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BACKGROUND Adequate real-world safety and efficacy of leadless pacemakers (LPs) have been demonstrated up to 3 years after implantation. Longer-term data are warranted to assess the net clinical benefit of leadless pacing.

OBJECTIVE The purpose of this study was to evaluate the long-term safety and efficacy of LP therapy in a real-world cohort.

METHODS In this retrospective cohort study, all consecutive patients with a first LP implantation from December 21, 2012, to December 13, 2016, in 6 Dutch high-volume centers were included. The primary safety endpoint was the rate of major procedure- or device-related complications (ie, requiring surgery) at 5-year follow-up. Analyses were performed with and without Nanostim battery advisory-related complications. The primary efficacy endpoint was the percentage of patients with a pacing capture threshold $\leq$2.0 V at implantation and without $\geq$1.5-V increase at the last follow-up visit.

RESULTS A total of 179 patients were included (mean age 79 $\pm$ 9 years), 93 (52%) with a Nanostim and 86 (48%) with a Micra VR LP. Mean follow-up duration was 44 $\pm$ 26 months. Forty-one major complications occurred, of which 7 were not advisory related. The 5-year major complication rate was 4% without advisory-related complications and 27% including advisory-related complications. No advisory-related major complications occurred a median 10 days (range 0–88 days) postimplantation. The pacing capture threshold was low in 163 of 167 patients (98%) and stable in 157 of 160 (98%).

CONCLUSION The long-term major complication rate without advisory-related complications was low with LPs. No complications occurred after the acute phase and no infections occurred, which may be a specific benefit of LPs. The performance was adequate with a stable pacing capture threshold.

KEYWORDS Complications; Efficacy; Leadless; Pacemaker; Safety

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Introduction

For patients with bradyarrhythmias, pacemaker therapy is the cornerstone of treatment.[1] Transvenous pacemakers have been the standard treatment for decades. However, this type of pacemaker is associated with a substantial rate of complications, particularly lead and pocket related.[2,3] To circumvent these complications, leadless pacemakers (LPs) have been developed. LPs are small capsulelike pacemakers that are implanted via the femoral or jugular vein and are fully contained in the right ventricle. Initially, 2 LP models were commercially available: the Nanostim LP (Abbott Medical Inc., Abbott Park, IL) with a helix-based fixation mechanism; and the Micra VR LP (Medtronic, Minneapolis, MN) with a tine-based fixation mechanism and a smaller length (42 vs 26 mm).[4,5] Nanostim LP implantations were halted due to premature battery failures. However, without battery-related complications, mid-term safety and efficacy were adequate.[6] Large-scale, real-world data of Micra VR LPs demonstrated adequate safety and efficacy, with follow-up durations up to 3

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years after implantation in selected populations.[7–9] Compared to transvenous pacemakers, more acute perforations but fewer device-related complications occurred. Because the needed duration of pacemaker therapy is much longer than 3 years in most patients, the net clinical benefit of leadless pacing can only be assessed with long-term data. Although Nanostim LPs currently are not being implanted, long-term data of this model are warranted because its successor, the Aveir VR (Abbott Medical Inc.), has a similar fixation mechanism and shape. In The Netherlands, LP technology was adopted early, resulting in the availability of a unique cohort with long-term follow-up data. The aim of this study was to evaluate the safety and efficacy of LP therapy in the long term in this real-world cohort.

Methods

Design, patients, and procedures

In this retrospective cohort study, all consecutive patients who were implanted with a primary LP (Nanostim LP or Micra VR LP) from December 21, 2012, to December 13, 2016, in 6 Dutch high-volume centers were included. All patients provided informed consent. The study was approved by the local Ethics Institutional Committee on Human Research. The implantation procedure for both LPs has been described previously.[4,5] Baseline characteristics, procedural details, and follow-up data were collected from patient files up to July 1, 2022. The management of patients with Nanostim battery failures at the Isala Clinics (Zwolle, The Netherlands) was previously reported.[10]

Outcomes

The primary safety endpoint was the rate of major procedure- or device-related complications during 5 years of follow-up after implantation. The classification of complications was as follows: minor complications were defined as complications requiring no action and potentially observation; intermediate complications were defined as complications requiring a nonsurgical medical intervention (eg, drugs or transfusion); and major complications were defined as complications requiring surgery. The secondary safety endpoint was the rate of all procedure- or device-related complications through 5 years after implantation.

The primary efficacy endpoint was the percentage of patients with a pacing capture threshold (PCT) $\leq$2.0 V at implantation at the nominal pulse width (Nanostim LP 0.40 ms; Micra VR LP 0.24 ms) and without $\geq$1.5-V increase at the last follow-up visit. The secondary efficacy endpoint was electrical performance (PCT, impedance, and R-wave amplitude) during follow-up.

Complication status and electrical parameters were retrospectively collected from patient files. Data from implantation and follow-up visits at prehospital discharge, 3 months after implantation, and yearly after implantation were included in this study.

Battery advisory-related complications

During the study, an advisory was issued for the Nanostim LP due to premature battery failures. This led to several events that met the complication criteria: replacement for a different (leadless) pacemaker due to battery failure or prophylactic replacement in pacemaker-dependent patients were defined as major complications, and battery failure without replacement pacemaker as a minor complication. This specific battery problem does not occur in the Micra VR LP and thus is not expected to be inherent to leadless pacing *per se*. Therefore, we performed separate analyses: with and without complications related to this technical problem.

Statistical analysis

For summary statistics, continuous variables are given as mean $\pm$ SD or median [interquartile range], and categorical variables as frequency. Kaplan-Meier estimates were used to estimate the rate of complications at 5 years after implantation. Patients were censored at death, replacement of the LP, battery depletion without replacement LP, or end of study. Changes in parameters of electrical performance were assessed using mixed models. Differences in groups were tested for using the Student's *t* test for continuous, normally distributed variables, and the Mann-Whitney *U* test for continuous, non-normally distributed variables. The association between extraction success and time to extraction was estimated with logistic regression.

Results

Clinical characteristics

A total of 179 patients with an implantation before December 13, 2016, from 6 high-volume centers in The Netherlands were included. Baseline characteristics are summarized in Table 1. The cohort reflects a common single-chamber pacemaker population with an average age at implantation of 79 $\pm$ 9 years and the primary pacing indication being mostly persistent or permanent atrial tachyarrhythmia with slow ventricular rate (40%) or complete atrioventricular (AV) block (17%). Sixty-two of the patients (35%) were female.

Procedural details

Details of the implantation are listed in Table 2. Of the 179 implanted LPs, 93 (52%) were Nanostim LPs and 86 (48%) were Micra VR LPs. The majority of patients used anticoagulants (70%), which were discontinued during the implantation in most patients. Repositioning was required in 24%.

Safety

Mean follow-up duration was 44 $\pm$ 26 months, with 66 patients having $\geq$5 years of follow-up. A total of 41 major complications occurred in 41 patients: 7 not advisory related and 34 advisory related. The Kaplan-Meier estimate for major complications at 5-year follow-up without advisory-related major complications was 4% (95% confidence interval 1%–7%) (Figure 1A). Including advisory-related major complications, the 5-year Kaplan-Meier estimate for major

Table 1 Baseline characteristics (N = 179)

Female	62 (35)
Age at implantation (y)	79 ± 9
Body mass index (kg/m^2)	26 ± 4
Pacing indication	
Persistent/permanent atrial tachyarrhythmia with slow ventricular rate	71 (40)
Persistent/permanent atrial tachyarrhythmia with complete AV block	31 (17)
AV block	36 (20)
Sinus nodal dysfunction	35 (20)
Other	6 (3)
Pacemaker dependent	26 (15)
Previous cardiac rhythm device	
VVI(R) pacemaker	7 (4)
DDD(R) pacemaker	11 (6)
DDD(R) ICD	3 (2)
CRT-P	1 (0.6)
Cardiomyopathy	
Dilated	1 (0.6)
Hypertrophic	6 (3)
Ischemic	11 (6)
Restrictive	1 (0.6)
Other	4 (2)
Coronary artery disease	53 (30)
Previous CABG	21 (12)
Previous PCI	28 (16)
Previous valve surgery	
Aortic	31 (17)
Pulmonary	0
Mitral	12 (7)
Tricuspid	5 (3)
Hypertension	94 (53)
Diabetes mellitus	35 (20)
Renal failure	
Yes, without dialysis	40 (23)
Yes, dialysis	5 (3)
Stroke	14 (8)
Peripheral artery disease	13 (7)
COPD	19 (11)

Values are given as n (%) or mean ± SD.

Body mass index missing in 21 patients, cardiomyopathy missing in 5 patients, renal failure missing in 2 patients, pacemaker dependent missing in 2 patients.

AV = atrioventricular; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; CRT-P = cardiac resynchronization therapy–pacemaker; ICD = implantable cardioverter-defibrillator; PCI = percutaneous coronary intervention.

Table 2 Procedural characteristics (N = 179)

Model LP	
Nanostim	93 (52)
Micra VR	86 (48)
Anticoagulation during implant	
VKA	108 (60)
DOAC	13 (7)
Therapeutic heparin	5 (3)
Anticoagulation management*†	
Discontinued	65 (68)
Discontinued, bridged with LMWH/heparin	2 (2.1)
Continued	29 (30)
Venous access site†	
Right femoral vein	159 (89)
Left femoral vein	5 (3)
Right jugular vein	1 (0.6)
Reposition required	42 (24)
Implant location‡	
Apex	88 (49)
Septum	38 (21)
Apicoseptal	29 (16)
Other	12 (7)

Values are given as n (%).

DOAC = direct oral anticoagulant; LMWH = low-molecular-weight heparin; LP = leadless pacemaker; VKA = vitamin K antagonist.

*Missing in 30 patients.

†Missing in 14 patients.

‡Missing in 12 patients.

complications was 27% (95% confidence interval 19%–35%) (Figure 1B). All major complications are listed in Table 3. The 7 not advisory-related complications occurred a median 10 days (range 0–88 days) after implantation: 3 during the hospitalization for implantation and 4 during follow-up. During implantation, 2 Nanostim LPs dislocated without embolization, after which the LPs were retrieved and another Nanostim implanted. There was 1 case of pericardial effusion on the day of implantation in a patient with a Micra VR LP, and percutaneous drainage was successfully performed. During follow-up, there were 2 patients with loss of capture of their Nanostim LP. In both cases, the LP was retrieved and another Nanostim LP implanted. In addition, 1 patient presented 65 days postimplantation with dyspnea due to embolization of the Nanostim LP to the proximal pulmonary artery. The LP was retrieved using a gooseneck snare, and another Nanostim LP was implanted successfully. Lastly, there was 1 case of pacemaker syndrome due to unexpected return of sinus rhythm in a patient with a Micra VR LP. Atrial flutter was reinduced during electrophysiological study with subsequent symptom resolution. The occurrence of major complications without advisory-related complications did not differ significantly between patients with a Nanostim LP or Micra VR LP (Supplemental Table 1). The 34 advisory-related complications included 27 replacements due to (impending) battery failure and 7 prophylactic replacements in pacemaker-dependent patients, after a median of 1150 days (range 304–2909 days).

All device-related complications are listed in Supplemental Table 2. The Kaplan-Meier estimate of 5-year complications was 10% (95% confidence interval 5%–14%) without advisory-related complications and 37% (95% confidence interval 28%–45%) including advisory-related complications (Supplemental Figure 1). No intermediate complications occurred. The not advisory-related minor complications included groin bleedings (n = 7), arrhythmias during implantation (n = 2), and worsening tricuspid regurgitation potentially due to the LP (n = 1). Advisory-related minor complications included 5 cases of premature battery depletion for which, in consultation with the patients, no replacement device was implanted. Three of these patients no longer met a guideline indication for pacing therapy, and 2 had a low ventricular pacing burden.

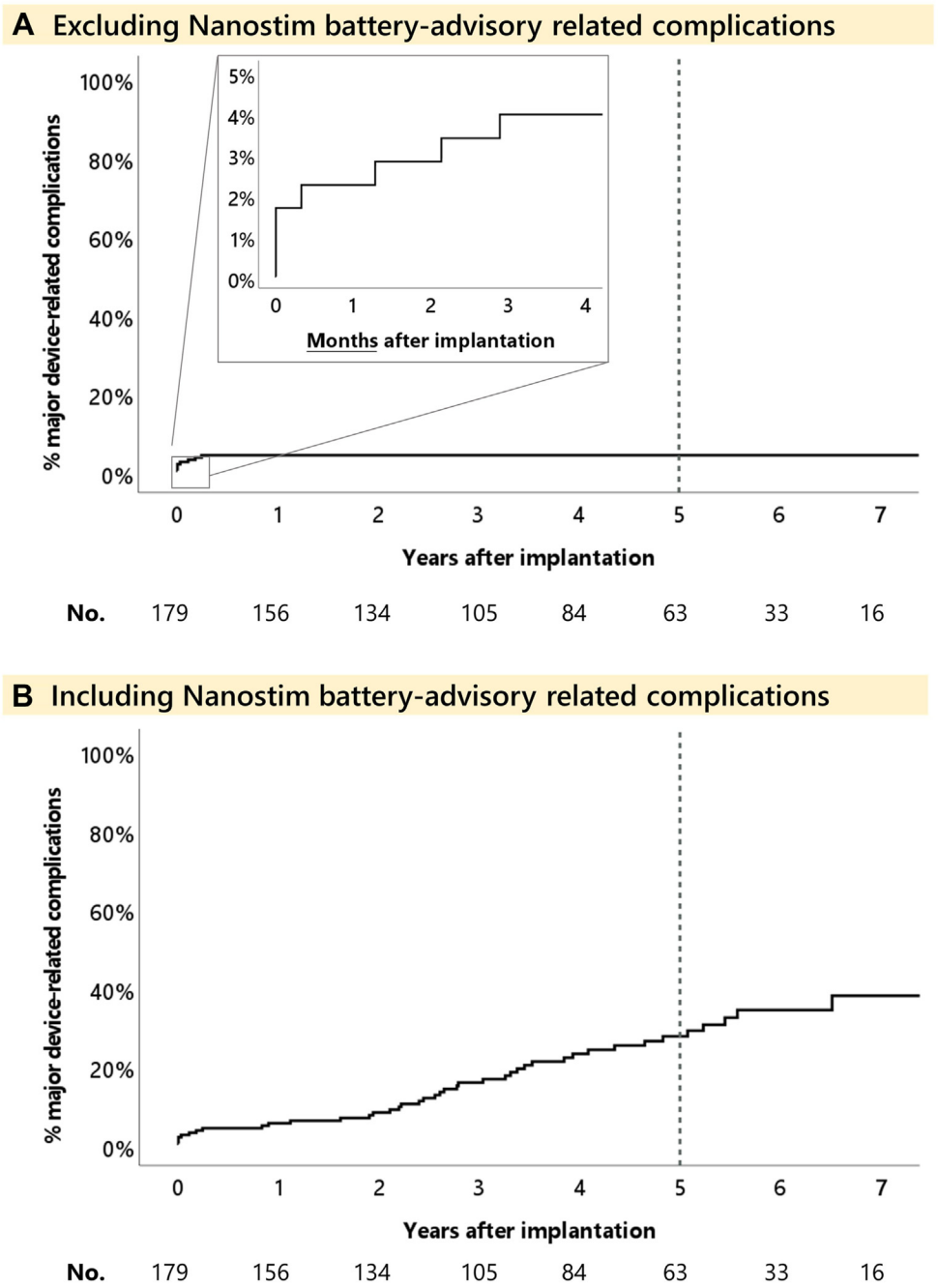


Figure 1 Major device-related complications. **A:** Without Nanostim battery advisory-related complications. **B:** Including Nanostim battery advisory-related complications.

Efficacy

PCT was ≤2 V at implantation in 163 of 167 patients (98%) with available PCT at nominal pulse width. PCT was stable (≤1.5-V increase) up to the last follow-up visit in 157 of 160 patients (98%). Of the 6 patients who did not reach the efficacy endpoint, 3 had PCT >2 V at implantation, 2 had an increase >1.5 V (1 with loss of capture after 88 days), and 1 had PCT >2 V at implantation with loss of capture after 9 days. In 12 subjects (7%), no implantation PCT was available at the nominal pulse width: 1 Micra patient with PCT of 3.25 V at 0.4 ms; 2 patients with no available PCT; and 9 with PCT range 0.25–1.1 V at 0.5–1 ms. In 19 subjects (11%), the difference in PCT could not be estimated exactly because of differences in pulse widths or unavailable data. In 2 of those subjects, there may have been an increase >1.5 V. At implantation, PCT was 0.75 V at 0.4 ms in both subjects, and at the last follow-up visit, PCTs were 0.75 and 1 V, both with pulse width of 1.5 ms. PCTs of both Nanostim and Micra LPs were stable ($P = .066$ and $P = .390$, respectively), R-wave amplitude increased over time ($P = .002$), and impedance decreased over time ($P < .001$) (Figure 2). The rate-response feature was activated in 60 patients (40%) at 1 year. The lower rate was

Table 3 Major device-related complications (N = 179)

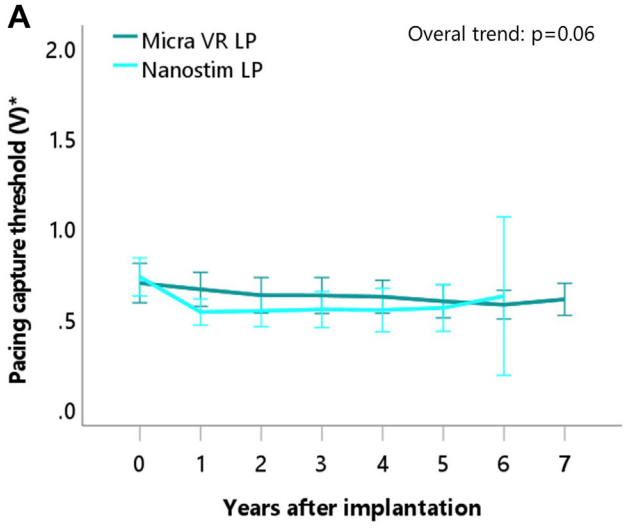
Complication	Advisory-related complications excluded	Advisory-related complications included
Implantation-related	3 (1.7)	3 (1.7)
Periprocedural dislocation	2 (1.1)	2 (1.1)
Pericardial effusion	1 (0.6)	1 (0.6)
Device-related	4 (2.2)	4 (2.2)
Loss of capture	2 (1.1)	2 (1.1)
Dislocation during follow-up	1 (0.6)	1 (0.6)
Pacemaker syndrome	1 (0.6)	1 (0.6)
Advisory-related complications	—	34 (19)
Replacement due to (impending) battery failure	—	27 (15)
Prophylactic replacement	—	7 (3.9)
Total	7 (3.9)	41 (23)

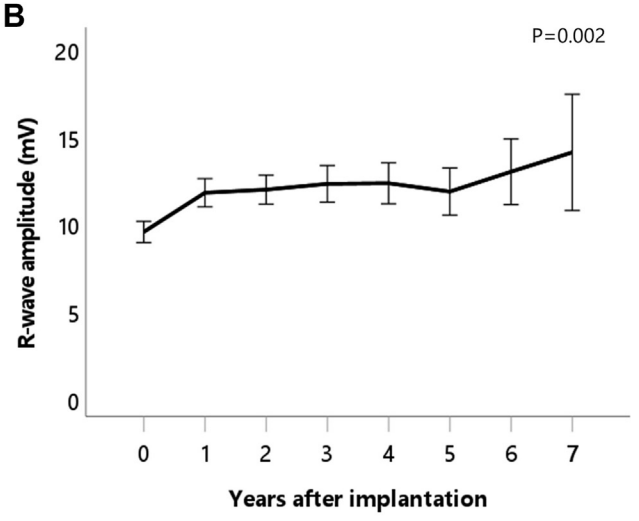
Values are given as n (%).

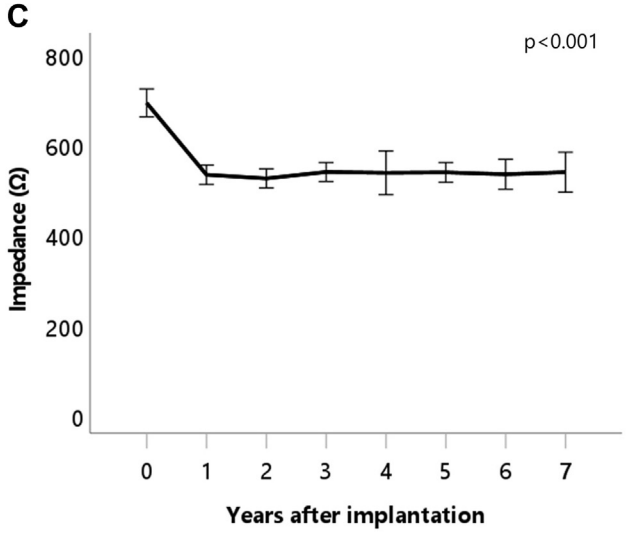
programmed <50/min in 17 patients (11%), 50–60/min in 127 (82%), and >60/min in 10 (7%) at 1 year. Ventricular pacing percentage was 0%–25% in 70 patients (47%), 25%–50% in 21 (14%), 50%–75% in 14 (10%), and >75% in 43 (28%) at 1 year (shown over time in Supplemental Figure 2). During follow-up, 3 LPs (Nanostim LP 1; Micra VR LP 2) were replaced because of battery depletion (after mean 60 ± 13 months) that was not deemed premature.

Replacement strategies

During this study, a replacement strategy (extraction, coimplantation, or deactivation and no further action) was required for nondislocated LPs in 48 patients. Figure 3 shows different strategies that were taken. In 5 patients with a Nanostim LP with premature battery depletion, the LP was deactivated and no further action was taken. Extraction was







D

	Implantation	Five years	P-value overall trend
Pacing capture threshold, overall (V)	0.70±0.49	0.57±0.27	0.06
Micra VR LPs (V)	0.68±0.50	0.58±0.27	0.390
Nanostim LPs (V)	0.71±0.49	0.54±0.26	0.066
R-wave amplitude (mV)	9.4±4.0	11.7±5.1	0.002
Impedance (Ω)	689±209	535±76	<0.001

Totals differ between parameters due to missing values.
*pulse width for Micra VR LPs 0.24ms, for Nanostim LPs 0.4ms

Figure 2 Electrical parameters over time. **A**, pacing capture threshold (V), shown separately for Micra VR leadless pacemakers (LPs) and Nanostim LPs due to different pulse widths; **B**, R-wave amplitude (mV); **C**, impedance (Ω); **D**, means and standard deviations of the electrical parameters at implantation and at five years of follow-up. Vertical lines represent 95% confidence interval (panel **A-C**).

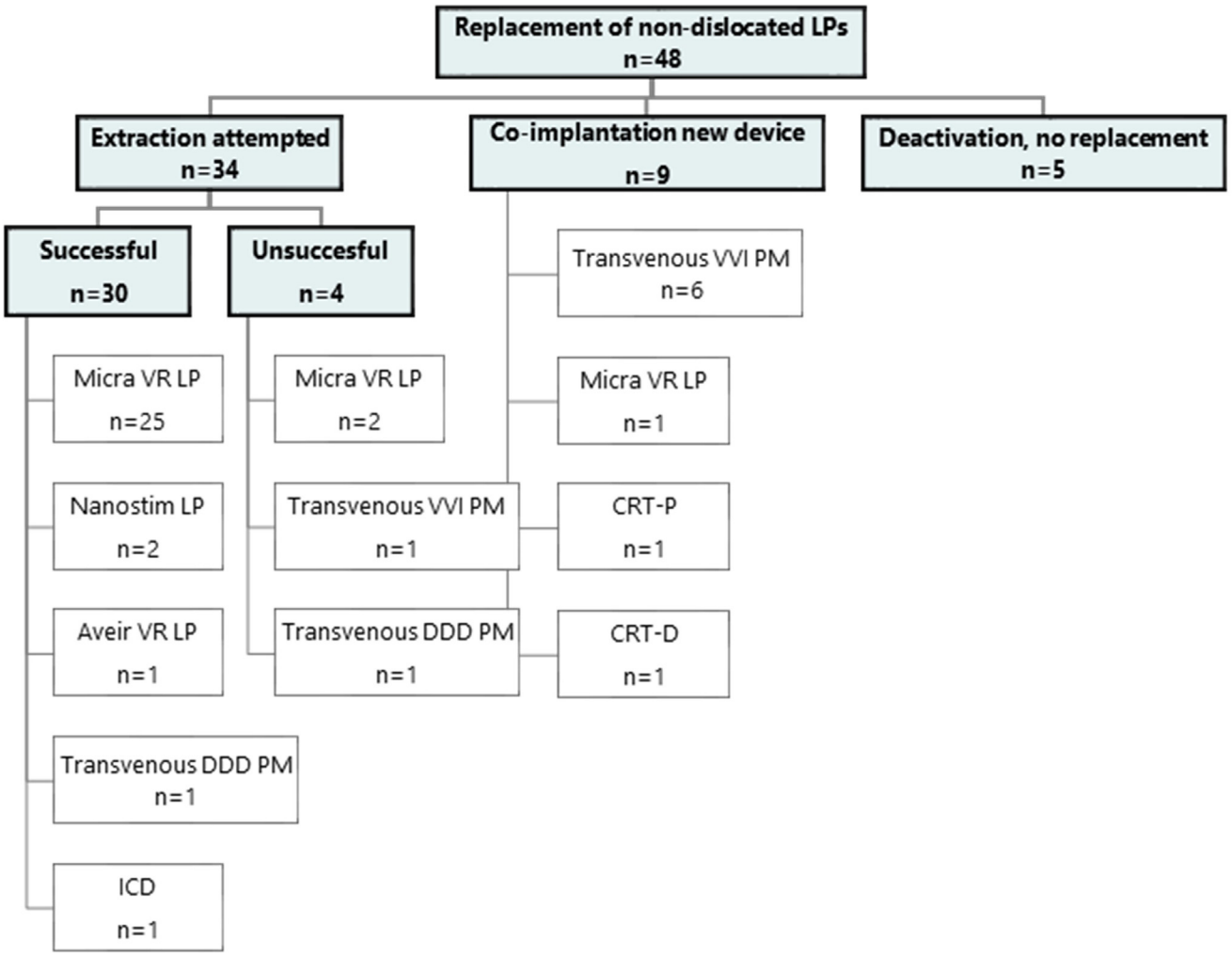


Figure 3 Different replacement strategies used in this study, including the device types that were implanted after extraction or coimplanted with the primary implanted leadless pacemaker (LP). CRT-D = cardiac resynchronization therapy–defibrillator; CRT-P = cardiac resynchronization therapy–pacemaker; ICD = implantable cardioverter-defibrillator; PM = pacemaker.

attempted in 34 patients and was successful in 30 (88%). All 34 LPs were Nanostim LPs, and time to extraction was mean 37 ± 22 months. There was no significant difference in time to extraction between the successful and unsuccessful extractions (36 ± 22 months vs 45 ± 19 months; $P = .49$). Extraction success by time to extraction is shown in Figure 4. Three of the unsuccessful retrievals were due to the inability to snare the docking button because of the position of the docking button behind the tricuspid valve in 1, adhesions in 1, and one of both in 1. In the other unsuccessful retrieval, catheter rotations were not converted to pacemaker rotations because of fibrotic overgrowth. The 9 patients with no extraction attempt (Micra VR LPs 3; Nanostim LPs 6) all were coimplanted with another device. No intermediate or major complications occurred during replacement or coimplantation.

Different clinical scenarios required a replacement strategy. The most common was (impending) premature battery failure due to the Nanostim battery or pacemaker dependency with a Nanostim *in situ* (n = 39 [5 without reimplantation]). Furthermore, in 4 patients, the device was replaced with a transvenous device because of a change of indication. One was replaced with an implantable cardioverter-defibrillator because of the occurrence of ventricular tachycardias, 1 with a cardiac resynchronization therapy–defibrillator because of deterioration

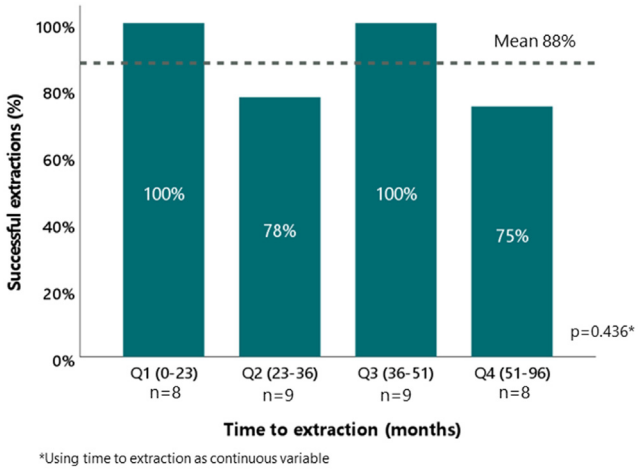


Figure 4 Extraction success by time to extraction (in months). Time to extraction is shown in quartiles with cutoff points at 23, 36, and 51 months.

of left ventricular function after myocardial infarction, and 1 with a cardiac resynchronization therapy–pacemaker because of high ventricular pacing percentage (77%) and heart failure with midrange ejection fraction. In the last patient, the LP was replaced with a dual-chamber pacemaker per the patient's request because of highly atypical chest symptoms. Three patients underwent replacement due to recommended replacement time (see section on Efficacy). Extraction was attempted in 1 patient, and the LP was successfully replaced with a Micra VR LP. The remaining 2 patients were coimplanted, 1 with a Micra VR LP and the other with a transvenous VVI pacemaker. Two LPs were replaced because of loss of capture (see sections on Safety and Efficacy).

End of follow-up

Of the 179 patients, 96 reached end of follow-up before either having a complication or reaching the end of the study. Eighty-three patients (46%) died a mean 34 ± 23 months after implantation, none deemed to be device related. Seven device replacements (4%) were unrelated to a complication (recommended replacement time 3; change of indication 4). Six patients (3%) were lost to follow-up.

Discussion

These real-world results in a general LP population demonstrate a low major complication rate, with all complications unrelated to the battery advisory occurring within 90 days of implantation, and a stable performance up to 7 years after implantation. Multiple replacement strategies were feasible, and extraction was successful in 88%, with a time to extraction of approximately 3 years without a declining success rate over time. This study confirms previous results of industry-initiated studies and studies with selected populations.[7–9]

In this study, we focused on major device-related complications defined as those requiring surgery, as those are thought to be most important to the patient. The most common were perforation (0.6%), dislodgment (1.7%), and loss of capture (1.1%). These complications occurred at rates very comparable to those in early LP studies, which was to be expected given that this study included LPs implanted early in the adoption of their use worldwide.[4,5] The rates of complications did not differ between the 2 LP types studied, although all dislodgments and cases of loss of capture occurred in patients with Nanostim LPs. Potentially, differences between the 2 LP types, such as the different fixation mechanisms, may have played at role. Compared to transvenous pacemakers, the perforation rate of LPs is higher but is decreasing as a result of more refined implantation techniques and the operator learning curve.[7,8] The incidences of dislodgments and loss of capture are similar for LPs and transvenous pacemakers.[2] Of note, in this study, 2 of 3 dislodgments (66%) occurred during implantation and therefore posed less risk to the patient than out-of-hospital dislodgments. Device infection, another important complication of pacemaker therapy that may require surgery, did not occur in this study, which is in line with previous studies on LPs.[11] Furthermore, an important finding of this study is the absence of complications requiring surgery between 88 days and 7 years postimplantation. In comparison, there was a 4% reintervention rate after 2 months in a large transvenous pacemaker study.[2] Because most of the transvenous pacemaker complications requiring reintervention are pocket and lead related, the low major complication rate after the acute phase may be a specific benefit of LP therapy.

Our results also demonstrated stable pacing parameters in the long term, confirming earlier studies with shorter follow-up.[6,7] The efficacy endpoint was met in nearly all patients. Importantly, PCT remained stable up to 7 years postimplantation. In contrast, PCT of transvenous pacemakers rises slowly over time.[12] Of note, the rate of procedural repositioning was 24% in our cohort, reflecting the early implementation phase of LPs. This rate may be lower in current clinical practice, as PCTs proved to decrease often after LP implantation.[13] Furthermore, the results of this study add to the limited experience on the feasibility and risks of different replacement strategies. First, we demonstrated good long-term extraction success without a decline with longer time to extraction. Second, our results emphasize the utmost importance in reassessing the pacemaker indication before extraction, because significant changes to pacemaker indication can occur in the long term (eg, progression of brady-tachy syndrome to permanent atrial fibrillation eliminating the pacemaker indication).

Study limitations

First, the design was retrospective, which introduces the risk of information bias. Second, there may have been differential attrition rates among patients, as patients with more comorbidities or higher age may have been more likely to drop out of the study. Third, we did not collect data on the safety and efficacy of LPs or transvenous devices that replaced primary LPs. Therefore, we are not able to provide data on the strategy of LP implantation and subsequent revisions as a whole. Fourth, data were collected from all follow-up visits without standard echocardiographic examinations, so we are not able to provide the exact number of patients with pacing-induced cardiomyopathy.

This study reports the first real-world long-term results of LP therapy in a general LP population. Long-term results are important because pacemakers are a long-term therapy. Our expectation is that the reported complication rate will hold for the lifetime of LPs given the encapsulation of LPs, which probably diminishes the risk of dislodgments and perforations, and the stable threshold shown in this and other studies.[7,14] The inclusion of Nanostim LPs is important given that use of LPs with a helix-based fixation mechanism has returned with the Aveir VR, and long-term results of the Aveir VR will not be available in the upcoming years. Use of LPs with a helix-based fixation mechanism may become even greater, as the first dual-chamber LP, the Aveir DR, consists of the Aveir VR and a similar atrial LP. A clinical study of the Aveir DR is currently in progress (Aveir DR i2i Study; ClinicalTrials.gov Identifier NCT05252702.). The results of this study are derived from 2 LP models with different

morphologies, so this study provides a more robust reflection of LP therapy in general.

Conclusion

The long-term safety (excluding advisory-related complications) and efficacy of LPs were adequate. No complications occurred more than 3 months after implantation, which may be a specific benefit of LPs. The pacing threshold of LPs is stable over time, in contrast to the gradually rising threshold of transvenous pacemakers. Our study results confirm the findings of previous studies and are promising for longer-term data on leadless pacing.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2023.05.031.

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