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**FASTTRACK CLINICAL RESEARCH**
*Clinical trials*

# Atrial pacing minimization in sinus node dysfunction and risk of incident atrial fibrillation: a randomized trial

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**See the editorial comment for this article 'Atrial pacing and atrial fibrillation in sinus node dysfunction: a relationship that remains elusive', by R. Parkash, https://doi.org/10.1093/eurheartj/ehad569.**

## Abstract

**Background and Aims** High percentages of atrial pacing have been associated with an increased risk of atrial fibrillation. This study is aimed at evaluating whether atrial pacing minimization in patients with sinus node dysfunction reduces the incidence of atrial fibrillation.

**Methods** In a nationwide, randomized controlled trial, 540 patients with sinus node dysfunction and an indication for first pacemaker implantation were assigned to pacing programmed to a base rate of 60 bpm and rate-adaptive pacing (DDDR-60) or pacing programmed to a base rate of 40 bpm without rate-adaptive pacing (DDD-40). Patients were followed on remote monitoring for 2 years. The primary endpoint was time to first episode of atrial fibrillation longer than 6 min. Secondary endpoints included longer episodes of atrial fibrillation, and the safety endpoint comprised a composite of syncope or presyncope.

**Results** The median percentage of atrial pacing was 1% in patients assigned to DDD-40 and 49% in patients assigned to DDDR-60. The primary endpoint occurred in 124 patients (46%) in each treatment group (hazard ratio [HR] 0.97, 95% confidence interval [CI] 0.76–1.25, $P = .83$). There were no between-group differences in atrial fibrillation exceeding 6 or 24 h, persistent atrial fibrillation, or cardioversions for atrial fibrillation. The incidence of syncope or presyncope was higher in patients assigned to DDD-40 (HR 1.71, 95% CI 1.13–2.59, $P = .01$).

**Conclusions** Atrial pacing minimization in patients with sinus node dysfunction does not reduce the incidence of atrial fibrillation. Programming a base rate of 40 bpm without rate-adaptive pacing is associated with an increased risk of syncope or presyncope.

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## Structured Graphical Abstract

**Key Question**

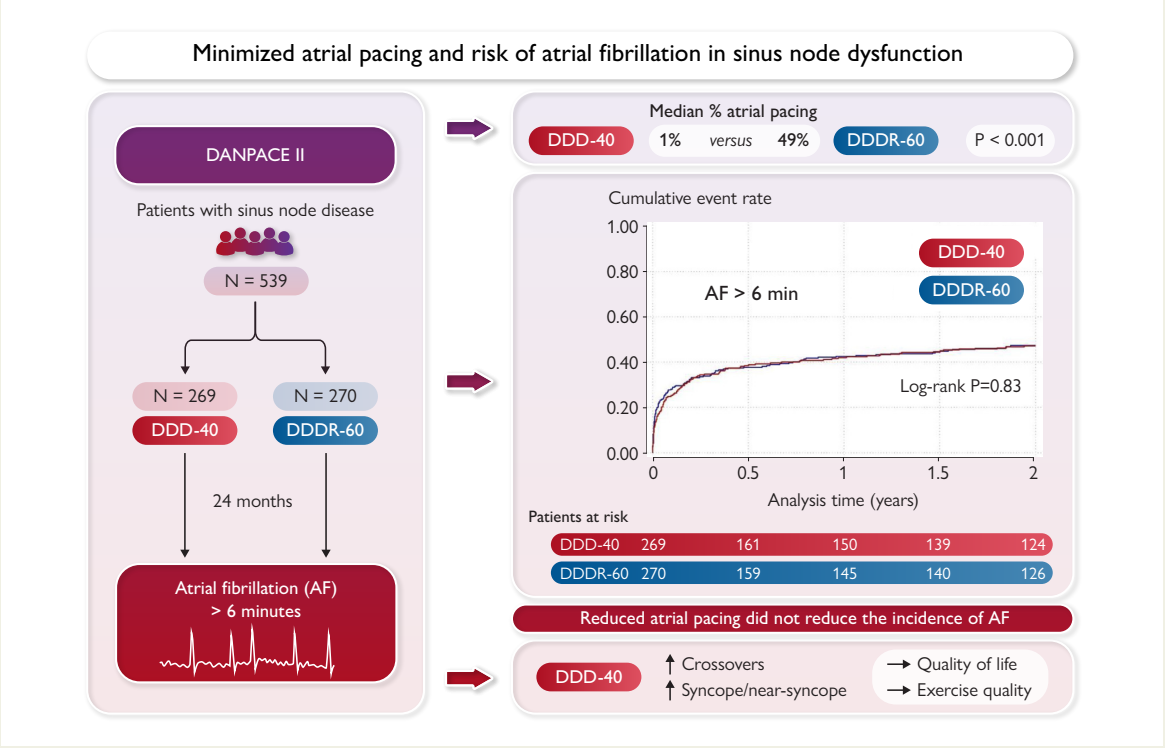
Does reduction of atrial pacing percentage lowers the risk of incident atrial fibrillation (AF) in sinus node disease?

**Key Finding**

In this randomized controlled trial randomization to a rate of 40 bpm without rate-adaptive pacing vs a rate of 60 bpm and rate-adaptive pacing was associated to a similar rate of AF at 2-year follow-up but a higher rate of syncope/presyncope.

**Take Home Message**

In patients with sinus node disease, reducing atrial pacing percentage does not reduce the risk of incident atrial fibrillation while it increases the risk of syncope/presyncope.




Consort diagram of the DANPACE II trial. Median percentage of atrial pacing in the two groups. Primary endpoint defined as time to first episode of atrial fibrillation > 6 min. Secondary and safety endpoints including syncope/presyncope, crossover, quality of life assessment, and 6 min walk test.

**Keywords** Sinus node disease • Pacemaker • Atrial fibrillation • Atrial pacing • Syncope • Quality of life

# Introduction

Atrial fibrillation is common in patients with sinus node dysfunction; approximately 40% of patients with pacemakers due to sinus node dysfunction have a history of atrial fibrillation[1,2] and 24%–68% experience atrial fibrillation after pacemaker implantation.[1–3] Previous trials demonstrated that pacing modes that preserve atrioventricular synchrony, promote intrinsic ventricular conduction, and prevent prolonged atrioventricular conduction delays can reduce the incidence of atrial fibrillation.[1,2,4–6] Current guidelines recommend dual-chamber pacing (DDD) to avoid unnecessary ventricular pacing but without programming of excessively long atrioventricular delays.[7] Different pacemaker algorithms using triggered or continuous overdrive atrial pacing were developed to prevent AF.[8–13] The clear effect of these algorithms has not been demonstrated in larger randomized studies. In addition, they are not well tolerated by patients and they accelerate battery depletion.[8] Higher percentages of atrial pacing have also been linked to an increased risk of atrial fibrillation.[14–16] However, this was never tested in a randomized controlled trial and it is not known whether the association is caused by abnormal prolongation and propagation of atrial depolarization induced by pacing or whether it may result from an increased need for pacing in more progressive atrial disease. Mostly, pacemakers are programmed to a base rate of 60 bpm with activated rate-adaptive pacing to increase the heart rate during physical activity. Programming a lower base rate and avoiding rate-adaptive pacing can reduce the proportion of atrial pacing in patients with pacemakers.[14,15] This trial was designed to determine whether minimizing atrial pacing in patients with sinus node dysfunction reduces the risk of atrial fibrillation.

# Methods

## Trial design and oversight

The DANPACE II trial was a national, multi-centre, open-label, investigator-initiated, randomized controlled trial designed to investigate whether minimized atrial pacing reduces the incidence of atrial fibrillation in patients with sinus node dysfunction. Patients were recruited from 11 pacemaker implanting centres in Denmark. Recruitment was initiated in May 2014 and concluded in June 2021.

The trial was designed and overseen by the Steering Committee (see Supplementary data online, *Appendix*), and daily monitoring and management were undertaken by the Trial Coordinating Centre at Aarhus University Hospital, Denmark. This trial was approved by the Ethics Committees of Central Denmark Region and registered under the Danish Data Protection Agency.

## Patients

We enrolled adults (aged 18 years or older) with sinus node dysfunction who were undergoing a first-time pacemaker implantation. Patients were not eligible for inclusion if they had permanent or persistent atrial fibrillation longer than 7 days before or at randomization, persistent sinus bradycardia, and/or chronotropic incompetence which would contraindicate a base rate of 40 bpm, had an indication for an implantable cardioverter defibrillator or cardiac resynchronization device, were pregnant, had a life expectancy of less than 1 year, or participated in another interventional study. Medical history was assessed from medical records or reported by patients and later confirmed in medical records when possible. The estimated glomerular filtration rate (eGFR) was calculated based on plasma creatinine levels. All participants gave written informed consent.

## Trial intervention and procedures

In this trial, we randomly assigned patients to pacing programmed to a base rate of 60 bpm with rate-adaptive pacing (DDDR-60) or pacing programmed to a base rate of 40 bpm without rate-adaptive pacing (DDD-40) on a 1:1 basis. Randomization was accomplished using a web-based system and was stratified for sex and prior atrial fibrillation and/or atrial flutter.

All patients received a standard, commercially available dual-chamber pacemaker with transvenous pacing leads placed in the right atrium and ventricle. The device was programmed according to randomization with atrioventricular delays set to 150–160 ms after a paced atrial complex and 130–140 ms after a sensed atrial complex with active atrioventricular hysteresis to promote intrinsic conduction to a maximum atrioventricular delay prolongation of 80–100 ms and rate-adaptive atrioventricular delay. The mode-switch criterion was an atrial rate of 190 bpm. This would result in mode switch to DDIR or VVIR with a basic pacing rate of 60 bpm. Atrial sensitivity was programmed between 0.1 and 0.5 mV. No atrial fibrillation suppression algorithms were used in this trial.

Patients were followed for 2 years after randomization. Remote monitoring was established for all patients and managed from a central core lab located at Aarhus University Hospital. Atrial high-rate episodes were transmitted automatically or manually on a weekly basis. All electrograms were adjudicated by experienced device specialists, and only those determined to represent atrial fibrillation were included as endpoints. In-hospital visits including device interrogations were scheduled after 3, 12, and 24 months. At the 12 month follow-up visit, patients answered a quality-of-life questionnaire, the 36-Item Short Form Health Survey (SF-36), and performed a 6 min walk test. From the SF-36 questionnaire, we report the summarized physical and mental component scores (ranging from 0 to 100). In case patients in the intervention group (DDD-40) displayed symptoms consistent with chronotropic incompetence, they crossed to the control group (DDDR-60). To avoid unnecessary crossovers, symptoms were reassessed 1 month after reprogramming.

## Endpoints

The primary endpoint was time to first device-detected episode of atrial fibrillation lasting longer than 6 min.[17] Secondary endpoints included time to first episode of device-detected atrial fibrillation with a duration longer than 6 or 24 h, persistent atrial fibrillation, chemical or electrical cardioversion for atrial fibrillation, stroke, transitory cerebral ischaemia or thromboembolic event, and all-cause mortality. Additional endpoints included quality of life and exercise capacity at 12 months and the need for pacemaker reprogramming (crossover) during follow-up. Safety endpoints included a composite of syncope or presyncope and implant-related complications.

## Statistical analyses

We anticipated that 50% of patients in the control group would develop atrial fibrillation within 2 years and estimated that enrolment of 540 patients would provide 80% power to detect a 25% reduction in the absolute incidence of the primary endpoint using a two-sided alpha of 0.05. All primary and secondary analyses were conducted according to the intention-to-treat principle. Differences in treatment outcomes were compared using time-to-event methods. Kaplan–Meier curves were used to display differences in event rates between treatment groups over follow-up and compared using a two-sided log-rank test. We used a Cox proportional hazard regression model to compute cause-specific hazard ratios (HRs) with 95% confidence intervals (CIs) for the primary and secondary endpoints. The appropriateness of the assumption of proportionality was assessed using conventional graphical techniques. In a pre-specified analysis, we used a multivariable Cox proportional hazard regression model to identify predictors for the primary endpoint. The following *a priori* selected baseline covariates were included in model 1: age, sex, PR interval in the electrocardiogram, prior atrial fibrillation or atrial flutter, and left ventricular ejection fraction, and in model 2: history of heart failure, hypertension, age, sex, diabetes, history of stroke, vascular disease, and prior atrial fibrillation or atrial flutter. Subgroup analyses were performed for patients with or without prior atrial fibrillation or flutter, a baseline PR interval and age above or below the median in the population, and sex. The heterogeneity of treatment effects was assessed by inclusion of an interaction term in the Cox model, and models were tested using the likelihood ratio test. In a post-hoc analysis, atrial fibrillation burden (assessed by % time spent in mode switch) was compared between the two treatment groups. Between-group differences in 6 min walk test performance and quality of life as assessed by the SF-36 were compared using Student's *t*-test and the Mann–Whitney two-sample test, respectively. Missing values in covariates used in the multivariable Cox analysis and in subcomponents of the SF-36 questionnaires were imputed using chained multiple imputation (10 imputed sets). All secondary analyses were considered exploratory, and the widths of the CIs were not adjusted for multiplicity. Two-sided $P \leq .05$ was considered statistically significant. All analyses were performed in Stata version 17.0 (StataCorp LLC, USA).

# Results

## Patients and follow-up

A total of 540 patients were enrolled from 11 centres; 270 were assigned to DDD-40 and 270 were assigned to DDDR-60 (*Figure 1*). One patient (randomized to DDD-40) withdrew consent before pacemaker implantation. Hence, the intention-to-treat population comprised 539 patients. Overall, demographic and clinical characteristics including medical history were well balanced between treatment groups (*Table 1*). Among included patients, just over 40% had a history of atrial tachyarrhythmias—115 (43%) patients in the DDDR-60 group and 121 (45%) patients in the DDD-40 group. The median follow-up time was 732 days (interquartile range [IQR] 710–771) and 734 (IQR 718–777) for DDD-40 and DDDR-60 ($P = .22$), respectively.

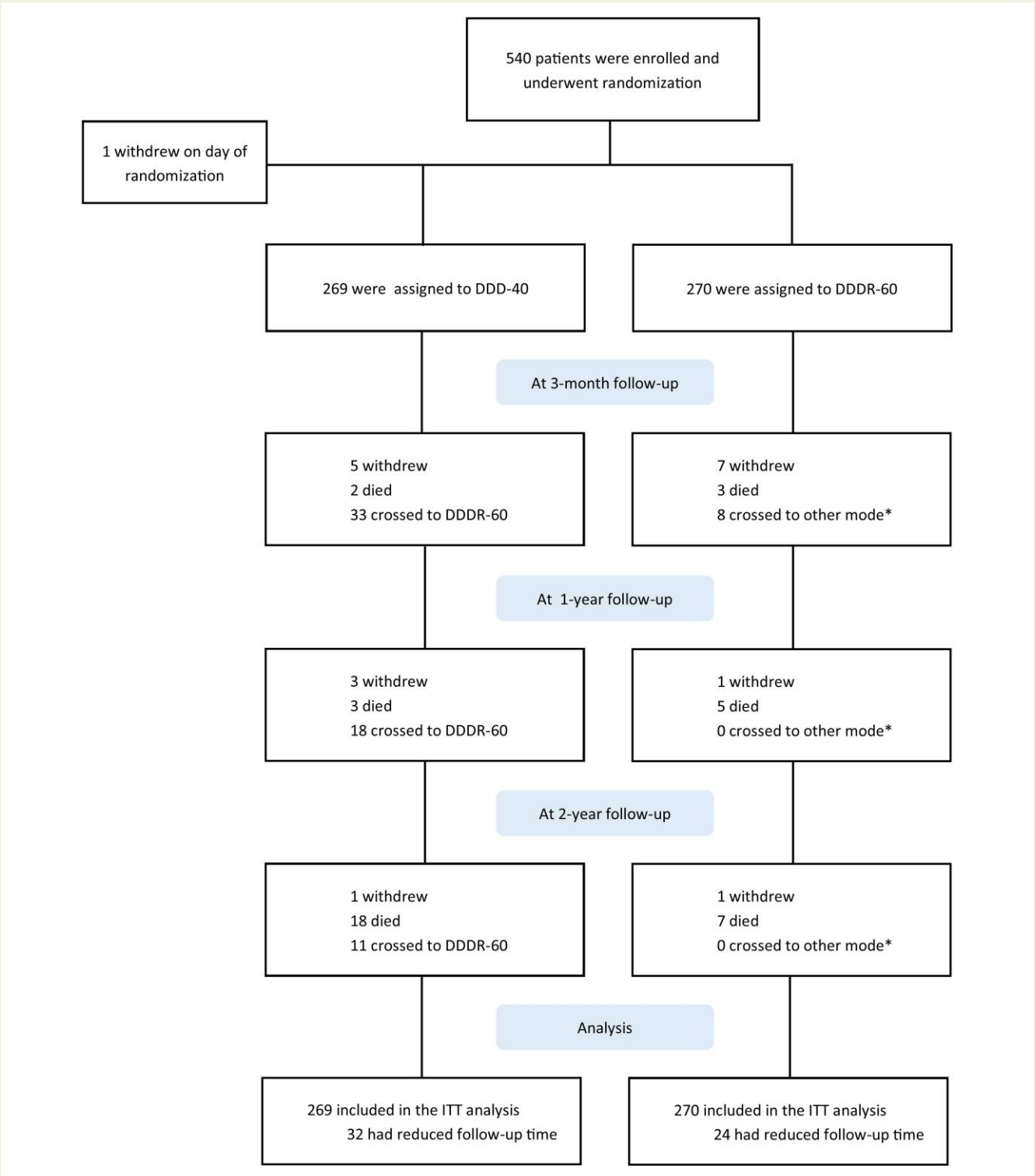



**Figure 1** CONSORT diagram

After 2 years of follow-up, 19 (4%) patients withdrew consent—9 (3%) assigned to DDDR-60 and 10 (4%) assigned to DDD-40. A total of 38 (7%) patients died during follow-up—15 (6%) in the DDDR-60 group and 23 (9%) in the DDD-40 group. None were lost to follow-up (*Figure 1*). The crossover rate was significantly higher for patients randomized to DDD-40 compared with DDDR-60 (*Figure 2C*). Among the 62 (23%) patients who crossed from DDD-40 to DDDR-60, the indication was syncope or presyncope in 18 (29%) patients, chronotropic incompetence in 38 (61%) patients, and not specified in 5 (8%) patients. Only eight (3%) patients in the control group

**Table 1 Demographic and clinical characteristics ($n = 539$)**

| | DDDR-60 ($n = 270$) | DDD-40 ($n = 269$) |
|---|---|---|
| Female sex, *n* (%) | 130 (48) | 140 (52) |
| Age, years (median [IQR]) | 73 (67–79) | 74(67–80) |
| Indication, *n* (%) | | |
| Sinus node dysfunction | 152 (56) | 151 (56) |
| Brady–tachy syndrome | 103 (38) | 105 (39) |
| Sinus node dysfunction and AVB | 15 (6) | 14 (5) |
| History of atrial fibrillation, flutter, or tachycardia, *n* (%) | 115 (43) | 121 (45) |
| Previous myocardial infarction, *n* (%) | 22 (8) | 23 (9) |
| Previous PCI or CABG, *n* (%) | 37 (14) | 32 (12) |
| Previous stroke, *n* (%) | 24 (9) | 28 (10) |
| Previous TCI, *n* (%) | 16 (6) | 14 (5) |
| Previous peripheral embolism, *n* (%) | 6 (2) | 4 (2) |
| Diabetes, *n* (%) | 27 (10) | 37 (14) |
| Heart failure, *n* (%) | 9 (3) | 8 (3) |
| Chronic obstructive pulmonary disease, *n* (%) | 23 (9) | 19 (7) |
| Peripheral atherosclerosis, *n* (%) | 6 (2) | 12 (5) |
| Hyperthyroidisms, *n* (%) | 9 (3) | 10 (4) |
| History of heart valve disease, *n* (%) | 9 (3) | 19 (7) |
| Previous pulmonary vein isolation, *n* (%) | 15 (6) | 9 (3) |
| Hypertension, *n* (%) | 141 (52) | 148 (55) |
| Symptoms, *n* (%) | | |
| Syncope | 144 (53) | 160 (59) |
| Presyncope | 143 (53) | 151 (56) |
| Dizziness | 180 (67) | 174 (65) |
| Palpitations | 89 (33) | 81 (30) |
| Dyspnoea | 80 (30) | 83 (31) |
| Fatigue | 66 (24) | 61 (23) |
| Echocardiography | | |
| LVEF, mean ± SD | 58 ± 7 | 58 ± 7 |
| LVEF < 50%, *n* (%) | 15 (6) | 14 (5) |
| Glomerular filtration rate, mL/min/1.73 $m^2$ (mean [SD]) | 73 (±24) | 72 (±24) |
| Medical therapy, *n* (%) | | |
| NOAC | 72 (27) | 76(28) |
| Warfarin | 24 (9) | 21 (8) |
| Aspirin | 44 (16) | 48 (18) |
| Other antiplatelet therapy | 25 (9) | 20 (7) |
| Beta blocker | 87 (32) | 101 (38) |
| ACE-I/ARB | 108 (40) | 120 (45) |
| Diuretics | 65 (24) | 77 (29) |
| Calcium channel blocker | 58 (22) | 71 (26) |

*Continued*

**Table 1** *Continued*

| | DDDR-60 ($n = 270$) | DDD-40 ($n = 269$) |
|---|---|---|
| Amiodarone | 10 (4) | 9 (3) |
| Digoxin | 3 (1) | 4 (2) |
| Class 1C antiarrhythmics | 2 (1) | 2 (1) |

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AVB, atrioventricular block; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NOAC, non-vitamin K oral anticoagulant; PCI, percutaneous coronary intervention; TCI, transitory cerebral ischaemia. Count data are reported as absolute frequencies and percentages. Continuous variables are reported as means ± standard deviation (SD) or medians and interquartile ranges (IQRs) in case of non-normal distribution. Data were missing for LVEF ($n = 91$ missing).

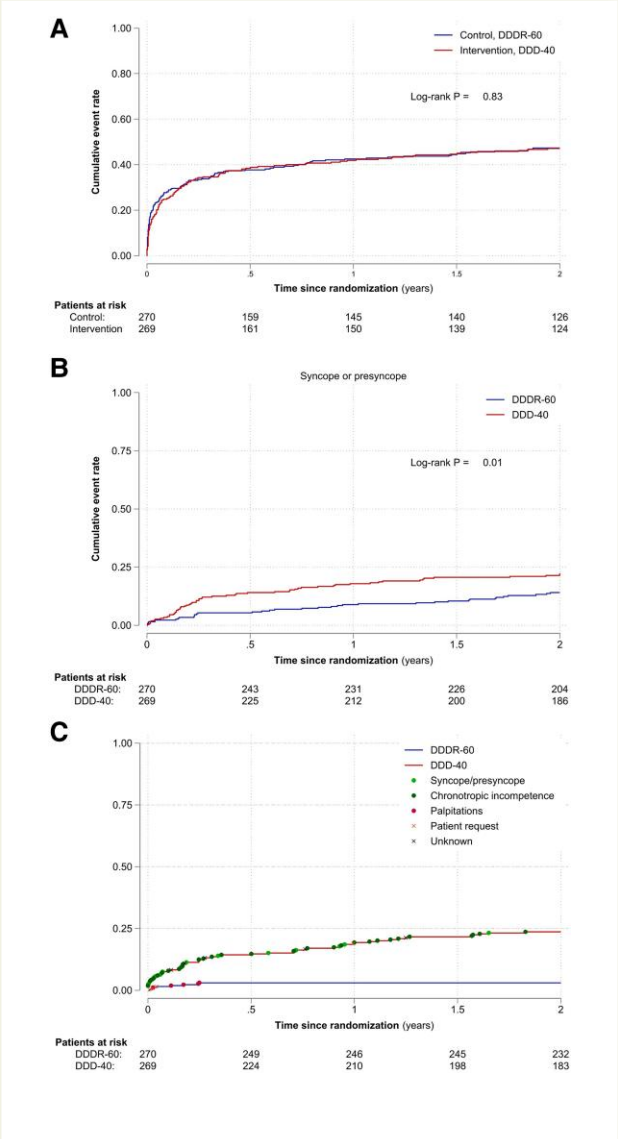



**Figure 2** (*A*) Time to first episode of atrial fibrillation longer than 6 min. (*B*) Time to first episode of syncope or presyncope. (*C*) Time to crossover including indication for crossover

had their device reprogrammed to a lower base rate. Four of 70 (6%) crossovers (one in the DDD-40 group and three in the DDDR-60 group) occurred per patient request.

## Intervention and endpoints

The median percentage of atrial pacing was 1% (IQR 0%–14%) in the DDD-40 group compared with 49% (IQR 22%–75%) in the DDDR-60 group. Likewise, the median percentage of ventricular pacing was lower with DDD-40 than DDDR-60 (9% [IQR 1%–54%] vs. 34% [IQR 8%–66%]).

After 2 years, the primary endpoint had occurred in 248 (46%) patients—in 124 of 270 (46%) patients assigned to DDDR-60 and in 124 of 269 (46%) assigned to DDD-40 (HR 0.97, 95% CI 0.76–1.25, $P = .83$) (*Figure 2A* and *Table 2*). No significant difference in the incidence of the primary endpoint was observed across subgroups (*Figure 3*). In the multivariable Cox analysis, only prior atrial fibrillation or atrial flutter was identified as a predictor for the primary endpoint (HR 7.31, 95% CI 5.44–9.84, $P < .001$) (*Table 3*).

In the secondary analyses, episodes of atrial fibrillation with a duration longer than 6 or 24 h, progression to permanent or persistent atrial fibrillation, cardioversions for atrial fibrillation, and all-cause mortality occurred at similar rates in both treatment groups. A total of seven patients experienced stroke, transitory cerebral ischaemia, or thromboembolic event. These were evenly distributed between the two groups—four in the DDDR-60 and three in the DDD-40 group. Total atrial fibrillation burden was 0% (IQR 0–1.8) in the DDDR-60 group and 0% (IQR 0–2.6) in the DDD-40 group ($P = .99$). Results for the primary and secondary endpoints are summarized in *Table 2*.

At 12 month follow-up, 447 (83%) patients responded to the SF-36 questionnaire. Imputation of missing values in incomplete questionnaires was performed for 98 (22%) patients. The quality of life was similar between patients randomized to DDDR-60 and to DDD-40 with no significant between-group differences in either the physical or mental component summary scores of the SF-36 (59 ± 7 vs. 60 ± 7 for physical components, $P = .37$, and 49 ± 4 vs. 49 ± 4 for mental components, $P = .66$) (*Figure 4*). A total of 414 (77%) patients performed a 6 min walk test, and no differences were observed between the treatment groups (466 ± 8 m vs. 464 ± 8 m, $P = .85$).

## Adverse events and safety

The composite safety endpoint comprised by syncope or presyncope occurred in 94 (17%) patients. Significantly more patients assigned to DDD-40 than to DDDR-60 experienced syncope or presyncope—58 (22%) in DDD-40 vs. 36 in DDDR-60 (13%) (HR 1.71; 95% CI 1.13–2.59; $P = .01$) (*Figure 2B*). A total of 16 (17%) events occurred in patients who crossed from DDD-40 to DDDR-60 during follow-up with three occurring after crossover. During follow-up, syncope occurred in 38 (7%) patients—22 (8%) in DDD-40 vs. 16 (6%) in DDDR-60 (HR 1.40, 95% CI 0.73–2.66, $P = .31$)—and 66 (12%)

**Table 2 Primary and secondary endpoints**

| | DDDR-60 ($n = 270$) | DDD-40 ($n = 269$) | HR | 95% CI | SE | *P*-value |
|---|---|---|---|---|---|---|
| Primary endpoint | | | | | | |
| Atrial fibrillation > 6 min | 124 | 124 | 0.97 | 0.76–1.25 | 0.12 | .83 |
| Secondary endpoints | | | | | | |
| Atrial fibrillation > 6 h | 87 | 98 | 1.15 | 0.86–1.53 | 0.17 | .35 |
| Atrial fibrillation > 24 h | 51 | 69 | 1.37 | 0.96–1.97 | 0.25 | .09 |
| Persistent atrial fibrillation | 36 | 40 | 1.12 | 0.71–1.76 | 0.26 | .63 |
| Cardioversion for atrial fibrillation | 12 | 14 | 1.16 | 0.54–2.50 | 0.46 | .71 |
| Thromboembolic event | 4 | 3 | 0.76 | 0.17–3.40 | 0.58 | .72 |
| All-cause mortality | 15 | 24 | 1.60 | 0.84–3.06 | 0.53 | .15 |
| Crossover | 8 | 62 | 8.50 | 4.07–17.74 | 3.19 | <.001 |
| Safety endpoints | | | | | | |
| Syncope or presyncope | 36 | 58 | 1.71 | 1.13–2.59 | 0.36 | .01 |

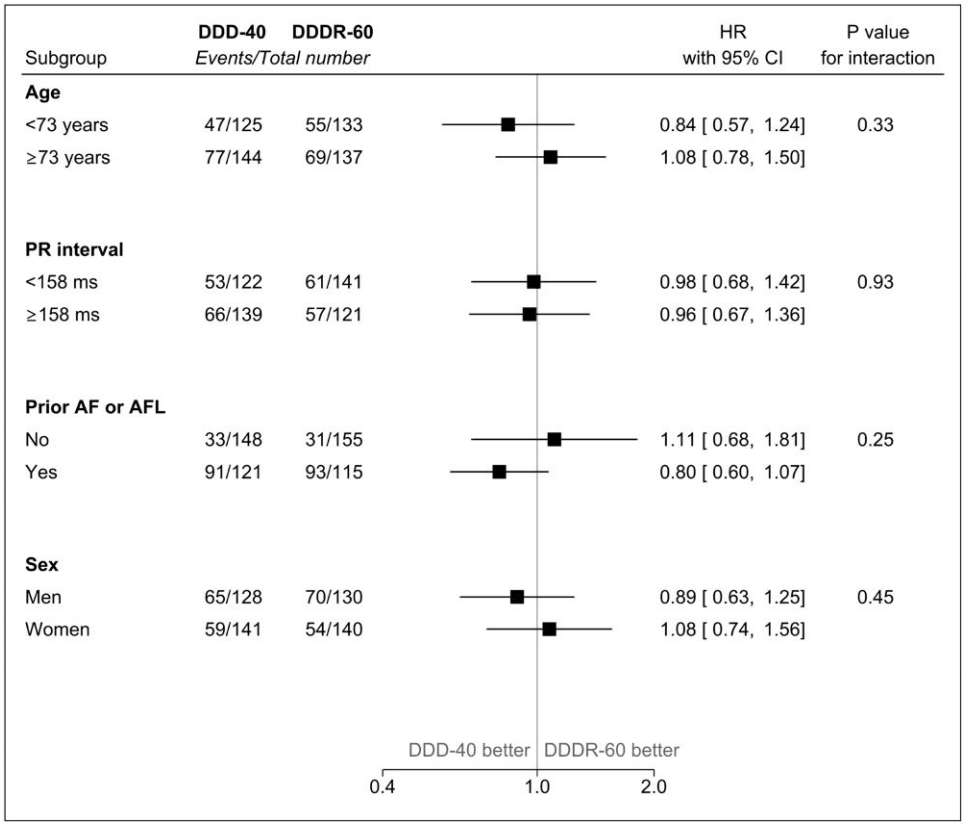



**Figure 3** Risk of atrial fibrillation longer than 6 min according to selected baseline characteristics

patients experienced presyncope—44 (16%) in DDD-40 vs. 22 (8%) in DDDR-60 (HR 2.1, 95% CI 1.26–3.52, $P = .004$).

Device-related complications requiring reoperation were registered in 19 (4%) patients—10 (4%) patients in the DDDR-60 group and 9 (3%) patients in the DDD-40 group.

# Discussion

In this multicentre, randomized controlled trial, we tested the hypothesis that minimizing atrial pacing by programming a base rate of 40 bpm and deactivating the rate-adaptive function reduce the risk of atrial

**Table 3 Predictors of a first episode of atrial fibrillation longer than 6 min**

| | HR | 95% CI | SE | *P*-value |
|---|---|---|---|---|
| Model 1 | | | | |
| DDD-40 | 0.86 | 0.67–1.11 | 0.11 | .26 |
| Age (>median) | 1.00 | 0.78–1.30 | 0.13 | .98 |
| Sex (female) | 1.18 | 0.92–1.52 | 0.15 | .20 |
| PR interval (>median) | 1.04 | 0.80–1.34 | 0.13 | .78 |
| Left ventricular ejection fraction (>median) | 0.97 | 0.74–1.27 | 0.13 | .84 |
| Prior atrial fibrillation/flutter | 7.31 | 5.44–9.84 | 1.11 | <.001 |
| Model 2 | | | | |
| DDD-40 | 0.86 | 0.67–1.10 | 0.11 | .23 |
| History of heart failure | 0.77 | 0.43–1.36 | 0.22 | .36 |
| Hypertension | 0.97 | 0.75–1.27 | 0.13 | .85 |
| Age > 75 | 1.23 | 0.81–1.86 | 0.26 | .34 |
| Diabetes | 0.92 | 0.63–1.35 | 0.18 | .68 |
| History of stroke | 1.02 | 0.72–1.46 | 0.19 | .91 |
| Age 65–74 | 1.12 | 0.74–1.70 | 0.24 | .60 |
| Vascular disease | 0.80 | 0.57–1.13 | 0.14 | .21 |
| Sex (female) | 1.16 | 0.89–1.50 | 0.15 | .27 |
| Prior atrial fibrillation/flutter | 7.17 | 5.31–9.69 | 1.10 | <.001 |

fibrillation in patients with sinus node dysfunction. Although this strategy successfully minimized the percentage of atrial pacing, it did not reduce the cumulative incidence of atrial fibrillation, regardless of episode duration. The incidence of syncope or presyncope was significantly higher in patients randomized to minimized atrial pacing. No effect was observed on the quality of life or exercise capacity (*Structured Graphical Abstract*). This trial indicates that programming intended to minimize atrial pacing should not be used as routine in unselected patients with sinus node dysfunction.

We used episodes of device-detected atrial fibrillation lasting longer than 6 min as a proxy for clinical atrial fibrillation. In the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT), subclinical device-detected tachyarrhythmias lasting longer than 6 min were associated with a significantly increased risk of thromboembolic events and identified as independent predictors of ischaemic stroke and clinical atrial fibrillation,[17] although a later study on the ASSERT population demonstrated that only episodes > 24 h were associated with an increased risk of stroke or systemic embolism.[18] Even with restriction to longer episodes, minimized atrial pacing did not appear to influence the incidence of atrial fibrillation in our study, albeit these analyses were not powered for final conclusions.

Several trials suggested that choice in pacing mode can influence the risk of atrial fibrillation in patients with sinus node dysfunction; preservation of atrioventricular synchrony and intrinsic ventricular conduction using atrial-based single-chamber pacing[2,4,5] and programming to minimize ventricular pacing have been shown to reduce the incidence of atrial fibrillation.[6] Meanwhile, in the Danish Multicenter Randomized Trial on Single Lead Atrial Pacing vs. Dual Chamber Pacing in Sick Sinus Syndrome (DANPACE),[1] the rate of atrial fibrillation was higher with single-lead atrial pacing, thus indicating that in

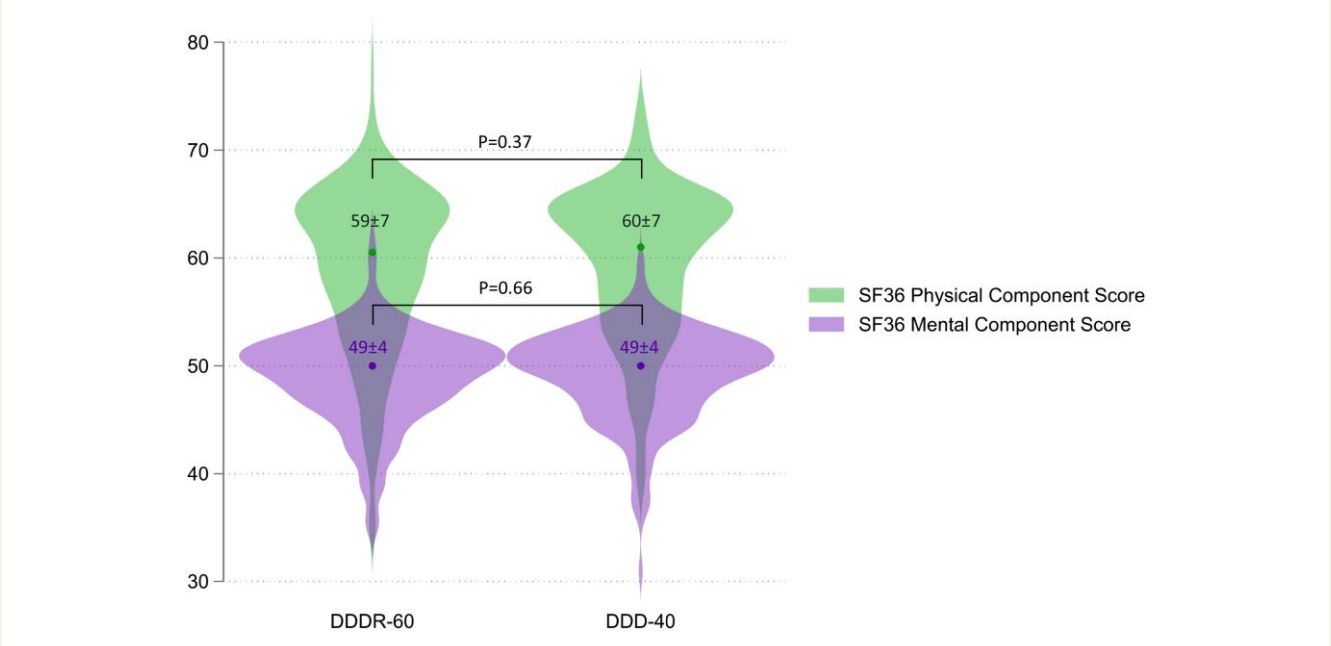



**Figure 4** Quality of life assessed by SF-36 at 12 months including the mental and physical scores

the context of atrial fibrillation, it may be more important to avoid long atrioventricular delays than to avoid ventricular pacing in patients with sinus node dysfunction. Different pacemaker-specific algorithms including triggered pacing and continuous overdrive atrial pacing were developed to reduce atrial fibrillation.[9–11,13] However, the evidence favouring routine use of these algorithms is not convincing. The ASSERT trial showed no benefit of an atrial overdrive pacing algorithm in reducing atrial fibrillation, but a non-significant trend suggested that increased atrial pacing increases the risk of atrial fibrillation.[8,17] In the MINimizE Right Ventricular pacing to prevent Atrial fibrillation and heart failure (MINERVA) trial, a combination of algorithms to prevent atrial fibrillation including atrial antitachycardia pacing reduced the risk of permanent atrial fibrillation in patients with a previous history of atrial fibrillation.[12] Shorter episodes were not reduced using these algorithms, which could indicate that results were mostly driven by the earlier termination of longer episodes with atrial antitachycardia pacing. An association between atrial pacing burden and incident atrial fibrillation was shown in a meta-analysis including 1507 patients.[14] In this analysis, patients receiving atrial pacing burden in the three upper quartiles had a four-fold higher risk of atrial fibrillation compared with the lower quartile and use of the rate response function increased the median proportion of atrial pacing burden from 29% to 72%. In contrast, a substudy of the DANPACE trial found no association between atrial fibrillation and percentages of atrial or ventricular pacing.[19] Based on the novel results from the present study, we can conclude that lowering the amount of atrial pacing has no impact on the incidence of atrial fibrillation in patients with sinus node dysfunction. The association found in previous studies likely reflects an increased need for pacing in patients with more progressive atrial disease, in whom the *a priori* risk of atrial fibrillation is also higher. In line with the current literature, a history of atrial arrhythmias at time of implantation was the strongest predictor of new episodes of atrial fibrillation. In both the DANPACE and the MOST trial,[1,2] the association between the pacing mode and atrial fibrillation was only significant in the subgroup without a history of atrial arrhythmias. In the present study, half of the patients had a history of atrial arrhythmias and most (74%) of the primary endpoints occurred in those patients. In the subgroup analysis, patients without a history of atrial arrhythmias had a higher HR for incidence of atrial fibrillation in the DDDR-60 group. Although this study is not powered for conclusions about this subgroup, this group may be studied in another trial to determine whether this group may actually benefit from DDD-40 pacing.

Despite implantation of a pacemaker, a considerable proportion of patients experience recurrent syncope.[20–22] In the DANPACE trial, the cumulative incidence of post-implantation syncope after a mean follow-up of 5.4 years was 17.5% and no significant difference was observed between patients randomized to AAIR or DDDR.[20] In a more recent registry-based study including patients undergoing a pacemaker implantation for bradyarrhythmia syncope, the cumulative incidence of syncope recurrence was 15.6%, as well as 12.5% with restriction to patients with sinus node dysfunction.[22] Common causes were reflex syncope (30%) and orthostatic hypotension (32%). In the present study, the rate of syncope or presyncope was comparable with previous reports for patients randomized to DDDR-60 but it was markedly higher for patients randomized to DDD-40. It is likely that a higher base rate could prevent both reflex and orthostatic syncope in some of these patients. Careful evaluation of patients and their risk of syncope is therefore advised before lowering the base rate to minimize atrial pacing.

Another concern with lower base rates is a presumed negative impact on exercise capacity and quality of life. In patients who completed the 6 min walk test and the SF-36 quality-of-life questionnaire after 12 months, we observed no significant differences between groups. This is in line with results from previous randomized studies where no beneficial effect of routine rate-adaptive pacing on exercise capacity and quality-of-life was reported.[23,24] However, it is noteworthy that 38 patients randomized to DDD-40 crossed to DDD-60 due to chronotropic incompetence, the majority within 6 months of implantation. An attenuated heart rate response to exercise in patients with sinus node dysfunction and implanted pacemakers can be alleviated with rate-adaptive pacing.

### Limitations

The primary endpoint of atrial fibrillation was defined as atrial high-rate episodes > 190 bpm with a duration of >6 min which has a false positive rate of 17%.[25] To reassure that all episodes were true atrial fibrillation, all episodes were adjudicated by an experienced device expert at a central remote monitoring centre. Due to the open design of the study, observers responsible for quality-of-life assessment, crossover between treatments, and exercise test were not blinded to the group assignment, which is a potential source of bias.

## Conclusion

In conclusion, minimizing atrial pacing in patients with sinus node dysfunction does not reduce incidence of atrial fibrillation. Programming a base rate of 40 bpm without rate-adaptive pacing is associated with a higher incidence of syncope or presyncope.

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## Supplementary Data

Supplementary data are available at *European Heart Journal* online.

## Declarations

### Disclosure of Interest

M.B.K. received speakers fee from Abbot, M.H.J.P.F. received consulting fees from Medtronic outside this work, J.B.J. received consulting fees from Medtronic outside this work, and J.C.N. received grants from the Novo Nordisk Foundation and the Danish Heart Foundation outside this work.

### Data Availability

Data are available upon reasonable request to Mads Brix Kronborg at mads.brix.kronborg@au.dk.

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## Ethical Approval

This trial was approved by the Ethics Committees of Central Denmark Region and registered under the Danish Data Protection Agency.

## Pre-registered Clinical Trial Number

ClinicalTrials.gov number, NCT02034526.

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