

Prospective Randomized Study to Assess the Efficacy of Site and Rate of Atrial Pacing on Long-Term Progression of Atrial Fibrillation in Sick Sinus Syndrome

Septal Pacing for Atrial Fibrillation Suppression Evaluation (SAFE) Study

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Background—Atrial-based pacing is associated with lower risk of atrial fibrillation (AF) in sick sinus syndrome compared with ventricular pacing; nevertheless, the impact of site and rate of atrial pacing on progression of AF remains unclear. We evaluated whether long-term atrial pacing at the right atrial (RA) appendage versus the low RA septum with (ON) or without (OFF) a continuous atrial overdrive pacing algorithm can prevent the development of persistent AF.

Methods and Results—We randomized 385 patients with paroxysmal AF and sick sinus syndrome in whom a pacemaker was indicated to pacing at RA appendage ON (n=98), RA appendage OFF (n=99), RA septum ON (n=92), or RA septum OFF (n=96). The primary outcome was the occurrence of persistent AF (AF documented at least 7 days apart or need for cardioversion). Demographic data were homogeneous across both pacing site (RA appendage/RA septum) and atrial overdrive pacing (ON/OFF). After a mean follow-up of 3.1 years, persistent AF occurred in 99 patients (25.8%; annual rate of persistent AF, 8.3%). Alternative site pacing at the RA septum versus conventional RA appendage (hazard ratio=1.18; 95% confidence interval, 0.79–1.75; $P=0.65$) or continuous atrial overdrive pacing ON versus OFF (hazard ratio=1.17; 95% confidence interval, 0.79–1.74; $P=0.69$) did not prevent the development of persistent AF.

Conclusions—In patients with paroxysmal AF and sick sinus syndrome requiring pacemaker implantation, an alternative atrial pacing site at the RA septum or continuous atrial overdrive pacing did not prevent the development of persistent AF.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00419640.

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Key Words: atrial fibrillation ■ cardiac pacing, artificial ■ sick sinus syndrome

Sick sinus syndrome (SSS) is common in the elderly and constitutes one of the most common indications for permanent cardiac pacemaker implantation.¹ In addition to abnormalities at the sinus node, SSS is associated with widespread

structural and electrophysiological changes in the atria.² Up to ≈40% of patients with SSS have a history of atrial fibrillation (AF) before pacemaker implantation.^{3–5} The occurrence of AF after pacemaker implantation in SSS is associated with

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an increased risk of stroke, systemic embolism, heart failure, and mortality.^{4,6,7} It is thus important to determine whether the pacing modality can be optimized to prevent AF after pacemaker implantation for SSS.

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Randomized clinical trials^{3,8,9} and a meta-analysis¹⁰ have demonstrated that atrial-based pacing modes reduce the incidence of AF compared with single-chamber right ventricular apical pacing. In addition, minimizing the percentage of ventricular pacing in patients with SSS who receive a dual-chamber DDDR is associated with a low risk of developing persistent AF.¹¹ Nevertheless, it is unknown whether selecting the atrial pacing site can prevent the progression of AF. It has been proposed that reduction of total atrial conduction times and dispersion of atrial refractoriness by atrial septal pacing can prevent AF.¹² Prior investigations^{13–18} that compared septal site pacing with right atrial (RA) appendage pacing in the pacemaker population for AF prevention have yielded mixed results. Whether the use of atrial pacing algorithms that ensure a high percentage of atrial pacing at sites other than the RA appendage can prevent progression of AF remains unclear.¹⁴ These studies were limited by their relatively small sample size, short duration of follow-up, including both primary and secondary AF prevention, and the use of surrogate markers of pacemaker-detected atrial arrhythmias as end points. Thus, the role of selective atrial pacing at a septal location for AF reduction has yet to be elucidated by an adequately powered randomized, controlled trial with clinical AF used as the end point. The Septal Pacing for AF Suppression Evaluation (SAFE) study¹⁹ was designed to address these uncertainties in pacing strategies for the secondary prevention of progression to persistent AF in patients with SSS. We hypothesized that RA septal pacing with an atrial pacing algorithm to ensure a high percentage of atrial pacing can prevent the development of persistent AF in patients with SSS and paroxysmal AF.

Methods

Study Protocol

The protocol of SAFE has been published previously.¹⁹ Briefly, SAFE was a single-blinded, 2×2 factorial randomized, multicenter study of patients with SSS and paroxysmal AF in whom a pacemaker was indicated.²⁰ In this study, all patients had documented paroxysmal AF by a 12-lead ECG within 6 months before the implantation. The objective of SAFE was to evaluate whether the site of atrial pacing (ie, conventional RA appendage versus low RA septal site) and the continuous atrial overdrive pacing algorithm (ie, ON versus OFF) can prevent the development of persistent AF in SSS. This was a physician-initiated study such that the randomization, data collection, and adjudication were performed by the primary investigators. Data monitoring, project management, and data analysis were performed by the Core Laboratory at Queen Mary Hospital, Hong Kong; St Jude Medical Inc; and the SAFE Study Coordination Group (Appendix I in the online-only Data Supplement).

Eligible patients underwent implantation of an IDENTITY ADx DR (model 5386/5380, St Jude Medical) DDDR pacemaker or a later model with similar AF Suppression Algorithm (AFx, St Jude Medical, Sylmar, CA) and atrial high-rate episode (AHRE) registration. They were randomized to receive atrial pacing at the RA appendage or low RA septum, with the ventricular lead positioned in the right ventricular apex. At 6 to 8 weeks after implantation, the overdrive atrial

pacing algorithm was activated (ON or OFF) in accordance with the prior randomized order. These 4 groups of patients (RA appendage OFF, RA appendage ON, RA septum OFF, and RA septum ON) were reviewed every 6 months for at least 3 years.

Study Population

Patients were eligible for the study if they (1) had a history of paroxysmal AF with AF documented on ECG in the 6 months preceding pacemaker implantation; (2) had a conventional indication for pacing because of SSS with or without atrioventricular node disease; (3) provided written informed consent for study participation and were willing to comply with the prescribed follow-up tests and schedule of evaluations; and (4) were at least 18 years old.

Patients were excluded if they (1) already had an implanted pacemaker or an implantable cardioverter-defibrillator; (2) were expected to have heart surgery within the next 6 months; (3) had class III or class IV angina pectoris; (4) were expected not to be able to tolerate high-rate pacing; (5) had <12 months of life expectancy; (6) were on the cardiac transplantation list; (7) were in chronic AF; or (8) had a reversible etiology of AF.

Implantation Procedure and Device Programming

Implantation of atrial leads to the RA appendage was performed by the conventional method. For RA septal lead placement, the position of the active fixation atrial lead was verified fluoroscopically in several planes as described.¹⁹ The pacemakers were programmed according to the specific programming requirements with DDD/DDDR mode for all patients.¹⁹ Briefly, the atrial tachycardia detection rate was programmed to 225 ppm to define the AHRE⁶ and to affect automatic mode switching. If atrioventricular conduction was intact and the native QRS complex was normal (<120 ms), the autointrinsic conduction search was activated with a maximum of 120 ms longer than the programmed sensed and paced atrioventricular interval as determined by the attending physician to maximize intrinsic conduction. Because a nominally high atrial sensitivity (0.5 mV) was programmed to register AF events, myopotential and far-field R-wave oversensing tests were performed in each patient to ensure accurate detection of AHRE.

Follow-Up and Assessment

Study follow-up visits were scheduled 6 to 8 weeks after implantation, then every 6 months for a minimum of 3 years. At each scheduled follow-up visit, data on the use of concomitant medication, clinical signs or symptoms of AF, hospitalization, and the occurrence of major cardiovascular events were recorded. All episodes of clinical and device-recorded AF were documented. Patients with ECG-documented AF during the follow-up visit or at unscheduled visits precipitated by AF symptoms were seen 1 week later to determine whether AF had become persistent.

Echocardiographic data on left ventricular end-systolic and -diastolic volumes and ejection fraction and left atrial size (parasternal long-axis view) measured within 3 months before implantation were required for all patients. These echocardiographic parameters were also measured at every 12-month visit. The quality-of-life questionnaire (Medical Outcomes Study 36-Item Short-Form General Health Survey²¹ with the validated local language version for each country/region) was completed by all patients at enrollment, at 6 to 8 weeks, and at the 12-month visit. The questionnaire determined the quality of life of a patient with the summary scores of the physical and mental components. Pacemakers were interrogated at every scheduled and unscheduled follow-up visit to retrieve any stored electrograms and to determine the number of AHRE >6 minutes since the last visit, the number of device-detected mode switch episodes since the last visit, and the AF burden.

Sample Size Justification

For the sample size calculation, it was assumed that after 3 years, 50% of patients enrolled would develop persistent AF^{3,4} and that this would be reduced to 30% by differences in lead position or overdrive pacing switched ON. With a significance level of 5% for the 2-sided

hypothesis and to achieve 91% power and an R^2 of 0.9 when explanatory variables are regressed with each other, with the use of the logistic model, a total of 380 patients were needed to achieve the purpose of this study (see Methods in the online-only Data Supplement).

Statistical Analysis

All analyses followed intention-to-treat principles and incorporated all available data from patients who had been randomized. Although this trial proposed to use logistic regression as initial analysis, subsequent post hoc review (see Methods in the online-only Data Supplement) of the results showed that logistic regression analysis was suboptimal and that survival analysis was needed. Therefore, time to develop persistent AF and cumulative survival rates for each of the 2 factors (RA septal versus RA appendage pacing and continuous atrial pacing algorithm ON versus OFF) were estimated as the primary end point with the use of the Kaplan-Meier method. Analysis of the survival curves are expressed in terms of log-rank statistics, hazard ratios, confidence intervals, and P values. All statistical analyses were performed with the use of SAS software (version 9.2). P values were considered significant if <0.05 .

Results

Study Population

The study drew patients from 21 centers from 9 regions or countries in Asia and Europe (Appendix I in the online-only Data Supplement). During the period May 2005 to November 2011, 385 patients were enrolled. These patients were randomized to receive atrial pacing at the RA appendage with (RA appendage ON, $n=98$) or without (RA appendage OFF, $n=99$) continuous atrial overdrive pacing or to receive atrial pacing at the RA septum with (RA septum ON, $n=92$) or without (RA septum OFF, $n=96$) continuous atrial overdrive pacing (Figure 1). Successful implantation according to the randomized site was achieved in

99% of patients. Of the 4 remaining patients (1%), 3 of those randomized to RA septum were paced at the RA appendage, and 1 patient from the RA appendage group was paced at the RA septum. There was no crossover between the overdrive pacing switched ON and OFF in this study. The dropout rate during the trial did not differ significantly among groups (10% for RA appendage ON, 13% for RA appendage OFF, 17% for RA septum ON, and 9% for RA septum OFF).

Baseline demographic data are summarized in the Table. Demographics were homogeneous across each factor analyzed. The majority of patients had SSS (94.3%), and high-grade atrioventricular block was the primary indication for pacemaker implantation in 9.6%. More patients were treated with aspirin (35%) than warfarin (11.7%). The left atrial size was 39.6 (SD=7.7) cm, and most patients had a normal left ventricular ejection fraction (mean, 65.3% [SD=11.5]). Heart failure symptoms (defined as New York Heart Association class above II) were present in only 6.2%.

Pacing and Device Parameters

At implantation, RA septal pacing significantly reduced P-wave duration compared with RA appendage pacing (97.3 [SD=24.1] versus 129.3 [SD=31.0] ms; $P<0.001$). At 6-month follow-up, programming continuous atrial overdrive pacing algorithm ON significantly increased the percentage of atrial pacing (92% [SD=13] versus 56% [SD=30]; $P<0.001$) but not the percentage of ventricular pacing (26.1% [SD=35.3] versus 26.0% [SD=33.3]; $P=0.90$) compared with algorithm OFF. There was no difference in the percentage of atrial pacing between RA septal and RA appendage pacing (74.6% [SD=29.4] versus 73.2% [SD, 30.0]; $P=0.89$), but

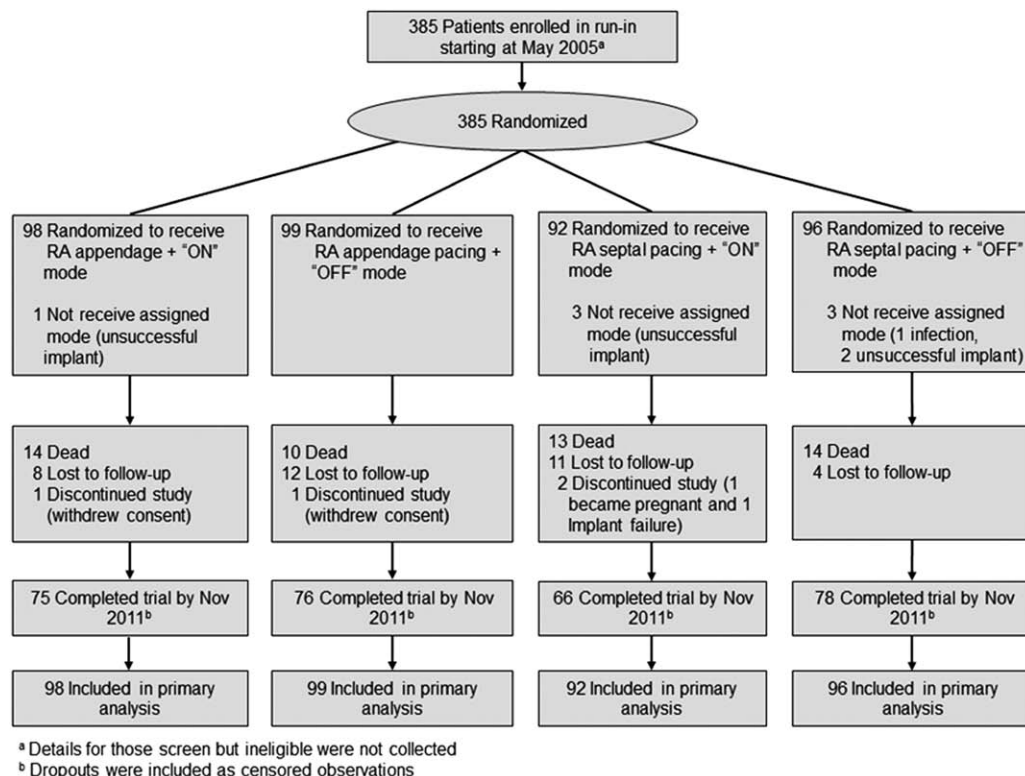


Figure 1. Participant allocation in Septal Pacing for AF Suppression Evaluation (SAFE) study. Nov indicates November; RA, right atrial.

Table. Demographics of Study Population

	Pacing Site		Pacing Rate	
	Low RA Septum (n=188)	RA Appendage (n=197)	Atrial Overdrive Algorithm OFF (n=195)	Atrial Overdrive Algorithm ON (n=190)
Female sex, %	57.45	58.88	53.85	62.63
Age, y (SD)	70.30 (10.18)	71.13 (9.96)	70.89 (10.19)	70.55 (9.95)
Hypertension, %	53.72	49.75	50.77	52.63
Coronary artery disease, %	18.62	19.29	21.54	16.32
Diabetes mellitus, %	15.96	17.26	16.92	16.32
NYHA class >II, %	7.45	5.08	5.64	6.84
Previous MI, %	4.26	2.03	2.56	3.68
Previous stroke or TIA, %	7.45	11.17	10.26	8.42
Sick sinus syndrome, %	95.21	93.40	93.33	95.26
Atrioventricular block, %	7.98	11.17	13.33	5.79
P-wave duration, ms (SD)	122.08 (66.16)	118.9 (38.62)	123.53 (64.52)	117.34 (40.13)
Medications				
β-Blockers, %	19.68	18.27	15.38	22.63
Sotalol, %	2.66	1.52	2.05	2.11
Amiodarone, %	11.70	12.18	8.21	15.79
Aspirin, %	36.70	33.50	38.97	31.05
Warfarin, %	11.17	12.18	9.23	14.21
Echocardiography				
LVEF, % (SD)	65.02 (11.45)	65.94 (10.83)	65.74 (11.13)	65.24 (11.15)
Left atrial size, mm (SD)	38.59 (6.70)	40.63 (8.47)	39.21 (7.23)	39.90 (8.02)

LVEF indicates left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; RA, right atrial; and TIA, transient ischemic attack.

the percentage of ventricular pacing was significantly lower with RA septal pacing at 6 months (22.9% [SD=33.8] versus 29.2% [SD=34.5]; $P=0.006$).

Persistent AF and AF Burden

The mean follow-up was 3.1 (SD=0.6) years. During this period, 35 patients (9.1%) defaulted. Early crossover to an alternative site occurred in 1% of patients. Persistent AF developed in 99 patients (25.8%) after a mean of 23.0 [SD=15.7] months (range, 0–66 months). Of the 99 patients who had persistent AF, restoration of sinus rhythm was attempted in 20 (20.2%), and the remaining 79 patients (79.8%) were managed with rate control. The annual rate of persistent AF was 8.3%. Persistent AF developed at the end of follow-up in 20.0%, 26.3%, 30.3%, and 23.0% for patients randomized to RA appendage ON, RA appendage OFF, RA septum ON, and RA septum OFF, respectively.

Survival analysis using the time to develop persistent AF and based on the atrial pacing site with RA septal versus RA appendage (hazard ratio=1.18; 95% confidence interval, 0.79–1.75; $P=0.65$; Figure 2A) or with (algorithm ON) or without (algorithm OFF) continuous atrial overdrive pacing (hazard ratio=1.17; 95% confidence interval, 0.79–1.74; $P=0.61$; Figure 2B) also failed to show any difference in the incidence of persistent AF.

An exploratory analysis of different subgroups was made, with the use of baseline demographics and implantation and device data at 6 months, of the time to develop persistent AF with RA appendage versus RA septal pacing site independent of the use of continuous atrial overdrive pacing. None of these parameters predicted the development of persistent

AF (Figure 3A). Similarly, when continuous atrial overdrive pacing (algorithm ON) was compared with backup pacing (algorithm OFF) independent of the atrial pacing sites, none of the parameters were predictive of long-term development of persistent AF (Figure 3B).

At 6 months, there was no difference in the AHRE (>6 minutes) or AF burden between the 4 modes of pacing (Table I in the online-only Data Supplement). Moreover, further analysis based on atrial pacing site (ie, RA septal versus RA appendage) or with (algorithm ON) or without (algorithm OFF) continuous atrial overdrive pacing showed no difference in the AF burden or AHRE (Table I in the online-only Data Supplement).

At baseline, the quality-of-life scores were similar between the 4 groups (data not shown). At 12 months, there was no difference in the quality-of-life scores between the 4 modes of pacing (Table II in the online-only Data Supplement). Moreover, further analysis based on atrial pacing site (ie, RA septal versus RA appendage) or with (algorithm ON) or without (algorithm OFF) continuous atrial overdrive pacing showed no difference in the quality-of-life scores (Table II in the online-only Data Supplement).

Complications and Major Adverse Events

An insignificant increase in the incidence of atrial lead repositioning was observed with RA septal pacing compared with RA appendage pacing ($n=9$; 4.8% versus $n=3$; 1.5%; $P=0.08$): A change from RA septum to RA appendage occurred in 3 patients and from RA appendage to RA septum in 1 patient. In addition, 6 patients required repositioning of the ventricular

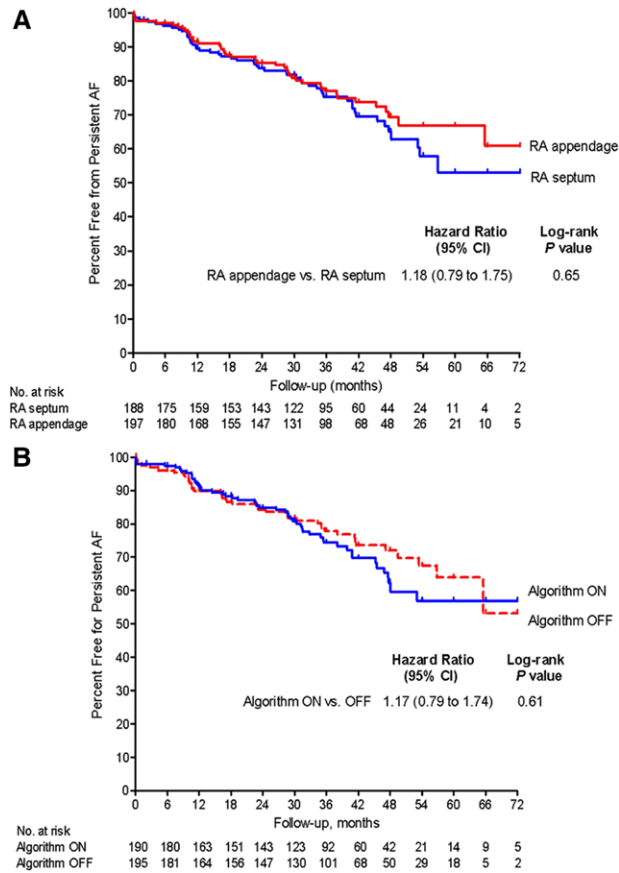


Figure 2. **A**, Comparison between right atrial (RA) septal vs RA appendage pacing on time to persistent atrial fibrillation. **B**, Comparison between continuous atrial overdrive pacing algorithm ON vs OFF on time to persistent atrial fibrillation. CI indicates confidence interval.

lead. Stroke or transient ischemic attack occurred in 19 patients. Death occurred in 51 patients, of which 14 deaths were attributable to cardiovascular events. Adverse events did not differ between the 4 patient groups ($P>0.05$).

Discussion

Main Findings

The SAFE study addresses the role of the atrial pacing site and the rate above backup pacing to prevent AF in a large pacemaker population with SSS and paroxysmal AF. We found that RA septal pacing reduced paced P-wave duration and encouraged intrinsic atrioventricular conduction in patients with SSS. Nevertheless, low RA septal pacing did not significantly affect the long-term development of persistent AF. We also showed that the use of continuous atrial overdrive pacing significantly increased atrial pacing without increasing ventricular pacing. The use of atrial pacing algorithms that ensure a high percentage of atrial pacing at different RA sites nonetheless did not reduce long-term development of persistent AF compared with conventional backup pacing. In this study, a clinically relevant end point of progression to persistent AF was used. No clinical variables could predict any potential benefit of either alternative site pacing or rate on progression to persistent AF. Other secondary end points, including AF

burden, AHRE >6 minutes, quality of life, and adverse events, were unaffected by the atrial pacing site and rate.

Alternative Pacing Site and AF

One of the mechanisms of AF is multiple reentry wavelets in the atrium²² that can be initiated by atrial triggers such as those from the pulmonary veins.^{23,24} A zone of slow conduction is a prerequisite for reentry: In patients with paroxysmal AF, it has been suggested that such a slow conducting zone is located in the triangle of Koch outside the coronary sinus.²⁵ Thus, septal pacing can preexcite the slow-conduction regions and potentially ameliorate AF occurrence. In this study, patients paced in the low RA septal area had significantly shorter P-wave duration, suggesting that RA septal pacing indeed shortened interatrial conduction time either because of its septal position or because of homogenizing conduction time at a potentially slow-conduction area. Moreover, because of the proximity to the atrioventricular node, intrinsic conduction was promoted, over and above the automatic intrinsic search algorithm in this device.²⁶ Nonetheless, despite a combination of these benefits, RA septal pacing did not affect the long-term development of persistent AF in this study.

A recent study on progressive atrial electrophysiological property changes in patients with devices without a history of AF has also identified P-wave duration as a marker of future AF development²⁷ rather than a change in the atrial effective refractory period. This emphasizes the importance of atrial conduction as an electrophysiological mechanism of AF development. In the present interventional trial, shortening of P-wave duration by low RA septal pacing in patients with SSS and paroxysmal AF did not affect recurrence of AF. This may be attributable to a difference in study populations (history of AF or no such history) and the ineffectiveness of low RA septal pacing or both. Low RA septal pacing may be effective only in a subgroup of patients with SSS with intra-atrial conduction delay.¹⁸

Continuous Atrial Overdrive Pacing and AF

In addition to suppressing bradycardia-dependent AF, continuous atrial overdrive pacing above the sinus rate may further reduce AF by a variety of mechanisms, including overdrive suppression of atrial triggers that initiate AF. If delivered at sites of conduction delay, it may induce absolute refractoriness in such areas, rendering them immune to ectopics that can induce reentry.²⁸ The continuous atrial pacing algorithm used in this study automatically overdrives the sinus rate by 5 to 10 bpm up to 130/min and appears to be durable over time.²⁹ Despite this, long-term progression to persistent AF was not suppressed over backup pacing. Consistent with our findings, recent data from the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) also showed that continuous atrial overdrive pacing did not prevent new-onset AF in a pacemaker population.³⁰ The reasons for this are speculative. Despite continuous atrial overdrive pacing, very early atrial ectopics are not consistently suppressible, and it is such early coupled ectopics that induce AF.³¹ In addition, a high percentage of atrial pacing may be harmful.⁵

In summary, among patients with SSS and paroxysmal AF who required pacemaker implantation, the use of an alternative atrial pacing site at the lower RA septum or continuous

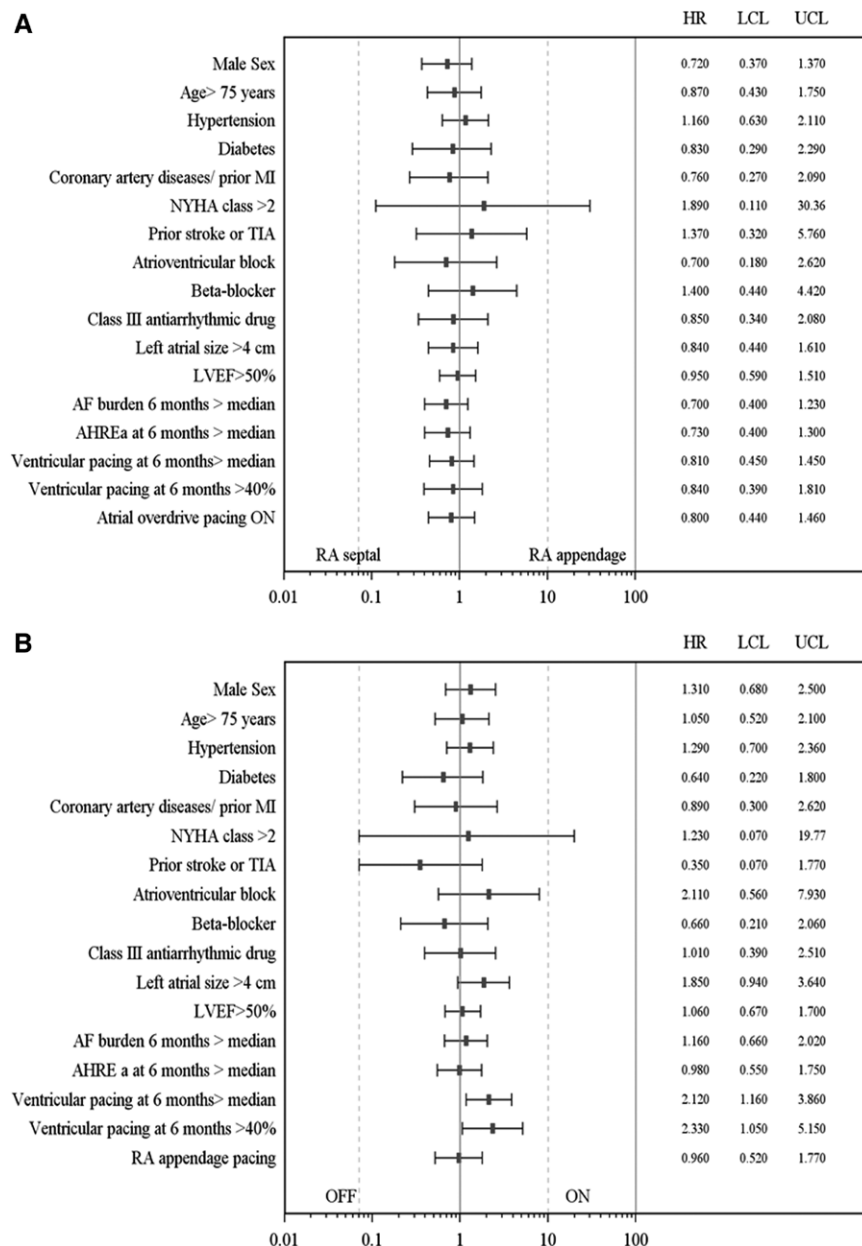


Figure 3. A, Comparison between right atrial (RA) septal vs RA appendage pacing on relative risks for development of persistent atrial fibrillation (AF), according to different subgroups.

B, Comparison between continuous atrial overdrive pacing algorithm ON vs OFF on relative risks for development of persistent AF, according to different subgroups. AHRE indicates atrial high-rate episode; HR, hazard ratio; LCL, lower 95% confidence level; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; TIA, transient ischemic attack; and UCL, upper 95% confidence level.

atrial overdrive pacing provided no incremental benefit to atrial-based pacing with minimized ventricular pacing in preventing the development of persistent AF.

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Disclosures

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CLINICAL PERSPECTIVE

In patients with sick sinus syndrome, the occurrence of atrial fibrillation (AF) after pacemaker implantation is associated with an increased risk of stroke, systemic embolism, heart failure, and mortality. The present study, a single-blinded, 2x2 factorial randomized, multicenter trial in 385 patients with sick sinus syndrome and paroxysmal AF and a 3.1-year follow-up, investigated whether long-term atrial pacing at the right atrial appendage versus the low right atrial septum with or without a continuous atrial overdrive pacing algorithm can prevent the development of persistent AF. Our results showed that neither low right atrial septal pacing to reduce P-wave duration nor the use of continuous atrial overdrive pacing to increase atrial pacing significantly affect the long-term development of persistent AF. No clinical variables could predict any potential benefit of either alternative site pacing or rate on progression to persistent AF. Other secondary end points, including AF burden, atrial high-rate episode >6 minutes, quality of life, and adverse events, were unaffected by the atrial pacing site and rate. In conclusions, among patients with sick sinus syndrome and paroxysmal AF who required pacemaker implantation, the use of an alternative atrial pacing site at the lower right atrial septum or continuous atrial overdrive pacing provided no incremental benefit to atrial-based pacing with minimized ventricular pacing in preventing the development of persistent AF.

Prospective Randomized Study to Assess the Efficacy of Site and Rate of Atrial Pacing on Long-Term Progression of Atrial Fibrillation in Sick Sinus Syndrome: Septal Pacing for Atrial Fibrillation Suppression Evaluation (SAFE) Study

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Supplemental Material

Sample Size Justification

For the sample size calculation, the significance of the effect of atrial pacing site and use of continuous atrial overdrive pacing and their interaction, on the freedom from persistent AF was determined as in the equation:

$$\log\left(\frac{P}{1-P}\right) = \beta_0 + \beta_1 RAA + \beta_2 ON + \beta_3 (RAA * ON)$$

Where P is the probability that $Y = 1$

$Y_i=1$ (Freedom from persistent AF= yes) and $Y_i=0$ (Freedom from persistent AF=no)

β_1 Represents the effect of pacing site on freedom from persistent AF

β_2 Represents the effect of AF Suppression on freedom from persistent AF

β_3 Represents the effect of the interaction term between pacing site and AF Suppression on freedom from persistent AF.

Statistical Analysis Using Logistic Regression

The choice of atrial pacing site and/or the use of continuous atrial overdrive pacing on the development of persistent AF was analysis using a logistic regression model. The effects of all the explanatory variables are expressed in terms of Wald statistics, odds ratios, corresponding confidence intervals and p-values. The effect of each explanatory variable will be considered significant if its p-value <0.05. Chi-square goodness of fit and likelihood ratio tests were used to verify the significance of the logistic regression model.

Post-Hoc power calculation was performed to determine the potential impact of the

dropout of the study population. A Logistic regression, as in the sample size calculation, was used, with 324 observations, and including the effect of pacing site (RA appendage/RA septal) and atrial overdrive pacing (ON/OFF), and interaction between the two factors in the model, at a 5% significance level to detect a change in proportion of patients with Persistent AF from the baseline value of 50% to 25.3%. The R-Squared of 0.004 between factors provides a study power of 87%.

Based on the logistic regression analysis, there were no significant effect of the pacing site (RA appendage/RA septal) ($P=0.72$) or atrial overdrive (ON/OFF) ($P=0.49$) or their interaction ($P=0.43$) in the incidence of persistent AF.

Author Contribution

Dr. Lau and Dr. Tse had full access to all the data in the study and take responsibility for the data integrity of the data and the data analysis.

Study concept and design: Lau; Tachapong; Wang; Kong; Kim; Omar;
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Statistical analysis: Lau; Bailleul; Tse

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Study supervision: Lau; Tachapong; Wang; Kong; Kim; Omar; Sriratanasathavorn;
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Funding/Support

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Role of Sponsor

Data monitoring, project management and data analysis.

Additional Contributions

We gratefully acknowledge the diligent and responsible oversight of the Data Safety Monitoring Board during the execution and analysis of this trial. Yassine El Hahi provided supports on the statistical analysis of the data. We thank the individuals who worked at the core laboratory and the study coordinators in each centers for the data collection.

Supplementary Table 1. Comparison between Different Groups on Atrial Fibrillation (AF) Burden and Atrial High Rate Episodes (AHRE)

	RA Appendage		RA Septum		P Value	
Atrial overdrive algorithm	ON (n=84)	OFF (n=81)	ON (n=74)	OFF (n=90)		
AF burden, % (SD)	7.5 (16.3)	9.1 (19.3)	6.8 (13.3)	7.7 (16.1)	0.73	
AHRE, % (SD) ^a	290.0 (849.5)	712 (2314.2)	458.5 (1018.0)	643.2 (1944.7)	0.43	
	Pacing Site		P Value	Algorithm		P Value
Atrial overdrive algorithm	RA Appendage (n=165)	RA septum (n=163)		ON (n=157)	OFF (n=171)	
AF burden, % (SD)	8.3 (17.8)%	7.3 (14.9)%	0.68	7.2 (14.9)%	8.4 (17.7)%	0.67
AHRE, number (SD) ^a	497.2 (1738.5)	558.0 (1584.5)	0.59	370.6 (934.7)	675.9 (2121.6)	0.82

^a Number of AHRE > 6 minutes

Supplementary Table 2. Comparison between Different Groups on Quality of Life Scores

		RA Appendage		RA Septum		P Value	
SF36 scores, mean (SD)		ON (n=77)	OFF (n=78)	ON (n=76)	OFF (n=77)		
Physical		63.0 (27.0)	66.4 (27.4)	64.7 (24.9)	67.9 (25.1)	0.62	
Mental		66.1 (16.7)	66.5 (18.0)	67.3 (19.4)	65.4 (19.4)	0.88	
	Pacing Site			P Value	Algorithm		P Value
SF36 scores, mean (SD)	RA Appendage (n=155)		RA septum (n=151)		ON (n=153)	OFF (n=153)	
Physical	64.7 (27.1)		66.3 (25.0)	0.27	63.9 (25.9)	67.1 (26.2)	0.49
Mental	66.3 (17.3)		66.3 (19.4)	0.90	66.7 (18.0)	65.9 (18.7)	0.89

Appendix 1

The SAFE Committee members and investigators are as follows:

Steering Committee: Chu-Pak Lau, Hung-Fat Tse, Ruth Kam, You-Ho Kim, Chi-Woon Kong, Muhammad Munawar, Razali Omar, Charn Sriratanasathavorn and Chun-Chieh Wang;

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