LVADs as a long term or destination therapy for the advanced heart failure

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DISCLOSURES

• Consultancies & lectures within last 2 y:

Boehringer Ingelheim, Merck, Pfizer, MSD, Sanofi Aventis, Pliva, Krka, Genzyme, Sandoz, Belupo, JGL, Astra Zeneca, Berlin Chemie Menarini, PharmaS, Medtronic, Medis Adria, Marck Medical, Thoratec
Idea of replacing a failing heart

1966. – first VAD - postcardiotomy support for 10 days (De Bakey)

1967. - first human heart transplantation (Bernard)
Heart transplantation

• HTx remains the only curative method for pts with end stage heart failure
• The rate of HTx remained relatively steady during the last 20 y
• Major imbalance between organ supply and demand
• 20% mortality rate among Htx waiting list candidates
Technical break through in VAD technology

First full implantable, miniaturized axial-pump for clinical application

diameter 30.5 mm
length 76.2 mm
weight 93 g
<table>
<thead>
<tr>
<th>Terms</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bridge to decision (BTD):</td>
<td>Use of MCS in patients with drug-refractory acute circulatory collapse and at immediate risk of death to sustain life until a full clinical evaluation can be completed and additional therapeutic options can be evaluated.</td>
</tr>
<tr>
<td>Bridge to candidacy (BTC):</td>
<td>Use of MCS to improve end-organ function in order to make an ineligible patient eligible for transplantation.</td>
</tr>
<tr>
<td>Bridge to transplantation (BTT):</td>
<td>Use of MCS to keep a patient at high risk of death before transplantation alive until a donor organ becomes available.</td>
</tr>
<tr>
<td>Bridge to recovery (BTR):</td>
<td>Use of MCS to keep patient alive until intrinsic cardiac function recovers sufficiently to remove MCS.</td>
</tr>
<tr>
<td>Destination therapy (DT):</td>
<td>Long-term use of MCS as an alternative to transplantation in patients with end-stage heart failure ineligible for transplantation.</td>
</tr>
</tbody>
</table>

MCS = mechanical circulatory support.
1st generation

- Large pulsatile, positive displacement pumps with a lot of moving parts, limited to the pts with BSA > 1.5m2
- Novacor LVAS
- Thoratec IVAD
- Thoratec HM XVE
- Extracorporeal: Thoratec PVAD, Berlin Heart Excor, Toyobo LVAS
1994. - FDA approved the pulsatile ventricular assist device (VAD) HeartMate XVE later called HeartMate I as the first VAD for bridge to transplantation (Thoratec Corporation, Pleasanton, CA)
REMATCH
Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure

The New England Journal of Medicine

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LONG-TERM USE OF A LEFT VENTRICULAR ASSIST DEVICE FOR END-STAGE HEART FAILURE

ERIC A. ROSE, M.D., ANNETINE C. GELIJNS, PH.D., ALAN J. MOSKOWITZ, M.D., DANIEL F. HEITJAN, PH.D., LINNE W. STEVENSON, M.D., WALTER DEMBITSKY, M.D., JAMES W. LONG, M.D., PH.D., DEBORAH D. ASCHEIM, M.D., ANITA R. TIERNEY, M.P.H., RONALD G. LEVITAN, M.SC., JOHN T. WATSON, PH.D., AND PAUL MEIER, PH.D., FOR THE RANDOMIZED EVALUATION OF MECHANICAL ASSISTANCE FOR THE TREATMENT OF CONGESTIVE HEART FAILURE (REMATCH) STUDY GROUP*
Overal reduction of mortality with 48% with LVAD. Survival at 1 y 52% vs 25%; at 2 y 23% vs 8% 2 y survival increases to 32% at FU Mean survival 408 vs 150 days

REMATCH

post REMATCH DT trial


Long JW et al. Destination Therapy with the HeartMate XVE LVAS: improved outcomes since the REMATCH study. CHF. 2005; 11:133-138
• INTrEPI D (Rogers et al. JACC 2007; 50:741-47)
  - Similar population as in the REMATCH
  - Advanced HF on inotropes
  - Except younger age: 60 vs 66 y
  - 55 pts enrolled
  - Result: superior survival in
  - 6 mo (46% vs 22%) and 12 mo (27% vs 11%)

RELIANT (Novacor vs HM XVE) - stopped
2nd generation

- Axial pumps which utilize continuous flow

- Continuous pusless flow is well tolerated and improves neurocognitive disturbances just as pulsatile LVADs

- Single moving rotor minimizes devices tear resulting to mechanical stability for years

- Due to smaller size less prone to infections and enable implantation in pts with smaller BSA
2nd generation: smaller in size, continuous flow

- Jarvik 2000
- HeartMate II
- MicroMed
- DeBakey
Heart Mate II

- Small, advanced axial flow blood pump
- Constructed of a medical-grade titanium alloy
HeartMate II BTT Clinical Trial – non-randomized trial in which all subjects received the HeartMate II LVAS and were compared to an objective performance criterion.

Outcomes at 6 months

- Transplantation, Recovery or Ongoing Device Support: 105 (79%)
- Transplantation: 56 (42%)
- Ongoing Device Support: 48 (36%)
- Died: 25 (19%)
- Withdrawal: 3 (2%)
- Recovery: 1 (1%)

**HeartMate II BTT – Hemodynamic and Functional Status Response**

*Cardiac Index*

- Baseline: 2.5 ± 0.5 ml/kg/min
- Day 1: 3.5 ± 0.5 ml/kg/min

*Pulmonary Capillary Wedge Pressure (PCWP)*

- Baseline: 20 ± 5 mmHg
- Day 1: 10 ± 5 mmHg

**Improvement in Heart Failure Symptoms**

- 83% Improved to NYHA Class I or II from Class IV
- 14% Improved to NYHA Class III from Class IV
- 3% No change

*Based on improvement in New York Heart Association Heart Failure Classification 3 months after implantation.*

6 min. walk

HM II DT Pivotal Trial

- Randomization 200 pts with NYHA IIIb or IV
- EF ≤ 25%
- VO2 max. ≤ 14 ml/kg/min
- or: inotropes at least 14 days
- or: IABP for 7 days
- HM II (134) vs. HM XVE (66)
- Primary end point: 24 m survival without disabling stroke and the need for an operation/repairing/replacing the VAD

Slaughter et al. NEJM 2009; 361:2241-2251
In a randomized clinical study of 200 participants at 38 centers, 46 percent of 134 participants with the HeartMate II were still living after two years with no disabling stroke or need for a reoperation for device replacement or repair compared with 11 percent of 66 participants in the control group.

In addition, data collected in a separate registry of smaller stature women and men indicated that the device worked well in this specific population.

## HeartMate II vs HeartMate I

<table>
<thead>
<tr>
<th>End Point</th>
<th>Continuous-Flow LVAD (N=134)</th>
<th>Pulsatile-Flow LVAD (N=66)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival free from disabling stroke and reoperation to repair or replace LVAD at 2 yr (primary composite end point)</td>
<td>62 (46 [38–55])</td>
<td>7 (11 [3–18])</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>First event that prevented patient from reaching the primary end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disabling stroke†</td>
<td>15 (11 [6–17])</td>
<td>8 (12 [4–20])</td>
<td>0.78 (0.33–1.82)</td>
<td>0.56</td>
</tr>
<tr>
<td>Reoperation to repair or replace pump‡</td>
<td>13 (10 [5–15])</td>
<td>24 (36 [25–48])</td>
<td>0.18 (0.09–0.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death within 2 yr after implantation</td>
<td>44 (33 [25–41])</td>
<td>27 (41 [29–53])</td>
<td>0.59 (0.35–0.99)</td>
<td>0.048</td>
</tr>
<tr>
<td>Any</td>
<td>72 (54 [45–62])</td>
<td>59 (89 [82–97])</td>
<td>0.38 (0.27–0.54)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Post approval study for HeartMate II® in destination therapy (DT)

- prospective evaluation of the first 247 patients with HM II implanted as DT
- enrollment from Jan – Sep 2010
- follow up - two years
- comparison group 133 patients enrolled in the primary data cohort in the DT pivotal trial

Jorde et al. Two-Year Outcomes in the Destination Therapy Post-FDA-Approval Study with a Continuous Flow Left Ventricular Assist Device: A Prospective Study Using the INTERMACS Registry 2013 Apr;32(Suppl):S10
## Adverse events and outcomes

<table>
<thead>
<tr>
<th></th>
<th>Length of stay (d)</th>
<th>Bleeding req surg.</th>
<th>Isch. Stroke (events/pt-yr)</th>
<th>Hem. Stroke (events/pt-yr)</th>
<th>Device infection (events/pt-yr)</th>
<th>1 yr survival</th>
<th>2 yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR (n=133)</td>
<td>27</td>
<td>30%</td>
<td>0.06</td>
<td>0.07</td>
<td>0.48</td>
<td>68±4%</td>
<td>58±4%</td>
</tr>
<tr>
<td>PA (n=247)</td>
<td>21</td>
<td>11%</td>
<td>0.04</td>
<td>0.05</td>
<td>0.22</td>
<td>76±3%</td>
<td>62±3%</td>
</tr>
</tbody>
</table>

Jorde et al. Two-Year Outcomes in the Destination Therapy Post-FDA-Approval Study with a Continuous Flow Left Ventricular Assist Device: A Prospective Study Using the INTERMACS Registry 2013 Apr;32(Suppl):S10
3rd generation – miniaturized continuous flow centrifugal or axial pumps

- Levacor VAD (WorldHeart)
- HeartWare (HVAD)
- VentrAssist
- DuraHeart
- Berlin Heart Incor
3rd generation VADs

- WorldHeart Levacor VAD → terminated

- Terumo Dura Heart
  - CE mark
  - in 2011. German pt. surpasses 5 years of support on DuraHeart LVAS
HeartWare Ventricular Assist system (HW VAS)

- 2009. CE mark for BTT
- May 2012. addendum to CE mark for DT
- November 2012. FDA approved for BTT
- June 2013. FDA approved to enroll pts. in DT trial

- so far cca. 2500 HVADs were implanted worldwide
Clinically relevant evidence-based data

ADVANCE

Objective: to evaluate safety and efficacy of HVAD in pts. listed for HTx with refractory advanced HF

- multi-center, prospective, non-randomized, two arm study
- HVAD (N=332 - pivotal trial + continuous access protocol) vs. control (INTERMACS, N=499)
- primary endpoint: non-inferiority to control
- secondary endpoints: descriptive statistics (survival, QoL, functional class, SAE)
ADVANCE secondary endpoints

- Survival at 360 days
- Functional status by 6MWT

**Survival on Device**

- HVAD: 90.6%
- Control: 85.7%

**Number at Risk**

<table>
<thead>
<tr>
<th></th>
<th>HVAD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>140</td>
<td>499</td>
</tr>
<tr>
<td>60</td>
<td>128</td>
<td>440</td>
</tr>
<tr>
<td>120</td>
<td>108</td>
<td>370</td>
</tr>
<tr>
<td>180</td>
<td>92</td>
<td>305</td>
</tr>
<tr>
<td>240</td>
<td>63</td>
<td>228</td>
</tr>
<tr>
<td>300</td>
<td>36</td>
<td>176</td>
</tr>
<tr>
<td>360</td>
<td>26</td>
<td>127</td>
</tr>
</tbody>
</table>

**Meters walked**

- Baseline: 89 ± 141 (N=132)
- 6 month Follow-up: 246 ± 204 (N=75)
- Baseline: 94 ± 149 (N=74)
- 6 month Follow-up: 244 ± 205 (Δ=150, N=74)

Clinically relevant evidence-based data

ADVANCE

- HeartWare VAD met the criterion of noninferiority to the control (p < 0.001) but not superiority:
  - The treatment-group success was 92.0%
  - Control-group success was 90.1%
- There appears to be less bleeding and infection with the new device
- The incidence of stroke was higher than might have been expected with the smaller size of the device
Clinically relevant evidence-based data

ENDURANCE

• “first-in-kind” trial (head-to-head VAD trial)
• a prospective, randomized, un-blinded, multi-center, non-inferiority clinical trial to evaluate the use of the HeartWare® Ventricular Assist System as a destination therapy in advanced HF pts.
• N=450 (June 2010- May 2012)
• Primary endpoint: stroke-free survival at two years (follow up ends in May 2014.!!)
• Secondary endpoints: incidence of bleeding, major infection, device failure, as well as health and functional status improvement.
• the largest trial to date for the long-term use of a left ventricular assist device
• EXPECTING RESULTS.....

manufacturers’ data: www.heartware.com
INCOR Berlin Heart design
INCOR Berlin Heart
Clinical update information - May 2013

- data from BerlinHeart database (from 44 implant centers)*

*manufacturers’ data, not indep. trial data

Data from: http://www.berlinheart.de/index.
INCOR Berlin Heart
Clinical update information- May 2013

- data from BerlinHeart database (N=646)
TRENDS
INTERMACS Implants per year by device strategy

INTERMACS - Implants per Year by Device Strategy
Primary Prospective Implants: June 23, 2006 to March 31, 2013

- Bridge to Transplant - Listed
- Bridge to Candidacy
- Destination Therapy
- Bridge to Recovery
- Other

Quarterly Report – 2013 Q1; 06/24/2013
Adult Primary Continuous Flow LVADs & BLVADs, DT and BTT, n = 5436
Implants: June 2006 – June 2012

n = 5436, Deaths = 1120

<table>
<thead>
<tr>
<th>Months</th>
<th>% Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>95%</td>
</tr>
<tr>
<td>12</td>
<td>80%</td>
</tr>
<tr>
<td>24</td>
<td>70%</td>
</tr>
<tr>
<td>36</td>
<td>59%</td>
</tr>
<tr>
<td>48</td>
<td>47%</td>
</tr>
</tbody>
</table>

Kirklin et al. Fifth INTERMACS annual report Feb 2013
### 10-y Survival, University Hospital Centre Zagreb

<table>
<thead>
<tr>
<th></th>
<th>1988-1999</th>
<th>2000-2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 d:</td>
<td>73%</td>
<td>85%</td>
</tr>
<tr>
<td>1 y:</td>
<td>63%</td>
<td>80%</td>
</tr>
<tr>
<td>5 y:</td>
<td>49%</td>
<td>64%</td>
</tr>
<tr>
<td>10 y:</td>
<td>35%</td>
<td>54%</td>
</tr>
</tbody>
</table>
INTERMACS
Implants per year by device type

Year

<table>
<thead>
<tr>
<th>Year</th>
<th>LVAD</th>
<th>BiVAD</th>
<th>TAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006 (Jun-Dec)</td>
<td>81</td>
<td>2</td>
<td>258</td>
</tr>
<tr>
<td>2007</td>
<td>72</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>2008</td>
<td>80</td>
<td>30</td>
<td>649</td>
</tr>
<tr>
<td>2009</td>
<td>94</td>
<td>24</td>
<td>907</td>
</tr>
<tr>
<td>2010</td>
<td>80</td>
<td>29</td>
<td>1561</td>
</tr>
<tr>
<td>2011</td>
<td>95</td>
<td>27</td>
<td>1823</td>
</tr>
<tr>
<td>2012</td>
<td>64</td>
<td>40</td>
<td>2113</td>
</tr>
<tr>
<td>2013 (Jan-Mar)</td>
<td>508</td>
<td>12</td>
<td>18</td>
</tr>
</tbody>
</table>
Technological improvements

- Fully implantable miniaturized durable VAD with percutaneously charging battery
- TETS (LionHeart 2000 LVAD; AbioCor TAH)
- Synergy Pocket Micro Pump; partial support up to 4.25 L/min, pacemaker like implantation
New indications

• VADs in less sick patients e.g. stable NYHA III patients/ambulatory patients

• Ongoing studies:
  
  - ROADMAP (HM II) – ending Dec. 2015
Conclusion

- LVADs of 2nd and 3rd generation are an accepted long term BTT and for DT for patients with advanced HF not eligible for HTx
- As the need for HTx constantly increases and HTx rates do not increase, LVAD can be an acceptable alternative to HTx
- Adequate RVAD and BVAD still remains an unsolved issue
Conclusion (cont.)

- New technological development will bring TETS and less invasive implantation strategies
- VADs are going to be tested against OMT and CRT in less sick patients
- The need for VADs will exponentially grow and require lowering prices and high volume production
• I never think of the Future. It comes soon enough.

*Albert Einstein,*
(1930)
Thank you!