ORIGINAL ARTICLE

A Dual-Chamber Leadless Pacemaker

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ABSTRACT

BACKGROUND

Single-chamber ventricular leadless pacemakers do not support atrial pacing or consistent atrioventricular synchrony. A dual-chamber leadless pacemaker system consisting of two devices implanted percutaneously, one in the right atrium and one in the right ventricle, would make leadless pacemaker therapy a treatment option for a wider range of indications.

METHODS

We conducted a prospective, multicenter, single-group study to evaluate the safety and performance of a dual-chamber leadless pacemaker system. Patients with a conventional indication for dual-chamber pacing were eligible for participation. The primary safety end point was freedom from complications (i.e., device- or procedure-related serious adverse events) at 90 days. The first primary performance end point was a combination of adequate atrial capture threshold and sensing amplitude at 3 months. The second primary performance end point was at least 70% atrioventricular synchrony at 3 months while the patient was sitting.

RESULTS

Among the 300 patients enrolled, 190 (63.3%) had sinus-node dysfunction and 100 (33.3%) had atrioventricular block as the primary pacing indication. The implantation procedure was successful (i.e., two functioning leadless pacemakers were implanted and had established implant-to-implant communication) in 295 patients (98.3%). A total of 35 device- or procedure-related serious adverse events occurred in 29 patients. The primary safety end point was met in 271 patients (90.3%; 95% confidence interval [CI], 87.0 to 93.7), which exceeded the performance goal of 78% (P<0.001). The first primary performance end point was met in 90.2% of the patients (95% CI, 86.8 to 93.6), which exceeded the performance goal of 82.5% (P<0.001). The mean (±SD) atrial capture threshold was 0.82±0.70 V, and the mean P-wave amplitude was 3.58±1.88 mV. Of the 21 patients (7%) with a P-wave amplitude of less than 1.0 mV, none required device revision for inadequate sensing. At least 70% atrioventricular synchrony was achieved in 97.3% of the patients (95% CI, 95.4 to 99.3), which exceeded the performance goal of 83% (P<0.001).

CONCLUSIONS

The dual-chamber leadless pacemaker system met the primary safety end point and provided atrial pacing and reliable atrioventricular synchrony for 3 months after implantation. (Funded by Abbott Medical; Aveir DR i2i ClinicalTrials.gov number, NCT05252702.)

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*The Aveir DR i2i Study Investigators are listed in the Supplementary Appendix, available at NEJM.org.

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Conventional pacemakers consist of a surgically implanted pulse generator with transvenous leads. Although effective, these transvenous pacemakers are subject to lead- and pocket-related complications.[1] Self-contained leadless pacemakers were designed to be placed in the right ventricle to mitigate these complications.[2,3] Observational studies of leadless single-chamber right ventricular pacemakers have shown them to have fewer associated complications than transvenous pacemakers.[4-7] However, single-chamber ventricular pacemakers do not provide atrial pacing or consistent atrioventricular synchrony, thus limiting leadless pacemaker therapy to approximately 20% of patients who have an indication for a pacemaker.[8] A ventricular leadless pacemaker with mechanical sensing of atrial contraction can provide imperfect atrioventricular synchrony but does not provide atrial pacing support.[9] The most common indications for a pacemaker, sinus-node dysfunction and heart block, require rate-adaptive atrial pacing and reliable atrioventricular synchronous pacing. To accommodate all pacing indications, a modular dual-chamber leadless pacemaker system with bidirectional communication and a fixation mechanism enabling placement of a right atrial leadless pacemaker was developed and tested in a preclinical model.[10] In this study, we assessed the safety and performance of this dual-chamber leadless pacemaker system in humans.

Methods

Study Design and Oversight

We evaluated the leadless pacemaker system (Aveir, Abbott Medical) in a prospective, international, multicenter, single-group investigation. The primary end-point analyses through 3 months of follow-up for the first 300 enrolled patients in whom implantation was attempted are reported here. The study was approved by relevant regulatory agencies, including the Food and Drug Administration, Technischer Überwachungsverein, and Health Canada, as well as by the institutional review board or ethics committee at each center. An international steering committee designed the study with input from the sponsor (Abbott Medical). An independent data and safety monitoring board oversaw participant safety and study conduct (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

The sponsor collected and monitored the study data and performed analyses in collaboration with the steering committee; several authors had full access to the raw data. The study was performed in accordance with the ethical principles of the Declaration of Helsinki and applicable good clinical practice guidelines and regulations. The sponsor assisted in preparing the submitted manuscript; the first draft was written by three of the authors, one of whom is an employee of the sponsor, and was reviewed and edited by the other authors. The authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol, available at NEJM.org.

Patient Population

After providing written informed consent, enrolled patients who met eligibility criteria underwent implantation of the dual-chamber leadless pacemaker system. Among the inclusion criteria were a standard indication for dual-chamber pacing and an age of at least 18 years.[11,12] Among the exclusion criteria were a mechanical tricuspid-valve prosthesis, inferior vena cava filter, preexisting pacing or defibrillation leads, and electrically active implantable medical devices. A full list of the inclusion and exclusion criteria is provided in the Supplementary Appendix.

Device Implantation

The leadless pacemaker system is a programmable, modular system made up of two devices that provide dual-chamber rate-responsive bradycardia pacing. Each leadless pacemaker is an entirely self-contained, fixed helix device that is delivered percutaneously by catheter through the femoral vein into the target chamber (Fig. 1 and video, available at NEJM.org; additional details are provided in the Supplementary Appendix). The right ventricular leadless pacemaker is physically identical to a commercially available single-chamber leadless pacemaker (Abbott Medical). A dedicated retrieval catheter allows removal and replacement of each leadless pacemaker as necessary. The leadless pacemakers wirelessly communicate bidirectionally on a beat-to-beat basis (implant-to-implant communication), with a series of short pulses delivered through the blood and myocardial tissue after each locally paced or sensed event to maintain atrioventricular synchrony.

A video showing the pacemaker system is available at NEJM.org

In this study, both leadless pacemakers were

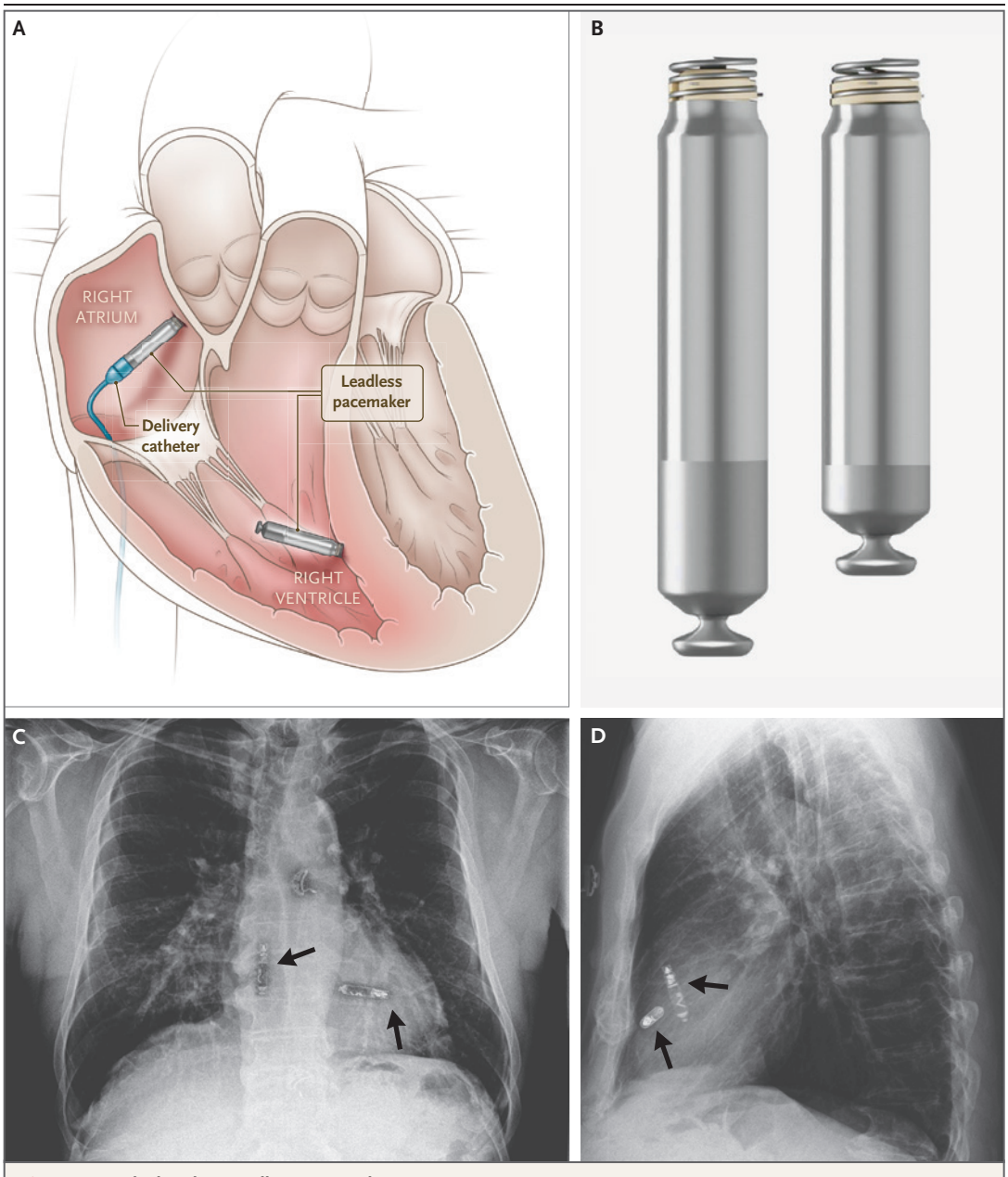


Figure 1. Dual-Chamber Leadless Pacemaker System.

Panel A shows the position of the dual-chamber leadless pacemaker system within the heart. A ventricular leadless pacemaker has already been implanted, and the delivery catheter is in the right atrium to implant the atrial leadless pacemaker. Panel B provides a closer view of the pacemakers. Each leadless pacemaker is 6.5 mm in diameter and affixes to the endocardium through an active fixation helix. The ventricular leadless pacemaker measures 38 mm in length and has a target site for implantation in the lower to mid-septal area of the right ventricle. The atrial leadless pacemaker measures 32.2 mm in length and has a target site at the base of the right atrial appendage. Panels C and D show chest radiographs of a patient with the leadless pacemaker system implanted in posteroanterior (Panel C) and lateral (Panel D) views. Images are contrast-enhanced to highlight the leadless pacemakers. The arrows indicate the locations of the devices.

implanted in a single procedure to provide dual-chamber pacing. Fluoroscopy was required for all procedures, contrast injection in the chambers was recommended, and the use of intracardiac echocardiography to assist with guiding implantation was optional.

SAFETY AND PERFORMANCE END POINTS

The primary safety end point was freedom from complications (i.e., device- or procedure-related serious adverse events) through 90 days after implantation. All adverse events were adjudicated by an independent clinical events committee (see the Supplementary Appendix).

The first primary performance end point was a combination of adequate atrial capture threshold (≤3.0 V at 0.4 msec) and atrial sensing amplitude (P wave of ≥1.0 mV) at the 3-month visit. The electrical performance of the right ventricular leadless pacemaker had previously met an analogous performance end point.[4] The second primary performance end point was atrioventricular synchrony success at the 3-month visit, defined as a paced or sensed ventricular beat within 300 msec of a paced or sensed atrial beat in 70% or more of the cardiac cycles that could be evaluated during a 5-minute seated recording. Secondary safety and performance end points, which were formulated to support regulatory approval of a single-chamber atrial pacemaker, are described in the Supplementary Appendix.

STATISTICAL ANALYSIS

We calculated that a sample of 300 patients would provide 90% power at a one-sided 2.5% significance level to determine whether the primary end points met the predetermined performance goals for safety and performance, accounting for attrition through 3 months. It was prespecified that all three primary end points were required to meet the criteria for study success, and the secondary end-point hypothesis tests were only to be evaluated, through a hierarchical testing procedure, if the primary end points were met. An adaptive design for sample-size reestimation was used to confirm the assumptions used in the sample-size calculations. The adaptive design included one preplanned interim analysis to be conducted when approximately 150 patients had completed their 3-month follow-up visits (see the Supplementary Appendix). The interim analysis supported the originally planned sample size.

For the primary safety end point, we assumed that 85% of the patients would be free from complications; the performance goal of 78% was based on published data on transvenous pacemaker complications.[1] We assumed that the atrial electrical performance end point would be met in 89.5% of the patients; the performance goal of 82.5% was based on two previous studies of single-chamber leadless pacemakers.[3,4] Finally, we assumed that the atrioventricular synchrony performance end point would be met in 90% of the patients; the performance goal of 83% was based on a previous study evaluating atrioventricular synchrony in a ventricular leadless pacemaker (see the Supplementary Appendix).[13]

For the primary safety end point, the P value was calculated with the use of the one-sided z-test and an alpha level of 0.025. Patients who withdrew from the study or died before the entry window of the 3-month follow-up visit without having a complication were excluded. Both performance end points were evaluated within the prespecified population in whom both leadless pacemakers were implanted (with or without adequate implant-to-implant communication). Implantation procedures that did not result in both leadless pacemakers being implanted were imputed as failures. A multiple imputation method based on a fully conditional specification method with the use of logistic regression was used to handle missing data for both performance end points because it reflected the uncertainty about the values to impute. Statistical analyses were performed with SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENT AND PROCEDURAL CHARACTERISTICS

From February through August 2022, a total of 300 enrolled patients underwent an implantation attempt across 55 centers in the United States, Canada, and Europe (Fig. S1 in the Supplementary Appendix). The devices were implanted by 82 different physicians (range, 1 to 25 implants per physician). The baseline and procedural char-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Full Analysis Population (N=300)
Sex — no. (%)	
Male	187 (62.3)
Female	113 (37.7)
Age — yr	69.2±13.5
Height — cm	171.6±10.1
Weight — kg	82.9±19.1
Body-mass index†	28.1±5.6
Race or ethnic group — no. (%)‡	
American Indian or Alaska Native	1 (0.3)
Asian	5 (1.7)
Black	6 (2.0)
White	200 (66.7)
Declined or unable to disclose	89 (29.7)
Geographic region of enrolling center — no. (%)	
United States	184 (61.3)
Europe	89 (29.7)
Canada	27 (9.0)
Primary pacemaker indication — no. (%)	
Sinus-node dysfunction	190 (63.3)
Atrioventricular block	100 (33.3)
Conduction disorder with 1:1 atrioventricular conduction	4 (1.3)
Vasovagal (reflex) syncope	6 (2.0)
Previous ablation — no. (%)	60 (20.0)
Tricuspid-valve disease — no. (%)	
Insufficiency, prolapse, or regurgitation	72 (24.0)
Repair or replacement	3 (1.0)
Arrhythmia history — no. (%)	
Ventricular	13 (4.3)
Nonventricular or supraventricular	135 (45.0)
Previous extractions — no. (%)	
Transvenous lead extraction	24 (8.0)
Leadless pacemaker extraction	2 (0.7)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Data on race and ethnic group were reported by the patients. Patients could select more than one category, and the sum of the numbers may exceed 300. The "Declined or unable to disclose" category represents data from European centers only, where race and ethnic group could not be reported because of local data privacy regulations. Data on race and ethnic group were reported by all other centers.

acteristics of the study population are shown in Tables 1 and 2 and Table S1; the patients' representativeness of the general population is shown in Table S2. Cardiac medication use at baseline and at 3 months is shown in Table S3. The most common indications for dual-chamber pacemaker implantation were sinus-node dysfunction (190 patients [63.3%]) and atrioventricular block (100 patients [33.3%]). Overall, 20.0% of the study population had previously undergone an ablation procedure, and 8.7% had undergone previous extraction of a transvenous lead or leadless pacemaker.

A successful procedure (i.e., implantation of two functioning leadless pacemakers with established implant-to-implant communication) was performed in 295 of 300 patients (98.3%); the atrial leadless pacemaker was not implanted in 2 patients, and 3 patients had inadequate implant-to-implant communication. The mean (±SD) procedural and fluoroscopy times were 86.3±36.5 and 18.3±10.7 minutes, respectively. The mean duration of the hospital stay after pacemaker implantation was 1.0±1.2 days. Intraprocedural repositioning of the atrial device was required in 72 patients (24.2%); in 31 patients (10.4%), more than one intraprocedural repositioning of the atrial device was needed. Intraprocedural repositioning of the ventricular device was required in 40 patients (13.4%); in 6 patients (2.0%), more than one intraprocedural repositioning of the ventricular device was needed.

DEVICE SAFETY

Thirty-five complications (i.e., device- or procedure-related serious adverse events) occurred in 29 patients within 90 days after implantation (Table 3). A total of 271 patients were free from complications (90.3%; 95% confidence interval [CI], 87.0 to 93.7); the one-sided 97.5% lower confidence boundary exceeded the performance goal of 78% (P<0.001).

Twenty-eight complications (80% of the total complications) occurred within 2 days after implantation (Fig. S2). Atrial fibrillation developed in 9 patients, 5 of whom had a history of atrial arrhythmias. Atrial fibrillation occurred during or immediately after implantation of the atrial leadless pacemaker in 8 patients; all 8 patients underwent successful electrical or pharmacologic

cardioversion. Two serious cardiac injury events — pericardial effusion related to the atrial leadless pacemaker — occurred in 2 patients (0.7%); in one patient it was treated with pericardiocentesis, and in the other it was managed conservatively.

Six intraprocedural dislodgements of a leadless pacemaker (5 atrial and 1 ventricular) occurred in 5 patients; in 2 cases, the pacemaker migrated outside the chamber into which it had been implanted — one into the pulmonary artery and the other through a suspected patent foramen ovale into the left ventricle. Five dislodgements were related to inadequate fixation, and in one case the pacemaker was mechanically dislodged by an intracardiac echocardiography catheter. In all cases, the dislodged leadless pacemaker was retrieved successfully and reimplanted during the initial procedure. Five atrial leadless pacemaker dislodgements (in 5 patients) occurred after the implantation procedure and were identified at a mean of 26±17 days after implantation (range, 0 to 40); these devices were retrieved percutaneously. In 4 of these 5 cases, the pacemaker migrated outside the right atrium to either the right ventricle (3 cases) or the right pulmonary artery (1 case). Investigators elected to reimplant another atrial leadless pacemaker in 3 of these patients. Leadless pacemakers implanted in the middle or distal right atrial appendage were associated with a numerically higher percentage of patients with postprocedural dislodgement than those implanted in other locations (3 of 68 [4%] and 2 of 232 [1%], respectively), a finding that reinforces previous guidance to preferentially target the ostium of the appendage in order to optimize implant-to-implant communication (Figs. S3 and S4).

Four deaths occurred during follow-up, between 46 and 86 days after implantation; the mean age of the four patients was 74±10 years (range, 62 to 84). Two deaths occurred after cardiac arrest; one was related to a malignant tumor and the other to sepsis (narratives are provided in the Supplementary Appendix). None of the deaths were considered to be device- or procedure-related, including the two deaths from cardiac arrest. Neither patient who died from cardiac arrest was pacemaker-dependent, and neither bradycardia nor device malfunction was reported from the sites preceding the deaths.

Table 2. Procedural Characteristics.*

Characteristic	Population with Pacemakers Implanted (N=298)†
Time from sheath insertion to removal — min	86.3±36.5
Time from delivery catheter insertion to removal — min	70.9±30.5
Ventricular leadless pacemaker	24.0±16.2
Atrial leadless pacemaker	40.2±22.6
Total fluoroscopic duration — min‡	18.3±10.7
Length of hospital stay — days	1.0±1.2
Atrial leadless pacemaker repositioning — no. (%)	
None	226 (75.8)
1	41 (13.8)
>1	31 (10.4)
Ventricular leadless pacemaker repositioning — no. (%)	
None	258 (86.6)
1	34 (11.4)
>1	6 (2.0)
Final leadless pacemaker placement in the right atrium — no. (%)	
RAA medial antral	140 (47.0)
RAA saccular	54 (18.1)
RAA lateral antral	42 (14.1)
RA lateral wall	32 (10.7)
RAA distal saccular	14 (4.7)
RA posterior wall	5 (1.7)
RA septum	2 (0.7)
Other	9 (3.0)
Final leadless pacemaker placement in the right ventricle — no. (%)	
RV apical septum	165 (55.4)
RV mid septum	101 (33.9)
RV apex	21 (7.0)
RV anterolateral free wall	3 (1.0)
RV inferior or diaphragmatic wall	1 (0.3)
Other	7 (2.3)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. RA denotes right atrium, RAA right atrial appendage, and RV right ventricle.
† This population includes the patients who had atrial and ventricular leadless pacemakers implanted (with or without adequate implant-to-implant communication).
‡ Data were missing for 1 patient.

Table 3. Complications within 90 Days.*

Event†	Population with Attempted Implantation (N=300)‡	
	No. of Events	No. of Patients with an Event (%)
Cardiac arrhythmia	10	10 (3.3)
Atrial fibrillation	9	9 (3.0)
Transient complete atrioventricular block	1	1 (0.3)
Intermittent or complete loss of implant-to-implant communication	1	1 (0.3)
Intraprocedural dislodgement	6	5 (1.7)
Due to inadequate fixation	5	4 (1.3)
Due to mechanical dislodgement§	1	1 (0.3)
Postprocedural dislodgement¶	5	5 (1.7)
Urinary retention	3	3 (1.0)
Pericardial effusion	2	2 (0.7)
Treated with percutaneous pericardiocentesis	1	1 (0.3)
Managed conservatively	1	1 (0.3)
Capture threshold issues	2	2 (0.7)
Threshold elevation in the atrial leadless pacemaker	1	1 (0.3)
Intermittent capture in the ventricular leadless pacemaker	1	1 (0.3)
Access site bleeding	1	1 (0.3)
Retroperitoneal hematoma	1	1 (0.3)
Syncope‖	1	1 (0.3)
Heart failure	1	1 (0.3)
Oral pain**	1	1 (0.3)
Pleural effusion	1	1 (0.3)
Total	35	29 (9.7)

* Complications were defined as device- or procedure-related serious adverse events. Events were classified as device- or procedure-related if they were considered by the clinical events committee to be possibly, probably, or causally related to any investigational device or procedure. Some patients had more than one event, and therefore the number of patients is smaller than the number of events.

† One pulmonary embolism that occurred 28 days after implantation was excluded from the primary safety end-point analysis per protocol because it was related to coronavirus disease 2019, but the event occurred in one of the 29 patients who had an adverse event.

‡ Attempted implantation was defined as a procedure in which the introducer sheath or dilator was inserted through the skin of the access site.

§ The atrial leadless pacemaker was mechanically dislodged by manipulation of an intracardiac echocardiography catheter during the implantation procedure.

¶ All dislodgements after the implantation procedure were dislodgements of atrial leadless pacemakers. The count excludes 1 additional atrial leadless pacemaker mechanical dislodgement that occurred during a coronary artery bypass surgery that was not related to the study. The device was successfully retrieved, and the event was not considered to be device- or procedure-related by the clinical events committee.

‖ Syncope resulted in fracture of the patient's right distal phalanx.

** Oral pain after the procedure, possibly a result of oral instrumentation associated with anesthesia, led to tooth extraction.

Serious adverse events not related to the device occurred within 90 days in 11.7% of the patients (Table S4 in the Supplementary Appendix).

SYSTEM REVISIONS

Within 90 days after implantation, eight revision procedures were performed: all eight involved successful percutaneous retrieval, and in six new leadless pacemakers were implanted successfully. Two patients did not receive a replacement atrial leadless pacemaker at the discretion of the investigator. The indications for these eight revisions were atrial dislodgement (in six cases), suboptimal implant-to-implant

communication (one case), and intermittent ventricular capture (one case).

ATRIAL LEADLESS PACEMAKER ELECTRICAL PERFORMANCE

Among the 300 patients, 299 were evaluated for the first primary performance end point, a combination of adequate atrial capture threshold and atrial sensing amplitude. One patient was excluded because the 3-month sensing amplitude and capture threshold were unmeasurable as a result of atrial tachyarrhythmia. Data for 2 patients in whom the atrial device was not implanted were imputed as failures. Measurable 3-month data were available for 290 patients; 7 patients had missing data, for which a multiple imputation method was used.

Success with respect to the first primary performance end point occurred in 90.2% of the patients (95% CI, 86.8 to 93.6); the one-sided 97.5% lower confidence boundary exceeded the performance goal of 82.5% (P<0.001), thereby meeting the first performance end point. The mean atrial pacing capture threshold (at 0.4 msec) was 0.82±0.70 V, and the mean P-wave amplitude was 3.58±1.88 mV (electrical measurements through 3 months are provided in Figs. S5 and S6).

The reasons for failure to meet this performance criterion included inadequate pacing threshold (in 6 patients) and inadequate P-wave amplitudes (in 22 patients). In 1 patient, failure with respect to both the capture threshold and the sensing criteria occurred. System revision within 90 days after implantation was not required in any of the 6 patients with an elevated atrial capture threshold. The capture and sensing performance of the ventricular leadless pacemaker was evaluated at 6 weeks in a previous study, and pacing threshold failure was found in 2% of patients.[4]

Among the 22 patients with sensing criteria failure, 21 had a measured P-wave amplitude of less than 1.0 mV, and 1 patient had undetectable P waves despite an absence of atrial tachyarrhythmia. Sensing failure for the atrial leadless pacemaker had occurred in 22 of 290 patients (7.6%) at 3 months; in a historical study, sensing failure for the ventricular leadless pacemaker had occurred and in 4 of 196 patients (2.0%) at 6 weeks.[4] System revision as a result of inadequate atrial sensing was not required in any patient. The results of sensitivity analyses and other additional analyses are provided in the Supplementary Appendix.

ATRIOVENTRICULAR SYNCHRONY PERFORMANCE

Among the 300 patients, 294 were evaluated for the second primary performance end point, a measure of atrioventricular synchrony performance. Six patients were excluded because of a lack of data that could be evaluated. Data from 2 patients in whom the atrial device was not implanted were imputed as failures. Measurable atrioventricular synchrony data were available for 277 patients; 15 patients had missing data, for which a multiple imputation method was used.

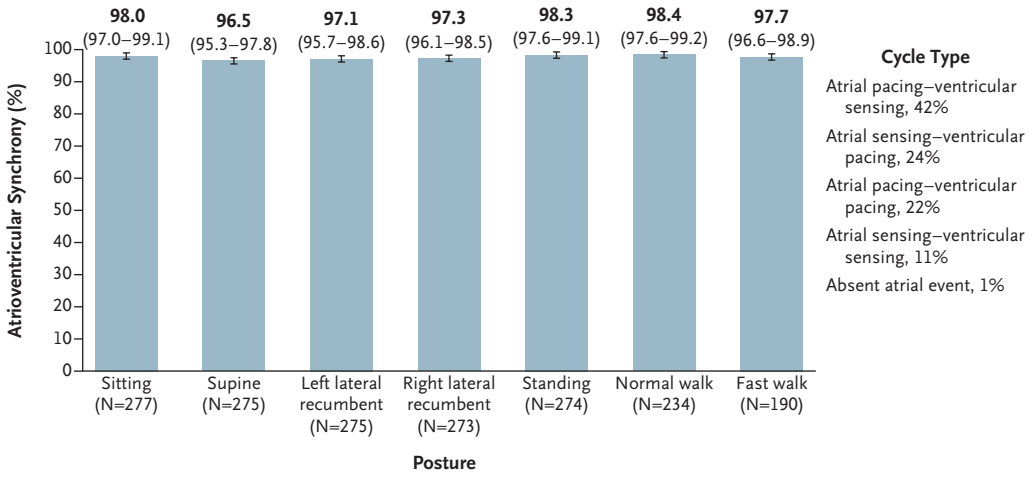
At least 70% atrioventricular synchrony was found in 97.3% (95% CI, 95.4 to 99.3) of the patients; the one-sided 97.5% lower confidence boundary exceeded the performance goal of 83% (P<0.001), thereby meeting the second performance end point. When all cardiac cycles that could be evaluated were considered across multiple postures and gaits, the mean atrioventricular synchrony percentage remained above 95%; the analyzed cycles were predominantly cycles with pacing in at least one chamber (Fig. 2; see Fig. S7 for patients with high ventricular pacing burden).

DISCUSSION

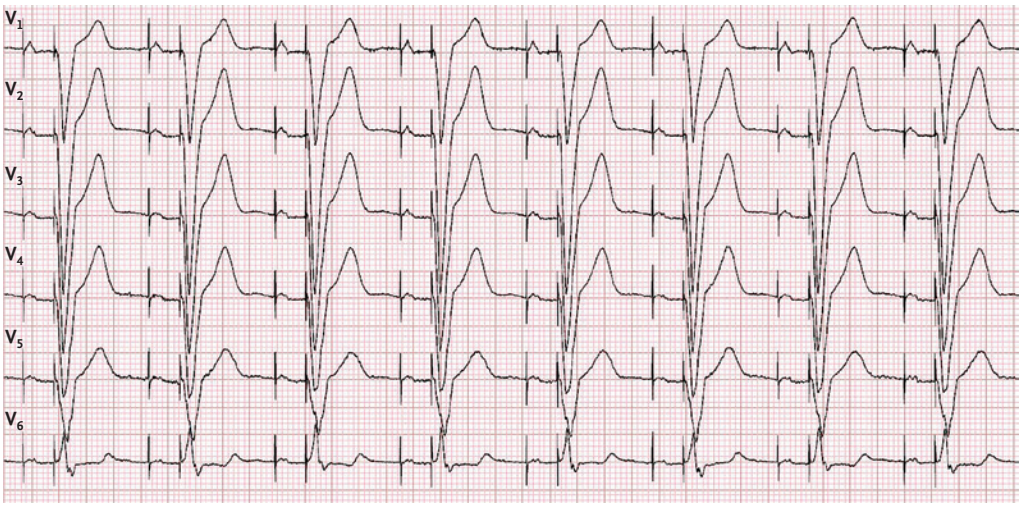
In this international, multicenter, single-group study, the safety and performance of a dual-chamber leadless pacemaker system was studied in a prospective population of 300 patients. The implantation procedure was successful in 295 patients (98.3%), and 3-month safety and performance results exceeded the prespecified boundaries for success, with the results for all three meeting the criteria for significance. In the analysis of the primary safety end point, 90.3% of the patients (95% CI, 87.0 to 93.7) were free from device- or procedure-related serious adverse events at 90 days after implantation. In the analysis of the primary performance end point, atrial capture threshold and sensing amplitude were adequate in 90.2% of the patients (95% CI, 86.8 to 93.6) at 3 months. No patients required system revision due to inadequate atrial sensing. In the analysis of the second primary performance end point at least 70% atrioventricular synchrony was achieved in 97.3% of the patients (95% CI, 95.4 to 99.3). Overall atrioventricular synchrony exceeded 95% when all cycles that could be evaluated were considered.

This modular dual-chamber pacing system requires the implantation of two separate active-fixation leadless pacemakers in the ventricle and

A Mean Atrioventricular Synchrony



B Surface Electrocardiogram



C Freeze Capture (sweep speed, 25 mm/sec)

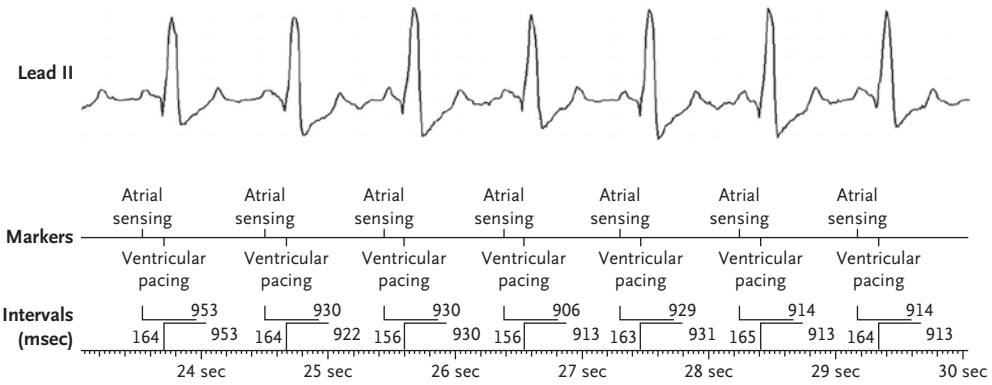


Figure 2 (facing page). Atrioventricular Synchrony.
Panel A shows the mean percentages of atrioventricular synchrony during various postures assumed by the patient at the 3-month visit. I bars indicate 95% confidence intervals; the widths of the confidence intervals have not been adjusted for multiplicity and therefore should not be used in place of a hypothesis test. The distribution of cycle types that could be evaluated are aggregated across all postures, with 88.7% of all cycles containing either an atrial paced beat or a ventricular paced beat. An absent atrial event is defined as an absence of a detectable P wave or atrial pacing spike. Panel B is a patient's surface electrocardiogram recorded with the use of a Holter monitor while the patient was sitting, showing active atrial and ventricular pacing with the leadless pacemaker system during the atrioventricular synchrony assessment at the 3-month follow-up visit. Panel C is a different patient's rhythm strip as recorded by the system programmer, showing atrial sensing with synchronous ventricular pacing during a follow-up device interrogation. For the intervals shown in Panel C, the top number indicates the interval between two consecutive atrial events, the bottom left number the interval between a sensed or paced atrial event and the next sensed or paced ventricular event, and the bottom right number the interval between two consecutive ventricular events.

atrium, potentially increasing procedural risk. Before this first-in-human experience, safety and performance data for an atrial leadless pacemaker were lacking. In this study, no procedure- or device-related deaths occurred. The incidence of acute complications was similar to that observed in studies of transvenous dual-chamber pacemakers.[1,14,15] In our study, serious cardiac injury (pericardial effusion) occurred in 0.7% of the patients, which compares favorably to both the 0.8% incidence (range, 0 to 6.4) of perforation in a recent meta-analysis of transvenous pacemaker studies and the 1.5% incidence of perforation in the initial single-chamber leadless pacemaker trials.[2,3,16] Although this dual-chamber system requires implantation of two devices, the low percentage of patients with perforation in our study most likely stems in part from the selection of investigators who had substantial experience with leadless pacemaker implantation and rigorous prestudy training. We observed a higher-than-expected incidence of dislodgement during and after the implantation procedure: 1.7% for each, as compared with the 1.1% in the initial trial of the ventricular leadless pacemaker, 0.11% in real-world experience with ventricular leadless pacemakers, and 1.9% for atrial lead dislocation within 2 months in real-world experience with transvenous pacemakers.[1,2,17] In our study, all dislodgements that occurred after the procedure was complete occurred with the atrial leadless pacemaker, and these devices were successfully retrieved. Limited data suggest that avoiding a deep atrial appendage location may reduce the incidence of dislodgement, but further study is needed.

Atrial fibrillation was the most common periprocedural complication; nine patients (3.0%) had this complication, which was treated with medications and cardioversion; five of these patients had a history of atrial arrhythmia. In eight of these patients, atrial fibrillation occurred during the procedure. Periprocedural atrial arrhythmias often occur after conventional pacemaker implantation because of the arrhythmogenic mechanical effects of atrial leads.[18,19] The inclusion of arrhythmias as a safety end point increased the overall incidence of complications as compared with other studies of leadless pacemakers, which excluded arrhythmias from the end point. The electrical performance of both the atrial and ventricular leadless pacemakers appears to be similar to that of transvenous dual-chamber pacemakers.[20-22]

Beat-to-beat wireless bidirectional communication is key to dual-chamber leadless pacemaker technology. The atrioventricular synchrony end point was successfully achieved in 98.2% of the patients. Moreover, the mean atrioventricular synchrony was high (at least 95%) in each posture evaluated, including fast walking, which suggested excellent dual chamber sensing, pacing, and rate response with activity and elevated heart rates (Fig. 2). There is a commercially available single-chamber ventricular leadless pacemaker that uses a mechanical sensor to indirectly sense atrial contraction and trigger ventricular pacing. However, the percentage of atrioventricular synchrony was reported as 89% during supine or sitting resting conditions and as 73 to 75% under ambulatory conditions with higher heart rates.[13] Moreover, this leadless pacemaker is incapable of atrial pacing, rendering it inappropriate for patients with sinus-node dysfunction.

Eliminating transvenous leads and the gen-

erator pocket reduces the long-term risk of infection and lead malfunction that affects one in six patients during 3 years of follow-up.[23] Wireless communication enables modular device therapy, in which components can be implanted as needed. The leadless pacemaker platform can be used as a single device for atrial-only or ventricular-only pacing indications or can be combined as an atrioventricular-synchronous system.

Our study is limited by its single-group nature, which precluded a direct comparison of its safety and performance with those of conventional transvenous pacemakers. Second, the use of multiple imputation to address missing performance data does not adequately account for competing risks such as death. In addition, only short-term follow-up data are reported, thus limiting our current understanding of longer-term safety and projected battery-longevity data (Table S5). From a safety perspective, however, previous studies of leadless pacemakers have suggested that after the early follow-up period, long-term complications are rare.[17] Data on race and ethnic group were also not collected from patients enrolled at European centers because of local data privacy regulations. Data on pacemaker dependency status were not collected prospectively. Finally, ambulatory atrioventricular synchrony data outside the clinical environment are needed.

In this study, a leadless dual-chamber pacemaker with bidirectional wireless communication met the primary safety and performance end points at 3 months in patients with standard indications for dual-chamber pacing.

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