Incidence of atrial fibrillation and thromboembolism in a randomised trial of atrial versus dual chamber pacing in 177 patients with sick sinus syndrome

L Kristensen, J C Nielsen, P T Mortensen, O L Pedersen, A K Pedersen, H R Andersen

Objective: To analyse the occurrence of atrial fibrillation (AF) and thromboembolism in a randomised comparison of rate adaptive single chamber atrial pacing (AAIR) and dual chamber pacing (DDDR) in patients with sick sinus syndrome and normal atrioventricular (AV) conduction, in which left atrial dilatation and decreased left ventricular fractional shortening had been observed in the DDDR group.

Methods: 177 consecutive patients with sick sinus syndrome (mean (SD) age 74 (9) years, 104 women) were randomly assigned to treatment with one of three pacemakers: AAIR (n = 54), DDDR with a short rate adaptive AV delay (n = 60) (DDDR-s); or DDDR with a fixed long AV delay (n = 63) (DDDR-l).

Analysis was intention to treat.

Results: Mean follow up was 2.9 (1.1) years. AF at one or more ambulatory visits was significantly less common in the AAIR group (4 (7.4%) v 14 (23.3%) in the DDDR-s group v 11 (17.5%) in the DDDR-l group; p = 0.03, log rank test). The risk of developing AF in the AAIR group compared with the DDDR-s group was significantly decreased after adjustment for brady-tachy syndrome in a Cox regression analysis (relative risk 0.27, 95% confidence interval (CI) 0.09 to 0.83, p = 0.02). The benefit of AAIR was highest among patients with brady-tachy syndrome. Brady-tachy syndrome and a thromboembolic event before pacemaker implantation were independent predictors of thromboembolism during follow up (relative risk 7.5, 95% CI 1.6 to 36.2, p = 0.01, and relative risk 4.7, 95% CI 1.2 to 17.9, p = 0.02, respectively).

Conclusions: During a mean follow up of 2.9 years AAIR was associated with significantly less AF. The beneficial effect of AAIR was still significant after adjustment for brady-tachy syndrome. Brady-tachy syndrome was associated with an increased risk of thromboembolism.

In patients with sick sinus syndrome (SSS), normal atrioventricular (AV) conduction, and no bundle branch block, bradycardia related symptoms can be treated successfully with any pacemaker—a single chamber atrial (AAI) pacemaker, a single chamber ventricular (VVI) pacemaker, or a dual chamber (DDDR) pacemaker. In a previous randomised trial of 225 patients with SSS, AAI pacing was superior to VVI pacing due to lower mortality, less atrial fibrillation (AF), less arterial thromboembolism, and less congestive heart failure.1,2 AV block was rare. Therefore, VVI pacing should no longer be used in these patients.

In contrast to VVI pacing, both AAI and DDD pacing preserve AV synchrony and are therefore referred to as physiological pacing. However, there are differences between the two pacing modes, which may be so important that the two modes should not be regarded as similar. AAI pacing preserves the normal ventricular activation and contraction pattern, whereas DDD pacing changes both. This difference may have a major impact on treatment outcome with the two different physiological pacing modes. It is still not clear whether AAI or DDD pacing is the optimal pacing mode in SSS. In a randomised comparison of AAI (AAIR) and DDD rate adaptive pacing (DDDR) in patients with SSS, we found that DDDR caused left atrial dilatation and decreased left ventricular fractional shortening—changes identical to those previously observed during VVI pacing.3,4 The present study aimed at analysing the occurrence of AF and thromboembolism in the randomised trial of AAIR and DDDR.

METHODS

Protocol

From December 1994 to March 1999 consecutive patients with SSS, who were referred for primary pacemaker implantation at Skejby Hospital, Aarhus, Denmark, were asked to participate in the trial. In a one year period patients were furthermore enrolled at the neighbouring Viborg County Hospital. The primary end points, previously reported,4 were changes in left atrial size and in left ventricular size and function measured by echocardiography.

The inclusion criteria were symptomatic bradycardia < 40 beats/min or symptomatic QRS pauses of more than two seconds, normal AV conduction (PQ interval ≤ 220 ms for patients ≤ 70 years and a PQ interval ≤ 260 ms for patients > 70 years), and no bundle branch block (QRS width < 120 ms). Exclusion criteria have been reported previously.4 Brady-tachy syndrome was defined as bradycardia and at least one episode of a supraventricular tachyarrhythmia.4

Abbreviations: AAI v VVI trial, Danish prospective randomised trial of atrial versus ventricular pacing in sick sinus syndrome; AAI, single chamber atrial pacemaker; AAIIR, rate adaptive single chamber atrial pacing; AF, atrial fibrillation; AFFIRM, atrial fibrillation follow-up investigation of rhythm management; AV, atrioventricular; CI, confidence interval; CTOPP, Canadian trial of physiologic pacing; DANPACE, Danish multicentre randomised study on AAIR versus DDDR pacing in sick sinus syndrome; DC, direct current; DDD, dual chamber pacemaker; DDD, rate adaptive dual chamber pacing; DDDR, rate adaptive dual chamber pacing; DDDR-s, DDDR with a short rate adaptive atrioventricular delay; DDDR-l, DDDR with a fixed long atrioventricular delay; SSS, sick sinus syndrome; VVI, single chamber ventricular pacemaker.
After giving written informed consent, patients were randomly assigned to three arms: AAIR pacemaker, DDDR pacemaker programmed with a conventional short rate adaptive AV delay (110–150 ms) (DDDR-s), and DDDR pacemaker programmed with a fixed long AV delay (≥ 250 ms) (DDDR-l).

Medical history, physical examination, and echocardiography were done before implantation. Follow up visits were after three months, after 12 months, and then once a year, each including physical examination, ECG recordings, pacemaker check up, and echocardiography. Physical examination and echocardiography were done unblinded regarding randomisation and pacing mode. Pacemaker telemetry data were collected at each follow up visit. Mean percentages of pacing in the atrium and ventricle during the follow up period were calculated for each patient. The last patient enrolled was to be followed up for at least one year, which was March 2000, before data were analysed.

End points
AF was diagnosed by a standard 12 lead ECG obtained at scheduled follow up visits. Episodes of AF between the follow up visits were not recorded. AF was categorised as chronic if recorded at two consecutive follow up visits and no sinus rhythm was observed subsequently. The decision to perform direct current (DC) conversion and to start anticoagulation was made on a clinical basis in the individual patient.

Stroke was diagnosed when neurological symptoms of presumably cerebral ischaemic origin persisted for more than 24 hours or if patients died within 24 hours after an acute cerebrovascular event. Peripheral embolus was diagnosed only if verified at embolectomy or necropsy.

Pacemaker implantation and programming
Standard AAIR and DDDR pacemakers (Cardiac Pacemakers Inc, Guidant Corp, Indianapolis, USA; Pacemaker, St Jude Medical Inc, St Paul, USA; Medtronic, Minneapolis, USA) were used, all fulfilling the study requirements for reporting cumulative numbers of paced and sensed events for a 12 month period.

All atrial leads were implanted in the upper parts of the right atrial wall. All patients randomly assigned to DDDR pacing had unipolar leads with passive fixation implanted in the right ventricular apex. AF at the time of pacemaker implantation was not a reason for implanting a pacemaker other than the randomised mode.

During implantation an atrial pacing test at 100 beats/min was performed; 1:1 AV conduction was required for an atrial pacemaker to be implanted. If Wenckebach block occurred at a rate below 100 beats/min the patient received a DDDR pacemaker.

The rate response function was active in all but two patients. Lower and upper rates were programmed individually. Mode switch function was active in all patients with DDD pacemakers implanted.

In patients randomly assigned to DDDR-l the AV delay was fixed at 300 ms and the rate adaptive shortening of the AV interval was programmed off. This setting was programmed in an attempt to avoid pacing the ventricles. In four patients a shorter AV delay had to be programmed to avoid induction of endless loop tachycardia. In patients randomly assigned to DDDR-s, the AV delay was set to 150 ms or shorter to obtain ventricular pacing with full capture. The rate adaptive shortening of the AV interval was programmed on.

Analysis
Power calculations were based on echocardiographic data from the previous AAI v VVI trial (Danish prospective randomised trial of atrial versus ventricular pacing in sick sinus syndrome).1 A total of 450 patients were planned to be enrolled in the study. However, enrolment was stopped prematurely after random assignment of 177 patients because at that time a national multicentre trial of AAIR versus DDDR pacing in patients with SSS was initiated and started in Denmark (DANPACE—Danish multicentre randomised study on AAIR versus DDDR pacing in sick sinus syndrome).2 Patients in the present study were not rolled over into DANPACE.

Analysis was intention to treat. Continuous variables were expressed as mean (SD). Treatment groups were compared by \( \chi^2 \) test for discrete variables and by two tailed t test, one way analysis of variance, or non-parametric tests for continuous variables. Kaplan-Meier plots were compared by log rank test. Cox regression analysis was used for multivariate analyses. An additional analysis was done to compare the AAIR group with the merged DDDR-s and DDDR-l groups (n = 123) with respect to incidences of AF and thromboembolism.

A probability value of \( p < 0.05 \) was deemed significant. SPSS 10.0 (SPSS Inc, Chicago, Illinois, USA) was used for statistical analysis.

The institutional scientific ethical committee approved the trial.

RESULTS
Patients
A total of 952 consecutive patients received their first pacemaker at the two hospitals during the recruitment period. Of these, 775 patients were excluded and 177 patients were included (fig 1). At Skejby Hospital 166 patients were included and at Viborg County Hospital 11 patients were included (20% and 11% of the screened populations, respectively).

The study participants (mean age 74 (9) years, range 44–93 years, 104 women) were randomly assigned to AAIR (n = 54), DDDR-s (n = 60), or DDDR-l (n = 63). Mean follow up was 2.9 (1.1) years (range six days to 5.3 years) and was similar in the three groups. No patients were lost to follow up. Baseline characteristics of the three groups were similar (table 1).

A total of 174 patients (98.3%) had a pacemaker implanted as randomly assigned. All patients randomly assigned to a DDDR pacemaker were discharged from hospital with a DDDR pacemaker. Three patients randomly assigned to AAIR pacemaker received DDDR pacemakers at primary implantation, which subsequently were programmed to DDDR-l mode. In two patients the reason was a Wenckebach block point below 100 beats/min at implantation. In one patient it was impossible to obtain an acceptable atrial sensing value during AF and a ventricular lead was implanted for safety reasons. During follow up three patients randomly assigned to AAIR had ventricular leads implanted because a high degree AV block developed (1.9% per year).

Four patients randomly assigned to DDDR had their pacing mode changed to VVI because persistent AF developed after three months, four and a half months, two years, and five years, respectively. One patient was changed from DDDR mode to AAIR mode after 13 months because the ventricular lead malfunctioned. The operation was not repeated in this patient because of lung cancer.

Atrial fibrillation
Twenty nine patients had AF at one or more follow up visits. AF was significantly less common in the AAIR group (7.4% (n = 4) v 23.3% (n = 14) in the DDDR-s group v 17.5% (n = 11) in the DDDR-l group; \( p = 0.03 \), log rank test) (fig 1). After stratification for brady-tachy syndrome the log rank test was still significant (\( p = 0.04 \)). Brady-tachy
Figure 1  Numbers of patients in the study population and in the three randomisation groups are listed together with the numbers of events during follow up in each randomisation group. The patients are further divided into groups with (+BTS) and without brady-tachy syndrome (−BTS). AAIR, rate adaptive single chamber atrial pacing; AF, atrial fibrillation; DDDR-I, rate adaptive dual chamber pacing with the pacemaker programmed with a fixed atrioventricular (AV) delay of 300 ms; DDDR-s, rate adaptive dual chamber pacing with the pacemaker programmed with a rate adaptive AV delay < 150 ms and ventricular capture; TE, thromboembolic event.

<table>
<thead>
<tr>
<th>Events during follow up</th>
<th>+ BTS</th>
<th>− BTS</th>
<th>+ BTS</th>
<th>− BTS</th>
<th>+ BTS</th>
<th>− BTS</th>
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<tbody>
<tr>
<td>AF</td>
<td>3</td>
<td>1</td>
<td>11</td>
<td>3</td>
<td>9</td>
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<tr>
<td>TE</td>
<td>3</td>
<td>0</td>
<td>6</td>
<td>1</td>
<td>3</td>
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Table 1 Baseline characteristics at the time of pacemaker implantation

<table>
<thead>
<tr>
<th>Patient’s characteristics</th>
<th>AAIR</th>
<th>DDDR-s</th>
<th>DDDR-I</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>54</td>
<td>60</td>
<td>63</td>
</tr>
<tr>
<td>Age (years)</td>
<td>74 (9)</td>
<td>74 (9)</td>
<td>74 (99)</td>
</tr>
<tr>
<td>Women</td>
<td>31</td>
<td>34</td>
<td>39</td>
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<tr>
<td>Mean follow up (years)</td>
<td>3.1 (1.3)</td>
<td>2.8 (1.5)</td>
<td>2.8 (1.4)</td>
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<td>Blood pressure (mm Hg)</td>
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<td>Systolic</td>
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<td>139 (22)</td>
<td>144 (22)</td>
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<tr>
<td>Diastolic</td>
<td>80 (13)</td>
<td>75 (12)</td>
<td>80 (10)</td>
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<td>Arrhythmia indicating pacemaker treatment</td>
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<td>Sinus bradycardia</td>
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<td>Brady-tachy syndrome</td>
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<td>Symptoms indicating pacemaker treatment</td>
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<td>Dizzy spells</td>
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<td>PQI interval (ms)</td>
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<td>183 (28)</td>
<td>184 (27)</td>
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<td>7</td>
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<td>Warfarin</td>
<td>5</td>
<td>5</td>
<td>11</td>
</tr>
</tbody>
</table>

Continuous data are mean (SD), other variables reported as number of patients. AAIR, rate adaptive single chamber atrial pacing; DDDR-I, DDDR with a fixed long atrioventricular delay; DDDR-s, DDDR with a short rate adaptive atrioventricular delay; NYHA, New York Heart Association.
syndrome at pacemaker implantation was strongly associated with AF during follow-up (relative risk 3.3, 95% confidence interval (CI) 1.3 to 8.1; p = 0.01). The risk of developing AF in the AAIR group compared with the DDDR-s group was still significantly decreased after adjustment for brady-tachy syndrome (relative risk 0.27, 95% CI 0.09 to 0.83; p = 0.02). Relative risk in the DDDR-l group was 0.78 (95% CI 0.36 to 1.75; p = 0.56) compared with the DDDR-s group. The annual risk of developing AF was 3% v 11.9% v 8.2% in the AAIR, DDDR-s, and DDDR-l groups, respectively. Kaplan-Meier curves of the proportion of patients in each randomisation group without AF during follow-up were plotted separately for patients with and without brady-tachy syndrome. As compared with the merged DDDR groups, the relative risk of AF was significantly reduced in the AAIR group (relative risk 0.30, 95% CI 0.11 to 0.87; p = 0.026), even after adjustment for brady-tachy syndrome (relative risk 0.30, 95% CI 0.11 to 0.87; p = 0.027).

Ten patients developed chronic AF: three patients (5.6%) from the AAIR group, four patients (6.7%) from the DDDR-s group, and three patients (4.8%) from the DDDR-l group (p = 0.64, log rank test).

During follow-up 14 patients underwent DC conversion because of persistent AF. One patient from the DDDR-s group underwent DC conversion twice. The annual risk of undergoing DC conversions was 1.8% in the AAIR group (n = 3), 4.2% in the DDDR-s group (n = 7), and 1.7% in the DDDR-l group (n = 3) (p = 0.28, log rank test).

Brady-tachy syndrome at implantation or AF during follow-up was not associated with increased risk of death (relative risk 1.4, 95% CI 0.71 to 2.75, p = 0.34, and relative risk 0.86, 95% CI 0.37 to 2.0, p = 0.73, respectively).

Thromboembolism

During follow-up 16 thromboembolic events occurred in 14 patients: three patients in the AAIR group (5.6%), seven patients in the DDDR-s group (11.7%), and four patients in the DDDR-l group (6.3%) (p = 0.32, log rank test) (fig 1). Time from pacemaker implantation to thromboembolic event was a mean of 1.35 (1.4) years (range 0.13–4.1 years). All events were strokes; four of these strokes were fatal. Of the 14 patients who had strokes, 12 had brady-tachy syndrome at pacemaker implantation (relative risk 5.2, 95% CI 1.2 to 23.3; p = 0.03). Figure 3 shows Kaplan-Meier plots of freedom from thromboembolism during follow-up for patients with and without brady-tachy syndrome. In two of the 14 patients AF was recorded during follow-up before the thromboembolic event. There was no significant difference in incidence of thromboembolism between the AAIR group and the merged DDDR groups (relative risk in the AAIR group 0.91, 95% CI 0.24 to 3.53; p = 0.9).

In a multivariate analysis brady-tachy syndrome and prior thromboembolism were both significant predictors of thromboembolism (relative risk 7.5, 95% CI 1.6 to 36.2, p = 0.01, and relative risk 4.7, 95% CI 1.2 to 17.9, p = 0.02, respectively).

Warfarin treatment

Thirty-one patients were treated with warfarin at one or more ambulatory visits: 21 patients were treated with warfarin at...
the time of pacemaker implantation but only 12 patients were treated at their last follow up.

Of the 29 patients having AF at one or more follow up visits, nine patients had their first episode of AF at their last ambulatory visit. Of the remaining 20 patients, eight patients (40%) were treated with warfarin at the ambulatory visit after their first episode of AF. Warfarin treatment was not started for 50% of the patients who developed chronic AF during follow up, mainly due to increased age or poor compliance.

Only one of the patients who had thromboembolic events was being treated with warfarin at the time of his event.

**Telemetry data**

The mean percentage of atrial pacing was not different between the three groups: 69% in the AAIR group, 57% in the DDDR-s group, and 67% in the DDDR-I group (p = 0.08, analysis of variance). The mean percentage of ventricular pacing was 90% in the DDDR-s group and 17% in the DDDR-I group (p < 0.01, analysis of variance). The percentage of atrial pacing was lower in patients with AF than in patients without AF during follow up, although the difference was significant only in the DDDR-I group (table 2). In the DDDR-s group, the percentage of pacing in the ventricle was lower in patients with AF than in those without AF (p < 0.01, Mann-Whitney test). In the DDDR-I group, in contrast, the percentage of pacing in the ventricle was higher in patients with episodes of AF (p = 0.02, Mann-Whitney test) (table 2).

**DISCUSSION**

This study is the first randomised trial comparing AAIR with DDDR in patients with SSS and normal AV conduction. During a mean follow up of 2.9 years AAIR was associated with significantly less AF than was DDDR. The beneficial effect of AAIR pacing was still significant after adjustment for brady-tachy syndrome. Brady-tachy syndrome was associated with an increased risk of thromboembolism.

In previous randomised trials of patients with SSS, VVI pacing increased the risk of AF as compared with AAI pacing and DDD pacing. In the present trial the incidence of AF was higher in the DDDR group than in the AAIR group, indicating that ventricular pacing per se may promote development of AF.

The mechanisms causing more AF during DDDR than during AAIR are not fully known. Right ventricular pacing during DDDR causes an altered activation sequence of the ventricles and consequently a change in the ventricular mechanical contraction pattern. This is associated with a decrease in left ventricular systolic function and diastolic function and an increase in both the right atrial pressure and pulmonary capillary wedge pressure, which may cause left atrial dilatation promoting AF. In fact, left atrial dilatation was observed in the DDDR groups in the present trial.

In the present trial, in the AAIR v VVI trial, and in the large CTOPP trial (Canadian trial of physiologic pacing), the difference in AF incidence first emerged after about two years of follow up. These similar patterns of delayed development of AF indicate that there is a considerable delay after pacemaker implantation before a possible deleterious effect of ventricular pacing or a beneficial effect of atrial pacing or physiological pacing becomes evident.

In the present study, the annual incidences of AF in the DDDR groups were slightly higher than the annual incidence found in the VVI group in the AAIR v VVI trial, whereas the AAIR groups had similar incidences of AF. This finding supports the hypothesis that ventricular stimulation in the DDD mode may be of major importance for the development of AF in patients with SSS. In the DDDR-I group significantly more ventricular pacing was observed among patients developing AF during follow up than among patients without AF. A similar pattern was not seen in the DDDR-s group. In this group, however, the percentage of ventricular pacing was quite high in both patients with and those without AF. DDD pacing in patients with SSS and normal AV conduction causes more ventricular stimulation than VVI pacing does because the ventricular pacing in the DDD mode is driven by the sensed and the paced beats in the atrium. The detrimental effect of more ventricular stimulation in the DDD mode may abolish the beneficial effect of preserved AV synchrony, as was also indicated by a subgroup analysis in CTOPP.

The percentage of time during which the atrium was paced was lower in patients with AF than in those without AF, though significant only in the DDDR-I group. This may indicate that atrial overdrive pacing can prevent AF. However, it may also merely reflect the higher number of sensed atrial events in the group of patients with AF.

When our study population was divided into two groups—patients without AF and those with atrial fibrillation or flutter—the percentage of time the atrium was paced was in the range of 30% to 35% with atrial fibrillation or flutter.

The percentage of time during which the atrium was paced was lower in patients with AF than in those without AF, although the difference was not significant. This may indicate that atrial fibrillation or flutter decreases the percentage of time the atrium is paced.

**Table 2**

<table>
<thead>
<tr>
<th>Randomisation</th>
<th>-AF</th>
<th>-AF</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacing in the atrium</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AAIR</td>
<td>70% *</td>
<td>51% **</td>
<td>0.14</td>
</tr>
<tr>
<td>DDDR-s</td>
<td>69% *</td>
<td>51% **</td>
<td>0.02</td>
</tr>
<tr>
<td>DDDR-I</td>
<td>70% *</td>
<td>49% **</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Pacing in the ventricle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AAIR</td>
<td>94%</td>
<td>78%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>DDDR-s</td>
<td>14%</td>
<td>26%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* p = 0.11, analysis of variance between randomisation groups; ** p = 0.99, analysis of variance between randomisation groups. The p value indicates comparison between patients without [-AF] and with atrial fibrillation (=AF) during follow up within each randomisation group. In the AAIR group, five patients had DDDR pacemakers. The percentages of pacing in the ventricle have not been included for these patients.
underused in the present trial, as also reported previously and described in patients with AF without pacing. The mean age of the patients at pacemaker implantation is approximately 75 years. Apparently anticoagulation is difficult to achieve in these elderly patients, most likely because of such contraindications as poor compliance and falling tendency. Therefore, it seems to be important if at all possible to avoid the development of AF in these patients.

Limitations

The study was powered to enrol 450 patients but inclusion was stopped prematurely after random assignment of only 177 patients.

In our previous study the differences between pacing modes increased greatly during long term follow up. In the present study the mean follow up was just below three years.

The data from the pacemaker telemetries do not indicate the number of AF episodes or total time in AF. The true incidence of AF in these patients is expected to be higher than indicated by the present findings, where AF was scored only at the planned follow up visits.

We cannot rule out that individual optimisation of the AV delay could have influenced the present results.

Future studies

It is still unsettled whether there are any differences in mortality, thromboembolism, heart failure, and quality of life between AAIR and DDDR on the long term. To investigate this problem DANPACE was started in 1999. In that trial 1900 patients with SSS and normal AV conduction are equally randomly assigned to AAIR or DDDR and will be followed up for a mean of 5.5 years. The primary end point is all cause mortality and secondary end points are AF, thromboembolism, congestive heart failure, cardiovascular mortality, repeat operations, quality of life, and cost effectiveness. Enrolment is expected to be complete in 2008.

Conclusion

This study is the first randomised trial comparing AAIR with DDDR in patients with SSS and normal AV conduction. During a mean follow up of 2.9 years AAIR was associated with significantly less AF. The beneficial effect of AAIR was still significant after adjustment for brady-tachy syndrome. Brady-tachy syndrome was associated with an increased risk of thromboembolism.

Authors’ affiliations

L Kristensen, J C Nielsen, P T Mortensen, A K Pedersen, H R Andersen, Department of Cardiology, Skejby Hospital, Aarhus University Hospital, Aarhus, Denmark

O I Pedersen, Department of Medicine, Viborg County Hospital, Viborg, Denmark

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