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ORIGINAL ARTICLE

A Leadless Intracardiac Transcatheter Pacing System

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For more than half a century, permanent cardiac pacing for symptomatic bradycardia has been achieved with systems that consist of a surgically implanted subcutaneous electrical generator connected to one or more transvenous leads that deliver the pacing therapy to the heart. Although these devices are effective, approximately one in eight patients has an early complication, frequently related to the lead or leads or to the subcutaneous “pocket.”¹ Complications include problems with the subcutaneous pocket, such as hematomas and infections; lead-insertion problems, such as pneumothoraxes and hemothoraxes; lead dislodgements and integrity problems; infections, including septicemia and endocarditis; vascular obstructions; and reduced vascular access. The pursuit of leadless pacing options has long been of interest^{2,3} to reduce the complications that can lead to interruption of pacemaker therapy, to hospitalization, or to death. As a result of advances in battery chemistry and component design, pacemakers are now small enough to place within the heart. In this report, we describe an international study of the performance of a self-contained pacemaker that is designed to avoid the need for a subcutaneous pocket and transvenous leads.

METHODS

Study Design and Oversight

The study is a prospective, nonrandomized, single-study-group, multisite, international clinical study to evaluate the safety and efficacy of the Micra Transcatheter Pacemaker System (Medtronic). The study is ongoing; the analysis reported here is a planned interim analysis. The design of the study has been described previously.⁴

The steering committee (the members are listed in the [Supplementary Appendix](#), available with the full text of this article at NEJM.org) designed and oversaw the conduct of the study and the data analysis in collaboration with the sponsor, Medtronic. The sponsor assisted in data analyses and in preparing this report. The [protocol](#) was approved by the ethics committee at each participating institution and associated national and local regulatory agencies and, along with the statistical analysis plan, is available at NEJM.org. Adjudications of adverse events were conducted by an independent clinical events committee. Oversight of safety and of study conduct are provided by an independent data and safety monitoring committee. The first draft of the manuscript was prepared by the first author, who had unrestricted access to the data, and was reviewed and edited by all the authors. All the authors take responsibility for the accuracy and completeness of the analysis and for the fidelity of this report to the study [protocol](#).

Patients and Study Procedures

We enrolled patients who met class I or II guideline-based indications for pacing (i.e., for bradycardia due to atrial tachyarrhythmia, sinus-node dysfunction, atrioventricular node dysfunction, or other causes).^{5,6} were considered to be suitable candidates for single-chamber ventricular demand (VVI) pacing, were not prevented from participating as a result of coexisting conditions, and provided written informed consent. Patients with an existing pacemaker or implantable cardioverter–defibrillator were not included in the study. Detailed inclusion and exclusion criteria are provided in Table S1 in the [Supplementary Appendix](#).

Study Device and Procedures

The Micra transcatheter pacemaker, a single-chamber ventricular pacemaker, is self-contained in a hermetically enclosed capsule with a volume of 0.8 cm³, a length of 25.9 mm, an outer diameter of 6.7 mm, and a weight of 2.0 g. Its functionality and features are similar to those of existing ventricular pacemakers, with features that include accelerometer-based rate-adaptive pacing and automated pacing capture threshold management to maximize battery longevity.

The implantation procedure for the transcatheter pacemaker has been described previously.^{4,7,8}

The device sits in a steerable catheter delivery system and is inserted through a femoral vein with the use of a 23-French introducer. The catheter is advanced into the right ventricle, and the device is affixed to the myocardium through four electrically inactive nitinol tines located at the distal end of the device ([Figure 1](#), and the [Supplementary Appendix](#)). After verification of device fixation and adequate electrical measurements, a tether is cut, and the delivery system is removed.

FIGURE 1

Follow-up and End Points

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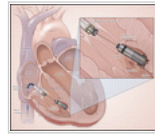
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Patients in whom the device was implanted were evaluated for adverse events and device function at hospital discharge and at follow-up assessments at 1, 3, and 6 months and every 6 months thereafter. The study had two primary end points that were assessed at 6 months of follow-up. The primary safety end point was freedom from system-related or procedure-related major complications. Major complications were defined as events resulting in death, permanent loss of device function as a result of mechanical or electrical dysfunction, hospitalization, prolongation of hospitalization by at least 48 hours, or system revision. The primary efficacy end point was the combination of a low (≤ 2 V at a pulse width of 0.24 msec) and stable (increase of ≤ 1.5 V from the time of implantation) pacing capture threshold at the 6-month visit.



Micra Transcatheter Pacing System Positioned in the Right Ventricle.

Statistical Analysis

We calculated that a sample of 720 patients with the device successfully implanted would provide more than 90% power to test the two primary end points relative to the specific performance goals as described below. With respect to the safety objective, we assumed that the rate of freedom from major complications would be greater than 90%, and with respect to the efficacy end point, we assumed that more than 89% of the patients would meet the criteria for the pacing capture threshold. The sample size and statistical analysis plan allowed for up to three planned interim analyses of the two primary end points, when 300, 450, and 600 patients had completed the 6-month follow-up visit. It was prespecified that, for each interim analysis, if both primary objectives were met, subsequent interim analyses would not be performed, and longer-term patient follow-up would continue. The boundaries defining success with regard to both primary objectives were based on a group sequential design⁹ to maintain an overall alpha level of 2.5%. A prespecified early performance assessment of the initial 60 patients who were followed for 3 months was completed for regulatory reasons and has been reported previously.⁸

The analysis of the safety objective included all 725 patients who underwent an implantation attempt. The 6-month Kaplan–Meier estimate of the freedom from major complications was evaluated against a performance goal of 83% with the use of a one-sample Wald test. The safety performance goal was based on data from 977 patients who were enrolled in six previous pacemaker studies, as described in the Methods section and Figure S1 of the [Supplementary Appendix](#). For the efficacy objective, the prespecified cohort included all patients who underwent successful implantation and for whom pacing threshold data at implantation and at 6 months were available or who had system revisions because of high thresholds before 6 months (with these system revisions designated as treatment failures). An exact binomial test was used to compare the percentage of patients meeting the primary efficacy end point against the performance goal of 80%. The efficacy performance goal was based on data on 322 pacing systems from the Medtronic CareLink database, as described in the Methods section and Figure S2 of the [Supplementary Appendix](#).

In addition to the comparisons against performance goals for the efficacy and safety analyses, we conducted a post hoc analysis to compare the risk of major complications through 6 months with the risk in a historical control group that consisted of 2667 patients from the six previous pacemaker studies cited above (Table S2 in the [Supplementary Appendix](#)). The Fine–Gray¹⁰ competing risk model was used to compare the patients who received the transcatheter pacemaker with those in the historical control group. A 1:1 propensity-matched subgroup of the control patients was used as the comparator group in an additional analysis (details are provided in the [Supplementary Appendix](#)). All analyses were conducted with SAS software, version 9.4 (SAS Institute), or the R statistical package (R Project for Statistical Computing).¹¹

RESULTS

Patients

Enrollment was completed in May 2015, with 744 patients enrolled at 56 centers in 19 countries in North America, Europe, Asia, Australia, and Africa. Nineteen patients exited the study before pacemaker implantation was attempted, because they withdrew consent (11 patients) or because they did not meet eligibility criteria (8 patients). A total of 725 patients underwent an implantation attempt (Fig. S3 in the [Supplementary Appendix](#)).

The primary indications among patients undergoing attempted implantation of the transcatheter pacemaker were bradycardia associated with persistent or permanent atrial tachyarrhythmia (64.0%), sinus-node dysfunction (17.5%), atrioventricular block (14.8%), and other reasons (3.7%). The reasons for the selection of VVI pacing included indications associated with atrial tachyarrhythmia (65.0%), an expectation that pacing would not be frequent (29.7%), the patient's advanced age (18.2%), and patient preference for new technology (12.3%). In 45 patients (6.2%), leadless pacing was chosen because of conditions that precluded implantation of a transvenous pacemaker system, such as compromised venous access, the need to preserve veins for hemodialysis, thrombosis, a history of infection, or the need for an indwelling venous catheter. The baseline characteristics of the 725 patients who underwent an implantation attempt are shown in [Table 1](#).

Of the 725 attempted implantations, 719 (99.2%) were successfully performed by 94 physicians. The six patients who underwent unsuccessful implantation attempts included four patients with major complications (three with cardiac perforations and one with pericardial effusion), one patient with tortuous venous anatomy, and one patient in whom a satisfactory pacing capture threshold could not be obtained. Details regarding the implantation procedures are provided in Table S3 in the [Supplementary Appendix](#). The recipients of successful implants were followed for a mean of 4 months (range, 0 to 14).

Evaluation of Safety against the Performance Goal

Among the 725 patients included in the safety analysis, the Kaplan–Meier estimate for freedom from major complications related to the system or procedure was 96.0% at 6 months after implantation (95% confidence interval [CI], 93.9 to 97.3%; $P < 0.001$ for the comparison with the



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TABLE 1

Characteristic	Number of Patients	Percentage
Age, mean (SD)	67.5 (11.5)	
Male	488	67.3
Female	237	32.7
White	508	69.9
Black	102	14.1
Hispanic	102	14.1
Other	13	1.8
Median follow-up, months	4.0	
Median time to implantation, days	14.0	
Median time to follow-up, days	14.0	
Median time to last follow-up, days	14.0	
Median time to death, days	14.0	
Median time to hospitalization, days	14.0	
Median time to system revision, days	14.0	
Median time to major complication, days	14.0	
Median time to death, days	14.0	
Median time to hospitalization, days	14.0	
Median time to system revision, days	14.0	
Median time to major complication, days	14.0	

Characteristics of the Patients at Baseline.

safety performance goal of 83%) (Figure 2). There were no radiographically visible device dislodgements, no telemetry failures, and no systemic infections. There were 28 major complications in 25 patients, including 4 of the 6 patients who underwent the unsuccessful implantation attempts described above (Table 2). The major complications included 11 cardiac injuries, 5 complications at the groin puncture site, 2 cases of thromboembolism, 2 pacing issues, and 8 other complications. All the major complications met the criteria for the safety end point because they resulted in hospitalization or prolongation of hospitalization, with the exception of one that was due to death (caused by metabolic acidosis, as described in the Supplementary Appendix). There were three system revisions: in 2 patients, the device was turned off (OOO mode) (in 1 patient because of an elevated pacing capture threshold and in 1 patient because the patient had symptoms of pacemaker syndrome) and remained in the right ventricle, and a concomitant transvenous system was implanted, and in 1 patient the device was retrieved when intermittent loss of capture was noted without radiographic evidence of dislodgement. This device was retrieved with the use of a percutaneous snare 17 days after implantation and was replaced with a new transcatheter device. Additional information concerning cardiac injuries and all deaths is provided in the Results section and Tables S4 and S5 in the Supplementary Appendix.

Evaluation of Efficacy against the Performance Goal

Of the 297 patients who were included in the primary efficacy analysis (Fig. S3 in the Supplementary Appendix), 292 (98.3%; 95% CI, 96.1 to 99.5) had an adequate 6-month pacing capture threshold; that is, they had a 6-month pacing capture threshold of no greater than 2.0 V and had an increase of no more than 1.5 V in pacing capture threshold from implantation to 6 months ($P < 0.001$ for the comparison with the efficacy performance goal of 80%). Among all patients who underwent implantation and for whom follow-up data were available, the pacing capture threshold tended to decrease shortly after implantation and remained stable thereafter; the mean pacing capture threshold was 0.63 V at a pulse width of 0.24 msec at implantation and 0.54 V at a pulse width of 0.24 msec at the 6-month visit (Figure 3A). The mean R-wave amplitude was 11.2 mV at implantation and 15.3 mV at the 6-month visit (Figure 3B). The mean pacing impedance was 724 ohms at implantation and decreased to 627 ohms at the 6-month visit (Figure 3C).

Evaluation of Safety against the Control Group

In a post hoc analysis, the 725 patients in our study (study patients) were compared with the 2667 patients who received transvenous pacemakers in the historical control cohort (control patients). There were significant differences between the study patients and the control patients with regard to baseline characteristics (Table S6 in the Supplementary Appendix): the study patients were older and had more coexisting conditions than did the control patients. The control patients in the propensity-matched subgroup were similar to the study patients with respect to baseline characteristics (Table S7 in the Supplementary Appendix).

Through 6 months of follow-up, the study patients had fewer major complications than did the patients in the historical control cohort (4.0% vs. 7.4%; hazard ratio, 0.49; 95% CI, 0.33 to 0.75; $P = 0.001$) (Fig. S4 in the Supplementary Appendix). A similar result was obtained in the analysis with adjustment for differences in the patient populations, in which the propensity-matched control subgroup was used (hazard ratio, 0.46; 95% CI, 0.28 to 0.74). The patients in our study, as compared with patients in the control cohort, had significantly fewer hospitalizations (2.3% vs. 3.9%) and fewer system revisions (0.4% vs. 3.5%) due to complications (Table S8 in the Supplementary Appendix). The rates of major complications at 6 months among the study patients and in the control cohort, according to major complication category, are shown in Figure S5 and Table S9 in the Supplementary Appendix. The rates of fixation-related events (device or lead dislodgements) were significantly higher in the control cohort than in the study cohort. The rates of access-site events, pacing issues, and cardiac injury events did not differ significantly between the cohorts.

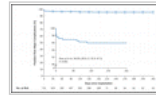
DISCUSSION

In this study, the Micra transcatheter pacing system was examined in a cohort of 725 patients. The device was successfully implanted in 719 patients (99.2%). During 6 months of follow-up, the efficacy and safety of the device were evaluated against performance goals that were based on data from recipients of conventional transvenous pacemakers. The efficacy and safety outcomes among the patients in our study met both performance goals, including freedom from major complications related to the system or procedure in 96.0% of the patients (95% CI, 93.9 to 97.3), as compared with a performance goal of 83%, and an adequate pacing capture threshold in 98.3% of the patients (95% CI, 96.1 to 99.5), as compared with a performance goal of 80%.

Data on the safety of transcatheter pacing are preliminary and have been limited to a few reports from nonrandomized studies.^{8,12,13} The technology currently provides single-chamber ventricular pacing, which serves only a subgroup of patients who require pacemakers.^{1,14} The delivery of the implant requires a different approach than that used for transvenous leads, with substantially larger venous access tools, and the longevity of the device, although estimated to be similar to that of subcutaneous generators, is not known.

In an effort to characterize the safety of the device in greater detail, we performed a post hoc comparison of the data on complications in the study patients with information on complications in a group of historical control patients. We observed significantly fewer hospitalizations and system revisions among the study patients, in part as a consequence of the fact that the transcatheter pacemaker has no pacemaker pocket or leads. In addition, the study patients had no systemic infections, no pneumothoraxes, and no radiographically visible dislodgements or device emboli. Experience with retrieval of the device was limited to one patient.

FIGURE 2



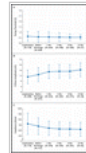
Kaplan-Meier Estimate of Absence of Major Complications Related to the Micra System or Implantation Procedure through 12 Months after Implantation.

TABLE 2

Complication Category	Number of Patients	Percentage of Patients
Cardiac Injuries	11	1.5%
Complications at Groin Puncture Site	5	0.7%
Thromboembolism	2	0.3%
Pacing Issues	2	0.3%
Other Complications	8	1.1%
Total Major Complications	28	3.9%

Major Complications in 725 Patients Who Underwent a Transcatheter Pacemaker Implantation Attempt.

FIGURE 3



Electrical Performance Characteristics of the Transcatheter Pacemaker, According to Study Visit.

Complications that led to death or that required invasive revision, termination of therapy, or hospitalization or extension of hospitalization occurred in 4.0% of the patients; this finding is in line with recent reports of transvenous systems¹⁵ and was significantly lower than the rate in the control group. However, cardiac injury occurred in 1.6% of the study patients, which is a higher frequency than that among the control patients (1.1%), although this difference was not significant. Whether the injury from transcatheter technology is specifically due to the delivery catheter, device design, cardiac anatomy, or the demographic characteristics of the patients is unclear. It is notable that the patients who had cardiac injury were elderly, more likely to be women, and more likely to have chronic lung disease or chronic obstructive pulmonary disease than were patients without injury and that these are also reported risk factors related to complications with transvenous leads.¹⁶⁻¹⁸

Pacing capture thresholds were low at implantation and remained stable through follow-up, with 91% of patients having a pacing output of less than 1.5 V at a pulse width of 0.24 msec. Projections based on the use conditions of patients who were followed for 6 months suggest an estimated battery longevity of 12.5 years, with 94% lasting more than 10 years, which is similar to the battery longevity of transvenous pacing systems.^{19,20}

Recently, an interim analysis of a differently designed transcatheter pacemaker (Nanostim, St. Jude Medical) was reported.¹³ Among implantation attempts in 526 patients, 95.8% were successful. In the primary cohort of 300 patients, 90% had adequate pacemaker function at 6 months. Device-related serious adverse events occurred in 6.7% of the patients and included device dislodgement and retrieval in 1.7%, cardiac perforation in 1.3%, and an elevated pacing capture threshold requiring percutaneous retrieval and device replacement in 1.3%. Direct comparison with our study should be performed cautiously, because of differences between the two studies in device design and study design, and because of the broader demographic and geographic profile of our patient population.

The primary limitation of our study is the lack of comparison with a randomized control group. Instead, we compared the outcomes in our patients against separately defined performance criteria for safety and efficacy, and in a post hoc analysis we compared them with outcomes in a group of control patients. Additional limitations were that the follow-up data were limited to 6 months and that implantation experience was limited to the 94 physicians who performed the implantations.

In conclusion, the Micra transcatheter pacing system, a leadless right ventricular pacemaker, was successfully implanted in 99.2% of 725 patients in whom implantation was attempted. The device met prespecified criteria for pacing capture threshold in 98.3% of the patients who were followed for 6 months. Although there were 28 major complications in 25 patients, the prespecified safety criteria were also met, and 96.0% of patients had no major complications at 6 months.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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A complete list of investigators in the Micra Transcatheter Pacing Study Group is provided in the [Supplementary Appendix](#), available at NEJM.org.

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