ORIGINAL ARTICLE

Percutaneous Implantation of an Entirely Intracardiac Leadless Pacemaker

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ABSTRACT

BACKGROUND

Cardiac pacemakers are limited by device-related complications, notably infection and problems related to pacemaker leads. We studied a miniaturized, fully self-contained leadless pacemaker that is nonsurgically implanted in the right ventricle with the use of a catheter.

METHODS

In this multicenter study, we implanted an active-fixation leadless cardiac pacemaker in patients who required permanent single-chamber ventricular pacing. The primary efficacy end point was both an acceptable pacing threshold (≤2.0 V at 0.4 msec) and an acceptable sensing amplitude (R wave ≥5.0 mV, or a value equal to or greater than the value at implantation) through 6 months. The primary safety end point was freedom from device-related serious adverse events through 6 months. In this ongoing study, the prespecified analysis of the primary end points was performed on data from the first 300 patients who completed 6 months of follow-up (primary cohort). The rates of the efficacy end point and safety end point were compared with performance goals (based on historical data) of 85% and 86%, respectively. Additional outcomes were assessed in all 526 patients who were enrolled as of June 2015 (the total cohort).

RESULTS

The leadless pacemaker was successfully implanted in 504 of the 526 patients in the total cohort (95.8%). The intention-to-treat primary efficacy end point was met in 270 of the 300 patients in the primary cohort (90.0%; 95% confidence interval [CI], 86.0 to 93.2, P=0.007), and the primary safety end point was met in 280 of the 300 patients (93.3%; 95% CI, 89.9 to 95.9; P<0.001). At 6 months, device-related serious adverse events were observed in 6.7% of the patients; events included device dislodgement with percutaneous retrieval (in 1.7%), cardiac perforation (in 1.3%), and pacing-threshold elevation requiring percutaneous retrieval and device replacement (in 1.3%).

CONCLUSIONS

The leadless cardiac pacemaker met prespecified pacing and sensing requirements in the large majority of patients. Device-related serious adverse events occurred in approximately 1 in 15 patients. (Funded by St. Jude Medical; LEADLESS II ClinicalTrials.gov number, NCT02030418.)

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Each year, nearly 1 million persons worldwide receive conventional transvenous cardiac pacemakers with active-fixation leads to treat bradycardia and heart block.[1,2] Despite considerable technological advancements since the clinical introduction of these pacemakers six decades ago, pacemaker-related adverse events occur in 1 in 10 patients.[3-11] These events are typically related to the transvenous lead, surgical pocket, or pulse generator.[3,4] The leads are susceptible to dislodgement, fracture, or insulation failure and can also cause infection, cardiac perforation, venous occlusion, and tricuspid regurgitation. Pulse generators have been associated with infection, pocket hematoma, and skin erosion.[3-9,12]

A recently developed device is a fully self-contained, leadless cardiac pacemaker with combined battery, electronics, and electrodes.[13,14] Encapsulated into a small unit (1.0 cc) and deliverable with the use of a catheter through the femoral vein, the leadless cardiac pacemaker is nonsurgically implanted directly within the right ventricle, thereby obviating repetitive lead flexion and potential lead damage with each cardiac cycle. Eliminating the device pocket and transvenous lead also potentially minimizes some long-term complications observed with conventional pacemakers, such as tricuspid valvular regurgitation and thromboembolism across a patent foramen ovale.[15] Feasibility of the leadless cardiac pacemaker in humans was shown in the LEADLESS trial.[13] We now report the outcomes of the LEADLESS II study, a nonrandomized trial examining the clinical safety and efficacy of nonsurgical implantation of the Nanostim leadless cardiac pacemaker in patients who require permanent ventricular pacing.

Methods

Study Design and Oversight

The LEADLESS II trial is a prospective, nonrandomized, multicenter clinical study. The trial is currently ongoing and enrolling patients. The planned interim analysis, reported here, includes the primary analysis of efficacy and safety in the initial 300 patients who were followed for 6 months (the primary cohort) and outcomes for all 526 patients who were enrolled as of June 2015 (the total cohort).

This premarket study was sponsored by the manufacturer of the Nanostim leadless cardiac pacemaker (St. Jude Medical) and was approved by the Food and Drug Administration and the institutional review board at each participating center. An international steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org), with the participation of the sponsor, was responsible for the design and conduct of the study and the reporting of the findings. Monitoring and collection of the data and initial data analyses were performed by the sponsor in partnership with the steering committee. All the authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of this report to the study protocol, available at NEJM.org. The first and last authors wrote the first draft of the manuscript, which was reviewed and edited by the other authors. The sponsor reviewed the manuscript before submission but was not involved in the writing of the manuscript or in the decision to submit it for publication.

Study Participants

After obtaining written informed consent, we enrolled patients with indications for permanent single-chamber ventricular pacing, including chronic atrial fibrillation with atrioventricular or bifascicular bundle-branch block, sinus rhythm with second-degree or third-degree atrioventricular block and a low level of physical activity or a shortened expected life span, or sinus bradycardia with infrequent pauses or unexplained syncope with an abnormal electrophysiological study. Patients were excluded if they had a mechanical tricuspid-valve prosthesis, pulmonary arterial hypertension, preexisting endocardial pacing or defibrillation leads, or an inferior vena cava filter or if they had undergone cardiovascular or peripheral vascular surgery within 30 days before enrollment (see the Supplementary Appendix for a full list of inclusion and exclusion criteria).

Device Implantation and Follow-up

The leadless cardiac pacemaker that we evaluated (Nanostim LP, St. Jude Medical) is an entirely self-contained, active-fixation, rate-adaptive pacemaker that is 42 mm in length and has a maximum diameter of 5.99 mm (Fig. 1). The pacemaker is delivered to the right ventricle at the end of a

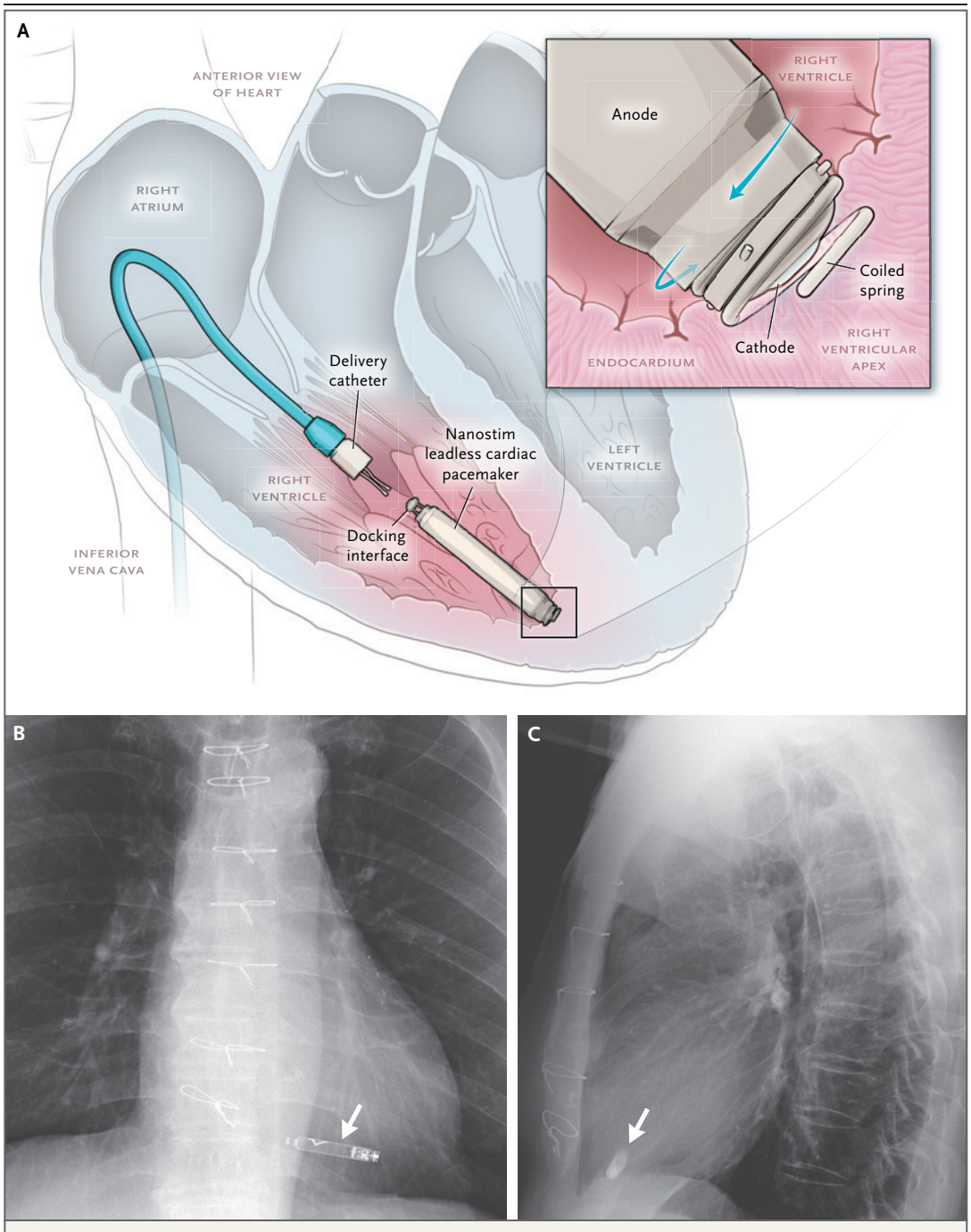

Figure 1. The Leadless Cardiac Pacemaker.

The Nanostim leadless cardiac pacemaker is shown attached to the right ventricular apex (Panel A). The cathode is in the center of the coiled spring, which affixes the device to the endocardium. The anode of the pacemaker is the uncoated part of the titanium case. The proximal portion of the device has a docking interface that enables attachment to the delivery and retrieval catheters. Chest radiographs of a patient who underwent implantation of this leadless cardiac pacemaker are shown in the posteroanterior (Panel B) and lateral (Panel C) projections. The arrows indicate the location of the device, which is situated in the region of the distal right ventricular septum and right ventricular apex.

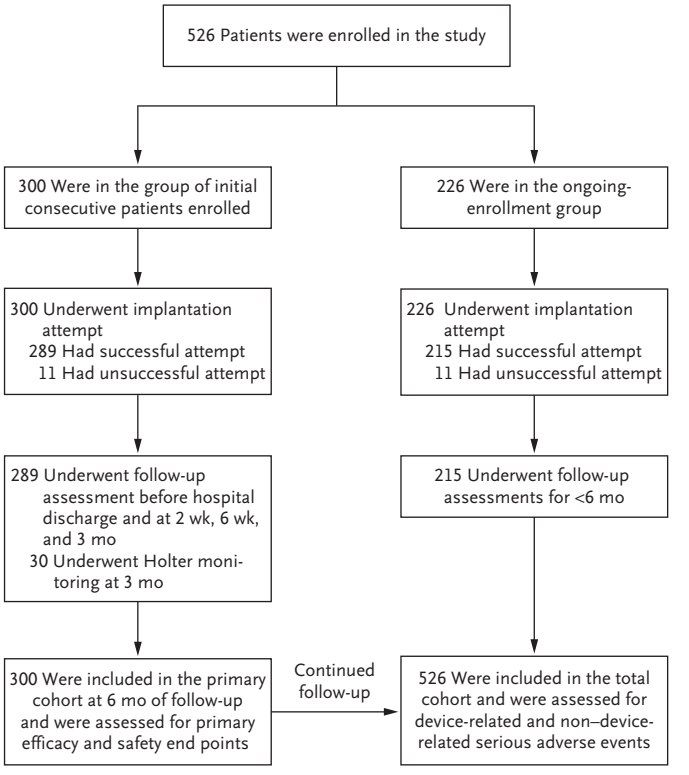

Figure 2. Enrollment, Study Intervention, and Follow-up.

The first 300 enrolled patients made up the primary cohort; data from these patients were analyzed for the primary efficacy and safety end points at 6 months, as prespecified in the protocol. An additional 226 patients were enrolled as part of the ongoing trial; data from these patients were analyzed together with data from the primary cohort that had extended follow-up beyond 6 months. This total cohort of 526 patients was assessed for device-related and non–device-related serious adverse events.

percutaneous delivery catheter and is anchored in the right ventricular apex with the use of a helical screw-in fixation electrode at the distal end of the device. Further details regarding this pacemaker and its implantation technique are provided in Video 1, and in Figure S1 in the Supplementary Appendix.

A video showing the leadless cardiac pacemaker is available at NEJM.org

After the device was implanted and before the patient was discharged from the hospital, the pacemaker was interrogated and the patient underwent chest radiography and standard 12-lead electrocardiography. Subsequent follow-up assessments were performed at 2 weeks, 6 weeks, 3 months, 6 months, and every 6 months thereafter. The programming of the pacemaker was left to the physician's discretion.

PRIMARY EFFICACY AND SAFETY END POINTS

The primary outcome analysis was a prespecified assessment of the primary efficacy and safety end points in the first 300 patients who were followed for 6 months (primary cohort) (Fig. 2). The composite primary efficacy end point was both a therapeutically acceptable pacing capture threshold (≤2.0 V at 0.4 msec) and a therapeutically acceptable sensing amplitude (R wave ≥5.0 mV, or a value equal to or greater than the value at implantation) through 6 months. The primary safety end point was freedom from device-related serious adverse events during the initial 6 months after implantation.

All adverse events were adjudicated by an independent clinical-events committee (see the Supplementary Appendix). A serious adverse event was defined as any untoward medical occurrence that led to death or to a serious deterioration in the health of a patient that resulted in life-threatening illness or injury, permanent impairment of a body structure or a body function, inpatient or prolonged hospitalization, or a medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. Serious adverse events were classified as device-related if they were considered by the clinical-events committee to be attributable to the investigational device or procedure.

SECONDARY OUTCOMES

The primary cohort was also evaluated for all non–device-related serious adverse events during 6 months of follow-up. Such events were considered to be unrelated to the investigational device or procedure. Because the LEADLESS II trial is ongoing, secondary analyses were performed on data from additional patients who were enrolled as of June 2015, combined with data from the first 300 patients, who had extended follow-up beyond 6 months (total cohort) (Fig. 2). Additional analyses in the total cohort included determination of all device-related and non–device-related serious adverse events during follow-up and the influence of operator experience.

STATISTICAL ANALYSIS

We estimated that if 300 patients were followed for 6 months, the study would have 90% power, at a two-sided 5.0% significance level, to show

rates of safety and efficacy that would be superior to predetermined performance goals for safety and efficacy. The performance goal for the primary efficacy end point of both a therapeutically acceptable pacing capture threshold and a therapeutically acceptable sensing amplitude through 6 months was 85%, and the study was powered under the assumption that the rate of this end point would be 91.5% or higher. The performance goal for efficacy was based on an ongoing pacemaker study (ClinicalTrials.gov number, NCT01576016) that is sponsored by St. Jude Medical. The performance goal for the primary safety end point of freedom from device-related serious adverse events through 6 months was 86%, and the study was powered under the assumption that the event-free rate would be 92%. (See the Supplementary Appendix for explanation of the performance goals.)

All the analyses were conducted with the use of exact confidence intervals for binomial proportions. The null hypotheses would be rejected if the lower boundaries of the two-sided 95% confidence intervals for the rate of the primary safety and efficacy end points would be greater than the respective performance goals. The primary safety and efficacy end points were assessed in the intention-to-treat population, which included the first 300 patients (primary cohort) who met the enrollment criteria and provided written informed consent and in whom the implantation of a leadless cardiac pacemaker was attempted. The primary efficacy end point was also analyzed in the subgroup of patients in whom implantation was successful. Statistical calculations were performed with the use of SAS software (SAS Institute) and were validated according to the operating procedures of the sponsor.

RESULTS

PATIENT AND PROCEDURAL CHARACTERISTICS

Between February 2014 and June 2015, a total of 526 patients were enrolled at 56 clinical sites (employing 100 operators) in three countries. The 300-patient primary cohort completed the 6-month follow-up in June 2015, thereby triggering the prespecified formal primary analyses (Fig. 2). The 526-patient total cohort was followed for a mean (±SD) of 6.9±4.2 months. The characteristics of these two cohorts are shown in Table 1. The mean age in the total cohort was 75.8±12.1 years, and 61.8% of the participants were male. Pacemaker indications were atrial fibrillation with atrioventricular block in 294 patients (55.9%), sinus rhythm with high-grade atrioventricular block in 46 patients (8.7%), and sinus bradycardia with infrequent pauses or syncope in 186 patients (35.4%).

Pacemaker implantation was successful in 504 of the 526 patients (95.8%). Procedural and fluoroscopy times were 28.6±17.8 minutes and 13.9±9.1 minutes, respectively. Most patients (70.2%) did not require device repositioning after initial deployment. The pacemaker required repositioning more than two times in 22 patients (4.4%). The duration of hospital stay from implantation to discharge was 1.1±1.7 days (range, 0 to 33).

DEVICE EFFICACY

In the intention-to-treat analysis, 270 of the 300 participants in the primary cohort (90.0%; two-sided 95% confidence interval [CI], 86.0 to 93.2) reached the primary efficacy end point; the lower boundary of the 95% CI exceeded the prespecified performance goal of 85% ($P=0.007$). Device implantation was unsuccessful in 11 patients; among the remaining 289 patients in whom implantation was successful, 270 reached the primary efficacy end point (93.4%; two-sided 95% CI, 89.9 to 96.0; $P<0.001$). The reasons for failure to reach the primary efficacy end point in the 19 patients with successful implantation included inadequate pacing capture threshold in 4 patients and inadequate sensed R-wave amplitudes in 16 patients. One patient had both inadequate pacing and inadequate sensing. Among the 289 patients with successful implantation, complete 6-month follow-up data were available for 266 patients and the last observation was carried forward for 23 patients (owing to death in 13 patients, missing data on the 6-month visit in 4 patients, and withdrawal from the study in 6 patients).

In the total cohort, the mean sensing and pacing threshold values improved significantly over time from the values observed at the time of pacemaker implantation; at 12 months, the mean R-wave amplitude was 9.2±2.9 mV, and the mean pacing capture threshold (at 0.4 msec) was 0.58±0.31 V (Fig. S2 in the Supplementary Appendix). The percentage of ventricular pacing was 38.7±36.9 before hospital discharge and 51.6±39.1 at 12 months.

Table 1. Patient Characteristics at Baseline and Procedural Characteristics.*

Characteristic	Primary Cohort (N=300)	Total Cohort (N=526)
Patient characteristics		
Age — yr		
Mean	75.7±11.6	75.8±12.1
Range	30–96	19–96
Body-mass index†		
Mean	29.2±7.3	28.7±6.8
Range	15.8–60.3	15.2–60.3
Sex — no. (%)		
Male	193 (64.3)	325 (61.8)
Female	107 (35.7)	201 (38.2)
Race or ethnic group — no. (%)‡		
White	269 (89.7)	478 (90.9)
Black	21 (7.0)	35 (6.7)
American Indian or Alaska Native	1 (0.3)	1 (0.2)
Asian	7 (2.3)	10 (1.9)
Other	2 (0.7)	2 (0.4)
Hispanic or Latino ethnic group — no. (%)‡		
Hispanic or Latino	13 (4.3)	17 (3.2)
Non-Hispanic or non-Latino	287 (95.7)	508 (96.6)
Unknown	0	1 (0.2)
Coronary artery disease — no. (%)	121 (40.3)	201 (38.2)
History of coronary-artery bypass grafting — no. (%)	48 (16.0)	84 (16.0)
History of myocardial infarction — no. (%)	42 (14.0)	73 (13.9)
History of percutaneous coronary intervention — no. (%)	47 (15.7)	86 (16.3)
Hypertension — no. (%)	252 (84.0)	420 (79.8)
Diabetes mellitus — no. (%)	82 (27.3)	143 (27.2)
Hyperlipidemia — no. (%)	208 (69.3)	355 (67.5)
Peripheral vascular disease — no. (%)	45 (15.0)	69 (13.1)
Congestive heart failure — no. (%)	43 (14.3)	82 (15.6)
NHYA class I	11 (3.7)	18 (3.4)
NYHA class II	20 (6.7)	36 (6.8)
NYHA class III	3 (1.0)	9 (1.7)
NYHA class IV	0	0
NYHA class unknown	9 (3.0)	19 (3.6)
History of arrhythmia — no. (%)		
Supraventricular	231 (77.0)	399 (75.9)
Ventricular	15 (5.0)	28 (5.3)
Tricuspid-valve disease — no. (%)		
Regurgitation or prolapse	59 (19.7)	106 (20.2)
Stenosis	0	0
Repair or replacement	3 (1.0)	3 (0.6)
Left ventricular ejection fraction — %	57.1±8.2	57.6±8.1
Medications — no. (%)		
Beta-blockers	120 (40.0)	199 (37.8)
Angiotensin-converting–enzyme inhibitors	80 (26.7)	149 (28.3)
Angiotensin-receptor blockers	62 (20.7)	91 (17.3)
Anticoagulants	180 (60.0)	310 (58.9)
Antiplatelets	143 (47.7)	247 (47.0)
Antiarrhythmic drugs: class I or III	28 (9.3)	48 (9.1)

Table 1. (Continued.)

Characteristic	Primary Cohort (N=300)	Total Cohort (N=526)
Procedural characteristics§		
Duration of implantation — min		
Total: sheath insertion to removal	50.0±27.3	46.5±25.3
Procedure: insertion of delivery catheter to removal	30.4±18.2	28.6±17.8
Duration of fluoroscopy — min	14.9±9.4	13.9±9.1
Device repositioning — no. of patients/total no. (%)		
None	199/289 (68.9)	354/504 (70.2)
1	53/289 (18.3)	89/504 (17.7)
2	24/289 (8.3)	39/504 (7.7)
>2	13/289 (4.5)	22/504 (4.4)
Final device position in right ventricle — no. of patients/total no. (%)		
Apex	140/289 (48.4)	192/504 (38.1)
Apical septum	5/289 (1.7)	96/504 (19.0)
Outflow, septum, or other	144/289 (49.8)	215/504 (42.7)
Missing data	0/289	1/504 (0.2)

* Plus–minus values are means ±SD. NYHA denotes New York Heart Association.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race and ethnic group were self-reported.
§ Data are for patients in whom implantation of the leadless cardiac pacemaker was successful (289 in the primary cohort and 504 in the total cohort).

DEVICE SAFETY

The primary safety end point was met in 280 of the 300 patients in the primary cohort (93.3%; two-sided 95% CI, 89.9 to 95.9); the lower boundary of the 95% CI exceeded the prespecified performance goal of 86% (P<0.001). A total of 22 device-related serious adverse events were observed in 20 patients (6.7%) over a period of 6 months (Table 2, and Fig. S3 in the Supplementary Appendix). The rates of cardiac perforation, device dislodgement, and elevated pacing thresholds necessitating device retrieval and replacement were 1.3%, 1.7%, and 1.3%, respectively. Vascular complications were reported in 1.3% of the patients.

In the total cohort of 526 patients, the rate of device-related serious adverse events was 6.5%, including cardiac perforation in 1.5% of the patients, device dislodgement in 1.1%, and device retrieval due to elevated pacing thresholds in 0.8% (Table 2, and Fig. S4 in the Supplementary Appendix). The six device dislodgements were identified at 8.0±6.4 days after implantation (range, 1 to 14). Device migration to the pulmonary artery or right femoral vein occurred in 4 and 2 patients, respectively. All six devices were retrieved percutaneously. There was no significant difference in the dislodgement rate between devices positioned in the right ventricular apex and those in non-apical positions (P=0.42).

In the total cohort, there were 28 deaths (5.3%) during follow-up; the mean age of patients who died was 79.1±10.9 years (range, 40 to 97). A total of 19 deaths (68%) occurred within 6 months, 8 (29%) between 6 and 12 months, and 1 (4%) beyond 12 months. The deaths were classified as having a cardiac cause in 4 patients, a noncardiac cause in 14 patients, and an unknown cause in 10 patients (Table S1 in the Supplementary Appendix). There were no deaths that were considered to be device-related. However there were 2 deaths (0.4%) that were classified by the clinical-events committee as procedure-related (see the Supplementary Appendix for details). The rate of non–device-related serious adverse events was 6.3% in the primary cohort and 5.5% in the total cohort (Table 3).

The influence of operator experience on the

Table 2. Device-Related Serious Adverse Events.*

Event	Primary Cohort (N=300)			Total Cohort (N=526)		
	No. of Events	No. of Patients	Event Rate	No. of Events	No. of Patients	Event Rate
			%			%
Total	22	20	6.7	40	34	6.5
Cardiac perforation						
Cardiac tamponade with intervention	1	1	0.3	5	5	1.0
Cardiac perforation requiring intervention	1	1	0.3	1	1	0.2
Pericardial effusion with no intervention	2	2	0.7	2	2	0.4
Vascular complication						
Bleeding	2	2	0.7	2	2	0.4
Arteriovenous fistula	1	1	0.3	1	1	0.2
Pseudoaneurysm	1	1	0.3	2	2	0.4
Failure of vascular closure device requiring intervention	0	0	0	1	1	0.2
Arrhythmia during device implantation						
Asystole	1	1	0.3	1	1	0.2
Ventricular tachycardia or ventricular fibrillation	1	1	0.3	2	2	0.4
Cardiopulmonary arrest during implantation procedure	0	0	0	1	1	0.2
Device dislodgement	5	5	1.7	6	6	1.1
Device migration during implantation owing to inadequate fixation	0	0	0	2	2	0.4
Pacing threshold elevation with retrieval and implantation of new device	4	4	1.3	4	4	0.8
Other						
Hemothorax	0	0	0	1	1	0.2
Angina pectoris	0	0	0	1	1	0.2
Pericarditis	1	1	0.3	1	1	0.2
Acute confusion and expressive aphasia	0	0	0	1	1	0.2
Dysarthria and lethargy after implantation	0	0	0	1	1	0.2
Contrast-induced nephropathy	0	0	0	1	1	0.2
Orthostatic hypotension with weakness	1	1	0.3	1	1	0.2
Left-leg weakness during implantation	0	0	0	1	1	0.2
Probable pulmonary embolism	1	1	0.3	1	1	0.2
Ischemic stroke	0	0	0	1	1	0.2

* Events were classified as device-related if they were considered by the clinical-events committee to be attributable to the investigational device or procedure. Some patients had more than one event, and therefore the number of patients is less than the number of events.

rate of device-related serious adverse events was assessed. Cases were stratified according to the first 10 devices implanted by an operator (470 implants) versus subsequent implants by the same operator (56 implants). The rate of device-related serious adverse events was 6.8% for the initial 10 cases versus 3.6% for the subsequent implants (P=0.56).

RETRIEVABILITY OF THE IMPLANTED DEVICES

In seven patients in the total cohort (excluding the six patients with dislodgements), the leadless cardiac pacemakers were successfully retrieved at 160±180 days (median, 100; range, 1 to 413) without complications. The reasons for retrieval were elevated pacing thresholds in four patients, worsening heart failure in two patients, and elective explantation in one patient. Three patients received new leadless cardiac pacemakers, two received conventional pacemakers, and the two patients with heart failure received cardiac-resynchronization therapy with either direct His-bundle pacing or biventricular pacing.

HOLTER-MONITOR FINDINGS

A prespecified subgroup of 30 patients underwent 24-hour ambulatory electrocardiography to assess pacing function. The percentage of ventricular pacing was 50.3±39.9 (range, 0 to 98). The mean minimum and maximum heart rates were 58.2±9.2 beats per minute and 111.1±21.1 beats per minute, respectively. The mean heart rate in all 30 patients was 71.2±9.8 beats per minute. The rate-adaptive feature was active in 16 patients. There were no pauses exceeding 2.0 seconds, no episodes of undersensing, and no instances of failure to capture. Four patients had T-wave oversensing, no instances of which resulted in a prolonged pause, symptoms in the patient, or reported adverse events.

DISCUSSION

This analysis from an ongoing multicenter study showed that the Nanostim leadless cardiac pacemaker was capable of providing effective pacemaker function in a varied group of patients who had indications for long-term pacing therapy. The coexisting conditions in this patient cohort were similar to those in patients who receive conventional single-chamber pacemakers, but the rates of hypertension, hyperlipidemia, and diabetes were higher in our cohort.[16] The rate of successful implantation was 95.8%, and the efficacy goals for pacing and sensing were met in 90% of the participants. The mean pacing threshold and sensing values at 6 months were similar to those observed with conventional transvenous leads,[17] and these values were stable over time. Furthermore, effective pacemaker function was verified in a subgroup of patients by means of ambulatory electrocardiography. Finally, this pacemaker was safely retrievable; however, most of the devices that were retrieved were explanted within 1 year after implantation, and there are few data on the feasibility of the removal of leadless cardiac pacemakers beyond this point.

Device-related serious adverse events were observed in 6.7% of the 300 patients in the primary cohort, including device dislodgement in 1.7%, cardiac perforation in 1.3%, elevated pacing thresholds requiring device retrieval and reimplantation in 1.3%, and vascular complications in 1.3%. For comparison, implantation of conventional ventricular pacemakers is associated with complications (excluding lead fracture) in 3.2% of patients, including pneumothorax in 1.1%, lead dislodgement in 0.8%, and infection in 0.5%.[18] The rate of cardiac perforation in our study (1.5% among the 526 patients in the total cohort) is similar to the rate observed with transvenous leads, which ranges from 0.6 to 5.0%.[3,19,20] Perforations related to leadless cardiac pacemakers may be due in part to the relatively large diameter of the device.

A recent report of the early performance of a different leadless cardiac pacemaker (Micra, Medtronic) that was implanted in 140 patients who were followed for a mean of 2 months showed an 18.6% rate of procedure-related adverse events.[21] Although the rate of cardiac perforation (0.7%) was somewhat lower than that observed in our study, the rate of vascular complications was higher, including bleeding in 2.1% of patients, hematoma in 1.4%, and pseudoaneurysm in 1.4%. It is difficult, however, to compare these two systems directly.

Premature battery depletion was not observed, but the limited duration of follow-up precludes robust confidence in the battery longevity of the leadless cardiac pacemaker. However, on the basis of the observed device-use conditions (e.g., heart rate, percentage of ventricular pacing, and pacing impedance) of the 300-patient cohort followed for 6 months, the battery longevity is estimated to be 15.0±6.7 years (95% CI, 14.2 to 15.8).

This study was limited by the observational design that did not directly compare the leadless cardiac pacemaker with conventional pacemakers, thereby limiting our ability to draw conclusions about the relative safety and efficacy of these devices. In addition, the performance goal for efficacy was based on an ongoing pacemaker

Table 3. Non–Device-Related Serious Adverse Events.*

Event	Primary Cohort (N=300)			Total Cohort (N=526)		
	No. of Events	No. of Patients	Event Rate	No. of Events	No. of Patients	Event Rate
			%			%
Total	22	19	6.3	36	29	5.5
Acute renal failure	1	1	0.3	2	2	0.4
Angina pectoris	1	1	0.3	2	2	0.4
Atrial fibrillation with rapid ventricular rates	1	1	0.3	1	1	0.2
Bacteremia	0	0	0	1	1	0.2
Bell's palsy	1	1	0.3	1	1	0.2
Bilateral pulmonary emboli with pulmonary infarction	1	1	0.3	1	1	0.2
Change in mental status	1	1	0.3	1	1	0.2
Dizziness	2	2	0.7	3	2	0.4
Heart failure	0	0	0	4	4	0.8
Heart failure and gout	1	1	0.3	1	1	0.2
Hypertensive emergency	1	1	0.3	1	1	0.2
Lung cancer	1	1	0.3	1	1	0.2
Mechanical fall	0	0	0	1	1	0.2
Methicillin-resistant *Staphylococcus aureus* infection	1	1	0.3	1	1	0.2
Myocardial infarction	1	1	0.3	1	1	0.2
Palpitations	1	1	0.3	1	1	0.2
Pericardial effusion after placement of epicardial lead	1	1	0.3	1	1	0.2
Reduction in ejection fraction: new onset	0	0	0	1	1	0.2
Seizure: new onset	0	0	0	1	1	0.2
Sepsis	2	2	0.7	2	2	0.4
Shortness of breath	1	1	0.3	1	1	0.2
Stroke	1	1	0.3	1	1	0.2
Syncope: unknown cause	1	1	0.3	1	1	0.2
Syncope: vasovagal	1	1	0.3	1	1	0.2
Urinary retention	1	1	0.3	1	1	0.2
Ventricular tachycardia or ventricular fibrillation	0	0	0	2	2	0.4
Vertigo	0	0	0	1	1	0.2

* These events were considered by the clinical-events committee to be unrelated to the investigational device or procedure. Some patients had more than one event, and therefore the number of patients is less than the number of events.

study, the data from which are not publicly available. Furthermore, the mean follow-up was only 6 months, again limiting our understanding of long-term efficacy and pacemaker-related complications, particularly in comparison with conventional pacemaker systems. Currently, the leadless cardiac pacemaker can serve as only a single-chamber ventricular pacemaker, which accounts for a minority of implanted pacemakers in the United States.[2] The leadless cardiac pacemaker

also cannot provide electrographic data. Refinements in device-to-device communication, atrial affixation, and device diagnostics would be necessary for this device to fully replace conventional dual-chamber pacemakers.

In summary, the Nanostim leadless cardiac pacemaker met prespecified pacing and sensing requirements in 90% of the patients in whom an implantation was attempted and in 93.4% of the patients in whom the implantation was successful. At 6 months, serious adverse events were observed in 6.7% of the patients.

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