Pacemaker therapy for patients with neurally-mediated syncope and documented asystole

A randomized controlled double-blind trial
**Study design**

**ILR screening phase**

Neurally-mediated syncopes

↓

ILR implantation (Reveal DX/XT)

↓

ILR follow-up (max 2 yrs)

**ISSUE 3 study phase**

ILR eligibility criteria:

- *Asystolic syncope* ≥3 s, or
- *Non-syncopal asystole* ≥6 s

R

\[ \text{Pm ON} \quad \text{Pm OFF} \]
Screening phase: documented events

- Tachycardia: 10%
- Normal SR: 23%
- Bradycardia: 10%
- Asystole: 56%

Total end-points: 158

Asystole (11 ± 4 s)
## Patient characteristics (I)

**Characteristics** | **Pm ON (n=38)** | **Pm OFF (n=39)** | **Registry (n=12)**
--- | --- | --- | ---
**Age, mean** | 63 | 63 | 63
**Men** | 53% | 41% | 58%

### Syncope events:

- **Total events, median** | 7 | 8 | 7
- **Events last 2 years, median** | 4 | 5 | 4
- **Events last 2 years without prodrome, median** | 3 | 3 | 1
- **Age at first syncope, mean** | 48 | 45 | 41
- **Interval between first and last episode, median** | 8 | 8 | 17
- **History of presyncope** | 50% | 56% | 75%
- **Hospitalization for syncope** | 63% | 64% | 58%
- **Injuries related to fainting:**
  - **Major (fractures, concussion)** | 5% | 10% | 17%
  - **Minor (bruises, contusion, hematoma)** | 39% | 46% | 50%
- **Typical vasovagal/situational presentation** | 47% | 41% | 58%
- **Atypical presentation (uncertain)** | 53% | 59% | 42%
Patient characteristics (II)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pm ON n=38</th>
<th>Pm OFF n=39</th>
<th>Registry n=12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ILR documentation</strong> (eligibility criteria):</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>- Syncope and asystole ≥3 s</td>
<td>79%</td>
<td>82%</td>
<td>77%</td>
</tr>
<tr>
<td>- Non-syncopal pause ≥6 s</td>
<td>21%</td>
<td>18%</td>
<td>17%</td>
</tr>
<tr>
<td>- Mean length of asystole, s</td>
<td>10</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td><strong>Tilt testing</strong>: performed</td>
<td>87%</td>
<td>82%</td>
<td>83%</td>
</tr>
<tr>
<td>- Positive of those performed</td>
<td>42%</td>
<td>72%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Structural heart disease</td>
<td>13%</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>- Hypertension</td>
<td>50%</td>
<td>49%</td>
<td>33%</td>
</tr>
<tr>
<td>- Diabetes</td>
<td>11%</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Concomitant medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Anti-hypertensive</td>
<td>47%</td>
<td>31%</td>
<td>25%</td>
</tr>
<tr>
<td>- Psychiatric</td>
<td>11%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>- Any other drugs</td>
<td>26%</td>
<td>25%</td>
<td>25%</td>
</tr>
</tbody>
</table>
First syncope recurrence
(intention-to-treat)

Kaplan-Meier survival estimates

<table>
<thead>
<tr>
<th>Months</th>
<th>Pm OFF</th>
<th>Pm ON</th>
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<tbody>
<tr>
<td>0</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
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<td>9</td>
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<td>12</td>
<td>21</td>
<td>16</td>
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<td>15</td>
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<tr>
<td>18</td>
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<td>13</td>
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<tr>
<td>21</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>24</td>
<td>8</td>
<td>11</td>
</tr>
</tbody>
</table>

Number at risk

log rank: p=0.039
RRR at 2 yrs: 57%
**Conclusions**

- Dual-chamber permanent pacing is effective in reducing recurrence of syncope in patients ≥40 years with severe asystolic NMS.

- The observed 32% absolute and 57% relative syncope reduction rate support the use of this invasive treatment for the relatively benign NMS.

- The overall strategy of using an ILR in order to determine indication for pacing likely contributed to the positive findings and explains the discrepancy with the negative results of some previous report.
Who gets an ILR and (eventually) a PM?

- 9% of patients affected by NMS referred to Syncope Clinic will receive an ILR.
- 18% of pts receiving an ILR will be candidates for pacemaker therapy within 1 year and approximately 40% within 4 years.
- 1 out of 3 pacemaker patients will benefit from pacing therapy within the subsequent 2 years (NNT=3).
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