Mechanical Assist Devices: From Bridge to transplant to destination therapy
Nothing to disclose
Less organs – more listings result in growing waiting lists for HTx

Widening gap
High Urgency Transplantation exceeds elective Transplantation

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Courtesy J. Gummert, Bad Oeynhausen
HTx issues – MCS a solution?

• Organ shortage
• In some countries already 90% of transplants are HU - worse outcomes, no hearts for elective patients
• Short-term support for BTT no realistic option for many patients
• BTT effectively means DT in many cases
• MCS an alternative to HTx?
First generation pulsatile devices
Züricher Patienten mit Berlin Heart
REMATCH-Trial (Heartmate I)

129 pts. randomized to LVAD (68) or medical therapy (61)
1998 – 2001; all pts. NYHA 4 non eligible for HTx

P=0.002
P=0.09

Med  n = 61
LVAD  n = 68
HTx

Rose NEJM 2001
## REMATCH

### Complications (n/Patient - year)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Contr.</th>
<th>LVAD</th>
<th>Rate Ratio</th>
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<tr>
<td>Cardiac arrest</td>
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<td>0.12</td>
<td>0.65</td>
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<tr>
<td>Myocardial infarct</td>
<td>0.03</td>
<td>0.02</td>
<td>0.65</td>
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<tr>
<td>Ventricular arrhythmia</td>
<td>0.56</td>
<td>0.25</td>
<td>0.45</td>
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</table>
Complications

• Mechanical wear
• Valve dysfunction
• Thrombembolic complications
Non pulsatile Devices

**Advantages**
- No valves
- No membranes
- Smaller housing
- Less moving parts
- Ease of implant

**Disadvantages**
- Non pulsatile
- AI in pump failure
- Afterload dependent
Improved patient comfort

- Less Trauma
- Less noise
- Smaller
- Longer battery charge
Inflow - Canula and LVAD
Implanted LVAD
Heartmate II vs. Heartmate I – Adverse Events
(US – Multicenter trial – Chronic Implant)

Slaughter NEJM 2010
Heartmate II vs. Heartmate I - Survival
(US – Multicenter trial – Chronic Implant)

1y 48% vs 70%
2y 17% vs 60%

P=0.008 by the log-rank test

Slaughter NEJM 2010
Improving Survival in DT trials

- Continuous-flow LVAD (2009)
- Pulsatile-flow LVAD (2001)
- Pulsatile-flow LVAD (2009)
- Medical therapy (2001)

P = 0.008 (2009)

P = 0.09 (2001)
ADULT HEART TRANSPLANTATION

Pulsatile vs. Continuous: p=0.0298
Pulsatile vs. No LVAD/No Inotropes: p < 0.0001
Pulsatile vs. No LVAD/Inotropes: p = 0.0032
No other pair-wise comparisons are statistically significant at p < 0.05

ISHLT 2011
Rapid growth in LVAD therapy
The rise of continuous flow pumps
Increase of LVAD vs BVAD support
Improved Survival by Implantation period
Improved Survival with Continuous Flow Pumps
Bridge to Candidacy with CF Devices
Destination Therapy with CF Devices
Outcomes of DT according to preoperative risk

Identification of risk factors for increased mortality (p<0.05)

- Older age
- Larger BMI
- Diabetes
- History of CABG
- INTERMACS level I / cardiogenic shock
- Lower sodium
- Increased bilirubin
- Use of pulsatile flow devices

<table>
<thead>
<tr>
<th></th>
<th>continuous</th>
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<th>overall</th>
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<tr>
<td>1 year survival</td>
<td>79%</td>
<td>61%</td>
<td>75%</td>
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<tr>
<td>2 year survival</td>
<td>78%</td>
<td>35%</td>
<td>51%</td>
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</table>

Kirklin JK presented at AATS 2012
DT competitive with HTx in current era

- DT accounts for 33% of implants in recent years
- Risk factors play a major role for survival outcome (DT therapy not appropriate for rapidly deteriorating patients or patients in shock)
- Mechanical circulatory provides competitive survival to heart transplantation in selected subsets:

  *Continuous flow LVAD / no diabetes / no cardiogenic shock / BUN <50*

  1 & 2 year survival with LVAD 85%
  comparable to 1 year survival after HTx 85-87%
Second generation non pulsatile devices

- Simplified Implantation Technique
- Electromagnetic bearing
- Less blood trauma
Freedom from Stroke or (Bleeding or embolic)


HeartMate II 81%
HeartWare 80%

 Courtesy J. Gummert, Bad Oyenhausen
Survival and preoperative Intermacs-Level


Intermacs level 1+2

Intermacs level 3-5

1 = Crash and burn
2 = Sliding on inotropes
3 = Dependent stability
4 = Frequent Flyer
5 = Homebound

Log Rank test: P=0.011

Courtesy J. Gummert, Bad Oyenhausen
New pumps / HeartMate

**Project Objectives**

- Develop a full-support, blood pump with full magnetic rotor levitation and wide gaps for optimized blood flow
  - Reduced adverse event profile

- Incorporate textured surfaces
  - Potential for reduced or no anticoagulation

- Capable of producing an artificial pulse
  - Physiologic blood flow with potential to help address late bleeding

- Operate at **lower power consumption**, allowing miniaturization of external components
Miniaturized VAD Design / MVAD

Project Objectives

• Three MVADS designs all showing strong results in preclinical studies.

• Wide bladed, axial flow technology allows significant miniaturization.

• Partial or full support attainable in all designs.

• All versions can eliminate full sternotomy.

• Wear-less impeller suspension.

• Versatile, configurable and scalable.
Miniaturized ventricular assist device (MVAD)

- Continuous axial flow pump
- Transapical implantation, Transaortic outflow
- 10 animals: 100% successful implantation, 100% normal end-organ perfusion, no significant hemolysis, no pump failures, no device-related complications
Miniaturized ventricular assist device (MVAD)
Infection Reduction Technology

Project Objectives

• Develop stabilization and exit site improvement technologies to significantly reduce percutaneous lead (driveline) infection.

• Pursuing device-based internal mechanical stability anchoring technologies
  – Focus on trauma-induced late-onset infection

• Advanced exit site material morphology and chemistry for improved tissue / percutaneous lead interface
Fully-Implantable LVAS (FILVAS)

Project Objectives

- LVAD incorporating **implantable battery and control system** enabling patients to have some duration of “un-tethered time” without external components.

- Mitigate the need for a standard **percutaneous “driveline”**, reducing infection.

- Minimize need for external components, enhancing quality of life.
Partial ventricular support
New philosophy and indications

Current therapy limitations

Big Gap due to
Normal QRS
Not sick enough for LVAD

NYHA II  NYHA III  NYHA IV  CGS

Disease Severity

Health Status / Prognosis

Wide QRS (~30%)

CRT

VAD

Highly Invasive

ICDs
## Partial ventricular support (CircuLite)

<table>
<thead>
<tr>
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<th>CircuLite</th>
<th>Current VADs</th>
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</table>
| **Patient**      | • Class IIIb and early Class IV  
                  • Cardiac Output: 2-3L/minute  
                  • Ambulatory, **home-bound**  
                  (INTERMACS Level >4)        | • Late Class IV and Shock  
                  • Cardiac Output: 1-2L/minute  
                  • Hospitalized, bed-bound   |
| **Design**       | • Partial Support, 2-3L/minute  
                  • **Supplements** native function | • Full Support, 5-6L/minute  
                  • Replaces native function   |
| **Procedure**    | • **Limited Access** procedure  
                  • **Off-pump** mini-thoracotomy | • Urgent, open heart procedure  
                  • Sternotomy and bypass      |
CircuLite – Clinical experience

- 27 pts. awaiting HTx (EF 21 ± 6%)
- Duration of support 6 to 281 days
- significant hemodynamic improvement:
  - increase in CI from 2.0 ± 0.4 to 2.8 ± 0.6 l min⁻¹ m⁻² (p < 0.001)
  - reduction in PCWP from 28 ± 6 to 18 ± 7 mm Hg (p = 0.002)
Endovascular VAD Implantation

**Project Objectives**

- Inflow cannula transeptally deployed in left atrium, via the subclavian vein and right atrium.
- Outflow graft attached to the subclavian artery.
- Pre-clinical evaluation underway.
Total Artificial Heart – Syncardia Cardiowest
Bridge to Transplant results

Non randomised US five center trial with historical controls

Copeland - NEJM 2004
CardioWest: Survival rate

Bad Oyenhausen 2/2001 – 8/2011; n = 150

12 months

5 year

Worldwide: 1020 pts (as of 12/13/2011)

Courtesy J. Gummert, Bad Oyenhausen
## TAH: Long-Term Experience

### Patient Duration Over 6 Months

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**82.4% survival**

113 alive on device or transplanted
ESC GL HF 2012: Indications for MCS

- Upgrade of LVAD indication for destination therapy

Pts. Eligible for LVAD or BiVAD implantation:

- Patients with >2 months of severe symptoms despite optimal medical and device therapy and more than one of the following:
  - LVEF ≤25% and, if measured, peak VO₂ < 12 mL/kg/min
  - ≥3 HF hospitalizations in previous 12 months without an obvious precipitating cause
  - Dependence on i.v. inotropic therapy
  - Progressive end-organ dysfunction (worsening renal and/or hepatic function) due to reduced perfusion and not to inadequate ventricular filling pressure (PCWP ≥20 mm Hg and SBP ≤80–90 mmHg or CI ≤2 L/min/m²)
  - Deteriorating right ventricular function
Conclusions

• Destination Therapy is an established therapy (>30% of implants)
• Results match HTx in selected subsets
• Organ shortage and growing heart failure population will increase need for LVADs
• Earlier implantation in pts. without end-organ failure yields better results
• Partial assist/smaller devices upcoming
ENDURANCE is a randomized, controlled, unblinded, multi-center clinical trial to evaluate the use of the HeartWare Destination Therapy. The non-inferiority study includes 450 patients with end-stage heart failure ineligible for cardiac transplantation.

Patients randomized to LVAD HeartWare LVAD against control group of any alternative LVAD approved by the FDA for DT in a 2:1 ratio. Primary endpoint at two years, with a subsequent follow-up period extending to five years post implant.
- Secondary endpoint of survival was 94% at six months; 91% projected survival at one-year for investigational device -

- Conference call today at 6:30 p.m. U.S. Central Time -

FRAMINGHAM, Mass. and SYDNEY, Nov. 14, 2010 /PRNewswire-FirstCall/ -- HeartWare International, Inc. (Nasdaq: HTWR) (ASX: HIN), a leading innovator of less invasive, miniaturized circulatory support technologies that are revolutionizing the treatment of advanced heart failure, today announced that data from its pivotal bridge to heart transplantation (BTT) study, ADVANCE, showed that 92% of the investigational device patients met the per protocol primary endpoint of the trial, which was defined as alive on the originally implanted