DANPACE: The Danish multicenter randomised trial on AAI/R versus DDDR pacing in sick sinus syndrome

Jens Cosedis Nielsen,
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on behalf of the DANPACE investigators
Conflicts of interest

• Jens Cosedis Nielsen has received speakers fees and/or consultant honoraries from Medtronic, St Jude Medical, Biotronik, Astra-Zeneca, and Sanofi-Aventis.
DANPACE investigators

**Steering Committee (numbers of patients included):**
- Henning Rud Andersen (chairman) and Jens Cosedis Nielsen (co-chairman), Aarhus University Hospital, Skejby (337);
- Poul-Erik Bloch-Thomsen, Gentofte Hospital (180);
- Søren Højberg, Bispebjerg Hospital (121);
- Mogens Møller, Odense University Hospital (114);
- Thomas Vesterlund, Aalborg Hospital (111);
- Dorthe Dalsgaard, Herning Hospital (108);
- Tonny Nielsen, Esbjerg Hospital (77);
- Mogens Asklund, Kolding Hospital (72);
- Elsebeth Vibeke Friis, Haderslev Hospital (70);
- Per Dahl Christensen, Viborg Hospital (56);
- Erik Hertel Simonsen, Hillerød Hospital (47);
- Ulrik Hedegaard Eriksen, Vejle Hospital (39);
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- Craig Barr, Andreas Tselios, Nicola Gordon, Russells Hall Hospital, Dudley (6);
- John Cleland, Andrew Clark, Sarah Hurren, Castle Hill Hospital, East Cottingham (3);
- David McEneaney, Andrew Moriarty, Anne Mackin, Craigavon Area Hospital, Craigavon (2);
- Arif Ahsan, Jane Burton, Ruth Oliver, Nottingham City Hospital (2);
- Barry Kneale, Lynda Huggins, Worthing Hospital (2).

**From Canada:**
- Jeffrey S. Healey, Hamilton (8).
In patients with sick sinus syndrome (SSS) bradycardia can be treated with any pacemaker: AAIR, VVIR, or DDDR.

VVIR pacing increases atrial fibrillation as compared with physiological pacing (DDDR or AAIR), and VVIR pacing was associated with increased mortality as compared with AAIR pacing in one small trial.¹

Ventricular pacing has been found to cause ventricular desynchronisation with lowering of LVEF and left atrial dilatation, resulting in heart failure and atrial fibrillation.

¹: Andersen HR et al., Lancet 1997
Aim

• To compare AAIR and DDDR pacing in SSS.

• Primary endpoint:
  – Death from any cause.

• Secondary endpoints:
  – Paroxysmal atrial fibrillation (at planned follow-up),
  – Chronic atrial fibrillation,
  – Stroke,
  – Heart failure,
  – Pacemaker reoperation.
Statistics

- 1,900 patients.
- Followed for in mean 5.5 years.
- Identify a 6% absolute difference in mortality.
- Power 80%, overall $\alpha=0.05$.

- Two planned interim analyses after $1/3$ and $2/3$ of the expected number of deaths.

- Intention to treat.
Methods

• Randomised controlled trial.

• **Inclusion criteria:**
  – symptomatic bradycardia and documented sinus-pause >2s or sinus bradycardia <40bpm >1 minute whilst awake,
  – PR-interval ≤0.22s (age 18-70 years) or PR-interval ≤0.26s (age ≥70 years),
  – QRS width <0.12s.

• **Exclusion criteria:**
  – AV block,
  – bundle branch block,
  – persistent atrial fibrillation >12 months,
  – atrial fibrillation with QRS rate <40 bpm for ≥1 min or pauses >3s,
  – a positive test for carotid sinus hypersensitivity.
Pacemaker programming

- Rate adaptive function was active.
- Lower rate 60 bpm.
- Upper rate 130 bpm.

- DDDR:
  - Paced AV-interval ≤220 ms.
  - Sensed AV-interval ≤200 ms.
  - Rate-adaptive shortening of the AV-interval.
Randomisation and pacing mode

1,415

AAIR 707

First PM:
AAIR 660
DDDR 46
VVIR 1

PM at last FU:
AAIR 585
DDDR 105
VVIR 17

93%

DDDR 708

First PM:
DDDR 700
AAIR 6
VVIR 2

PM at last FU:
DDDR 639
VVIR 49
AAIR 18
CRT 1
No PM 1

99%

83%

90%
<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>AAIR (N=707)</th>
<th>DDDR (N=708)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender no. (%)</td>
<td>472 (66.8)</td>
<td>441 (62.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Age (years, mean±SD)</td>
<td>73.5 ±11.2</td>
<td>72.4 ±11.4</td>
<td>0.054</td>
</tr>
<tr>
<td>Brady-tachy syndrome no. (%)</td>
<td>303 (42.9)</td>
<td>318 (44.9)</td>
<td>0.44</td>
</tr>
<tr>
<td>Hypertension</td>
<td>241 (34.1)</td>
<td>239 (33.8)</td>
<td>0.90</td>
</tr>
<tr>
<td>Previous myocardial infarction no. (%)</td>
<td>94 (13.3)</td>
<td>90 (12.7)</td>
<td>0.74</td>
</tr>
<tr>
<td>Diabetes no. (%)</td>
<td>68 (9.6)</td>
<td>72 (10.2)</td>
<td>0.73</td>
</tr>
<tr>
<td>Previous transient cerebral ischemia no. (%)</td>
<td>35 (5.0)</td>
<td>37 (5.2)</td>
<td>0.81</td>
</tr>
<tr>
<td>Previous stroke no. (%)</td>
<td>61 (8.6)</td>
<td>53 (7.5)</td>
<td>0.43</td>
</tr>
<tr>
<td>Left ventricular ejection fraction reduced (&lt; 50%) no. (%)</td>
<td>59 (10.6)</td>
<td>54 (9.5)</td>
<td>0.55</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter (mm, mean±SD)</td>
<td>47.7 ± 7.3</td>
<td>47.8 ± 7.3</td>
<td>0.45</td>
</tr>
<tr>
<td>Left atrial diameter (mm, mean±SD)</td>
<td>39.3 ± 6.5</td>
<td>38.8 ± 6.4</td>
<td>0.23</td>
</tr>
<tr>
<td>Symptoms before pacemaker no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>359 (50.8)</td>
<td>349 (49.3)</td>
<td>0.58</td>
</tr>
<tr>
<td>Dizzy spells</td>
<td>597 (84.4)</td>
<td>587 (82.9)</td>
<td>0.44</td>
</tr>
<tr>
<td>Heart failure</td>
<td>86 (12.2)</td>
<td>79 (11.2)</td>
<td>0.56</td>
</tr>
<tr>
<td>≥2 of the above three symptoms</td>
<td>317 (44.8)</td>
<td>291 (41.1)</td>
<td>0.16</td>
</tr>
<tr>
<td>Medication at randomization no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>108 (15.3)</td>
<td>89 (12.6)</td>
<td>0.14</td>
</tr>
<tr>
<td>Aspirin</td>
<td>369 (52.2)</td>
<td>361 (51.1)</td>
<td>0.67</td>
</tr>
<tr>
<td>Sotalol</td>
<td>43 (6.1)</td>
<td>44 (6.2)</td>
<td>0.91</td>
</tr>
<tr>
<td>Beta-blocker other than sotalol</td>
<td>159 (22.5)</td>
<td>132 (18.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>137 (19.4)</td>
<td>142 (20.1)</td>
<td>0.75</td>
</tr>
<tr>
<td>Digoxin</td>
<td>73 (10.3)</td>
<td>62 (8.8)</td>
<td>0.32</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>25 (3.5)</td>
<td>24 (3.4)</td>
<td>0.88</td>
</tr>
<tr>
<td>Class I Antiarrhythmics</td>
<td>14 (2.0)</td>
<td>20 (2.8)</td>
<td>0.30</td>
</tr>
<tr>
<td>Angiotensin-converting-enzyme inhibitors</td>
<td>160 (22.6)</td>
<td>170 (24.0)</td>
<td>0.53</td>
</tr>
<tr>
<td>Diuretics</td>
<td>304 (43.0)</td>
<td>263 (37.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>New York Heart Association functional class no. (%)</td>
<td></td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>I</td>
<td>503 (71.4)</td>
<td>522 (73.9)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>172 (24.4)</td>
<td>158 (22.4)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>29 (4.1)</td>
<td>24 (3.4)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>2 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Wenckebach block point (≥100 bpm, %)</td>
<td>611 (94.1)</td>
<td>581 (91.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>Treated as randomized</td>
<td>660 (93.4)</td>
<td>700 (98.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Results

• Follow-up 5.4±2.6 years.
• No patients lost for follow-up.

• Pacing in the atrium:
  – AAIR group: 58±29%
  – DDDR group: 59±31%

• Pacing in the ventricle:
  – DDDR group: 65±33%

\[ P = 0.52 \]
Survival

- Dual Chamber Pacing
- Single Lead Atrial Pacing

Survival (%)

Years from randomization

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Lead</td>
<td>707</td>
<td>648</td>
<td>466</td>
<td>298</td>
<td>147</td>
<td>25</td>
</tr>
<tr>
<td>Dual Chamber</td>
<td>708</td>
<td>629</td>
<td>462</td>
<td>287</td>
<td>136</td>
<td>24</td>
</tr>
</tbody>
</table>

p=0.53
Atrial fibrillation

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**No. at Risk**
- Single Lead: 707, 498, 301, 157, 47, 0
- Dual Chamber: 708, 504, 330, 158, 52, 0

**Years from randomization**

![Graph showing a comparison between Dual Chamber Pacing and Single Lead Atrial Pacing.](image)

- Dual Chamber Pacing
- Single Lead Atrial Pacing

**p=0.024**
Stroke

Dual Chamber Pacing
Single Lead Atrial Pacing

p=0.56

Years from randomization

No. at Risk
Single Lead 707 571 383 225 68 0
Dual Chamber 708 550 391 215 73 0
Reoperation

Reoperation

p<0.001

Dual Chamber Pacing

Single Lead Atrial Pacing

No. at Risk

<table>
<thead>
<tr>
<th>Years from randomization</th>
<th>Dual Chamber Pacing</th>
<th>Single Lead Atrial Pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>707</td>
<td>707</td>
</tr>
<tr>
<td>2</td>
<td>527</td>
<td>534</td>
</tr>
<tr>
<td>4</td>
<td>340</td>
<td>377</td>
</tr>
<tr>
<td>6</td>
<td>196</td>
<td>198</td>
</tr>
<tr>
<td>8</td>
<td>33</td>
<td>44</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Freedom from reoperation (%)

Dual Chamber 708
Single Lead 707
Heart failure

- NYHA class at last FU: $p=0.43$
- Diuretics at last follow-up: $p=0.89$
- Hospitalization for heart failure: $p=0.90$
## Clinical Outcomes – Multivariate analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.94</td>
<td>0.77-1.14</td>
<td>0.52</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>1.24</td>
<td>1.01-1.52</td>
<td>0.042</td>
</tr>
<tr>
<td>Chronic AF</td>
<td>1.01</td>
<td>0.74-1.39</td>
<td>0.93</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.05</td>
<td>0.70-1.59</td>
<td>0.80</td>
</tr>
<tr>
<td>Reoperation</td>
<td>2.00</td>
<td>1.54-2.61</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Conclusions

• No difference in survival between AAIR and DDDR pacing in SSS.

• Risk of reoperation is doubled with AAIR pacing.

• Paroxysmal atrial fibrillation is more common in AAIR pacing.

• DDDR pacing with an AV interval ≤220ms is the preferred pacing mode for SSS.

• AAIR pacing should no longer be used.
Financial support

Unrestricted grants from

– Medtronic,
– St Jude Medical,
– Boston Scientific,
– Ela Medical,
– Pfizer,
– The Danish Heart Foundation (10-04-R78-A2954-22779).