Recovery – from myocardium to patient quality of life

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Head, Section of Heart Failure, Transplant and MCS Director, ISHLT Transplant Registry
Disclosure statement

- I have no relevant financial conflicts of interest to disclose
- I will discuss off-label use of left ventricular assist devices
Clinical scenario

- 22-year-old female
- Non-ischemic cardiomyopathy
- HF NYHA IV / stage D, inotropic dependent

LVEDD = 64 mm, EF = 20 %
Expected survival
Expected survival - medical therapy

Clinical trials in NYHA III/IV HF
Survival in patients on inotropic support
Seattle HF Model
Expected survival – heart transplant

- **NYHA III-IV, medical therapy**
- **Heart transplant**

Survival (%) vs. Years

U HEALTH UNIVERSITY OF UTAH
Expected survival - BTT VAD

Survival (%)

Years

0 1 2 3 4 5 6 7 8 9 10

NYHA III-IV, medical therapy
Heart transplant
LVAD BTT strategy

BTT LVAD data courtesy of Kirklin JK, Naftel DC
Expected survival – DT VAD

Data courtesy of Kirklin JK, Naftel DC
Expected survival - general population

Adapted from National Vital Statistics Reports. 58 (21), 2010
Is aiming for recovery a better option?

Or could it be?

LV Structure

LV Function

Initial Insult

Reverse remodeling/Recovery

LVAD Unloading

LOAD

Cardiac Remodeling
Recovery rate in BTR investigations of chronic HF

No Adjuvant Drug Therapy Protocol

<table>
<thead>
<tr>
<th>Group</th>
<th>“Cardiac Recovery” Patients</th>
<th>Total Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berlin Group</td>
<td>19%</td>
<td></td>
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<tr>
<td>US LVAD Working Group</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Gothenburg Group</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Pittsburgh Group</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Vancouver Group</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Texas Heart Institute Group</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>US IMAC Group</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>Harefield University of Athens Group</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>Montefiore Group</td>
<td>24%</td>
<td></td>
</tr>
</tbody>
</table>

Aggressive Adjuvant Drug Therapy
INTERMACS - Competing Outcomes for Continuous Flow LVADs (without RVAD implant at time of LVAD operation)
Primary Prospective Implants: June 23, 2006 to June 30, 2014

- Alive (device still in place):
  - 61.8% at 12 months

- Death (before transplant): 19.9%

- Transplant: 17.5%

- Explanted (recovery): 0.7%
• **Known:**
  - LV recovery with mechanical unloading can happen

• **Unknown:**
  - mechanisms
  - incidence
  - likelihood HF recurrence

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**Patient selection?**
**Adjuvant therapy testing?**
Regression of structural changes

No signs of regression to atrophy

Hypertrophy regression during VAD unloading

VAD Unloading
Reverse Cardiac Remodeling

- Metabolic
- Molecular
- Structural
- Microstructural
- Ultrastructural

Cardiac Remodeling

Drakos SG et al. JACC 2010
Diakos N et al. JACC 2014
Microvessel density

Drakos SG et al. JACC 2011
Systolic functional response in time

‘Responder’ definition:
1. LVEF $\uparrow >40\%$
2. LVESV $\downarrow >20\%$

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Drakos, Stehlik, Kfoury et al. JACC 2013
Wever-Pinzon J et al. JACC 2016
Cardiac metabolism

Glycolysis Upregulation - Pyruvate Mitochondrial Oxidation Mismatch
Cardiac metabolism
### INTERMACS Recovery

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>No. of Patients (N = 14,338)</th>
<th>No. of Patients With CR (N = 185)</th>
<th>Incidence Rate of CR (Event per 100 Person-Years)</th>
<th>SHR (95% CI)</th>
<th>p Value</th>
<th>Regression Coefficient</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;50 yrs (vs. ≥ 50 yrs)</td>
<td>3,848 (26.8)</td>
<td>112 (60.5)</td>
<td>2.2 vs. 0.5</td>
<td>1.91 (1.36-2.68)</td>
<td>&lt;0.0001</td>
<td>0.65</td>
<td>1</td>
</tr>
<tr>
<td>Nonischemic CM (vs. ischemic CM)</td>
<td>7,427 (51.8)</td>
<td>155 (83.8)</td>
<td>1.6 vs. 0.3</td>
<td>4.67 (3.06-7.14)</td>
<td>&lt;0.0001</td>
<td>1.54</td>
<td>3</td>
</tr>
<tr>
<td>Time from cardiac diagnosis &lt;2 yrs (vs. ≥ 2 yrs)</td>
<td>3,310 (23.1)</td>
<td>114 (61.6)</td>
<td>2.7 vs. 0.5</td>
<td>2.18 (1.52-3.14)</td>
<td>&lt;0.0001</td>
<td>0.78</td>
<td>1</td>
</tr>
<tr>
<td>Implanted ICD (no vs. yes)</td>
<td>3,004 (21.0)</td>
<td>113 (61.1)</td>
<td>2.9 vs. 0.5</td>
<td>3.68 (2.59-5.23)</td>
<td>&lt;0.0001</td>
<td>1.30</td>
<td>2</td>
</tr>
<tr>
<td>Creatinine ≤1.2 mg/dl (vs. &gt;1.2 mg/dl)</td>
<td>6,702 (46.7)</td>
<td>132 (71.4)</td>
<td>1.4 vs. 0.5</td>
<td>1.97 (1.42-2.73)</td>
<td>&lt;0.0001</td>
<td>0.68</td>
<td>1</td>
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<tr>
<td>LVEDD &lt;6.5 cm (vs. ≥ 6.5 cm)</td>
<td>4,084 (28.5)</td>
<td>82 (44.3)</td>
<td>1.6 vs. 0.7</td>
<td>1.81 (1.33-2.46)</td>
<td>&lt;0.0001</td>
<td>0.59</td>
<td>1</td>
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**I-CARS: Derivation Cohort**

<table>
<thead>
<tr>
<th>Cardiac Recovery (%)</th>
<th>Overall</th>
<th>Non-BTR</th>
<th>BTR</th>
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<tbody>
<tr>
<td>Overall</td>
<td>0.2</td>
<td>0.2</td>
<td>0.0</td>
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<tr>
<td>Low probability</td>
<td>8.9</td>
<td>1.4</td>
<td>1.3</td>
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<tr>
<td>Intermediate probability</td>
<td>3</td>
<td>1.3</td>
<td>8.1</td>
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<tr>
<td>High probability</td>
<td>0.2</td>
<td>0.2</td>
<td>0.0</td>
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</tbody>
</table>

**I-CARS: Validation Cohort**

<table>
<thead>
<tr>
<th>Cardiac Recovery (%)</th>
<th>Patients (%)</th>
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</thead>
<tbody>
<tr>
<td>Cardiac Response</td>
<td>7.4</td>
</tr>
<tr>
<td>Cardiac Recovery</td>
<td>0.0</td>
</tr>
</tbody>
</table>

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Wever-Pinzon O, Drakos SG, Stehlik J, Selzman CH. JACC 2016
RESTAGE-HF

REmission from Stage D Heart Failure
(RESTAGE-HF)

• Bridge to recovery clinical trial, N=40
• Non-ischemic CM patients
• Med rx: carvedilol, lisinopril, spironolactone, digoxin, losartan

Explant criteria at 6,000 RPM (HMII):
- LVEDD <60mm, LVESD <50mm
- LVEF >45%
- LV filling pressure <15 mmHg
- cardiac index >2.4L/min/m²
- max VO₂ >16 ml/kg/min

U Louisville
U Pennsylvania
Cleveland Clinic
Montefiore/Einstein, NY
U Nebraska
U Utah

(Trial sponsored by St Jude/Abbott)
Integration of Patient Reported Outcomes Assessment Into Routine Clinical Care

**Novel Approaches to Health Status Assessment**

- Patient completes PRO instrument
- PRO results wirelessly uploaded to server, scored, graphed and linked to patient's EHR
- Provider reviews PRO results
- PRO results used in decision-making

**Instrument-**

<table>
<thead>
<tr>
<th>Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12)</th>
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</table>

**NIH Patient Reported Outcome Measurement Information System Computer Adaptive Testing (PROMIS CAT):**

- Fatigue – bank v1.0
- Depression – bank v1.0
- Physical Function – bank v1.2
- Satisfaction with Social Roles and Activities – bank v2.0.
Quality of life assessment

LVAD explant sustained recovery

LVAD explant, recurrence of HF
Expected survival – full recovery

- Healthy 22-year old
- Full recovery after explant
- Heart transplant
- LVAD BTR/BTT strategy

Survival (%) vs. Years
Expected survival – partial recovery

- Healthy 22-year old
- Partial recovery (NYHA II)
- Heart transplant
- LVAD BTR/BTT strategy
Expected survival – recovery and relapse

- Healthy 22-year old
- Recovery and delayed relaps
- Heart transplant
- LVAD BTR/BTT strategy

Need for intervention
Potential impact

Number of hospitals implanting VADs
Number of patients with LVAD implants

INTERMACS Hospital Activation and Patient Enrollment
Primary Prospective Implants: June 23, 2006 to June 30, 2014
Patient 9 months after LVAD implant

LVEDD = 43 mm, EF = 55 %
VO₂ max = 15.7 ml/kg/min
VE/VCO₂ at AT = 38
Goal
# Acknowledgements

## Clinical Team

<table>
<thead>
<tr>
<th>Cardiology</th>
<th>CT Surgery</th>
<th>Molecular Medicine &amp; CVRTI</th>
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<tbody>
<tr>
<td>University Utah &amp; VAMC</td>
<td></td>
<td>Drakos Lab, Li Lab, McKellar Lab, Rutter Lab, Sachse Lab, Selzman Lab</td>
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<tr>
<td>Fang, Jim</td>
<td>Selzman, Craig</td>
<td>UVRL &amp; Exercise Physiology</td>
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<tr>
<td>Drakos, Stavros</td>
<td>Bull, David</td>
<td>Richardson, Russ</td>
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<td>Gilbert, Edward</td>
<td>McKellar, Stephen</td>
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<tr>
<td>Movsesian, Maty</td>
<td>Koliopoulou, Antigone</td>
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<td>Nativi Nicolau, Jose</td>
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<tr>
<td>Stehlik, Josef</td>
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<td>U Utah Population Health</td>
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<tr>
<td>Weber Pinzon, Omar</td>
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<td>Hess, Rachel</td>
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<td>Biber, Josh</td>
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<tr>
<td>Intermountain Medical Center</td>
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<td>U of Iowa</td>
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<tr>
<td>Afshar, Kia</td>
<td>Caine, Bill</td>
<td>Abel Lab</td>
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<tr>
<td>Alharethi, Rami</td>
<td>Doty, John</td>
<td>University of Missouri-KC</td>
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<tr>
<td>Kfoury, Boudi</td>
<td>Reid, Bruce</td>
<td>Spertus, John</td>
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</tbody>
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## Cardiac Pathology

Hammond, Elizabeth
Revelo, Patricia