Failure

- QOL as much as survival will drive the paradigm
EQ5D Visual Analog Scale (VAS) across time (± SE)

Figure 17

Continuous Flow LVAD/BiVAD implants: 2008 – 2013, n= 9372

<table>
<thead>
<tr>
<th>Implant Eras</th>
<th>P values</th>
</tr>
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<tbody>
<tr>
<td>2008 – 2010</td>
<td>&lt; .0001</td>
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<tr>
<td>2011 - 2013</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Months Post Implant</th>
<th>Pre-Implant</th>
<th>3 month</th>
<th>6 month</th>
<th>12 month</th>
<th>18 month</th>
<th>24 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>P values</td>
<td>&lt; .0001</td>
<td>.05</td>
<td>.07</td>
<td>.12</td>
<td>.48</td>
<td>.65</td>
</tr>
</tbody>
</table>
Figure 19

Continuous Flow LVAD/BiVAD implants: 2008 – 2013, n= 9372

EQ5D Dimension: Usual Activities

By Era
2008-2010
2011-2013

% with Problems

Pre-Implant < .0001
3 mths .14
6 mths .86
12 mths .75
18 mths .78
24 mths .35

EQ5D Dimension: Usual Activities
Change in HRQOL from Before to After DT MCS is Similar for Older and Younger Patients: Analyses from INTERMACS

Kathleen L. Grady, David C. Naftel, Susan Myers, Mary Amada Dew, Gerdi Weidner, Kathy Idrissi, Hochang Lee, Edwin C. McGee Jr, and James K. Kirklin

"This project has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN268201100025C"
EQ5D Dimension: Usual Activities*

By Age Groups

P(across time):
- age < 60 years, p < .0001
- age 60–69 years, p < .0001
- age 70+ years, p < .0001

*N=118, N=145, N=153

87% 86% 79%

57% 57% 57%

48% 47% 42%

54% 41% 41%

Total N:
- Pre-Implant: 317, 375, 375
- 3 Month: 201, 231, 239
- 6 Month: 189, 232, 246
- 12 Month: 164, 203, 220

P value: .003

*‘Too Sick’ assigned as extreme problems
VADs for Ambulatory Heart Failure

- QOL as much as survival will drive the paradigm
- QOL is profoundly affected by adverse events
Specific Adverse Events that challenge the long-term implementation of MCS (even in the ambulatory patient)

- Early mortality and its causes
- Stroke
- Infection of driveline and pump pockets
- Right Ventricular Failure
- Pump malfunction/Thrombosis
- Renal Dysfunction

Plus Quality of Life and Functional Capacity
V. Adverse Event Definitions-
Precision in the definitions is critical to the accurate identification and quantification of adverse events

In moving from protocol v3.0 (May 2, 2012) to protocol v4.0 (June 2, 2014), all AE definitions were reviewed. The major modifications are shown in the next slides.
A plasma-free hemoglobin value that is greater than 40 mg/dl, in association with clinical signs associated with hemolysis (e.g., anemia, low hematocrit, hyperbilirubinemia) occurring after the first 72 hours post-implant. Hemolysis related to documented non-device-related causes (e.g. transfusion or drug) is excluded from this definition.
Minor Hemolysis: A plasma-free hemoglobin value greater than 20 mg/dl or a serum lactate dehydrogenase (LDH) level greater than two and one-half time (2.5x) the upper limits of the normal range at the implanting center occurring after the first 72 hours post-implant in the absence of clinical symptoms or findings of hemolysis or abnormal pump function.
4.0 Hemolysis Definition: Major Hemolysis

**Major Hemolysis:** A plasma-free hemoglobin value greater than 20 mg/dl or a serum lactate dehydrogenase (LDH) level greater than two and one-half times (2.5x) the upper limits of the normal range at the implanting center occurring after the first 72 hours post-implant and associated with clinical symptoms or findings of hemolysis or abnormal pump function. Major Hemolysis requires the presence of one or more of the following conditions:

- Hemoglobinuria (“tea-colored urine”)
- Anemia (decrease in hematocrit or hemoglobin level that is out of proportion to levels explainable by chronic illness or usual post-VAD state)
- Hyperbilirubinemia (total bilirubin above 2 mg%, with predominately indirect component)
- Pump malfunction and/or abnormal pump parameters
3.0 Right Heart Failure
Definition

Symptoms and signs of persistent right ventricular dysfunction [central venous pressure (CVP) > 18 mmHg with a cardiac index <2.3 L/min/m² in the absence of elevated left atrial/pulmonary capillary wedge pressure (greater than 18 mmhg), tamponade, ventricular arrhythmias or pneumothorax] requiring RVAD; implantation; or requiring inhaled nitric oxide or inotropic therapy for a duration of more than 1 week at any time after LVAD implantation.”
4.0 Right Heart Failure

Definition

Symptoms or findings of persistent right ventricular failure characterized by both of the following:
Documentation of elevated central venous pressure (CVP) by:

**Direct measurement** (e.g., right heart catheterization) with evidence of a central venous pressure (CVP) or right atrial pressure (RAP) > 16 mmHg.

or

Findings of significantly dilated inferior vena cava with absence of inspiratory variation by echocardiography,

or

Clinical findings of elevated jugular venous distension at least half way up the neck in an upright patient.

**Manifestations of elevated central venous pressure characterized by:**

Clinical findings of peripheral edema (≥2+ either new or unresolved),

or

Presence of ascites or palpable hepatomegaly on physical examination (unmistakable abdominal contour) or by diagnostic imaging,

or

Laboratory evidence of worsening hepatic (total bilirubin > 2.0) or renal dysfunction (creatinine > 2.0).

IF the patient meets the definition for right heart failure, the severity of the right heart failure will be graded according to the following scale below.

(NOTE: For right heart failure to meet severe or severe acute severity, direct measurement of central venous pressure or right atrial pressure must be one of the criteria)
Device Malfunction

Device malfunction denotes a failure of one or more of the components of the MCSD system which either directly causes or could potentially induce a state of inadequate circulatory support (low cardiac output state) or death. The manufacturer must confirm device failure. A failure that was iatrogenic or recipient-induced will be classified as an Iatrogenic/Recipient-Induced Failure.

Device failure should be classified according to which components fails as follows:

1) **Pump failure** (blood contacting components of pump and any motor or other pump actuating mechanism that is housed with the blood contacting components). In the special situation of **pump thrombosis**, thrombus is documented to be present within the device or its conduits that result in or could potentially induce circulatory failure.

2) **Non-pump failure** (e.g., external pneumatic drive unit, electric power supply unit, batteries, controller, interconnect cable, compliance chamber)
A **Device Malfunction** occurs when any component of the MCSD system ceases to operate to its designed performance specifications or otherwise fails to perform as intended. Performance specifications include all claims made in the Instructions for Use.

Device malfunctions can be further defined as **major** or **minor**:

**Major device malfunction**, otherwise known as failure, occurs when one or more of the components of the MCSD system either directly causes or could potentially induce a state of inadequate circulatory support (low cardiac output state) or death. A failure that was iatrogenic or recipient-induced will be classified as an Iatrogenic/Recipient-Induced Failure. A device malfunction or failure is considered major when one of the following conditions occurs:
- Suspected or confirmed pump thrombus (see below)
- Urgent transplantation (immediate 1A listing for transplant)
- Pump replacement
- Pump explant
- Breach of integrity of drive line that required repair
- Death

**Minor device malfunction** includes inadequately functioning external components which require repair or replacement but do not result in 1a-f. Device malfunction does not apply to “routine” maintenance which includes repair/replacement of: external controller, pneumatic drive unit, electric power supplies, batteries and interconnecting cables.
Pump Thrombus represents a special case of major device malfunction and can be delineated as suspected pump thrombus or confirmed pump thrombus. Pump thrombus will be classified as “SUSPECTED” (see definition below) based upon clinical, biochemical, or hemodynamic findings or “CONFIRMED” (see definition below) based upon device inspection or incontrovertible radiologic studies or absence of appropriate Doppler flow signals that confirms thrombus within the device or its conduits that results in or could potentially induce circulatory failure.

1. **Suspected pump thrombus** is a pump-related malfunction in which clinical or MCSD parameters suggest thrombus on the blood contacting components of the pump, cannulae, or grafts. Signs and symptoms should include at least 2 of the 3 following criteria:
   a) Presence of hemolysis
   b) Presence of heart failure not explained by structural heart disease
   c) Abnormal pump parameters

Suspected pump thrombus should be accompanied by 1 or more of the following events or interventions:
   i. treatment with intravenous anticoagulation (e.g., heparin), intravenous thrombolytics (e.g., tPA), or intravenous antiplatelet therapy (e.g., eptifibatide, tirofiban)
   ii. pump replacement
   iii. pump explantation
   iv. urgent transplantation (UNOS status 1A)
   v. stroke
   vi. arterial non-CNS thromboembolism
   vii. death
2. **Confirmed pump thrombus** is a major pump-related malfunction in which thrombus is confirmed within the blood contacting surfaces of device inflow cannula or outflow conduit or grafts. This can be reported via direct visual inspection or by incontrovertible contrast radiographic evidence or by the absence of an appropriate Doppler flow signal that results in or could potentially induce circulatory failure or result in thromboembolism.

If a Suspected Pump Thrombus event is ultimately confirmed through visual inspection following pump replacement, urgent transplantation or upon autopsy following death, the event will be adjudicated by the CEC for reclassification to Confirmed Pump Thrombus.
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Pulsatile (n=127)</th>
<th>Continuous (n=1160)</th>
<th>Hazard Ratio²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device malfunction</td>
<td>38 events, 3.69</td>
<td>100 events, 1.15</td>
<td>3.21</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Infection</td>
<td>236 events, 22.91</td>
<td>705 events, 8.09</td>
<td>2.83</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>30 events, 2.91</td>
<td>141 events, 1.62</td>
<td>1.80</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Venous thrombotic event</td>
<td>11 events, 1.07</td>
<td>56 events, 0.64</td>
<td>1.66</td>
<td>0.03</td>
</tr>
<tr>
<td>Neurologic dysfunction</td>
<td>30 events, 2.91</td>
<td>162 events, 1.86</td>
<td>1.57</td>
<td>0.006</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>41 events, 3.98</td>
<td>230 events, 2.64</td>
<td>1.51</td>
<td>0.004</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>55 events, 5.34</td>
<td>339 events, 3.89</td>
<td>1.37</td>
<td>0.009</td>
</tr>
<tr>
<td>Bleeding</td>
<td>150 events, 14.56</td>
<td>1040 events, 11.94</td>
<td>1.22</td>
<td>0.008</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>7 events, 0.68</td>
<td>50 events, 0.57</td>
<td>1.18</td>
<td>0.24</td>
</tr>
<tr>
<td>Right heart failure</td>
<td>14 events, 1.36</td>
<td>151 events, 1.73</td>
<td>0.78</td>
<td>0.75</td>
</tr>
</tbody>
</table>
VADs for Ambulatory Heart Failure

• QOL as much as survival will drive the paradigm

• QOL is profoundly affected by adverse events

• Do ambulatory patients have fewer adverse events than Intermacs level 1 and 2 patients?
Adult primary continuous flow LVADs, n=5366
Implants: June 2006 – 2012
Time to First Stroke

% Freedom  Months post implant
97% 1
95% 3
93% 6
89% 12
83% 24
81% 36

Event: Time to first Stroke (censored at death, transplant or explant recovery)
Adult Primary Continuous Intracorporeal LVADs: 896
By INTERMACS Patient Profile Levels

 Level 1, n=172, neuro events=23
 Level 2, n=396, neuro events=28
 Level 3, n=172, neuro events=12
 Level 4-7, n=156, neuro events=15

% Free from Neurological Events

0 3 6 9 12 15 18 21 24

Event: First Neurological Event

p = .08
Implants: June 2006 – June 2012
Adult primary continuous LVAD (includes RVADs at same operation): n=5515
First PRI Location: n=849

Freedom from PRI
Month after Device Implant

Event: First PRI (censored at death, transplant or explant recovery)

By Location of Pump Related Infection

p (overall) < 0.0001

First Pump Pocket Infection, n=108
First Pump Interior Infection, n=22
First Driveline infection n=719

Note: a patient can have multiple locations for a single infection episode, therefore the total number of infection locations will not add up to the total number of patients
Implants June 2006 – March 2011: Pump-related Infection Analysis

Adult primary continuous LVAD (includes RVADs at same operation): n=2900
First PRI: n=428

Freedom from PRI
Month after Device Implant

Event: First PRI (censored at death, transplant or explant recovery)

<table>
<thead>
<tr>
<th>Patient Profile Levels</th>
<th>n</th>
<th>First PRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1: Critical Cardiogenic Shock</td>
<td>428</td>
<td>71</td>
</tr>
<tr>
<td>Level 2: Progressive Decline</td>
<td>1256</td>
<td>184</td>
</tr>
<tr>
<td>Level 3: Stable but inotrope dependent</td>
<td>686</td>
<td>93</td>
</tr>
<tr>
<td>Level 4: Resting symptoms</td>
<td>361</td>
<td>56</td>
</tr>
<tr>
<td>Levels 5-7: (Exertion intolerant, Exertion limited, NYHA Class 3)</td>
<td>169</td>
<td>24</td>
</tr>
<tr>
<td>Totals</td>
<td>2900</td>
<td>428</td>
</tr>
</tbody>
</table>

\[ p \text{ (overall)} = 0.73 \]
Adult Primary Continuous Flow LVADs & BIVADs, DT and BTT, n=5436
Implants: June 2006 – June 2012
Time to First Major Event*

* Major Event: First occurrence of infection, bleeding, device malfunction, stroke or death

Patients=5436, Events=3611

<table>
<thead>
<tr>
<th>Months</th>
<th>% Freedom</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59%</td>
</tr>
<tr>
<td>3</td>
<td>48%</td>
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<td>6</td>
<td>40%</td>
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<tr>
<td>12</td>
<td>30%</td>
</tr>
<tr>
<td>24</td>
<td>19%</td>
</tr>
<tr>
<td>36</td>
<td>14%</td>
</tr>
</tbody>
</table>
Adult Primary Continuous Flow LVADs & BIVADs, DT and BTT, n=5436
Implants: June 2006 – June 2012
Time to First Major Event* by INTERMACS Level

* Major Event: First occurrence of infection, bleeding, device malfunction, stroke or death

Levels 4-7, n=1038
Events=680

Level 1: N=819
Events=585

Level 2: n=2180
Events=1477

Level 3: n=1399
Events=869

p < .0001

Figure 21
How do Readmissions Impact Survival among Patients with Continuous-Flow Left Ventricular Assist Devices? Findings from INTERMACS

03/31/2014

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### Risk Factors for Death after “90 days post discharge”

<table>
<thead>
<tr>
<th>Rehospitalizations during 90 days:</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>p-value</td>
</tr>
<tr>
<td>Total # Rehosp</td>
<td>1.41</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Infection Rehosp</td>
<td>2.77</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Bleeding Rehosp</td>
<td>1.35</td>
<td>.01</td>
</tr>
<tr>
<td>Cardiac Arrhythmia Rehosp</td>
<td>1.47</td>
<td>.03</td>
</tr>
<tr>
<td>Neurological Rehosp</td>
<td>2.03</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Pulmonary Disorder Rehosp</td>
<td>2.59</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Planned Procedure Rehosp</td>
<td>0.90</td>
<td>.59</td>
</tr>
<tr>
<td>RHF Rehosp</td>
<td>2.68</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

* Effect of rehospitalizations are adjusted for significant pre-implant risk factors (age, creatinine, INR, RA pressure, ascites, history of CABG, INTERMACS Level)
**Adult Primary Continuous Flow LVAD(+/−RVAD), n=3041**

**Event:** Time to 1\textsuperscript{st} Readmission

- **Level 1:** 435, readmissions = 309
- **Level 2:** 1288, readmissions = 955
- **Level 3:** 739, readmissions = 558
- **Levels 4-7:** 579, readmissions = 441

**overall p=.50**

*Patients discharged from index hospitalization*
In the current state of MCS technology, better “risk” status at implant provides limited or no “protection” against serious adverse events.
Interaction between Survival, Adverse Events, and Life Satisfaction in Decisions about Medical Rx vs Transplant vs VAD Therapy – the need for Quantification
Hypothesis: the SEMI-QUANTIFICATION of the subjective outcomes of “Is your life better with the device?” or “Are you functional with a good quality of life?” will become a critical component of the denominator of the Cost-effectiveness calculations.
Future of Tx/VAD Rx:
Refinement of “Cost-Effective Care Ratio

- Cost (new strategy) – Cost (current strategy)  
  Effect (new therapy) – Effect (current therapy)
Future of Tx/VAD Rx: Refinement of “Cost-Effective Care Ratio

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Effectiveness will be some combination of survival and life satisfaction
Future of Tx/VAD Rx: Refinement of “Cost-Effective Care”

- Cost (new strategy) – Cost (current strategy)

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Mathematical incorporation of INTERMACS Adverse Event Burden Score into denominator of the CEC equation.
Simplistic Grading of Adverse Event Burden: a platform for discussions on Quantification (1 is mild, 4 is bad):

**INTERMACS ADVERSE EVENT SCORE**

- Permanent Event-related disability – 4
- No disability but important impact on daily activities – 3
- Required a major operation, but no lasting disability – 2
- Resumption of pre-event activities - 1
Elements of Decision

- Survival estimate
- Life Satisfaction Score

A non-linear summation of these produces a Life Satisfaction/Survival Score
## Assumptions

<table>
<thead>
<tr>
<th>LSS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (worst)</td>
<td>While on waiting list, status 1</td>
</tr>
<tr>
<td>2</td>
<td>While on waiting list, status 2</td>
</tr>
<tr>
<td>3</td>
<td>After LVAD</td>
</tr>
<tr>
<td>4 (best)</td>
<td>After Cardiac Transplant</td>
</tr>
</tbody>
</table>

### Waiting Time (with co-morbidities):  
- Status 2 = 2 yrs  
- Status 1 = 1 yr

### Median Survival  
- CTx (with co-m) = 5 yrs  
- LVAD = 4 yrs
Status 2 with Co-morbidities

“Wait for Cardiac Transplantation”

Cum. LSS

LSS = 2

0

2 yrs

LSS = 4

4 yrs

LSS = 4

12

“Immediate LVAD Therapy”

Cum. LSS

LSS = 3

0

2 yrs

12

4 yrs
LVAD: Survival

Medical Survival before Tx

LVAD offers a survival benefit

% Survival

Time

6 mo 12 mo 18 mo 24 mo 30 mo 36 mo 42 mo 48 mo
LVAD offers a survival benefit

% Survival

Time

6 mo 12 mo 18 mo 24 mo 30 mo 36 mo 42 mo 48 mo

LVAD: Survival

Medical Survival before Tx
For the stable NYHA III/IV patient, LVAD could offer a survival benefit, but if the adverse event burden is high (and LSS is low), medical therapy might offer a better quality of life.
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For the stable NYHA III/IV patient, LVAD could offer a survival/LSS benefit if the adverse event burden is sufficient to preserve an advantage over medical therapy.
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• Final recommendations will weigh heavily on time-related depictions (curves) of mathematical solutions to these LSSS equations.
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• It will be our charge to develop the language and refine the equations to facilitate these complex decisions.