MCSD “Pump Thrombosis”: Industry Perspective

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Patients Supported by HeartMate II

Pumps implanted by quarter\(^1\)

![Graph showing cumulative pumps implanted by quarter from 2009 to 2013.]

Ongoing Patients at Year End\(^2\)

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>3,000</td>
</tr>
<tr>
<td>2011</td>
<td>4,100</td>
</tr>
<tr>
<td>2012</td>
<td>5,600</td>
</tr>
<tr>
<td>2013</td>
<td>6,700</td>
</tr>
</tbody>
</table>

\(^1\) Sundareswaran ISHLT 2014

\(^2\) Burbach, MCS Conference 2014
HeartMate II Clinical Trial Rates for Thrombus and Hemolysis

- **Pump Thrombus**
  - 5/133 (4%) primary data cohort \(^1\)
  - 16/281 (6%) CAP cohort \(^2\)

- **Hemolysis**
  - 5/133 (4%) primary data cohort \(^1\)
  - 13/281 (5%) CAP cohort \(^2\)

- **Combined Thrombus + Hemolysis**
  - 28/281 (10%), 0.07 events/pt-yr) CAP cohort

- **Pump Replacements – all cause**
  - 12/133 (9%) primary data cohort \(^1\)
  - 22/281 (8%) CAP cohort \(^2\)

- **Pump Replacements for thrombus**
  - 2/133 (2%) primary data cohort \(^1\)
  - 8/281 (3%) CAP cohort \(^2\)

\(^2\) Park et al *Circ Heart Fail.* 2012;5:241-248
Our Current Data - Suspected or Confirmed Pump thrombus within 6 months of implantation

Suspicious (includes hemolysis) or Confirmed Thrombus

- Clinical Trial ~1% at 6 Months
- 3 center study ~14% at 6 Months
- Clinical Trial ~3.6% at 6 Months

Pump Exchanges - Suspected Thrombus

- Clinical Trial ~1% at 6 Months

References:
1. Sundareswaran and Farrar ISHLT 2014
2. Data from Park et al. Circ HF 2012
3. Figure S10, Starling et al. NEJM 2014
Pump Thrombus Within 90 days of Implant

Overall Customer Complaints at 90 days

Three center analysis by Jan 1 2013 Starling et al (confirmed thrombus)

4.2% Complaint Database (Confirmed or suspected thrombus)

1Park et al Circ HF 2012
2 Starling et al NEJM 2013
3 Data on file as of January 31, 2014, Thoratec Corporation Pleasanton
Center to Center Variability
Prevalence of suspected thrombus / hemolysis within 6 Months - 2011 to 2013
Top 15 implanting centers in the commercial era with a minimum of 179 commercial implants

Data as of January 31st, 2014

Data on file, Thoratec Corporation.
Factors Related to Pump Thrombosis at Select Medium to High Volume Centers

• **Purpose**: Characterize events at 7 HMII centers (>100 HMII implants) whose device thrombosis rates are lower than those reported by INTERMACs.

• **Results:**
  - Suspected thrombus: 2.8% at 3 months and 5.3% at 6 months
  - 3% pump exchanges or death from suspected thrombosis at 6 months
  - Hemorrhagic stroke 0.04 eppy, Ischemic stroke 0.05 eppy at 6 months
  - Survival 88 ± 2% at 6 months

• **Conclusion**: This analysis demonstrates low event rates for thrombus at select medium to large volume centers.

Dynamic Factors Possibly Explaining the Increase in Pump Thrombosis

• The patient
• The pump
• The operation
• The management
What are some of the factors that may contribute towards this increase?

• Potential Device Related Factors
  – Introduction of Sealed Grafts – Q1, 2011
  – Manufacturing variability
  – Controller software changes

• Confounding Clinical Factors
  – Changing definitions of thrombosis and reporting practices
  – Anticoagulation (Movement towards lower target INRs[< 2.0]) to reduce risk of bleeding, and no heparin use post-op
  – Pump Speeds (Movement towards lower pump speeds) to reduce risk of Aortic Insufficiency
  – Variability in patient profiles post DT approval – a more diverse patient profile
Pump Thrombosis: Potential Contributing Factors

Patient Related
- Age
- Gender
- Race or Ethnicity
- BMI
- Compliance

Patient Management Related
- Constant Comorbidities
  - Hypo-Hyper tension
  - RV function
  - LA Pressure
  - Speed
  - Heparin?
  - INR
  - Aspirin
  - Off AC in 30, 60, 90 days?
  - Patient evaluated for recovery?

Anatomy Related
- LA Appendage
- LV Volume
- LV Geometric Shape
- Prior cardiac procedures

Device Related
- Mfg date
- Process changes
- Sealed Outflow
- Sealed Inflow
- Supplier changes

Center Related
- Surgeon
- # of Implants
- TEE at implant?
- Off pump
- Incision?
- Core and Sew or Sew and Core?
- Surgical Skills
- Coring technique
- LV coring site
- Inflow cannula placement
- Pump position
- Deairing
- Ring attachment
- Method

Implant Technique Related
- GI Bleed
- Infection
- Arrhythmia
- Hype-coagulable State
- HIT
- INR Outlier
- Trauma Surgery

Episodic Adverse Event Related
- Inflow Cannula Dimensions
- Blood Pathway Dimensions
- Inflow Cannula Degrees of freedom
- Blood contact surfaces
- Shear rate

Device Design Related
Pump Thrombosis: Device and Device Design Related Factors

High Shear
- Burrs
- Bearing gap
- Surface finish
- Diameters of conduits
- High flow
- Variable tip clearance
- Outside design point of pump
- Transition between uncoated and PM coated surfaces
- Clearance between inlet stator and blood bore
- Sharp edges
- Junctions between transition sections
- Variable PM coating

Heat
- Inflow/outflow obstruction
- Loose ball
- Improper flow
- Disconnection
- Kinking
- Rotor imbalance
- Turbulence/recirc
- Air
- Software
- Thermocoupling
- Biological depositions
- Bearings
- Sintered surfaces
- Small gap
- Friction
- Less washing
- Lack of lubrication
- Poor fit
- Variable fit
- Motor
- Diminished energy product

Stasis
- Inflow/outflow obstruction
- Loose ball
- Pump stop
- Disconnection
- Kinking
- Pump migration
- Implant procedure
- Malposition
- Neointima layer
- Sealed grafts
- PM coating
- Bearings
- EtO residuals
- Machine oil, coolants
- Contamination
- Si oil
- Pyrogens
- Variable graft coating
- Variable PM coating

Biocompatibility
- Debris
- Surface finish
- Graft textures
- Variable PM coating

Device-caused Thrombus
Design Change - Sealed Grafts

- Gelatin impregnated polyester grafts
  - Both inflow and outflow conduits
  - Introduced in first half of 2011
- Replaced conduits with the previous unsealed polyester vascular grafts.
- Goals of design change:
  - Remove the need to preclot the grafts prior to implantation,
  - Remove the variability in preclotting methods with fibrin glue, etc,
  - Reduce postoperative bleeding.
Impact of Sealed Grafts

Pumps Implanted
(Sealed vs. Unsealed Grafts)

Sealed Outflow
Limited launch: Feb, 2010
Sealed kit launch: March, 2011

Period of Overlap

Year of Implant

Number of Pumps Implanted

Sundaeswaran and Farrar ISHLT 2014
Impact of Sealed Grafts

Suspected or Confirmed Thrombosis at 6 months (Sealed vs. Unsealed Grafts)

Period of Overlap

Year of Implant

Percentage of Pumps (%)
Impact of Sealed Grafts Q1-Q2 2011

Freedom from Suspected or Confirmed Pump Thrombosis

- Unsealed Grafts (N=606)
  - 94.4 ±1.0%
  - 92.8 ±0.9%
- Sealed Grafts (N=895)
  - 90.9 ±1.3%
  - 88.9 ±1.2%

P (log rank test) = 0.41
Sealed Grafts

• Hypotheses
  – Sealed graft has different flow dynamics
  – Sealed inflow is more prone to kinking
  – Gelatin is released from sealed inflow graft and becoming lodged in inlet bearing or rotor
  – Neointima formed on inflow graft and detaches and becomes lodged in pump
Hypothesis: Bearing manufacturer has changed

- Bearings are manufactured by the same partner since 2004
- Manufacturer is located in the United States (not Mexico or China)
Variables analyzed

- **Forward Bearing Ball Surface Finish**: Surface finish of the forward bearing ball
- **Forward Bearing Cup Surface Finish**: Surface finish of the forward bearing cup
- **Aft Bearing Ball Surface Finish**: Surface finish of the aft bearing ball
- **Aft Cup Surface Finish**: Surface finish of the aft bearing cup
- **Bearing Gap**: The gap set between the rotor bearings and the inlet/outer stators
- **Stack Height Operator**: Individual responsible for assembling the bearings in the pump, including the gap
- **Stack Height Station**: The fixture utilized by the stack height operator for assembling the bearings
- **Burn in Cycles**: Number of 4 hour test-cycles it takes for the pump to reach stable power levels
Internal Investigations Summary

- Comprehensive analysis of the pump and its components
  - Reviewed by outside consultants
- Known changes
  - Analyzed multiple hypotheses for sealed grafts
  - Examined EPC SW
- Manufacturing consistency
  - All design specifications met
  - Analyzed manufacturing processes/scale-up
- Bearings
  - In depth analysis including materials, manufacturing information
  - Analysis of bearings with and without thrombus
- No device related factor has been identified
Pump Thrombosis/Hemolysis: A Multifactorial Issue

- Pump issues
  - No root cause discovered
  - Doesn’t explain variability
- Surgical implantation techniques
  - Malapposition of the inflow cannula
  - Pump pocket depth (lower) in thrombosis group
  - Pump migration
- Pre-pump factors (intracardiac thrombus)
- Post-pump factors (aortic root thrombus)
- Systemic factors (inflammation, infection, thrombophilia)
- Management issues
  - Pump speed (lower speeds – less heat dissipation)
  - Anticoagulation (heparin bridging, INR targets, antiplatelet therapy)

Modified from: Mehra et al. JHLT published online Dec 3, 2013
Algorithm for the Diagnosis and Management of Pump Thrombosis

- **Power Elevations**: Early or Late?
  - Early
    - Consider Echocardiogram (± Pump Speed Changes)
    - LV Unloading?
      - Yes
        - Close Follow Up
      - No
        - Isolated LDH Rise
          - Isolated LDH Rise?
            - Yes
              - Optimize Anticoagulation
              - Check Serum Indices of Hemolysis
              - Hemolysis?
                - Yes
                  - Consider Echocardiogram (± Pump Speed Changes)
                  - LV Unloading?
                    - Yes
                      - Increase INR
                      - ASA 325 mg
                      - Consider a Second Antiplatelet Agent
                    - No
                      - Chest CT Angiogram
                        - Inflow Cannula Malposition or Outflow Graft Obstruction?
                          - Yes
                            - Consider Surgical Correction
                          - No
                            - Resolved?
                              - Yes
                                - ICU – Add Inotropes, Diuresis as Needed
                              - No
                                - Surgical Candidate?
                                  - Yes
                                    - Consider: Direct Thrombin Inhibitors
                                  - No
                                    - Consider Thrombolitics in Patient with End Organ Dysfunction or Hemodynamic Compromise
                        - Resolved?
                          - No
                            - Pump Exchange or Urgent Transplantation or Explant for Recovery
          - No
            - Evidence of Hemolysis
              - Evidence of Hemolysis?
                - Yes
                  - Admit to Hospital
                  - Consider IV Heparin
                  - CXR
                  - Echocardiogram (± Pump Speed Changes), Consider RHC
                  - Monitor LDH, pHiHgb, indirect bilirubin, Haptoglobin, Renal Function
                - No
                  - LV Unloading?
                    - Yes
                      - Chest CT Angiogram
                    - No
                      - Resolved?
                        - Yes
                          - ICU – Add Inotropes, Diuresis as Needed
                        - No
                          - Surgical Candidate?
                            - Yes
                              - Consider: Direct Thrombin Inhibitors
                            - No
                              - Consider Thrombolitics in Patient with End Organ Dysfunction or Hemodynamic Compromise

Definitions:
- **Power Elevations**: Sustained (>24 hrs) Power > 10W; or Sustained (>24 hrs) Power increase > 2W from Baseline
- **Isolated LDH Rise**: LDH > 3x Upper Limit of Normal (ULN)
- **Hemolysis**: Clinical Diagnosis; or LDH > 3x ULN and pHiHgb > 40
- **Resolved**: Normal Powers, Normal LDHs, Sufficient LV Unloading, and No Clinical Evidence of Hemolysis

Abbreviations: LV, Left Ventricle; LDH, Lactate Dehydrogenase; pHiHgb, Plasma-free Hemoglobin; RHC, Right Heart Cath; CXR, Chest X-ray
What are we doing?

• Continue to investigate device related factors
• Multi-center pump thrombosis study in 2014 (PREVENT)
• Publication and podium strategy focused on prevention, diagnosis, and management of device thrombosis in the current era
• Updated recommendations in the current era of device thrombosis
  – Surgical technique, speed and anticoagulation
• More widespread dissemination of internal investigation data (ISHLT presentation- Sealed grafts; ASAIO presentation: bearings)
• Continued collaboration with centers, including the centers part of the NEJM publication
Next Steps

• **Updated Recommendations**
  – Implant technique
  – Pump speeds
  – Blood pressure
  – Anticoagulation

• **Prospective Multi-center Study on Pump Thrombosis**
  – Determine the incidence of pump thrombosis in the current HMII era, while adopting the above recommended practices
  – Identify the risk factors associated with these events
# PREVENTion of HeartMate II Pump Thrombosis Through Clinical Management (PREVENT)

<table>
<thead>
<tr>
<th>Study Objectives</th>
<th>(1) Determine the incidence of pump thrombosis in the current HMII era, while adopting recommended practices for reducing the risk of pump thrombosis (2) Identify the risk factors associated with these events</th>
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</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Prospective multi-center study</td>
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<tr>
<td>Patient Population</td>
<td>Consecutive patients implanted with the HeartMate II</td>
</tr>
</tbody>
</table>
| Recommended Patient Management                                                  | • Implant techniques  
• Anticoagulation  
• Pump speeds to avoid low flow                                                                                                                                                     |
| Estimated Number of patients                                                    | 200-300 Patients                                                                                                                                                                                  |
| Patient Follow-Up                                                              | Primary endpoint – 3 Months; Secondary endpoint – 6 Months                                                                                                                                           |
| Estimated Number of Sites                                                       | Up to 20                                                                                                                                                                                          |
| Inclusion Criteria                                                              | • Patients receiving the HeartMate II as their first device  
• Signed informed consent                                                                                                                                                                       |
| Exclusion Criteria                                                              | • Patients with prior mechanical circulatory support (e.g. ECMO, Impella), except for IABP                                                                                                                                                                   |
| Primary Study Endpoint                                                          | Incidence of confirmed pump thrombus at 3 Months                                                                                                                                                   |
| Secondary Study Endpoints                                                       | 1. Incidence of confirmed pump thrombus and suspected pump thrombosis (including unexplained hemolysis) within 6 months  
2. Incidence of pump exchange, urgent transplantation, or death due to pump thrombosis within 3 and 6 months  
3. Survival on LVAD support at 6 months post implantation  
4. Analysis of risk factors (e.g. patient related factors, management factors, recent infection, bleeding, atrial fibrillation, etc) for pump thrombosis including subgroup analysis of patients identified as having a hypercoagulable disorder  
5. Analysis of Chest-XRays to assess pump position over time  
6. Analysis of pump parameters and laboratory data (e.g. INR, LDH, PHGB etc) over time  
7. Analysis of adherence to recommended practices                                                                                                                                           |
Adverse event reduction remains a focus

... Since the trial, therapy understanding and adverse event occurrence continues to evolve

Note: 3x scale difference for Device infection and Bleeding requiring surgery compared to others

Jorde et al JACC online 2014
Summary of Post Approval Outcomes*

BTT*

DT**

*derived from INTERMACS

Slaughter, Rogers, Milano NEJM 2009;361:2241-51

1Slaughter, Rogers, Milano NEJM 2009;361:2241-51
The HeartMate II - Perspective

“The HeartMate II is a dramatic improvement over earlier devices, which had limited durability and higher associated mortality. *The HeartMate II gives patients who otherwise would die of terminal heart failure an excellent chance to have high-quality lives.* My colleagues and I will continue to implant this pump, which has already saved thousands of lives and which will remain an important advance in this field.”

O. Howard Frazier MD
Appendix
**Recommendations**

**Methods to Reduce Risk of Pump Thrombus**

- **Avoid low flow**
  - Implant techniques
    - Create unobstructed blood flow path
    - Prevent migration
  - Avoid low speeds
    - Use ramp speed and ECHO to set speed
  - Avoid high blood pressure (MAP < 90 mmHg)
  - Maintain adequate preload

- **Maintain adequate anticoagulation**
  - Heparin bridging
  - Warfarin anticoagulation
  - Address patient compliance issues

Highest Risk is a combination of:
- malpositioned pump
- low flow
- low anticoagulation
- Predisposed patient conditions
Implant Technique

- Creation of an adequately sized pump pocket, inferiorly deep, and lateral

- Inflow cannula should be parallel to the septum, oriented to the central LV
  - Core at the apex (not superior or anterior wall)

- Position outflow graft to avoid compression of the right ventricle

- Pump Position
  - Position should be below the diaphragm
  - Pump should be fixated to avoid migration
Pump Speeds and Blood Pressure

• Pump speeds coming out of the OR should be optimized
  – Not too high to impact the RV and not too low, which may result in low pump flow and pump thrombosis

• In most patients run pump speed above 9000 RPM and avoid speeds below 8600
  – Some cases, such as small patients, may require lower pump speeds

• Average pump speed during the clinical trial:
  – Day 1: 9150 ± 495 rpm
  – Day 180: 9405 ± 448 rpm

• Adjust pump speed to allow for AV opening only after the above goals are achieved

• Maintain a mean arterial pressure of <90 mmHg
Anticoagulation

- **Heparin Bridging**
  - In most patients without persistent bleeding, begin bridging with unfractionated heparin or LMWH within 48 hours of device implant with a goal PTT of 40-45 sec in the first 48 hr, titrated 50 to 60 sec by 96 hours.
  - When PO meds are tolerated, initiate warfarin support until an INR of 2.0-2.5 is obtained, at which time heparin therapy may be discontinued.

- **Warfarin Anticoagulation**
  - Initiate warfarin within 48 hr to obtain goal INR by POD 5-7
  - Goal INR 2.0 ± 0.5, with a preference towards 2.0-2.5

- **Antiplatelet Therapy**
  - ASA (81-325 mg daily)

- **Consider tailoring anticoagulation for specific patient profiles**