DANPACE: The Danish multicenter randomised trial on AAIR versus DDDR pacing in sick sinus syndrome

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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 Coseidis 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);
• Gunnar Vagn Hagemann Jensen, Roskilde Hospital (28);
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From United Kingdom:

• William D. Toff (UK coordinating investigator), J. Douglas Skehan, Kieran Brack, Glenfield Hospital, Leicester (8);
• 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).
Background

• 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 $\alpha=0.05$.
- Intention to treat.

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

90%

99%
<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>Syncope no. (%)</td>
<td>359 (50.8)</td>
<td>349 (49.3)</td>
<td>0.58</td>
</tr>
<tr>
<td>Dizzy spells no. (%)</td>
<td>597 (84.4)</td>
<td>587 (82.9)</td>
<td>0.44</td>
</tr>
<tr>
<td>Heart failure no. (%)</td>
<td>86 (12.2)</td>
<td>79 (11.2)</td>
<td>0.56</td>
</tr>
<tr>
<td>≥ 2 of the above three symptoms no. (%)</td>
<td>317 (44.8)</td>
<td>291 (41.1)</td>
<td>0.16</td>
</tr>
<tr>
<td>Anticoagulation no. (%)</td>
<td>108 (15.3)</td>
<td>89 (12.6)</td>
<td>0.14</td>
</tr>
<tr>
<td>Aspirin no. (%)</td>
<td>369 (52.2)</td>
<td>361 (51.1)</td>
<td>0.67</td>
</tr>
<tr>
<td>Sotalol no. (%)</td>
<td>43 (6.1)</td>
<td>44 (6.2)</td>
<td>0.91</td>
</tr>
<tr>
<td>Beta-blocker other than sotalol no. (%)</td>
<td>159 (22.5)</td>
<td>132 (18.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Calcium-channel blocker no.</td>
<td>137 (19.4)</td>
<td>142 (20.1)</td>
<td>0.75</td>
</tr>
<tr>
<td>Digoxin no. (%)</td>
<td>73 (10.3)</td>
<td>62 (8.8)</td>
<td>0.32</td>
</tr>
<tr>
<td>Amiodarone no. (%)</td>
<td>25 (3.5)</td>
<td>24 (3.4)</td>
<td>0.88</td>
</tr>
<tr>
<td>Class I Antiarrhythmics no.</td>
<td>14 (2.0)</td>
<td>20 (2.8)</td>
<td>0.30</td>
</tr>
<tr>
<td>Angiotensin-converting-enzyme inhibitors no.</td>
<td>160 (22.6)</td>
<td>170 (24.0)</td>
<td>0.53</td>
</tr>
<tr>
<td>Diuretics no. (%)</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% \( P=0.52 \)

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

- Dual Chamber Pacing
- Single Lead Atrial Pacing

Survival (%): 708, 629, 462, 287, 136, 24
- Single Lead:

<table>
<thead>
<tr>
<th>Years from randomization</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</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

No. at Risk

Single Lead 707 498 301 157 47 0
Dual Chamber 708 504 330 158 52 0

p=0.024
Stroke

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>571</td>
<td>383</td>
<td>225</td>
<td>68</td>
<td>0</td>
</tr>
<tr>
<td>Dual Chamber</td>
<td>708</td>
<td>550</td>
<td>391</td>
<td>215</td>
<td>73</td>
<td>0</td>
</tr>
</tbody>
</table>

p = 0.56
Reoperation

Years from randomization vs. % Freedom from reoperation. The graph shows two Kaplan-Meier curves: Dual Chamber Pacing (blue) and Single Lead Atrial Pacing (red). The log-rank test statistic for comparing the two is $p<0.001$.

<table>
<thead>
<tr>
<th>Years from randomization</th>
<th>Single Lead</th>
<th>Dual Chamber</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>707</td>
<td>708</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>

No. at Risk:
- Single Lead: 707
- Dual Chamber: 708
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></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 $\leq 220$ms is the preferred pacing mode for SSS.

• AAIR pacing should no longer be used.
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– Pfizer,
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