Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome

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Summary

Background In a previous study of 225 patients with sick-sinus syndrome randomised to either single-chamber atrial pacing (n=110) or single-chamber ventricular pacing (n=115), we found that after a mean follow-up of 3·3 years, atrial pacing was associated with significantly less atrial fibrillation and thromboembolism whereas there was no significant difference in mortality and heart failure between the two groups. We aimed to find out whether this beneficial effect of atrial pacing is maintained during extended follow-up of up to 8 years.

Methods Follow-up visits for all patients were at 3 months, 12 months, then once a year at which patients had a physical examination, ECG recording, and pacemaker check-up. Endpoints were mortality, cardiovascular death, atrial fibrillation, thromboembolic events, heart failure, and atrioventricular block. Data was analysed on Dec 31, 1996.

Findings At long-term follow-up, 39 patients from the atrial group had died versus 57 from the ventricular group (relative risk 0·66 [95% CI 0·44–0·99]; p=0·045). 19 patients from the atrial group and 39 patients from the ventricular group died from a cardiovascular cause (0·47 [0·27–0·82]; p=0·0065). The cumulative incidences of atrial fibrillation and chronic atrial fibrillation were also significantly lower in the atrial group than in the ventricular group (0·54 [0·33–0·89], p=0·012 and 0·35 [0·16–0·76], p=0·004, respectively). Thromboembolic events occurred in 13 patients in the atrial group and 26 in the ventricular group (0·47 [0·24–0·92], p=0·023). Heart failure was less severe in the atrial group than in the ventricular group (p<0·05). In multivariate analysis, atrial pacing was significantly associated with freedom from thromboembolic events (0·47 [0·24–0·92], p=0·028) and survival from cardiovascular death (0·52 [0·30–0·91], p=0·022), but no longer with overall survival (0·71 [0·46–1·08], p=0·11) or chronic atrial fibrillation (0·45 [0·20–1·05], p=0·063). Atrioventricular block occurred in four patients in the atrial group (0·6% annual risk).

Interpretation The beneficial effect of atrial pacing found in our previous study is enhanced substantially over time. Patients with sick-sinus syndrome should be treated with an atrial rather than ventricular-pacing system because after long-term follow-up, atrial pacing is associated with a significantly higher survival, less atrial fibrillation, fewer thromboembolic complications, less heart failure, and a low-risk of atrioventricular block.

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Introduction

We have previously reported,[1] that treatment with single-chamber atrial pacing in patients with sick-sinus syndrome was associated with less atrial fibrillation and thromboembolic events compared with single-chamber ventricular pacing, whereas there was no statistically significant difference in mortality and heart failure between the two treatment groups. Whether this beneficial effect of atrial pacing is maintained over long-term follow-up has never been evaluated in a randomised trial. The aim of the present study was to find out whether the advantages of atrial pacing on atrial fibrillation and thromboembolism was maintained after extended follow-up. The lack of significance in mortality and heart failure in our previous report could have been associated with the relatively low number of events during the first follow-up period. Therefore an additional aim was to find out if differences in mortality and heart failure occurred during long-term follow-up. To answer these questions, patients were followed up for up to 8 years. To identify predictors of death, cardiovascular death, chronic atrial fibrillation, and thromboembolic events multivariate analyses were done.

Methods

The trial was done as a one-centre study at Skejby University Hospital, Aarhus, Denmark. All patients who were referred to treatment with their first pacemaker during the recruitment period from May 15, 1988, to Dec 31, 1991, were evaluated for randomisation as previously reported.[1] Power calculations were published in 1994 in our previous report. In 1993, we decided to extend the follow-up period beyond the observation period set out in the protocol, and in 1995 it was decided that the last patient included should be followed up for at least 5 years before final data analysis, which was to be done on Dec 31, 1996. No additional power calculations were done before this extended follow-up.

Medical history, physical examination, and echocardiography were done before pacemaker implantation. Follow-up visits were after 3 months, 12 months, then once a year. Such visits included physical examination, electrocardiographic recording, and pacemaker check-up; they were not blinded.

During the recruitment period, 1052 patients (484 women, 568 men, age 71 [SD 17] years) had their first pacemaker implanted; 827 patients were excluded from randomisation.[1] Endpoints were mortality, cardiovascular death, atrial fibrillation, chronic atrial fibrillation, thromboembolic events, heart failure, and atrioventricular block in the atrial group. All endpoints were prespecified except cardiovascular death. Cause of death was obtained by interviewing the doctors who had care of the patient and by review of hospital files and necropsy reports. Cardiovascular death included sudden death and death due to congestive heart failure, thromboembolism, or a pulmonary embolus.

Atrial fibrillation was diagnosed by a standard 12-lead electrocardiogram (ECG) at the follow-up visits (not from ECGs taken at any other time). Atrial fibrillation was categorised as chronic if it was recorded at two consecutive follow-up visits and no sinus rhythm was observed subsequently. When a patient had atrial fibrillation, conversion to normal rhythm was always

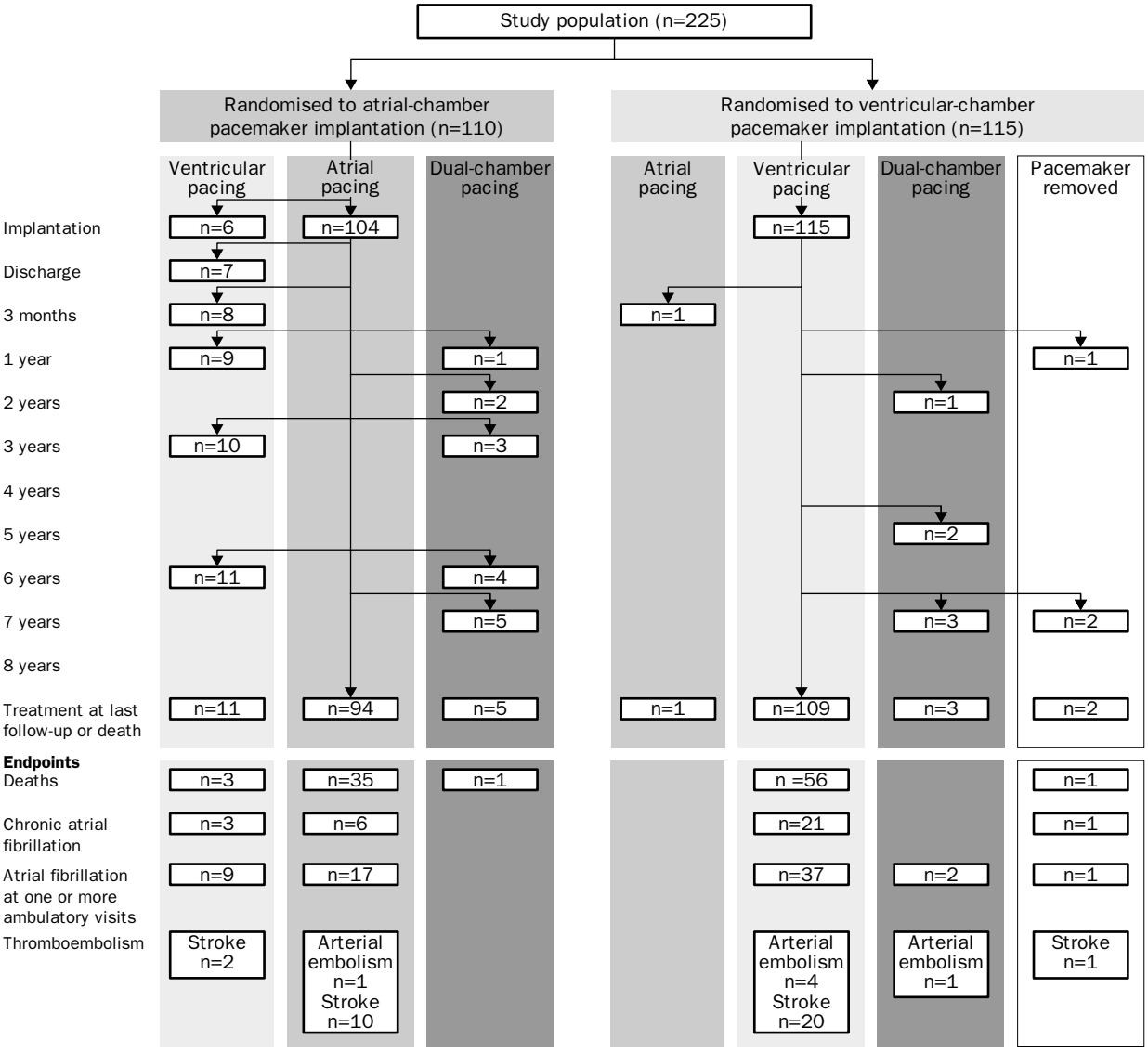


Figure 1 **Trial profile**

considered, and the decision to attempt medical conversion or defibrillation by DC discharge was done from clinical criterias. Brady-tachy syndrome was defined as bradycardia and at least one documented episode of a supraventricular tachyarrhythmia.[2]

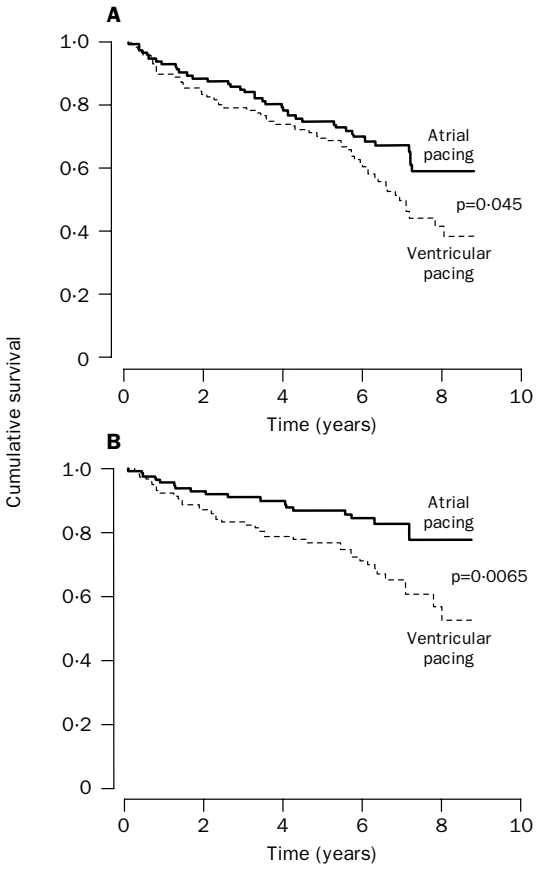
Patients had an atrial-pacing test during pacemaker implantation. 1:1 atrioventricular conduction at 100 beats/min was required for an atrial pacemaker to be implanted. Retrograde atrioventricular conduction was assessed only in patients randomised to ventricular pacing as previously reported.[1] Medical treatment was not discontinued before implantation.

After giving informed consent, patients were randomly allocated single-chamber atrial or single-chamber ventricular pacing stratified in blocks of 10-year age groups. To avoid an unequal allocation, the patients were randomised in blocks of ten (five atrial and five ventricular) in each age group. Allocation was concealed in opaque, sealed envelopes until the patient was randomised.

The study was approved by the National Danish Ethics Committee and was done in accordance with the rules of the Helsinki declaration. From the first follow-up period it was clear that ventricular pacing exposed the patients to more atrial fibrillation and thromboembolic events than atrial pacing.[1] It was deemed acceptable to extend the study period because there was no difference in mortality between the two treatment groups, and because a reoperation and insertion of an atrial electrode might possibly be associated with extra morbidity.

Statistical analyses

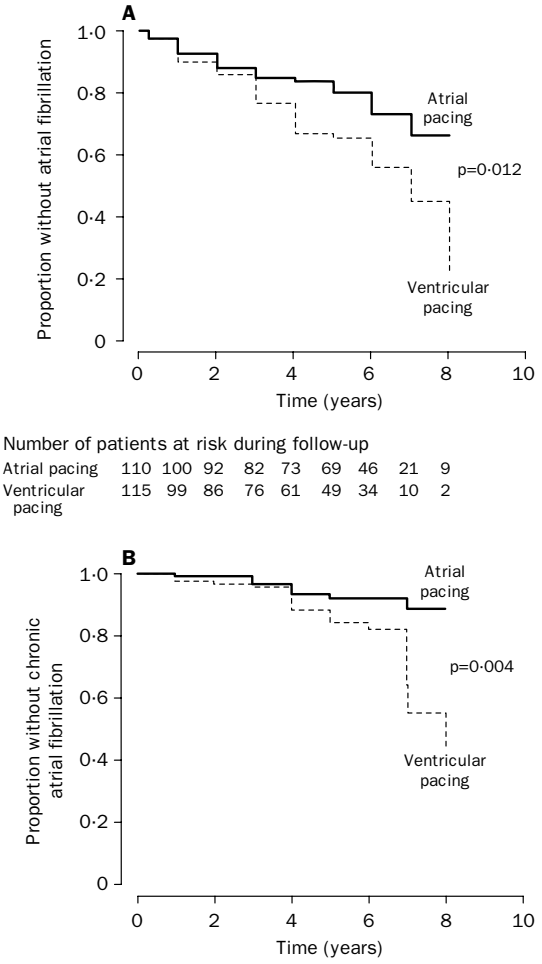
All analyses were done according to intention-to-treat. Continuous variables were expressed as mean (SD). Treatment groups were compared by χ^2 test or Fisher's exact test (two-tailed) for discrete variables and by two-tailed *t*-test for continuous variables. Kaplan-Meier plots were calculated for mortality, cardiovascular death, thromboembolism, atrial fibrillation, and chronic atrial fibrillation, and compared by log-rank test. For the identification of independent predictors of death, cardiovascular death, chronic atrial fibrillation, and thromboembolic events, univariate and multivariate analyses were done using the Cox proportional hazard regression method. Relative risk and 95% CIs are reported. Baseline covariates considered for inclusion in the multivariate analyses were: randomisation to atrial pacing, age, sex, brady-tachy syndrome, presenting symptom, previous myocardial infarction, left atrial diameter, left ventricular end-diastolic diameter, left ventricular fractional shortening, New York Heart Association (NYHA) class (in analysis of mortality and cardiovascular death), dose of diuretics (in analysis of mortality and cardiovascular death), retrograde atrioventricular conduction (in analysis of chronic atrial fibrillation and thrombombolic events), and previous thromboembolic event (in analysis of thromboembolic events). Moreover, in the analysis of thromboembolic events, the occurrence of atrial fibrillation and chronic atrial fibrillation during follow-up was considered. Only variables associated with



Number of patients at risk during follow-up

Atrial pacing	110	102	97	92	86	82	59	38	13
Ventricular pacing	115	103	96	91	85	80	56	29	12

Figure 2 **Kaplan-Meier survival plots of overall survival (A) and of survival from cardiovascular death (B)**



Number of patients at risk during follow-up

Atrial pacing	110	100	92	82	73	69	46	21	9
Ventricular pacing	115	99	86	76	61	49	34	10	2

Number of patients at risk during follow-up

Atrial pacing	110	102	96	91	80	74	49	26	10
Ventricular pacing	115	102	92	84	75	65	41	18	5

Figure 3 **Kaplan-Meier plots of freedom from atrial fibrillation (A) and chronic atrial fibrillation (B) during follow-up**

the endpoint in univariate analysis ($p<0·10$) were included in the multivariate analysis.

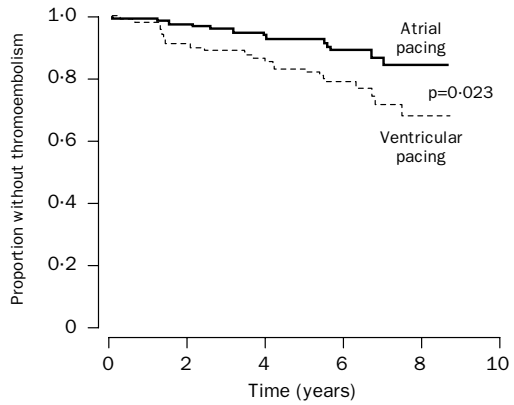
Results

Participant flow and follow-up

A total of 225 patients were randomly assigned atrial pacing (n=110, age 76 [8] years, 37 men) or ventricular pacing (n=115, age 75 [8] years, 46 men), respectively. Baseline patient characteristics have previously been reported,[1] and were similar in the two treatment groups. No patients were lost to follow-up. Mean follow-up was 5·5 [2·4] years for the total study population with similar follow-up in the atrial pacing (5·7 [2·3] years) and ventricular pacing (5·3 [2·5] years) groups. Pacing mode at implantation, during follow-up, and at the end of follow-up or death is shown in figure 1. Seven patients allocated atrial pacing had ventricular leads implanted before discharge from hospital. During follow-up, four patients had ventricular leads implanted because of infection after 3 months, lead fracture after 1 year, and insulation defect of a bipolar lead after 3 years. The fourth patient needed reoperation due to loss of atrial sensing after 6 years, and the physician in charge of the reoperation chose to implant a ventricular lead instead of a new atrial lead, although no atrioventricular block was documented.

The pacemaker system was upgraded to a dual-chamber system because of atrioventricular block in four patients, two of which had right-bundle-branch block at the time of randomisation. In one patient with brady-tachy syndrome, it was necessary to replace a defective pacemaker after 6 years. During pacemaker replacement, the patient had paroxysmal atrial fibrillation, and although the atrial lead was intact, the physician in charge of the operation chose to implant an additional ventricular lead and a new dual-chamber pacemaker.

During follow-up of the ventricular group, two patients, who developed severe pacemaker syndrome, had the pacing system altered to atrial and dual-chamber systems after 2 months and 2 years, respectively. In one patient, the upgrade to a dual-chamber system was done after 5 years to diminish symptomatic atrial tachycardia, and one patient needed reoperation after 7 years due to loss of sensing, and upgrading to a dual-chamber system was chosen. One patient had the pacemaker system removed 4 months after pacemaker implantation because of infection and declined implantation of another system. Another patient had the pacemaker system removed after 7 years because of infection. This patient had developed chronic atrial fibrillation 4 years after implantation, but had no bradycardia at subsequent follow-up, and therefore needed no new pacemaker system. Complications that required reoperation are shown in



Number of patients at risk during follow-up

Atrial pacing	110	102	96	89	83	79	56	34	12
Ventricular pacing	115	102	93	87	80	75	50	24	11

Figure 4 **Kaplan-Meier plots of thromboembolic events (stroke and peripheral arterial embolus)**

table 1. Medical treatments were similar during follow-up in the two groups. Warfarin was given to 16 patients in the ventricular group and ten patients in the atrial group (p=0·26). Of the 31 patients who developed chronic atrial fibrillation, 14 were treated with warfarin (mean age at inclusion 71 [6] years), while the remaining 17 patients (mean age at inclusion 78 [8] years) were not treated with warfarin because of contraindications to anticoagulation. These patients were instead treated with aspirin, which was given to 81 patients in the ventricular group and to 69 patients in the atrial group (n=0·22).

Mortality

A total of 96 patients died, 39 from the atrial group and 57 from the ventricular group (figure 1). The Kaplan-Meier survival plots are shown in figure 2A. All-cause mortality was significantly lower in the atrial group than in the ventricular group (relative risk 0·66 [95% CI 0·44–0·99], p=0·045). 46 patients died in hospital and 18 necropsies were done (table 2). Cardiovascular mortality was found in 19 of 110 in the atrial group versus 39 of 115 in the ventricular group (0·47 [0·27–0·82], p=0·0065). The Kaplan-Meier plots are shown in figure 2B. The number of thromboembolic deaths were five in the atrial group and 14 in the ventricular group (0·34 [0·12–0·96], p=0·032). In the multivariate analysis, age, previous myocardial infarction, left ventricular end-diastolic diameter, and brady-tachy syndrome at time of randomisation were significantly associated with increased risk of death, while ventricular pacing, age, previous myocardial infarction, and left ventricular end-diastolic diameter were significantly associated with cardiovascular death (table 3).

	Atrial-pacing group	Ventricular-pacing group
Lead displacement	9	2
Lead fracture	1	
Insulation defect	2	
Infection	1	3
Pneumothorax		1
Atrioventricular block	4	
Pacemaker syndrome		2
Excessive pocket mobility	1	2
Twiddlers syndrome	1	1
Loss of sensing	2	1
Muscular stimulation		1
Atrial tachycardia		1

Table 1: **Pacemaker complications necessitating reoperation**

	Atrial-pacing group	Ventricular-pacing group
Sudden cardiac death	7	13
Sudden death (unknown cause)	3	5
Chronic heart failure	3	7
Stroke	5	13
Arterial embolus	0	1
Pulmonary embolus	1	0
Cancer	5	7
Other reasons	15	11
Total	39	57

Table 2: **Causes of death**

Atrial fibrillation

All patients had sinus rhythm at the time of randomisation. In the atrial-pacing group, 26 patients had atrial fibrillation at one or more follow-up visits versus 40 patients in the ventricular-pacing group (p=0·066, χ^2 test). Kaplan-Meier plots of the proportions of patients in the two groups without atrial fibrillation during follow-up is shown in figure 3A. The proportion of patients with atrial fibrillation was significantly lower in the atrial group than in the ventricular group (relative risk 0·54 [95% CI 0·33–0·89], p=0·012). 21 patients died before the 1 year follow-up visit leaving 204 patients (102 in each group) at risk of developing chronic atrial fibrillation. In the atrial-pacing group, nine patients developed chronic atrial fibrillation versus 22 patients in the ventricular-pacing group (p=0·011, χ^2 test; table 4). Kaplan-Meier plots of proportions of patients without chronic atrial fibrillation during follow-up showed a significant difference between the two groups (relative risk for atrial group 0·35 [95% CI 0·16–0·76], p=0·004; figure 3B). The number of patients at risk of atrial fibrillation is lower than the number of patients alive at a certain time after implantation as indicated in figure 2. Once atrial fibrillation or chronic atrial fibrillation was diagnosed in a patient at a follow-up visit, this patient had reached the final end-point, and therefore was no longer at risk during subsequent follow-up. Atrial fibrillation was diagnosed by ECG at the follow-up visits, not from ECG's taken at any other time, which explains the large deflections of the Kaplan-Meier plots only at each follow-up visit. Thus, each deflection frequently represents several patients. The multivariate analysis identified brady-tachy syndrome and left ventricular end-diastolic diameter at the time of randomisation as the only variables associated with a significantly increased risk of development of chronic atrial fibrillation during follow-up (table 3). None of the patients with chronic atrial fibrillation in the atrial group developed bradycardia. Two of the nine patients in the atrial group who developed chronic atrial fibrillation were actually treated with ventricular pacing since initial implantation, and a third patient in the atrial group who developed chronic atrial fibrilation was treated with ventricular pacing from 3 months after initial implantation (figure 1).

Thromboembolism

During follow-up, thromboembolic events ocurred in 13 patients in the atrial group and in 26 patients in the ventricular group (p=0·033, χ^2 test). Kaplan-Meier plots of proportions of patients without thromboembolism in the two groups are shown in figure 4. Freedom from

	Relative risk of death [95% CI]; p	Relative risk of cardiovascular death [95% CI]; p	Relative risk of thrombo-embolic events [95% CI]; p	Relative risk of chronic atrial fibrillation [95% CI]; p
Preoperative clinical variables				
Randomisation to atrial pacing	0·71 (0·46–1·08); 0·111	0·52 (0·30–0·91); 0·022	0·47 (0·24–0·92); 0·028	0·45 (0·20–1·05); 0·063
Brady-tachy syndrome	1·56 (1·02–2·38); 0·038		2·08 (1·10–3·96); 0·025	3·92 (1·74–8·81); 0·001
Previous myocardial infarction	2·84 (1·74–4·64); <0·0001	3·15 (1·73–5·75); 0·0002		2·31 (0·85–6·27); 0·101
Left ventricular end-diastolic diameter	1·04 (1·01–1·06); 0·014	1·04 (1·01–1·08); 0·02		1·06 (1·01–1·12); 0·025
Age	1·10 (1·07–1·14); <0·0001	1·10 (1·05–1·14); <0·0001	1·04 (1·00–1·09); 0·054	
Clinical variables during follow-up				
Occurrence of atrial fibrillation			1·93 (0·67–5·58); 0·23	
Occurrence of chronic atrial fibrillation			1·48 (0·60–5·38); 0·55	

Table 3: **Multivariate Cox proportional hazard regression analysis of clinical variables evaluated as risk factors for development of death, thromboembolic events, and chronic atrial fibrillation during follow-up**

thromboembolic events during follow-up was more frequent in the atrial-pacing group than in the ventricular-pacing group (relative risk 0·47 [95% CI 0·24–0·92], p=0·023). The association between thromboembolism, brady-tachy syndrome at randomisation, and atrial fibrillation during follow-up is presented in table 4. The multivariate analysis identified randomisation to ventricular pacing and brady-tachy syndrome at time of randomisation as the only variables significantly associated with increased risk of developing thromboembolic events during follow-up (table 3). In univariate Cox regression analysis, the occurrence of atrial fibrillation during follow-up was significantly associated with an increased risk of thromboembolic events during follow-up (2·37 [1·11–5·06], p=0·04), but there was no significant association among these two variables in the multivariate analysis (table 3). Stroke before randomisation and occurrence of chronic atrial fibrillation was not significantly associated with thromboembolic events during follow-up.

Two of the patients randomised to atrial pacing but treated with ventricular pacing since initial implantation developed a thromboembolic event during follow-up (figure 1).

Heart failure

At randomisation, there was no difference in the NYHA classification and no difference in the use of diuretics between the two groups. During follow-up, the NYHA class was significantly higher in the ventricular group than in the atrial group at each follow-up visit from 3 months to 7 years ($p<0·05$, χ^2 test). There was no significant difference at 8 years follow-up, where NYHA class was scored for a total of only 20 patients. NYHA class at last follow-up (three patients died before their 3 months follow-up visit, leaving 222 patients) was significantly higher in the venticular group than in the atrial group (NYHA class I/II/III/IV: 65/44/four/zero *vs* 84/22/two/one patients, p=0·010, χ^2 test).

Use of diuretics was significantly higher in the ventricular group than in the atrial group at the 5 year, 6 year, 7 year, and 8 year follow-up vists ($p<0·05$, *t* test), while there was no difference at earlier follow-up visits. The increase in dose of diuretics from implantation to last follow-up was significantly higher in the ventricular group than in the atrial group (21 [49] mg/day *vs* 8 [42] mg/day furosemide, p=0·033).

	Follow-up	
	Atrial-pacing group (n=110)	Ventricular-pacing group (n=115)
	Thrombo-embolism/ patients in group	Thrombo-embolism/ patients in group
Brady-tachy syndrome at randomisation (n=94)		
No atrial fibrillation during follow-up	3/28	8/29
Paroxysmal atrial fibrillation during follow-up	1/9	3/8
Chronic atrial fibrillation during follow-up	3/6	4/14
No brady-tachy syndrome at randomisation (n=131)		
No atrial fibrillation during follow-up	3/56	9/46
Paroxysmal atrial fibrillation during follow-up	2/8	2/10
Chronic atrial fibrillation during follow-up	1/3	0/8

Table 4: **Association between thromboembolism, brady-tachy syndrome at randomisation, and atrial fibrillation during follow-up**

Atrioventricular conduction

Four patients in the atrial group developed atrioventricular block during follow-up (annual risk 0·6%). Two of these patients had right-bundle-branch block at randomisation. Retrograde atrioventricular conduction was present in 63 patients in the ventricular group. Univariate Cox regression analysis showed that retrograde atrioventricular conduction was not an independent risk factor for development of chronic atrial fibrillation or thromboembolic events during follow-up.

Discussion

The present study shows that the beneficial effect of atrial pacing is enhanced substantially after an extended follow-up. Consequently, atrial pacing is better than ventricular pacing, not only with regard to atrial fibrillation and thromboembolism, but also with regard to total mortality, cardiovascular mortality, and heart failure, which are all significantly reduced.

We found all-cause mortality and mortality due to cardiovascular causes significantly higher in the ventricular pacemaker group. After adjustment for other variables, randomisation to ventricular pacing was significantly associated with cardiovacular death, and there was a trend towards increased overall mortality in the ventricular group. These findings are in accordance with the retrospective studies by Rosenqvist and colleagues[3] and by Santini and colleagues[4] who both reported a higher total mortality and a higher cardiac mortality in patients treated with ventricular pacing. Sgarbossa and colleagues[5] found, that ventricular pacing was not a significant predictor of death or cardiovascular death compared with physiological pacing. However, in the study by Sgarbossa and colleagues, ventricular pacing (112 patients) was not compared with atrial pacing, but with physiological pacing (374 patients with dual-chamber pacemakers and only 19 patients with atrial pacemakers). Thus, in that study, most of the patients in the physiological group had a ventricular lead implanted, and therefore had their right ventricle stimulated very frequently.[6,7] The ventricular stimulation is potentially

harmful to cardiac function,[8–13] and even dual-chamber pacing might be associated with a similar risk of death as observed in the present study for ventricular pacing due to stimulation of the ventricular myocardium in both pacing modes.

In our previous report,[1] where patients were followed for a mean of 3·3 years, there was no significant difference in mortality. In the present study with extended follow-up, the two survival plots (figure 2) were nearly merging and parallel in the first years, but separated after about 5 years, where the survival in the ventricular group decreased more rapidly than in the atrial group. This difference might be a consequence of the year-long unfavourable stimulation of the ventricles, which in the long-term may lead to a progressive deterioration in cardiac function. This hypothesis is supported by the findings in the present study of a higher incidence of heart failure and need for treatment with diuretics in the ventricular group at extended follow-up, which was not present in our previous report.

The cumulative incidences of atrial fibrillation and chronic atrial fibrillation were significantly higher in the ventricular-pacing group than in the atrial-pacing group. Compared to our previous report, the difference between the two groups increased substantially at extended follow-up. In the present study, 22% of the patients treated with ventricular pacing developed chronic atrial fibrillation during follow-up. This is less than reported by Rosenqvist and colleagues[3] and Santini and colleagues,[4] probably because of our more strict definition of chronic atrial fibrillation.

Brady-tachy syndrome at the time of randomisation was the strongest predictor of chronic atrial fibrillation in the multivariate analysis. However, in patients without brady-tachy syndrome ventricular pacing was also associated with an increased risk of paroxysmal or chronic atrial fibrillation when compared with atrial pacing. The exact mechanisms linking ventricular pacing with the development of atrial fibrillation is not known. Ventricular pacing may increase or atrial pacing may decrase, delay, or prevent the natural evolution of chronic atrial fibrillation in patients with sick-sinus syndrome. However, the findings in the present study strongly indicate that the atrium should be sensed and paced in patients with sick-sinus syndrome—also in patients with paroxysmal atrial fibrillation.

In the present study, age was not an independent predictor of chronic atrial fibrillation, which contradicts findings in non-paced populations.[14] However, the present population of patients with sick-sinus syndrome and mainly sinus rhythm before pacemaker implantation is only a minority of the patients who develop chronic atrial fibrillation, and in this population, age does not seem to predict chronic atrial fibrillation.

The present study was designed to identify all thromboembolic events, and we found a higher frequency of thromboembolic complications than reported in retrospective analyses,[3,15] possibly because in retrospective analyses, many thromboembolic events have not been recorded in the pacemaker files, which often focus on pacemaker indices. We found, that thromboembolic events were significantly more frequent in the ventricular group than in the atrial group, which confirms findings from our previous report and several retrospective analyses.[4,16,17] Randomisation to ventricular pacing was an independent risk factor for subsequent occurrence of thromboembolic events during follow-up. This may partly reflect the higher frequency of atrial fibrillation observed with ventricular pacing. Brady-tachy syndrome at randomisation was an independent predictor of thrombo-embolism. Also, the incidence of thromboembolic events in patients without atrial fibrillation before implantation and during follow-up was significantly higher in the ventricular group. These findings indicate that venticular pacing per se increases the risk of thromboembolism.

Prevention of thromboembolic complications by anticoagulation has proved effective in patients with chronic atrial fibrillation,[18–20] and recently also in patients with paroxysmal atrial fibrillation.[21] In the present study, the number of patients treated with anticoagulation was rather low, which probably reflects, that many of the patients were elderly with contraindications to anticoagulation when chronic atrial fibrillation occurred. Furthermore, thromboembolism occurred in 12 patients where atrial fibrillation was never documented before the thromboembolic event. Consequently, no strict indication for anticoagulation was present in a substantial proportion of our patients. Anticoagulation is often underused in patients with atrial fibrillation who do not have pacemaker,[22–24] which could also be the case for our patients with sick-sinus syndrome.

The incidence of heart failure was higher in the ventricular group than in the atrial group, which is in agreement with retrospective[3,4,17] and experimental[8,25] findings. However, it was difficult to precisely define the NYHA class in our patients, many of which were very old and immobile, and moreover classification was not blinded, which introduced a possibility of observer bias. The significantly higher dose of diuretics in the ventricular group during long-term follow-up supports evidence that ventricular pacing was associated with a higher risk of heart failure.

Although most studies have shown a very low incidence of atrioventricular block during follow-up,[26–30] the risk of deterioration of atrioventricular conduction has been considered a contraindication to single-chamber atrial pacing.[31] The 0·6% annual incidence of atrioventricular block in our study confirms that atrial pacing is a safe treatment for patients with sick-sinus syndrome, also during long-term follow-up. It is now clear, that in patients with sick-sinus syndrome, right-bundle-branch block is associated with an increased risk of the development of symptomatic high-degree atrioventricular block,[3,28] and today such patients should be treated with a dual-chamber pacemaker.

The present trial proves that single-chamber ventricular pacing should be avoided in patients with sick-sinus syndrome. Now the crucial question for treatment of patients with this syndrome and with normal atrioventricular and intraventricular conduction is whether to implant atrial or dual-chamber pacemakers.

The advantage of dual-chamber pacing is its capability to protect the patients against bradycardia if significant atrioventricular block arises during follow-up. Another argument for dual-chamber pacing has been that 10–20% of patients develop chronic atrial fibrillation and may need pacing for bradycardia. However, if the sick-sinus node disease progresses to chronic atrial fibrillation, the paroxysmal atrial bradycardia disappears, and only very few patients need pacing for ventricular bradycardia. In the present study none of the patients in the atrial-pacing

group who developed chronic atrial fibrillation needed ventricular pacing.

The disadvantages of dual-chamber pacing are the numerous ventricular stimulations[6,7] that alter the ventricular contraction pattern, which may potentially compromise cardiac function.[8–13] Consequently, patients who have dual-chamber pacemakers may have the same less favourable prognosis as did the patients in the ventricular-pacing group in the present trial.

The extension of the follow-up period in our previous study was not protocolled in 1988 when the trial was started, but was decided in 1993, before the first study was reported, and at that time it was not preceded by new power calculations. Statistically, we consider the present report to be a new study. If the first analysis, published in 1994, is regarded as an interim analysis, the appropriate significance level in the present report would have been 0·035 instead of 0·05 (calculated by the α-spending function proposed by Pocock).[32] However, this does not change the overall interpretation of the present study, and does not change our conclusions. No adjustments were made for the multiplicity of the endpoints.

The beneficial effect of atrial pacing observed previously is enhanced substantially after extended follow-up. Patients with the sick-sinus syndrome and no signs of atrioventricular conduction abnormalities should be treated with atrial pacing instead of ventricular pacing because atrial pacing is associated with lower mortality, less atrial fibrillation, thromboembolic complications, and heart failure, and a low-risk of atrioventricular block. Based on the present study, we believe that treatment with a single-chamber ventricular pacemaker is contraindicated in this group of patients. Therefore, in our hospital, patients with sick-sinus syndrome already treated with ventricular pacing are now offered reoperation and upgrading of the pacemaker-system to atrial pacing.

Contributors

Henning Rud Andersen designed the study, secured funding, coordinated the study, randomised treatment to patients, and did most of the pacemaker implantations and the follow-up investigations until 1995. Jens Cosedis Nielsen did all the follow-up investigations in 1996, and undertook the statistical analysis of data. Poul Erik Bloch Thomsen, Leif Thuesen, Peter Thomas Mortensen, Thomas Vesterlund, and Anders Kirstein Pedersen implanted some of the pacemakers and did some of the follow-up investigations. The manuscript was written by Henning Rud Andersen and Jens Cosedis Nielsen with contributions from the other authors.

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