Miniaturized Transcatheter Delivered Cardiac Pacing: Primary Results of a Worldwide Clinical Trial

The Micra TPS Global Clinical Trial

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Permanent Cardiac Pacing Today

• Effective therapy for symptomatic bradycardia, with >350,000 procedures in the US annually *

• 1 in 8 patients may experience a complication with most occurring early after the implant procedure †
  – Lead related 2.4-5.5%
  – Pocket related 0.4-4.8%
  – Pneumothorax 0.9-2.2%
  – Infection 0.3-0.8%

The Micra Transcatheter Pacing System (TPS) Compared to transvenous pacemaker systems:

- >90% smaller (0.8 cc, 2.0 grams)
- Similar longevity and functionality with accelerometer-based rate response and automated pacing capture threshold management

The Micra TPS Global Clinical Trial

Study Design:
• Prospective, non-randomized, single-arm, multi-site, FDA IDE study*

Primary Objectives (6 months):
• Safety: Freedom-from device or procedure-related major complications
  – Death, permanent loss of therapy, hospitalization, prolonged hospitalization, or system revision
  – Target performance >90%, lower CI >83%
• Efficacy: Demonstrate low and stable pacing thresholds
  – ≤ 2V and no increase of >1.5V (relative to implant)
  – Target performance >89%, lower CI >80%

Comparison to Transvenous Pacemaker Systems:
• Safety performance comparison to predefined historical control†
  – 2667 patients from 6 trials of commercially available technology

†3830, 5076, EnRhythm, EnRhythm MRI, Advisa MRI, and SAVEPACe. Events related only to right atrial lead were excluded.
Study Recruitment

Patients:
• Candidates with Class I or II guideline indication* for *de novo* ventricular pacing with no restriction by comorbidity (e.g. COPD)

Enrollment:
• 744 patients from December 2013 to May 2015
• 56 centers in 19 countries in 5 continents
  – North America, Europe, Asia, Australia, and Africa

Patient Flow Diagram

Patients enrolled (n = 744)

Excluded
- Inclusion/exclusion criteria not met (n = 8)
- Withdrew consent (n = 11)

Implant attempted (n = 725)
- Successful implant (n = 719)
- Unsuccessful implant (n = 6)

No Micra 6 month visit
- Awaiting visit (n = 390)
- Death prior to 6-month visit (n = 23)
- Lost to follow-up (n = 1)
- Missed 6-month visit (n = 4)

System modified due to elevated PCT (n = 2)

Six month visit performed (n = 301)
- Paired PCT data not available (n = 6)

Safety objective (n = 725)

Efficacy objective (n = 297)

Analyzed when first 300 patients reached 6 month visit
## Baseline Characteristics

Micra patients older, more comorbidities

<table>
<thead>
<tr>
<th></th>
<th>Micra (N = 725)</th>
<th>Historical Control (N = 2667)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>75.9 ± 10.9</td>
<td>71.1 ± 12.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>58.8%</td>
<td>55.1%</td>
<td>0.08</td>
</tr>
<tr>
<td>Hypertension</td>
<td>78.6%</td>
<td>67.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AF</td>
<td>72.6%</td>
<td>36.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valvular Disease</td>
<td>42.2%</td>
<td>19.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>28.6%</td>
<td>21.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAD</td>
<td>28.0%</td>
<td>38.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHF</td>
<td>17.0%</td>
<td>15.0%</td>
<td>0.20</td>
</tr>
<tr>
<td>COPD</td>
<td>12.4%</td>
<td>7.2%†</td>
<td>0.001</td>
</tr>
<tr>
<td>Vascular Disease</td>
<td>7.3%</td>
<td>10.1%</td>
<td>0.032</td>
</tr>
</tbody>
</table>

*P-value from T-test (continuous variables) or Fisher’s Exact test (categorical variables).

†Data parameter not collected across all 6 trials.
Micra TPS Implant

• 99.2% implant success (719 of 725 attempts) with 94 implanters

• Median implant time was 28 min introducer in to introducer out
  – 22 min after 1st 10 implants
Primary Objectives Met

Safety (n = 725):

- 96.0% freedom from device and procedure-related major complication at 6 months (95% CI, 93.9 to 97.3; P<0.0001)
  - No dislodgements
  - No systemic infections

Efficacy (n = 297):

- 98.3% with adequate 6-month pacing capture threshold (95% CI, 96.1 to 99.5; P<0.0001)
Micra Major Complications (n = 725)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Death</th>
<th>Loss of Device Function</th>
<th>Hospitalization</th>
<th>Prolonged Hospitalization</th>
<th>System Revision</th>
<th>Total Events</th>
<th>No. Patients (Kaplan-Meier at 6 Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep vein thrombosis</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>AV fistula / pseudoaneurysm</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>5 (0.7%)</td>
</tr>
<tr>
<td>Cardiac perforation / effusion</td>
<td>3</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td>11</td>
<td>11 (1.6%)</td>
</tr>
<tr>
<td>Elevated thresholds</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td></td>
<td>2</td>
<td>2</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>3 (0.9%)</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Pacemaker syndrome</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Presyncope</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td><strong>TOTAL MAJOR COMPLICATIONS</strong></td>
<td>1</td>
<td>1</td>
<td>13</td>
<td>18</td>
<td>3</td>
<td>28</td>
<td>25 (4.0%)</td>
</tr>
</tbody>
</table>

Not mutually exclusive as a single event may meet more than one major complication criterion.
51% Fewer Major Complications with Micra vs Transvenous Pacemakers

To adjust for differences in patient populations, propensity matching to a subset of the historical control confirmed a reduction in major complications with Micra (HR: 0.46; 95% CI: 0.28 to 0.74).
Most Major Complications Reduced with Micra vs Transvenous Pacemakers within Subgroups

<table>
<thead>
<tr>
<th>SUBGROUP</th>
<th>No. OF PATIENTS</th>
<th>Micra Better</th>
<th>Transvenous Better</th>
<th>P-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>3392</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>1762</td>
<td></td>
<td></td>
<td>0.7427</td>
</tr>
<tr>
<td>≥75</td>
<td>1630</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>1497</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1895</td>
<td></td>
<td></td>
<td>0.3494</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
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<tr>
<td>No</td>
<td>1928</td>
<td></td>
<td></td>
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<td>Yes</td>
<td>602</td>
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</tr>
<tr>
<td>CAD</td>
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<tr>
<td>No</td>
<td>2164</td>
<td></td>
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<td>0.5507</td>
</tr>
<tr>
<td>Yes</td>
<td>1228</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>1889</td>
<td></td>
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<td>0.1458</td>
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<tr>
<td>Yes</td>
<td>1503</td>
<td></td>
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<tr>
<td>Congestive heart failure</td>
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<tr>
<td>No</td>
<td>2869</td>
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<tr>
<td>Yes</td>
<td>523</td>
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</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>1030</td>
<td></td>
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<td>0.944</td>
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<tr>
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<td>2362</td>
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<td>Valvular disease</td>
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<tr>
<td>No</td>
<td>2574</td>
<td></td>
<td></td>
<td>0.0582</td>
</tr>
<tr>
<td>Yes</td>
<td>818</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>COPD</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1317</td>
<td></td>
<td></td>
<td>0.2425</td>
</tr>
<tr>
<td>Yes</td>
<td>143</td>
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<tr>
<td>LBBB</td>
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<tr>
<td>No</td>
<td>2033</td>
<td></td>
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<td>0.8559</td>
</tr>
<tr>
<td>Yes</td>
<td>289</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Vascular disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2191</td>
<td></td>
<td></td>
<td>0.6414</td>
</tr>
<tr>
<td>Yes</td>
<td>223</td>
<td></td>
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</tr>
</tbody>
</table>
# Healthcare Utilization

54% Fewer Hospitalizations and 87% Fewer System Revisions with Micra versus Transvenous Pacemakers

<table>
<thead>
<tr>
<th>6-Month Kaplan-Meier Estimates</th>
<th>Micra (n=725)</th>
<th>Historical Control (n=2667)</th>
<th>Relative Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Major Complications</td>
<td>4.0%</td>
<td>7.4%</td>
<td>51%</td>
</tr>
<tr>
<td>Death</td>
<td>0.1%</td>
<td>0%</td>
<td>NS</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>2.3%</td>
<td>3.9%</td>
<td>54%</td>
</tr>
<tr>
<td>Prolonged Hospitalization</td>
<td>2.6%</td>
<td>2.4%</td>
<td>NS</td>
</tr>
<tr>
<td>System Revision</td>
<td>0.4%</td>
<td>3.5%</td>
<td>87%</td>
</tr>
<tr>
<td>Loss of device function</td>
<td>0.1%</td>
<td>0%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Not mutually exclusive as a single event may meet more than one major complication criteria.

NS = Not significant
Micra Pacing Thresholds

Battery Longevity Estimate:
• Based on use conditions of the 300 patients with 6-month data, median battery longevity estimate is 12.5 years*

*Use conditions included: median pacing 49%, median pacing threshold 0.50V, median impedance 573Ω; estimated longevity range of 6.0-14.6 years.
Micra Electrical Performance

**R-WAVE AMPLITUDE**

- **Implant** (n=690): 11.2
- **Discharge** (n=673): 12.8
- **1-month** (n=634): 15.0
- **3-month** (n=463): 15.3
- **6-month** (n=274): 15.3
- **12-month** (n=58): 16.4

Mean ± standard deviation

**PACING IMPEDANCE**

- **Implant** (n=719): 724
- **Discharge** (n=717): 679
- **1-month** (n=676): 643
- **3-month** (n=504): 629
- **6-month** (n=301): 627
- **12-month** (n=62): 621

Mean ± standard deviation
Conclusions

The Micra transcatheter ventricular pacemaker was successfully implanted (99.2%) in clinically diverse patients around the world, while meeting prespecified safety and efficacy endpoints.

Major complications occurred in 4% of patients, 51% less than the transvenous pacemaker control group.

Importantly, this resulted in 54% fewer hospitalizations and 87% fewer system revisions, led by the elimination of pneumothoraces and absence of Micra dislodgements.
Participating Centers

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