Biventricular Pacing for Atrio-ventricular Block to Prevent Cardiac Desynchronization

BioPace Trial Investigators and Coordinators
DISCLOSURE

St. Jude Medical : consultant
BOARDs AND COMMITTEES

Steering Committee
- Blanc J.J. – Brest, France
- Funck R.C. – Bad Hersfeld, Germany
- Lunati M. – Milano, Italy
- Hindricks G. – Leipzig, Germany
- De Roy L. – Yvoir, Belgium
- Paul V. – Perth, Australia

Echo Core Lab
- Henein M. – London, UK

Independent Event Adjudication Committee
- Daubert J.C. – Rennes, France
- Tavazzi I. – Cotignola, Italy
- Thygesen K. – Aarhus, Denmark

Data Safety Monitoring Board
- Linde C. – Stockholm, Sweden
- Leclercq C. – Rennes, France
- Trampisch H.J. – Bochum, Germany

Investigators

Trial Statistician
- Mueller H.H. – Munich, Germany

Sponsor
- St. Jude Medical

Data Management
- Coordinating Center for Clinical Trials (KKS) – Marburg, Germany

Clinical trials.gov identifier:
- NCT00187278
BACKGROUND

• Atrio-Ventricular Block (AVB) is a common disease currently treated with Right Ventricular (RV) pacing.

• However numerous trials (DAVID, MOST...) have shown that RV pacing may have deleterious long-term effects on Left Ventricular (LV) function and clinical outcome.
AIM OF STUDY

To investigate whether biventricular (BiV) pacing prevents the deleterious consequences of right ventricular (RV) pacing in patients with a standard indication for permanent ventricular pacing.
STUDY DESIGN

• International, multicenter

• Parallel group design

• Randomization (RV / BiV) prior to implant

• Blinded endpoint assessment
STUDY CENTERS

Number of sites per country
STUDY PURPOSE AND ENDPOINT

PURPOSE

• BiV pacing is superior to RV pacing in patients with AVB who require permanent ventricular pacing

PRIMARY ENDPOINT

• Combination of time-to-death or first hospitalization due to Heart Failure (HF)
SECONDARY ENDPOINTS

• Death due to cardiovascular causes
• Functional capacity (6-minute walk test) and Quality of Life (Minnesota Questionnaire) 12 months after implantation.
• Echo core laboratory results
  • Left ventricular end diastolic and end systolic diameters
  • Left ventricular ejection fraction
  • Left atrial dimensions
  • Amount of mitral and tricuspid regurgitation
• Adverse events related to
  • Implantation procedure
  • Left ventricular lead (successful implantation of the SJM LV lead)
  • All leads
INCLUSION CRITERIA

• Indication for implantation of a ventricular pacemaker according to guidelines and an anticipated need for frequent ventricular pacing
  • Permanent 3rd degree AV-block or
  • Intermittent 3rd degree AV-block in combination with 1st degree AV-block with a PR-interval $\geq 220$ ms or
  • 2nd degree AV-block in combination with 1st degree AV-block with a PR-interval $\geq 220$ ms or
  • 1st degree AV-block with a PR-interval $\geq 220$ ms and indication for ventricular pacing or
  • Chronic atrial fibrillation with a spontaneous ventricular rate at rest $\leq 60$/min

• Any left ventricular ejection fraction (LVEF) as measured by echocardiography
EXCLUSION CRITERIA

- Implanted ventricular pacing device
- Status 1 for heart transplantation
- Evidence of acute left ventricular dysfunction and high probability for its reversibility (e.g. acute myocarditis, tachy-cardiomyopathy)
- Implanted prosthetic tricuspid valve
- Severe musculoskeletal disorder(s)
- Age below 18 years
- Life expectancy of less than 6 months
STATISTICAL ANALYSIS

• Two-sided stratified logrank test
• Type I error level: $\alpha = 5\%$
• Power: $1 - \beta = 80\%$
• Detectable difference: Hazard Ratio = 0.8
• Intention-to-treat analysis
• Adjusted for differences in gender, age and AF
• 635 events required
• Maximum loss to follow-up: 15%
• 1800 subjects needed
• Pre-specified analysis stratified by LVEF
Enrollment period from May 2003 to September 2007

1810 patients

RV Group 908 patients

BiV Group: 902 patients

Mean FU: 5.6 years

689 combined events (439 Deaths + 250 HF Hospitalizations)
# Baseline Parameters

<table>
<thead>
<tr>
<th></th>
<th>Total 1810</th>
<th>RV 908 (50.2%)</th>
<th>BiV 902 (49.8%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [year]</td>
<td>73.5±9.2</td>
<td>73.3±9.3</td>
<td>73.8±9.0</td>
<td>0.27</td>
</tr>
<tr>
<td>Men</td>
<td>68.3%</td>
<td>67.4%</td>
<td>69.2%</td>
<td>0.42</td>
</tr>
<tr>
<td>% Ventricular pacing at 1 month</td>
<td>88.2</td>
<td>86.3</td>
<td>90.1</td>
<td>0.07</td>
</tr>
<tr>
<td>LVEF [%]</td>
<td>55.4±12.2</td>
<td>55.5±12.4</td>
<td>55.3±12.1</td>
<td>0.95</td>
</tr>
<tr>
<td>QRS Duration [ms]</td>
<td>118.4±30.5</td>
<td>118.8±30.3</td>
<td>118.1±30.8</td>
<td>0.61</td>
</tr>
<tr>
<td>Underlying Cardiac Disease</td>
<td>63.1%</td>
<td>63.0%</td>
<td>63.3%</td>
<td>0.92</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>24.9%</td>
<td>24.8%</td>
<td>24.9%</td>
<td>0.96</td>
</tr>
<tr>
<td>LBBB</td>
<td>17.2%</td>
<td>18.3%</td>
<td>16.6%</td>
<td>0.39</td>
</tr>
</tbody>
</table>
# BASELINE PARAMETERS

<table>
<thead>
<tr>
<th></th>
<th>TOTAL 1810</th>
<th>RV 908 (50.2%)</th>
<th>BiV 902 (49.8%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age [year]</strong></td>
<td>73.5±9.2</td>
<td>73.3±9.3</td>
<td>73.8±9.0</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>68.3%</td>
<td>67.4%</td>
<td>69.2%</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>% Ventricular pacing at 1 month</strong></td>
<td>88.2</td>
<td>86.3</td>
<td>90.1</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>LVEF [%]</strong></td>
<td>55.4±12.2</td>
<td>55.5±12.4</td>
<td>55.3±12.1</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>QRS Duration [ms]</strong></td>
<td>118.4±30.5</td>
<td>118.8±30.3</td>
<td>118.1±30.8</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Underlying Cardiac Disease</strong></td>
<td>63.1%</td>
<td>63.0%</td>
<td>63.3%</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Atrial Fibrillation</strong></td>
<td>24.9%</td>
<td>24.8%</td>
<td>24.9%</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>LBBB</strong></td>
<td>17.2%</td>
<td>18.3%</td>
<td>16.6%</td>
<td>0.39</td>
</tr>
</tbody>
</table>
## Baseline Parameters

<table>
<thead>
<tr>
<th></th>
<th>TOTAL 1810</th>
<th>RV 908 (50.2%)</th>
<th>BiV 902 (49.8%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age [year]</strong></td>
<td>73.5±9.2</td>
<td>73.3±9.3</td>
<td>73.8±9.0</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>68.3%</td>
<td>67.4%</td>
<td>69.2%</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>% Ventricular pacing at 1 month</strong></td>
<td>88.2</td>
<td>86.3</td>
<td>90.1</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>LVEF [%]</strong></td>
<td>55.4±12.2</td>
<td>55.5±12.4</td>
<td>55.3±12.1</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>QRS Duration [ms]</strong></td>
<td>118.4±30.5</td>
<td>118.8±30.3</td>
<td>118.1±30.8</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Underlying Cardiac Disease</strong></td>
<td>63.1%</td>
<td>63.0%</td>
<td>63.3%</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Atrial Fibrillation</strong></td>
<td>24.9%</td>
<td>24.8%</td>
<td>24.9%</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>LBBB</strong></td>
<td>17.2%</td>
<td>18.3%</td>
<td>16.6%</td>
<td>0.39</td>
</tr>
</tbody>
</table>
## BASELINE PARAMETERS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TOTAL</th>
<th>RV (50.2%)</th>
<th>BiV (49.8%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age [year]</td>
<td>73.5±9.2</td>
<td>73.3±9.3</td>
<td>73.8±9.0</td>
<td>0.27</td>
</tr>
<tr>
<td>• Men</td>
<td>68.3%</td>
<td>67.4%</td>
<td>69.2%</td>
<td>0.42</td>
</tr>
<tr>
<td>• % Ventricular pacing at 1 month</td>
<td>88.2</td>
<td>86.3</td>
<td>90.1</td>
<td>0.07</td>
</tr>
<tr>
<td>• LVEF [%]</td>
<td>55.4±12.2</td>
<td>55.5±12.4</td>
<td>55.3±12.1</td>
<td>0.95</td>
</tr>
<tr>
<td>• QRS Duration [ms]</td>
<td>118.4±30.5</td>
<td>118.8±30.3</td>
<td>118.1±30.8</td>
<td>0.61</td>
</tr>
<tr>
<td>• Underlying Cardiac Disease</td>
<td>63.1%</td>
<td>63.0%</td>
<td>63.3%</td>
<td>0.92</td>
</tr>
<tr>
<td>• Atrial Fibrillation</td>
<td>24.9%</td>
<td>24.8%</td>
<td>24.9%</td>
<td>0.96</td>
</tr>
<tr>
<td>• LBBB</td>
<td>17.2%</td>
<td>18.3%</td>
<td>16.6%</td>
<td>0.39</td>
</tr>
</tbody>
</table>
RESULTS
MORTALITY/HF HOSPITALIZATION

1810 patients / LVEF 55.4±12.2%

Event Free Rate

Time since randomization (months)

RV BiV

p (adjusted): 0.08, HR 0.871, 95%-CI: [0.75; 1.01]

Right ventricular (RV)
Biventricular (BiV)
MORTALITY/HF HOSPITALIZATION

HR 0.87, 95%-CI: [0.75; 1.01]

p = 0.08
MORTALITY/HF HOSPITALIZATION
(LVEF ≤ 50%)

571 patients / LVEF 41.2 ± 8.8%

Event Free Rate

Time since randomization (months)

Right ventricular (RV)
Biventricular (BiV)

p (adjusted): 0.48, HR 0.920, 95% CI: [0.73; 1.16]
MORTALITY/HF HOSPITALIZATION (LVEF>50%)

1239 patients / LVEF 61.9±7.0%

Event Free Rate

Time since randomization (months)

p (adjusted): 0.18, HR 0.876, 95%-CI: [0.72; 1.07]

Right ventricular (RV)
Biventricular (BiV)
MORTALITY / HF HOSPITALIZATION

Overall (1810/1810)
HR 0.87, 95%-CI: [0.75; 1.01]
p=0.08

LVEV ≤ 50% (571/1810)
HR 0.92, 95%-CI: [0.73; 1.16]
p=0.48

LVEV >50% (1239/1810)
HR 0.88, 95%-CI: [0.72; 1.07]
p=0.18
## ADVERSE EVENTS

<table>
<thead>
<tr>
<th></th>
<th>As treated (N=1774)</th>
<th>TOTAL (N=891) [95% CI]</th>
<th>RV (N=891) [95% CI]</th>
<th>BiV (N=883) [95% CI]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Implant Failure</strong></td>
<td>7.4%</td>
<td>0% [0.0%; 0.4%]</td>
<td>14.8% [11.7%; 16.4%]</td>
<td>&lt;0.0000</td>
<td>....</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td>1.6%</td>
<td>1.1%</td>
<td>2.1%</td>
<td>0.10</td>
<td></td>
</tr>
</tbody>
</table>
STRENGTHS AND LIMITATIONS

STRENGTHS

• Prospective, international, randomized, single-blind control
• Largest, longest follow-up trial to date
• Percentage of RV and BIV pacing measured
• Effect evaluated according to different baseline LVEF

LIMITATIONS

• Long study duration
• 14.8% initial failed implants in the BiV group
CONCLUSIONS

• In patients with AVB who need implantation of a permanent pacemaker there is a non statistically significant trend in favor of BiV over RV pacing mode.

• Additional analyses will perhaps identify sub-groups for which BiV confers a clear benefit.
LIST OF INVESTIGATORS

- **Australia:** Nadurata
- **Austria:** Siostrzonek, Grimm, Huber
- **Belgium:** Vrints, Mairesse, Vandekerckhove, Castadot, Zenagui, Stoupel, Deperon, Blommaert
- **Canada:** Paredes, Parker
- **Estonia:** Kolk
- **France:** Poulard, Rey, Dupuis, Etienne, Kacet, Graux, Deharo, Davy, Jauvert, Dennetièrè, Anselme
- **Germany:** Geller, Liebetrau, Dänschel, Meisel, Sievert, Reinig, Weissmüller, Hindricks, Pfeiffer, Szendey, Brömsen, Schmailzl, Axthelm, Czech, Daub, Sick, Steiner, Oltmanns, Ketteler, Grove, Hahlweg, Sabin, Schmitt, Zahn, Weitkamp, Rub, Perings, Lemke
- **Italy:** Padeletti, Vicentini, Luzzi, Verlato, Di Girolamo, Botto, Toselli, Leonzio, Solimene, Lunati, Vaccari, Carreras
- **Netherlands:** De Voogt, Van den Bos, Saïd, Dijkman, Widdershoven
- **Norway:** Haaland, Helleburst, Lappegard, Gjestvang, Nilsen
- **Poland:** Wilcck, Lewczuk
- **Sweden:** Frykman, Gadler, Kjellman, Aronsson
- **Serbia:** Milasinovic, Angelkov, Perisic, Kovačević
- **Tunisia:** Kachboura
- **UK:** Panthing, Yousef, Paul, Barr, Wright, Haywood