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ORIGINAL INVESTIGATIONS

Chronic Performance of a Leadless Cardiac Pacemaker

1-Year Follow-Up of the LEADLESS Trial

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ABSTRACT

BACKGROUND A leadless cardiac pacemaker (LCP) system was recently introduced to overcome lead-related complications of conventional pacing systems. To date, long-term results of an LCP system are unknown.

OBJECTIVES The aim of this study was to assess the complication incidence, electrical performance, and rate response characteristics within the first year of follow-up of patients implanted with an LCP.

METHODS We retrospectively assessed intermediate-term follow-up data for 31 of 33 patients from the LEADLESS trial cohort who had an indication for single-chamber pacing and received an LCP between December 2012 and April 2013.

RESULTS The mean age of the cohort was 76 ± 8 years, and 65% were male. Between 3 and 12 months of follow-up, there were no pacemaker-related adverse events reported. The pacing performance results at 6- and 12-month follow-up were, respectively, as follows: mean pacing threshold (at a 0.4-ms pulse width), 0.40 ± 0.26 V and 0.43 ± 0.30 V; R-wave amplitude 10.6 ± 2.6 mV and 10.3 ± 2.2 mV; and impedance 625 ± 205 Ω and 627 ± 209 Ω. At the 12-month follow-up in 61% of the patients (n = 19 of 31), the rate response sensor was activated, and an adequate rate response was observed in all patients.

CONCLUSIONS The LCP demonstrates very stable performance and reassuring safety results during intermediate-term follow-up. These results support the use of the LCP as a promising alternative to conventional pacemaker systems. Continued evaluation is warranted to further characterize this system. (Evaluation of a New Cardiac Pacemaker; NCT01700244) (J Am Coll Cardiol 2015;65:1497–504) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

LCP = leadless cardiac pacemaker

VVIR = single-chamber, rate-adaptive pacemaker

In the United States, nearly 250,000 new cardiac pacemakers are implanted annually, contributing to 700,000 new cardiac pacemakers implanted worldwide (1). For almost 60 years, pacemaker therapy has been the standard of care for various bradyarrhythmias, improving quality of life and reducing mortality in at-risk patients (2–5). Although the efficacy and safety of transvenous pacemaker therapy have incrementally improved, this therapy is associated with procedure- and device-related complications. Approximately 10% of patients experience a periprocedural complication related to transvenous implantation of a pacemaker (6,7). Most complications are related to the subcutaneous pocket of the pulse generator (e.g., hematoma, skin erosion, pocket infection) or venous access and lead implantation (e.g., pneumothorax, cardiac tamponade, lead dislodgment) (8–10). In the long term, transvenous leads, often considered the Achilles heel of the cardiac pacing system, can cause venous obstruction and are prone to insulation breaks, conductor fracture, and infection (9,11–14).

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Recently, a leadless cardiac pacemaker (LCP) has been introduced to potentially overcome some of these short- and long-term complications (15). The pulse generator and sensing/pacing electrodes are fully contained within a single unit. In the prospective, multicenter, nonrandomized LEADLESS trial, we reported the safety and feasibility of LCP implantation, and short-term (3-month) stability of measures of pacing performance (15). However, further follow-up is required to assess the intermediate- and long-term safety (e.g., risk of embolization, proarrhythmia, and other unanticipated adverse events) and performance (e.g., battery longevity, pacing thresholds over time, and rate response function) of this device. Herein, we report the 1-year follow-up results of the LEADLESS trial.

METHODS

LCP SYSTEM. The design, technical specifications, and method of implanting the LCP (Nanostim, St. Jude Medical, St. Paul, Minnesota) were described previously (15). The LCP is a temperature-responsive, single-chamber rate-adaptive pacemaker (VVIR) and can increase the pacing rate in response to exercise (16). The LCP uses 3 characteristics of the right ventricular temperature signal to provide an appropriate and proportional increase in pacing rate in response to exercise: 1) temperature in the right heart typically manifests a dip at the onset of exercise due to cooler blood flowing to the heart from the peripheral circulation; 2) as exercise continues, the positive slope of increasing temperature provides an indication of the rate at which skeletal muscles are working; and 3) in prolonged exercise, a steady-state temperature increase is often reached in which the heat input from the working muscles equals the heat lost by the body's natural processes for regulating temperature (positive magnitude).

STUDY PATIENT COHORT. The initial clinical experience with the LCP was reported previously (15). Briefly, the LEADLESS trial was conducted at 3 European centers. Thirty-three patients (older than 18 years of age with an indication for single-chamber pacing) were enrolled from December 2012 to April 2013 and followed for 12 weeks (15).

CHRONIC PERFORMANCE AND SAFETY STUDY. Patients implanted with a permanent LCP in the LEADLESS Trial were retrospectively included in this intermediate-term follow-up study to evaluate the safety and performance of this device, with a minimum of 1 year of follow-up. Medical records were analyzed from July 2013 to June 2014. The records were specifically evaluated for the following: 1) serious adverse events; 2) electrical performance of the LCP; and 3) rate response sensor activation (activated in selected patients only). This study was not designed to systematically evaluate the rate response function of the device. Nevertheless, all available data providing insight in sensor function were obtained for analysis. Similarly, echocardiographic evaluation was not performed systematically, but available echocardiograms were assessed. Permission of the local institutional review boards was obtained for this retrospective analysis.

STATISTICAL ANALYSIS. Categorical variables are presented as frequencies and continuous variables as mean ± SD or median (interquartile range), as appropriate. The paired Student *t* test was used to compare means of continuous variables at specific time points; change in the repeatedly measured variables was analyzed with linear mixed-effects models using time as a fixed factor and patient number as a random factor. All analyses were conducted with SPSS version 20.0 (SPSS Inc., Chicago, Illinois).

RESULTS

PATIENTS. Thirty-one patients were included in this 1-year follow-up study. Two patients from the initial study cohort (N = 33) were excluded. One patient had a perforation during the implantation procedure

leading to cardiac tamponade and was operated on successfully, but died of a massive cerebral artery ischemic infarct 5 days after the implantation. The second patient underwent successful LCP retrieval at day 7 post-implantation because of the need for an implantable cardioverter-defibrillator (15). The clinical characteristics of the patients of the present study are shown in Table 1.

PROCEDURE. All patients, available for 12-month follow-up (n = 31, 100%), had a successful LCP implantation in the apicoseptal region of the right ventricle. The median total implantation procedure time was 24 min (range 11 to 74 min). In the majority of patients (n = 22, 71%), the initial deployment of the device was successful, 9 patients (29%) required 1 or more reposition(s) during implantation due to inadequate electrical measurements (mean of 2 repositions; range 1 to 3). Procedure characteristics are shown in Table 1. The mean threshold at implantation was 0.83 ± 0.45 V for repositioned patients versus 0.75 ± 0.53 V and was not different from non-repositioned patients (p = 0.684). Similarly, at discharge, thresholds were 0.39 ± 0.18 V versus 0.42 ± 0.21 V (p = 0.696) and 0.39 ± 0.18 V versus 0.44 ± 0.34 V (p = 0.660) at 12-month follow-up, respectively.

SAFETY AT 1-YEAR FOLLOW-UP. The mean follow-up interval was 1.2 ± 0.1 years. At 12-month follow-up, all patients (n = 31) were alive. No pacemaker-related complications were observed in these 31 patients (Central Illustration). Furthermore, pacemaker syndrome developed in none of the patients, nor were there any device embolizations, late perforations, or patients with a device-related infection or an infection of unknown origin. There were no thrombi observed on echocardiography. Moreover, no device-induced ventricular arrhythmias were observed, and none of the patients required a reintervention. Figure 1 shows a chest x-ray at pre-discharge at 1-day post-implantation and at 12-month follow-up, showing no significant changes in position of the LCP.

Between 3 and 12 months of follow-up, 6 patients (19%) were hospitalized after LCP implantation; however, none related to either the implantation procedure or pacemaker function: 1 patient had a leg fracture, 1 patient was treated for breast cancer, 1 patient underwent surgery for pancreatic cancer, 2 patients were admitted with left-sided heart failure due to rapidly conducted atrial fibrillation (115 to 119 beats/min), and 1 patient was admitted because of disorientation. Examination in this last patient revealed a properly functioning LCP and a cerebral computed tomography scan revealed no abnormalities. The episode of disorientation was interpreted as being caused by temporary hypoperfusion of the brain due to low blood pressure. The 2 patients with rapidly conducted atrial fibrillation had a properly functioning LCP and were treated medically.

TABLE 1 Patient Characteristics, Procedural Details, and Outcome (N = 31)

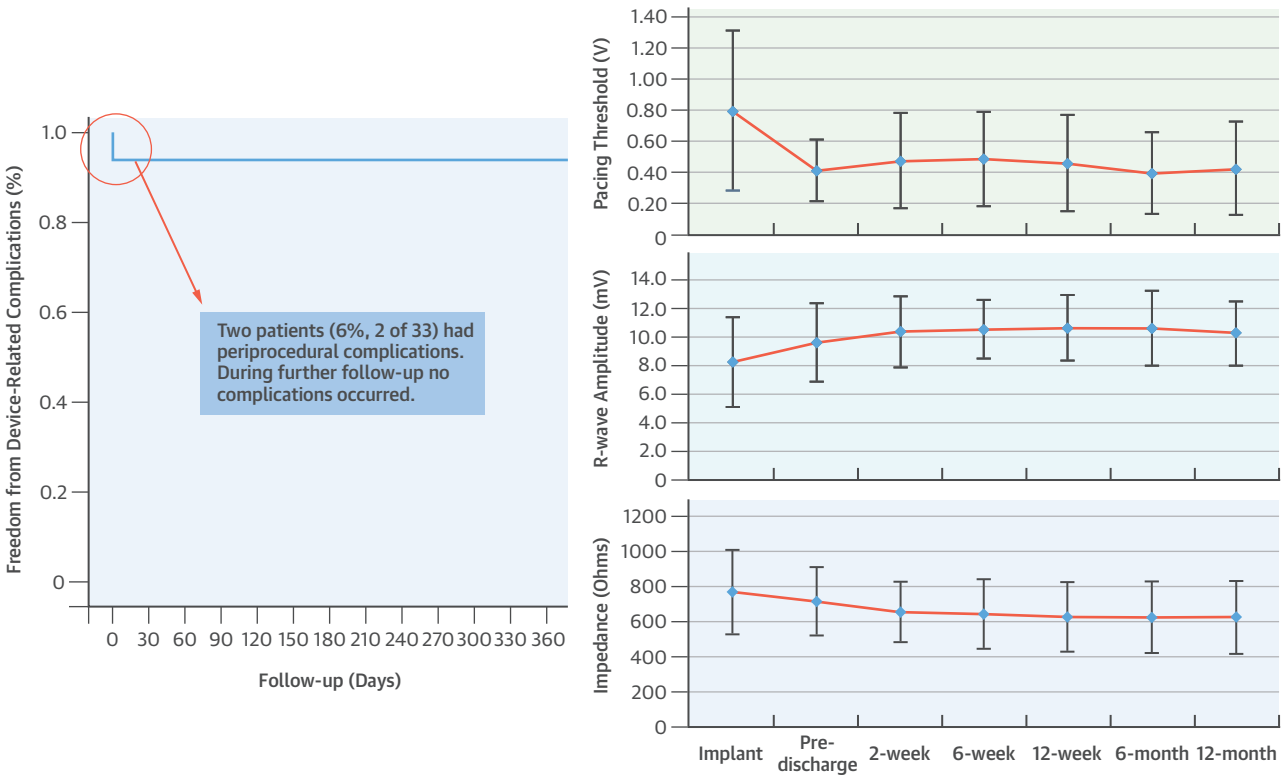
Age, yrs	76.4 ± 8.4
Male	20 (65)
Pacing indication	
Permanent AF with AV block (including AF with a slow ventricular response)	21 (68)
Sinus rhythm with second/third degree AV block and significant comorbidities	5 (16)
Sinus bradycardia with infrequent pauses or unexplained syncope	5 (16)
Repositioning attempts (to achieve final implantation position)	
0	23 (74)
1	3 (10)
2	3 (10)
3	2 (6)
Median implant procedure duration, min	24 (11-74)
Time to follow-up, yrs	1.2 ± 0.2
Rehospitalized between 3 and 12 months	6 (19)
Device-related adverse events between 3 and 12 months	0 (0)

Values are mean ± SD or median (total range).
AF = atrial fibrillation; AV = atrioventricular block.

PERFORMANCE MEASURES. After an initial drop of threshold, decrease in impedance, and increase in the R-wave at 1 day post-implantation, these performance measures remained very stable from the 3-month follow-up measurement onward (time effects between 3, 6, and 12 months: all p values >0.05). Mean pacing threshold (at a 0.4-ms pulse width) was 0.40 ± 0.26 V and 0.43 ± 0.30 V; R-wave amplitude was 10.6 ± 2.6 mV and 10.3 ± 2.2 mV; and impedance was 625 ± 205 Ω and 627 ± 209 Ω at 6- and 12-month follow-up, respectively. The Central Illustration shows the pacing threshold, R-wave amplitude, and impedance over time. Aside from a statistically significant decrease in mean threshold between implantation and discharge in all patients (0.77 ± 0.51 V vs. 0.41 ± 0.20 V; p = 0.001), no change in threshold more than 0.25 V was observed in any patient within the 3- to 12-month follow-up. No early battery depletion, under- or oversensing, or pacing capture issues were detected at the follow-up visits.

RATE RESPONSE. Initially, in all patients, the pacing mode was programmed to VVIR per protocol. From 6-week follow-up onward, the pacing mode setting was reprogrammed to VVIR after an individual patient pacing optimization assessment on the basis of exercise tolerance and rate histogram data. Figure 2 shows an example of the snapshot temperature data captured before, during, and after a 6-min walk test,

CENTRAL ILLUSTRATION **1-Year Follow-Up of Patients Implanted With a Leadless Cardiac Pacemaker: Safety and Device Performance**



Knops, R.E. et al. J Am Coll Cardiol. 2015; 65(15):1497–504.

(Left) Kaplan-Meier survival curve represents freedom from device-related complications: 2 patients had device-related complications (6%, 31 of 33), both periprocedurally. During further follow-up, no complications occurred in the remaining patients (n = 31). **(Right)** Device performance measurements of the leadless cardiac pacemaker. The mean value ± SD of pacing threshold (at 0.4 ms [V]) **(right top)**; the R-wave amplitude (mV) **(right middle)**; and the pacing impedance (Ω) **(right bottom)** at each follow-up assessment.

and the accompanying sensor-indicated rate (i.e., the rate-response that would have been provided). At 6-week, 12-week, 6-month, and 12-month follow-up, the total percent of patients with a pacemaker activated rate response set to activated rate response function were 35% (n = 11 of 31), 39% (n = 12 of 31), 58% (n = 18 of 31), and 61% (n = 19 of 31), respectively.

In patients with an activated sensor rate, histograms were obtained to assess adequate sensor-based heart rate, defined as 80% of the predicted maximal heart adjusted for age. In all 19 sensor-activated patients, an adequate rate response was obtained. In 3 patients (n = 3 of 19, 16%), the initial rate response sensor settings were adjusted during follow-up due to too steep sensor gain settings and too high maximal sensor rate. An example of adequate rate response function is shown in Online Figure 1. In all other patients (n = 16 of 19, 84%), the nominal sensor settings were sufficient.

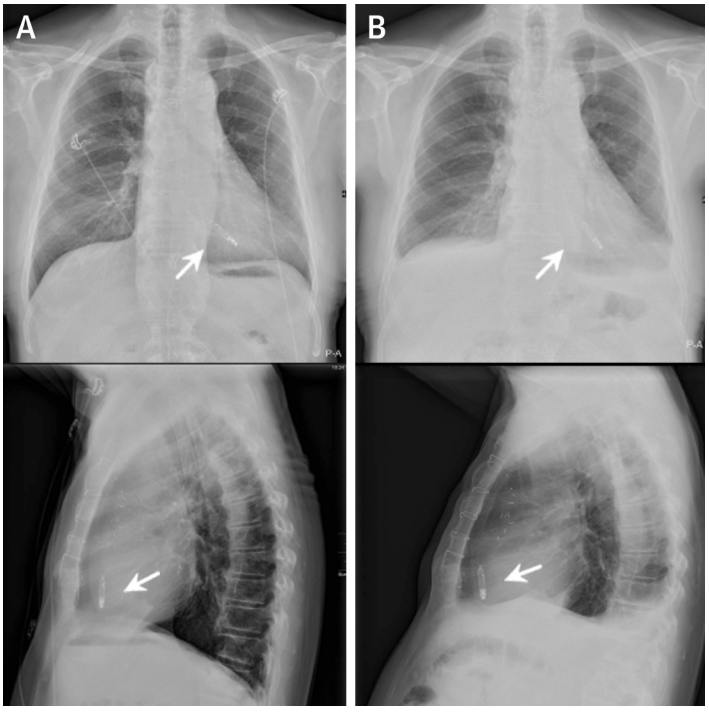
DISCUSSION

The intermediate-term safety and performance of a novel LCP with a minimum of 12-month follow-up shows the following: 1) there were no adverse events related to the device between 3- and 12-month follow-up; 2) the electrical performance measures of the LCP were stable between 3- and 12-month follow-up; and 3) the rate response feature was used and adequately functioning in the majority of patients (Central Illustration).

SAFETY. As reported previously, there were 2 complications associated with the implantation procedure (15). One patient died of a cerebrovascular accident

5 days after successful surgery for acute perforation, and in another patient, the device was inadvertently placed in the left ventricle through a persistent foramen ovale and had to be repositioned in the same procedure. The observed complication rates, both acute and intermediate term, were low compared with complication rates of conventional pacemaker systems, as reported in recent studies (6,7). Udo et al. (6) reported a 5-year complication rate of 19.7% in a Dutch cohort, consisting of 1,517 first implant pacemaker patients, of which 12.4% arose in the first 2 months after implantation and were mainly lead or pocket related. Of all lead-related complications (5.5%), lead dislocation or disconnection was the most common complication (3.3%), requiring a reoperation. In a large Danish cohort (5,918 consecutive cardiovascular implantable electronic device patients), Kirkfeldt et al. (7) reported 8.4% complications in single- and dual-chamber pacemaker patients within the first 6 months post-implantation. The largest contributors were lead-related reinterventions and pocket hematomas resulting in prolonged hospital stay, hospital readmission, or additional outpatient visits. With a leadless pacemaker design, lead and pocket complications can be eliminated, potentially resulting in lower complication rates. Femoral venous access prevents pulmonary complications such as a pneumothorax (8). Although not observed in the study, the occurrence of complications arising from the transfemoral approach, such as groin hematomas, has to be evaluated.

FIGURE 1 Position of the LCP on Chest Radiograph at 1-Day and 12-Month Post-Implantation

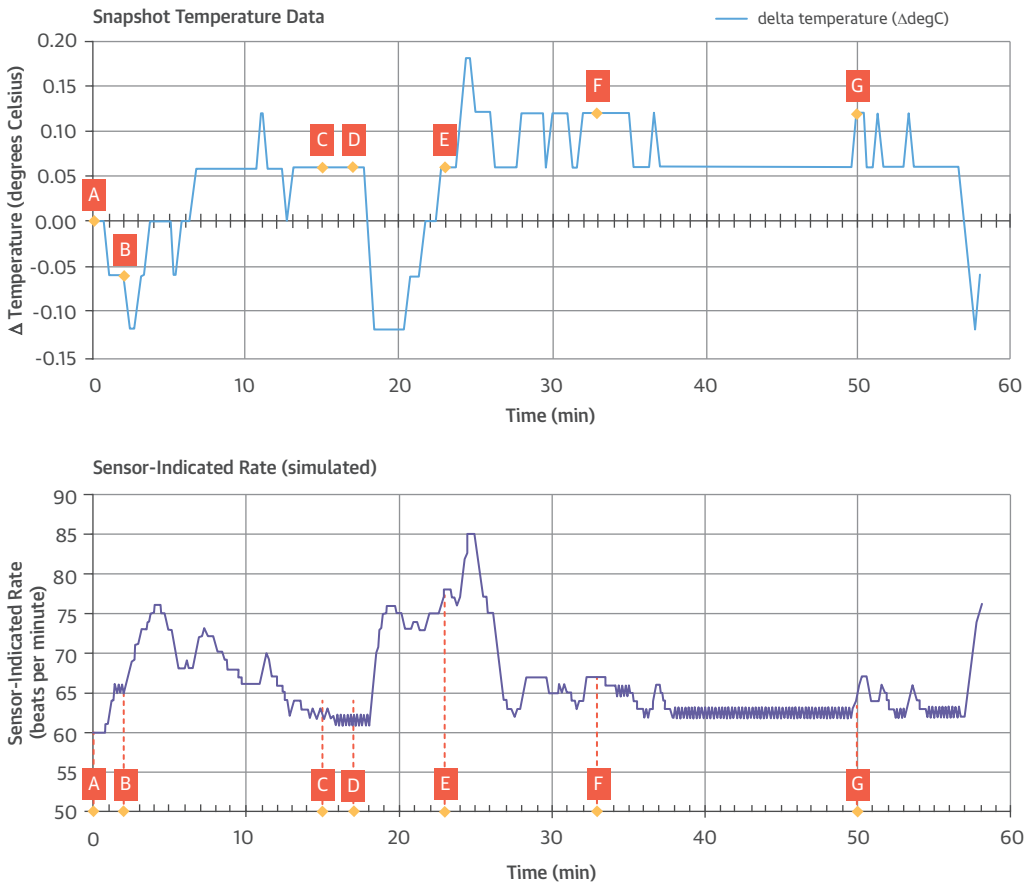


(A) Chest radiograph 1 day post-implantation; the LCP projects in the right ventricle **(arrow)**. **(B)** Chest radiograph 12-month post-implantation; position of the LCP is unchanged **(arrow)**, bilateral pleural effusion. LCP = leadless cardiac pacemaker.

The occurrence of cardiac perforations, device embolizations, device-induced arrhythmias, and the need for reintervention needs to be assessed in the long term and in larger cohorts to evaluate the overall safety of this device. In summary, both acute and intermediate-term complication rates observed in this cohort were low. To systematically address long-term safety, studies are ongoing in Europe (The LEADLESS Observational Study; NCT02051972) and in the United States (The LEADLESS Pacemaker II IDE [Leadless II]; NCT02030418). With this new percutaneous approach for leadless pacemaker implants, a learning curve for the operating physician has been observed with regard to procedure time. Therefore, this new technique necessitates a solid training program for new implanters.

PERFORMANCE. After 12 months of follow-up, we observed very stable electrical measures in all of our patients. Compared with time of implantation, the mean pacing threshold showed a 50% decrease 1 day later at hospital pre-discharge (15) and remained constant during follow-up (**Central Illustration**). The higher initial threshold could be due to an implant lesion of the 0.5-cm diameter screw-in helix. Although the pacing electrode is not part of the helix and is placed several millimeters away, tissue injury could still influence the acute pacing thresholds but appears to resolve entirely by pre-discharge. We observed a slightly higher, although not statistically significant, pacing threshold at implantation in patients with device repositioning compared with patients without, but this difference was not observed during follow-up. Potentially, the larger area of injured tissue, due to multiple device deployments, might influence acute pacing thresholds, but does not influence long-term thresholds. The stable threshold curve resembles previously described and commonly used steroid-eluting active pacemaker leads (16–18) and is expected to have a performance to equal that of conventional pacemaker leads after 12 months. First, influence of fibrosis formation on long-term threshold performance is less likely to occur than with conventional pacing systems because the electrode of the leadless system is separated from the screw-in helix by ~2 mm, instead of being part of the fixation mechanism. Second, no lead fractures or lead

FIGURE 2 Rate Response Calibration During a 6-Min Walk Test



Once single-chamber, rate-responsive pacemaker calibration mode is turned on, the leadless cardiac pacemaker stores temperature data every 20 s for 1 h without affecting pacing rate. The programmer then interrogates the pacemaker and retrieves the stored data, called snapshot temperature data. **(Top)** Each patient's analysis shows the snapshot temperature as a function of time. **(Bottom)** The pacing rate as a function of time, which the rate response would have provided. A = leadless cardiac pacemaker programmed to single-chamber, rate-responsive pacemaker calibration mode; B = patient walked to chair; C = stood up and received instructions; D = started 6-min walk test; E = completed 6-min walk test; F = sat back down on chair; G = walked back from chair to examination table.

dislocations are expected, and device embolization after intermediate-term implantation was not observed and is not likely to occur. Similarly, observed impedance measures were stable during follow-up (means ranging from 773 Ω to 625 Ω). Therefore, battery longevity is estimated to be 9.3 years, when programmed at nominal settings (60-beats/min pacing rate, 2.5-V output, 600-Ω impedance, and 100% pacing). We did not observe early battery depletion, which is consistent with the projected battery longevity outlook.

RATE RESPONSE. At 12-month follow-up in 61% of the patients (n = 19 of 31), the rate response sensor was activated (a 26% increase compared with the 12-week follow-up). Although the present study was not designed to assess adequate rate response function of the LCP, we observed an adequate rate response in all of the patients who had the rate response sensor activated. In 3 cases, the sensitivity of the sensor was adjusted to achieve the desired rates. No pacemaker syndrome was observed (19). As mentioned, the rate response sensor of the LCP registers the central venous blood temperature, which increases with exercise, after showing a dip in core body temperature at the onset of exercise because cooler peripheral blood is returned to the circulation. Because of the relatively slow response of the central venous temperature to exercise compared with activity sensors, the sensor reaction may be relatively slow and might deliver a suboptimal rate response at low workloads (20). Potentially, elderly patients with a low level of activity may not reach the level of

prolonged exercise, which is necessary for a sufficient increase in blood temperature to activate the sensor, but this was not observed. To shed further light on this issue, a prospective study to assess the function of this rate response sensor and its characteristics at low workloads needs to be undertaken.

LONG-TERM REPLACEMENT STRATEGY. It is unknown whether long-term retrieval of the pacemaker after several years of implantation in patients will be possible. Acute and subacute retrieval of the LCP is feasible, and preclinical evidence shows that the device can be extracted up to 5 months post-implantation (21). The device may get encapsulated over time and therefore may be difficult to capture and retrieve. Long-term animal studies are under way that will evaluate the feasibility of late device retrieval. An alternative replacement strategy could be to place an additional device next to the initial device, without compromising the right ventricular volume capacity and overall function. For this strategy, it is important to realize that the LCP only takes up 1.0 ml of volume in the right ventricle, but also that evidence of these strategies is currently lacking.

STUDY LIMITATIONS. In this initial patient cohort, we report no device-related adverse events during intermediate-term follow-up. This observational study was obviously not powered to compare adverse event and failure rates of this device with those of conventional pacemaker systems. However, the data presented here are the only data available to date. Hence, larger studies are needed to evaluate the safety of the leadless device design and implantation procedure and might reveal yet unknown risks. A randomized, controlled trial comparing conventional and leadless pacing systems would be needed to compare the overall complication rates.

The LCP is only appropriate for patients with a single-chamber pacing indication and not suitable for dual-chamber sensing and pacing. In Europe, VVIR indications account for 20% to 30% of all new pacemaker implantations, but on a global scale, the percentage of VVIR pacing is higher due to the high number of single-chamber pacemakers in developing countries (1). The development of a leadless dual-chamber pacing system is anticipated in the near future.

CONCLUSIONS

The LCP demonstrates stable performance and reassuring safety results during intermediate-term follow-up. These results support the use of the LCP as a promising alternative to conventional single-chamber pacemaker systems. Continued evaluation is warranted to further characterize this system.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Leadless cardiac pacemakers exhibited stable electrical performance without device-related adverse events 1 year after implantation in an initial cohort of 31 patients.

TRANSLATIONAL OUTLOOK: Comparative trials with longer follow-up are needed to assess the performance of leadless and conventional lead-based pacemakers and inform optimal case selection for each type of system.

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KEY WORDS arrhythmia, leadless pacing, pacing, rhythm disorders

APPENDIX For a supplemental figure, please see the online version of this article.