Updated performance of the Micra transcatheter pacemaker in the real-world setting: A comparison to the investigational study and a transvenous historical control

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BACKGROUND Early results of the Micra Investigational Device Exemption (IDE) study and Micra Post-Approval Registry (PAR) demonstrated excellent safety and efficacy performance; however, intermediate-term results across a large patient population in the real-world setting have not been evaluated.

OBJECTIVES We report updated performance of the Micra transcatheter pacemaker from a worldwide PAR and compare it with the IDE study as well as a transvenous historical control.

METHODS The safety objective of the analysis was system- or procedure-related major complications through 12 months postimplantation. We compared the major complication rate with that of the 726 patients from the IDE and with a reference data set of 2667 patients with transvenous pacemakers by using a Fine-Gray competing risk model.

RESULTS The Micra device was successfully implanted in 1801 of 1817 patients (99.1%). The mean follow-up period was 6.8 ± 6.9 months. Through 12 months, the major complication rate was 2.7% (95% confidence interval [CI] 2.0%–3.7%). The risk of major complications for Micra PAR patients was 63% lower than that for patients with transvenous pacemakers through 12 months postimplantation (hazard ratio 0.37; 95% CI 0.27–0.52; $P < .001$). The

The Micra Post-Approval Registry and Micra Transcatheter Pacing Study are funded by Medtronic, plc, USA. Dr El-Chami has received compensation for services from Boston Scientific and Medtronic. Dr Clementy, Dr Martinez-Sande, Dr Ritter have received compensation for services from Medtronic. Dr Garweg has received proctoring fees from Medtronic. Dr Piccini has received compensation for services from Medtronic and research grant from Abbott and Boston Scientific. Dr Lloyd has received compensation for services from Boston Scientific and Medtronic; speakers' bureau from Medtronic; and research grant from Abbott, Boston Scientific, and Medtronic. Dr Johansen has received compensation for services from Cook Medical and speakers' bureau from Medtronic and Merit Medical. Dr. Liu, Dr Fagan, and Ms Eakley are employees/shareholders of Medtronic. Dr Roberts has received compensation for services from Medtronic; speakers' bureau from Medtronic; and research grant from Medtronic. The rest of the authors report no conflicts of interest. **Address reprint requests and correspondence:** Dr Mikhael F. El-Chami, Division of Cardiology, Section of Electrophysiology, Emory University Hospital, 550 Peachtree St NE, Atlanta, GA 3308. E-mail address: melcham@emory.edu.

1547-5271/

https://doi.org/10.1016/j.hrthm.2018.08.005

major complication rate trended lower in the PAR than in the IDE study (hazard ratio 0.71; 95% CI 0.44–1.1; $P = .160$), driven by the lower pericardial effusion rate in the PAR. There were 3 cases of infection associated with the procedure, but none required device removal and there were no battery or telemetry issues. Pacing thresholds were low and stable through 12 months postimplantation.

CONCLUSION Performance of the Micra transcatheter pacemaker in international clinical practice remains consistent with previously reported data. Major complications were infrequent and occurred 63% less often compared to transvenous systems.

CLINICAL TRIAL REGISTRATION Micra Transcatheter Pacing System Post-Approval Registry ClinicalTrials.gov identifier: NCT02536118; Micra Transcatheter Pacing Study ClinicalTrials.gov identifier: NCT02004873.

KEYWORDS Leadless pacing; Real-world performance; Transcatheter pacemaker; Updated results; Transvenous pacemaker

Introduction

Transvenous pacing leads and subcutaneous pockets are frequently the source of complications with traditional transvenous pacemakers (TV-PPMs).[1,2] Leadless pacemakers were designed to minimize these complications.[3,4] The Micra Investigational Device Exemption (IDE) study established the safety and efficacy of the Micra transcatheter pacing system (TPS).[4] In the IDE study, the Micra TPS was successfully implanted in 99.2% of patients with a low rate of complications at 1-year follow-up (4%), which was 48% lower than that for patients with transvenous systems.[5] Remarkably, no infections or macro-dislodgments were encountered in this study. Pacing parameters remained excellent and stable through 24-month follow-up. While these early results were encouraging, it is not clear that the efficacy and safety are similar outside the confines of a clinical trial conducted at major pacing centers.

The Micra Post-Approval Registry (PAR), mandated by the Food and Drug Administration, was designed to study the safety and efficacy of this device in a real-world setting.[6] In this article, we report updated performance of the Micra TPS from a worldwide PAR and compare it with the IDE study as well as a transvenous historical control.

Methods

Study design

The design of the Micra PAR has been described previously.[6] Briefly, the aim of this active, prospective, nonrandomized, multicenter registry was to further evaluate short- and long-term safety performance of the Micra TPS when used as intended in "real-world" clinical practice after commercial release. The protocol was approved by an ethics committee at each of the participating centers, as applicable. All system- and procedure-related adverse events were adjudicated by a Clinical Events Committee of independent physicians.

Patients and procedures

All patients intended to be implanted with a market-approved Micra device at participating centers were eligible. Enrolled patients provided written informed consent. Patients who participated in a premarket trial (ie, IDE study) and consented to participate in the PAR for long-term follow-up were excluded from this analysis. The first new registry enrollment occurred on July 26, 2015, after regulatory approval of the Micra device in Europe, and global enrollment was closed on March 2, 2018. The required 9-year registry follow-up period is ongoing.

The Micra TPS is a single-chamber ventricular pacemaker and is 93% smaller than a TV-PPM system with a total volume of 0.8 mL. The device has similar functionality and features to existing single-chamber ventricular pacemakers, including rate adaptive pacing, remote monitoring capabilities, and automated pacing capture threshold management, designed to maximize battery longevity. Micra is inherently magnetic resonance imaging conditionally safe for full-body scans in both 1.5-T and 3-T scanners.[7] The device is implanted directly in the right ventricle through a femoral vein. The device is fixated in the myocardium via 4 flexible nitinol tines.[8,9]

Enrolled patients underwent implant attempt and are followed according to routine care practices of their provider. Patient and device status are reported at implant/prehospital discharge, 30 days postimplantation, and at least annually thereafter for a minimum follow-up period of 9 years. All system- and procedure-related adverse events or system revisions (eg, device extraction) are to be reported immediately after center awareness.

End points

The aim of this analysis was to assess system- or procedure-related major complications through 12 months postimplantation. Adopting the same criteria used in the Micra IDE study, major complications were defined as system- and procedure-related events resulting in death, permanent loss of device function, hospitalization, prolonged hospitalization by 48 hours, or system revision. The diagnoses of all events and any resulting clinical actions were reported by center investigators. The Clinical Events Committee reviewed and adjudicated, at a minimum, all system- and procedure-related adverse events to determine relatedness and whether the events met the criterion of a major complication. Major complication rates through 12 months were compared with those previously reported in the IDE study.[5] In addition, for a comparison of safety performance relative to

Table 1 Baseline characteristics

Characteristic	Postmarket (n = 1817)	IDE (n = 726)	Total (N = 2543)	*P*
Sex: male	1111 (61.1)	427 (58.8)	1538 (60.5)	.26
Atrial arrhythmia	1370 (75.4)	548 (75.5)	1918 (75.4)	>.99
CHF	234 (12.9)	131 (18.0)	365 (14.4)	.001
COPD	176 (9.7)	92 (12.7)	268 (10.5)	.032
CAD	402 (22.1)	205 (28.2)	607 (23.9)	.001
HTN	1165 (64.1)	571 (78.7)	1736 (68.3)	<.001
Diabetes	480 (26.4)	207 (28.5)	687 (27.0)	.30
Prior CIED	265 (14.6)	0 (0.0)	265 (10.4)	<.001
Condition that precludes the use of a TV-PPM	435 (23.9)	45 (6.2)	480 (18.9)	<.001
Pacing indication				
Bradyarrhythmia with AF	1127 (62.0)	464 (63.9)	1591 (62.6)	<.001
Sinus node dysfunction	177 (9.7)	126 (17.4)	303 (11.9)	
AV block	211 (11.6)	109 (15.0)	320 (12.6)	
Syncope	243 (13.4)	16 (2.2)	259 (10.2)	
Other	50 (2.8)	11 (1.5)	61 (2.4)	
Not reported	9 (0.5)	0 (0.0)	9 (0.4)	

Values are presented as n (%).

AF = atrial fibrillation; AV = atrioventricular; CAD = coronary artery disease; CHF =congestive heart failure; CIED = cardiac implantable electronic device; COPD = chronic obstructive pulmonary disease; HTN =hypertension; IDE = Micra Investigational Device Exemption; TV-PPM = transvenous pacemaker.

conventional pacemaker systems with transvenous leads, a data set of 2667 patients with de novo pacemakers from 6 recent Medtronic trials of dual-chamber pacing was assembled.[4] Events related only to the right atrial lead were excluded in order to approximate a single-chamber data set. Rates of major complications, including breakdown of major complication criteria, were compared between the Micra and transvenous control groups. Electrical performance at implantation/prehospital discharge and follow-up was also characterized.

Statistical analysis

At the time of the database freeze for this analysis, all but 6 successfully implanted patients were included because of delayed data entry. Summary statistics were obtained and reported using mean ± SD for continuous variables and frequency and percentage for categorical variables.

The major complication rate was calculated for each category and subcategory for both acute major complication (≤30 days of follow-up) and chronic major complication (>30 days of follow-up). The distribution of pacing percentage for Micra patients at the last follow-up visit was plotted. Battery longevity estimates were obtained from each patient's last device interrogation and normalized to the longevity remaining at 6 months (183 days) postimplantation. Kaplan-Meier methods were used to estimate the rate of major complication (and its components) at 12 months postimplantation. In addition, the Fine-Gray competing risk model was used to compare the risk of major complications (and its components) through 12 months between 2 groups: 2667 patients in the transvenous control group vs 1817 patients with an attempted Micra implantation procedure in the postmarket population and 726 patients with an attempted Micra implantation procedure in the IDE study. However, when comparing components of the major complication rate, the Fisher exact test was used if zero events were observed for one of the groups. All analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC) or the R statistical package (R Project for Statistical Computing, Vienna, Austria). Electrical parameters were summarized at each study visit using means and SDs.

Results

Patients

A total of 1817 enrolled patients underwent implant attempt from 179 centers in 23 countries from July 2015 through March 2018. Patients were on average 75.6 ± 13.5 years of age, were mostly (n=1111, 61.1%) men, and had multiple comorbidities, including hypertension (n=1165, 64.1%), diabetes (n=480, 26.4%), coronary artery disease (n=402, 22.1%), and chronic obstructive pulmonary disease (COPD) (n=176, 9.7%) (Table 1). Compared with patients in the IDE study, patients in the PAR had fewer comorbidities, including coronary artery disease, heart failure, and COPD. Nearly a quarter of patients (n=435, 23.9%) had a condition the implanting physician felt precluded the use of a transvenous system and 265 (14.6%) had a prior cardiac implantable electronic device implanted. The most common primary indication for pacing was bradyarrhythmia with atrial fibrillation (AF) (n=1127, 62.0%), followed by syncope (n=243, 13.4%), atrioventricular (AV) block (n=211, 11.6%), sinus node dysfunction (n=177, 9.7%), and other/not reported (n=59, 3.3%). Patients in the PAR tended to be older, were more likely to be male, and had a higher incidence of diabetes, COPD, and AF than did the historical TV-PPM cohort (Supplemental Table 1). The Micra device was successfully implanted in 1801 patients (99.1%). Devices were predominantly placed in the right ventricular (RV) septum (n=1156, 63.6%), followed by the RV apex (n=582, 32.0%). The median procedure time (time from the introducer

Table 2 Major complications for patients with an attempted Micra implantation procedure (n=1817)

Complication	No. of events (no. of patients, percentage)		
	≤30 d	>30 d	Total major complications
Total major complications	41 (36, 1.98)	5 (5, 0.28)	46 (41, 2.26)
Embolism and thrombosis	2 (2, 0.11)	0 (0, 0)	2 (2, 0.11)
Deep vein thrombosis	1 (1, 0.06)	0 (0, 0)	1 (1, 0.06)
Pulmonary embolism	1 (1, 0.06)	0 (0, 0)	1 (1, 0.06)
Events at the groin puncture site	10 (10, 0.55)	1 (1, 0.06)	11 (11, 0.61)
Arterial injury/atrioventricular fistula	6 (6, 0.33)	1 (1, 0.06)	7 (7, 0.39)
Hematoma	1 (1, 0.06)	0 (0, 0)	1 (1, 0.06)
Incision site hemorrhage	2 (2, 0.11)	0 (0, 0)	2 (2, 0.11)
Retroperitoneal hemorrhage	1 (1, 0.06)	0 (0, 0)	1 (1, 0.06)
Cardiac effusion/perforation	8 (8, 0.44)	0 (0, 0)	8 (8, 0.44)
Pacing issues	12 (11, 0.61)	2 (2, 0.11)	14 (13, 0.72)
Device capturing issue/elevated thresholds	9 (9, 0.50)	2 (2, 0.11)	11 (11, 0.61)
Device dislodgment	1 (1, 0.06)	0 (0, 0)	1 (1, 0.06)
Device embolization during an implant attempt	1 (1, 0.06)	0 (0, 0)	1 (1, 0.06)
Undersensing	1 (1, 0.06)	0 (0, 0)	1 (1, 0.06)
Infection	3 (3, 0.17)	0 (0, 0)	3 (3, 0.17)
Abdominal wall infection	1 (1, 0.06)	0 (0, 0)	1 (1, 0.06)
Hematoma infection	1 (1, 0.06)	0 (0, 0)	1 (1, 0.06)
Sepsis	1 (1, 0.06)	0 (0, 0)	1 (1, 0.06)
Other	6 (6, 0.33)	2 (2, 0.11)	8 (8, 0.44)
Blood pressure decreased	1 (1, 0.06)	0 (0, 0)	1 (1, 0.06)
Cardiac failure	1 (1, 0.06)	0 (0, 0)	1 (1, 0.06)
Cardiomyopathy	0 (0, 0)	1 (1, 0.06)	1 (1, 0.06)
Complication of device removal	1 (1, 0.06)	0 (0, 0)	1 (1, 0.06)
Noncardiac chest pain	1 (1, 0.06)	0 (0, 0)	1 (1, 0.06)
Pacemaker syndrome	0 (0, 0)	1 (1, 0.06)	1 (1, 0.06)
Pulmonary edema	1 (1, 0.06)	0 (0, 0)	1 (1, 0.06)
Syncope	1 (1, 0.06)	0 (0, 0)	1 (1, 0.06)

in to the introducer out) was 26.0 minutes (interquartile range [IQR] 19–40 minutes), and the majority of implants (n=1522, 83.8%) required ≤3 deployments. The mean follow-up duration was 6.8 ± 6.9 months (range 0–30 months), with 465 patients having at least 12 months of follow-up.

Safety

There were 46 major complications in 41 patients adjudicated as related to the Micra device or procedure (Table 2). The majority of major complications (89%) occurred within 30 days of implantation, with only 1 major complication reported >6 months postimplantation. Of the major complications, there were 14 device pacing issue events, 11 events at the groin puncture site, 8 cardiac effusion/perforation events, 3 infection events, and 8 other events (including 1 cardiac failure event, 1 cardiomyopathy event, and 1 pacemaker syndrome event).

One patient experienced a right groin hematoma infection that occurred after a Micra/AV nodal ablation concomitant procedure. The infection resolved with intravenous antibiotics. One patient underwent a percutaneous retrieval attempt on the day of implantation owing to elevated thresholds. During the retrieval, the device became entangled in the patient's inferior vena cava filter (a contraindication for Micra implantation), causing vascular trauma, which required surgical repair. A second Micra device was successfully implanted the same day. This patient experienced an abdominal wall infection 25 days postimplantation, was hospitalized, treated with intravenous antibiotics, and was discharged when the infection resolved 5 days later. The third infection event (sepsis, which resolved with antibiotics and did not require device removal) was previously described.[6]

There was 1 dislodgment without embolization. The device was attached to the RV myocardium in proximity to the papillary muscle. This device was retrieved and reimplanted 50 days after the original implantation procedure. Another device embolized during implantation, and it was snared and retrieved. This patient received another Micra device during the same procedure.

One pacemaker syndrome event occurred 186 days postimplantation. This patient underwent an upgrade to a cardiac resynchronization therapy device.

Major complication criteria were not mutually exclusive, and of the 46 events, 33 led to prolonged hospitalization by 48 hours, 17 led to hospitalization, 5 resulted in death, and 15 resulted in a system revision (Table 3). A subset of the system revisions (9 events) were associated with loss of device function due to high pacing thresholds or failure of the device to capture, resulting in the device being programmed to OOO mode or retrieved and replaced with a new Micra device or a transvenous device. Importantly, there were no unexpected device issues, no telemetry failures, and no battery issues.

Table 3 System- or procedure-related major complication breakdown for Micra and transvenous control patients

Major complication criterion	Micra (n = 1817)		Transvenous historical control (n = 2667)		Relative risk reduction (95% CI) (%)	*P*
	No. of events (no. of patients, percentage)	12-mo KM estimates (95% CI) (%)	No. of events (no. of patients, percentage)	12-mo KM estimates (95% CI) (%)		
Total major complications	46 (41, 2.26)	2.7 (2.0 to 3.7)	230 (196, 7.35)	7.6 (6.6 to 8.7)	63 (48 to 73)	<.0001
Death	5 (5, 0.28)	0.3 (0.1 to 0.8)	0 (0, 0.00)	0.0	NE	.0109
Hospitalization	17 (16, 0.88)	1.3 (0.8 to 2.1)	124 (106, 3.97)	4.1 (3.4 to 5.0)	71 (51 to 83)	<.0001
Prolonged hospitalization	33 (29, 1.60)	1.9 (1.3 to 2.7)	68 (64, 2.40)	2.4 (1.9 to 3.1)	24 (−18 to 51)	.2278
System revision	15 (13, 0.72)	0.9 (0.5 to 1.6)	102 (95, 3.56)	3.8 (3.1 to 4.6)	74 (54 to 85)	<.0001
Loss of device function	9 (9, 0.50)	0.7 (0.4 to 1.3)	0 (0, 0.00)	0.0	NE	.0003

Major complication end point criteria are not mutually exclusive. For example, an event resulting in a system revision may also result in hospitalization.
CI = confidence interval; KM = Kaplan-Meier; NE = not estimable.

Perforations/effusions

There were a total of 14 perforation/effusion events, and of these, 8 met the criteria for a major complication. Of the 14 perforation/effusion events, 8 required pericardiocentesis, 4 required no intervention, and 2 required surgical repair and ultimately led to death. The 6 perforation/effusion events that did not meet the major complication criteria resolved and did not lead to any long-term adverse events. The 2 perforation/effusion deaths were adjudicated as related to the implantation procedure and not to the Micra device. One patient was a 65-year-old woman with a low body mass index (BMI) (17.4 kg/m^2), hypertension, and renal dysfunction requiring dialysis. After multiple attempts to deploy the Micra device without successfully engaging the tines, an echocardiogram revealed pericardial effusion. An RV perforation was repaired surgically, but the patient experienced extensive blood loss and was pronounced dead the same day despite administration of blood products. The second patient was a 76-year-old woman with hypertension, diabetes, and renal dysfunction requiring dialysis. The implant attempt was unsuccessful because of tamponade that required surgical repair. This patient had a complicated postoperative course and developed sepsis 2 weeks later with documented bacteremia and died ∼3 weeks after the implant attempt owing to septic shock.

Previously reported risk factors for perforation/effusion with Micra include BMI <20 kg/m^2, advanced age (≥85 years), female sex, congestive heart failure, non-AF indication, and chronic lung disease.[10] Of the 14 patients with perforation/effusion events, 6 had >2 risk factors, 7 had 1–2 risk factors, and 1 had 0 risk factors.

Deaths

There were a total of 144 patient deaths reported in the PAR due to any cause, of which 13 were due to sudden cardiac death, 35 were due to nonsudden cardiac death, 77 were due to noncardiac death, and 19 were for unknown reasons. Three deaths were adjudicated as unknown relatedness to the procedure, and 5 deaths were adjudicated as related to the implantation procedure. One procedure-related death was previously published. In brief, this patient died of pulmonary edema in the setting of severe aortic valve disease the day after his procedure.[6] Two perforation-related deaths were described in detail above. The fourth patient with a procedure-related death was a 92-year-old woman with a low BMI (19.2 kg/m^2), hypertension, persistent AF, and COPD who underwent concomitant Micra implantation and AV node ablation. After the implantation procedure, a computed tomography scan revealed retroperitoneal bleeding and the patient's condition worsened despite blood transfusions and multiple rounds of epinephrine. The patient died the next day. The fifth procedure–related death involved an 84-year-old female patient on dialysis who was initially admitted to the hospital for scheduled brachiocephalic arteriovenous fistula creation. The patient experienced multiple episodes of AF with rapid ventricular response in the next 2 weeks and was consulted for Micra placement. During the implantation procedure, the patient became hypotensive and died the next day. There was no evidence of pericardial effusion or retroperitoneal bleeding, and the death was presumed to be due to RV failure, possibly from acute infarct.

Of the 3 patients with deaths adjudicated as unknown relatedness to the procedure, the first patient was a 94-year-old man who died at home 22 days postimplantation. The cause of death was labeled as heart failure and was adjudicated as unknown relatedness to the implantation procedure. The second patient with a death adjudicated as unknown relatedness to the procedure was a 74-year-old man who died after being hospitalized with fever 25 days postimplantation and was found dead in the hospital. The third patient was an 86-year-old man who presented to the hospital with cardiac arrest 6 days postimplantation. The patient had ventricular fibrillation arrest and was shocked 6 times from an external defibrillator. This patient also had a history of heart failure.

Electrical performance

The mean pacing capture threshold was 0.6 ± 0.55 V at 0.24 ms (n = 1661) at implantation and remained stable through 18 months of follow-up (0.66 ± 0.45 V) (n = 202) (Figure 1). Of the 566 patients with available pacing threshold data at 12 months, 97.0% had a pacing threshold of <2 V. The mean impedance was 730 ± 181 Ω at implantation and 568 ± 104 Ω at 18 months. The mean R-wave amplitude was

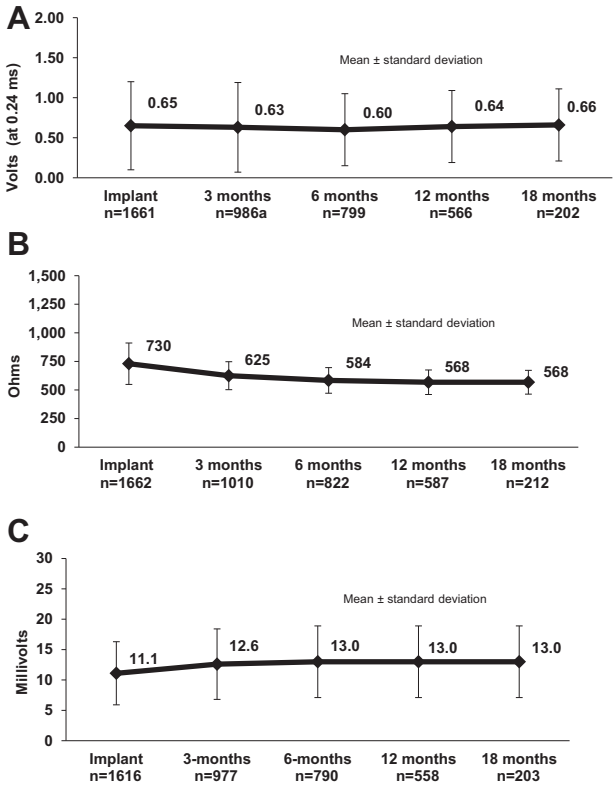

Figure 1 Electrical performance over time. **A:** Pacing capture thresholds. **B:** Impedance. **C:** Sensing. The *vertical solid lines* represent the SD. n values represent the number of patients with data available at each time point.

11.1 ± 5.2 mV at implantation and 13.0 ± 5.9 mV at 18 months. For the 713 patients with device interrogation data available, the median ventricular pacing percentage was 55.7% (IQR 7%–98%) (Figure 2) at the last follow-up visit. Of these 713 patients, 45.3% were programmed to rate-adaptive pacing and the lower pacing rate interval was ≤40, >40–≤60, or >60 beats/min for 10.5%, 68.0%, and 21.5% of patients, respectively. For the 451 patients with available

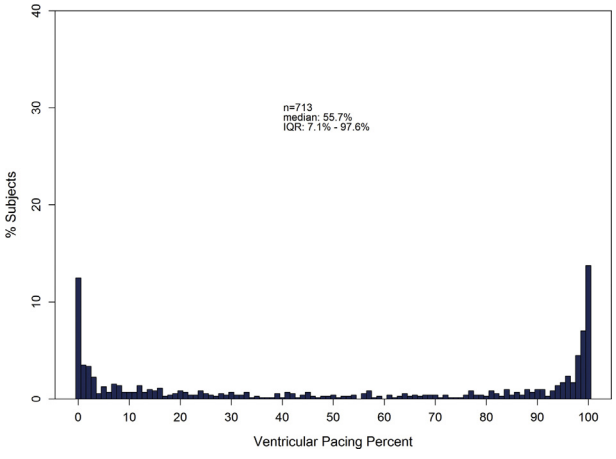

Figure 2 Ventricular pacing percentage obtained from the device memory at each patient's last follow-up visit for patients with at least 30 days of follow-up. IQR = interquartile range.

data at 6 months postimplantation, median battery longevity was estimated to be 13.6 years (IQR 11.9–15.4 years).

Safety: PAR cohort vs IDE and transvenous cohorts

Through 12 months postimplantation, the major complication rate in the Micra PAR cohort was 2.7% (95% confidence interval [CI] 2.0%–3.7%) as compared with 7.6% (95% CI 6.6%–8.7%) in the historical TV-PPM cohort. This represents a 63% lower risk of major complications (hazard ratio 0.37; 95% CI 0.27–0.52; $P < .001$). The reduction in major complications was primarily driven by a significant 74% relative risk reduction in system revisions and 71% relative risk reduction in hospitalizations (Table 3). The major complication rate trended lower in the Micra PAR than in the IDE study (hazard ratio 0.71; 95% CI 0.44–1.1; $P = .160$) (Figure 3). This was driven by significantly lower pericardial effusion rates in the PAR (0.44% vs 1.52%; $P = .009$).

Discussion

This is the largest report on leadless pacemakers to date. More than 1800 patients were enrolled and followed over a mean of ∼7 months, with >450 patients followed beyond 1 year. The results as detailed above show an excellent implant success rate (99.1%), stable pacing parameters, and reliable battery performance over the duration of follow-up. The rate of procedure-related infections was low. Most importantly, the 3 infections (an abdominal wall infection, an infected groin hematoma, and sepsis) responded to antibiotics and did not require device removal. This low rate of infection may be related to the absence of a subcutaneous pocket and hence a lower likelihood of bacterial translocation into the pacemaker site, in addition to the small surface area of leadless pacemakers relative to transvenous leads, and their tendency for encapsulation,[11] which could make bacterial adherence to the device less likely. Given the absence of infections requiring device removal across all leadless pacing data sets, more work to understand the clinical mechanisms for this observation is warranted.[3–5]

In addition, the rate of dislodgments was low and seen only in 1 patient (0.06%). This is conceivably a major advantage of the Micra TPS over the TV-PPM and appears to be a consistent finding. For instance, no dislodgments were reported in the Micra IDE study. In contrast, the rate of transvenous lead dislodgments was reported in 3.3% of patients within 2 months of implantation in the FOLLOWPACE study and in 1.2% of patients implanted with a single-lead pacemaker in the Danish registry.[12]

The rate of groin complications was low (0.61%), a finding consistent with the groin complication rate (0.7%) of the IDE study. This is a surprising, but reassuring, finding given the large caliber Micra introducer sheath (23 F). While the groin complication rate was low in the registry, a 92-year-old patient with a low BMI developed retroperitoneal bleeding, which eventually led to death. This highlights the importance of careful groin access and consideration of vascular ultrasound guidance for venous puncture, especially

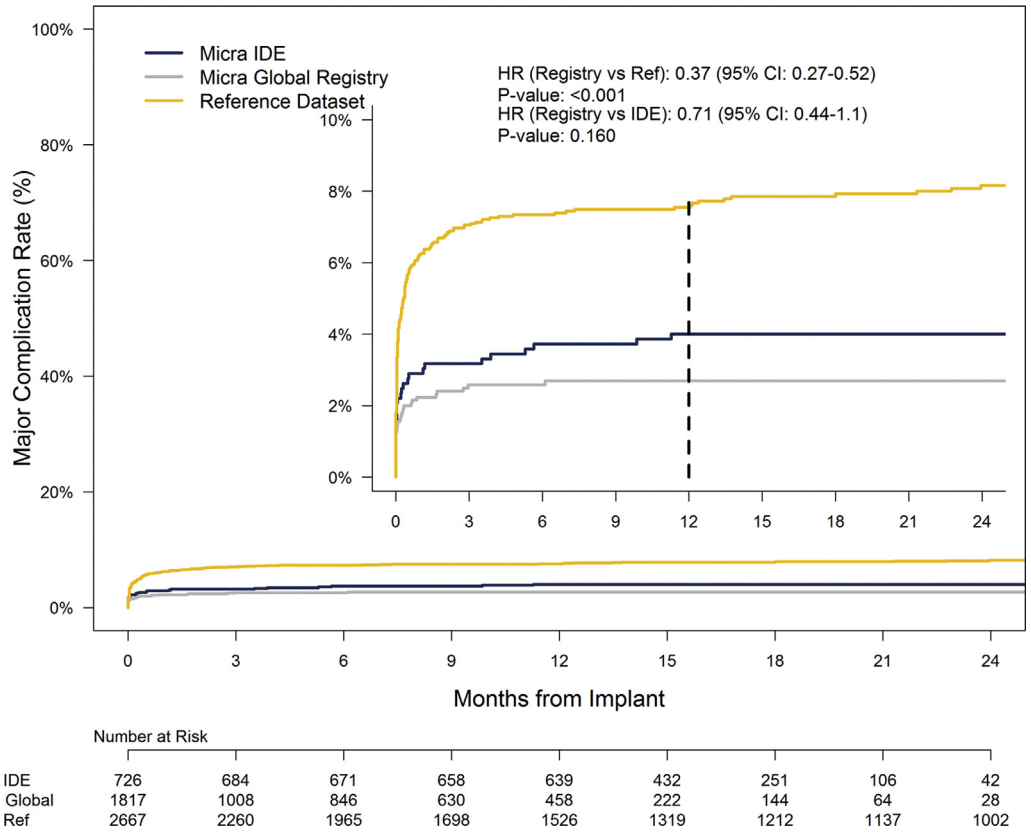

Figure 3 Major complication rates through 24 months postimplantation for Micra PAR, Micra IDE study, and transvenous reference cohorts. Subdistributional hazard ratio derived from data through 365 days postimplantation for each cohort by comparing the cumulative incidence functions given to the left of the *dashed line*. CI = confidence interval; HR = hazard ratio; IDE = Micra Investigational Device Exemption; PAR = Post-Approval Registry.

when dealing with octo- or nonagenarians, a population at increased risk of groin complications.

An important finding of the PAR is the significantly lower rate of perforation (0.77% total and 0.44% meeting the criterion for a major complication definition) as compared with the original Micra IDE study data (1.8% total and 1.5% meeting the criterion for a major complication definition). This possibly reflects the rigorous training programs that new implanters are exposed to. A major focus on implanting these devices in the septum and on the use of intravenous contrast with orthogonal radiographic views to confirm the position of the delivery system could explain the lower rate of perforation. As mentioned above, ~64% of Micra devices were positioned in the septum in the PAR as compared with 33% in the IDE study. This rate of perforation is comparable with the rate of perforation seen with the TV-PPM as reported in a meta-analysis of 28 studies reporting on lead perforation. In this meta-analysis, the mean rate of perforation with the TV-PPM was 0.8%.[12]

In this study, a total of 14 pericardial effusions were reported. Ten required an intervention (8 pericardiocentesis and 2 surgical repair), while 4 were small effusions that did not require drainage. It is important to note that most patients who developed perforation had ≥1 risk factors reported to be associated with perforation (older age, low BMI, female sex, congestive heart failure, non-AF indication, and chronic lung disease). Familiarity with these risk factors could help select patients at lower risk of perforation or allow physicians to exert an extra effort to avoid the RV apex in these patients.

We observed a total of 144 deaths (7.9%) over the duration of follow-up. This is on par with the reported mortality in similar cohorts of patients referred for single lead pacemaker implantation. For instance, in a study by Pyatt et al,[13] the 1-year mortality in such a cohort was ~20%.

Study limitations

This is a prospective registry comparing the outcomes of the Micra TPS to a historical transvenous pacing cohort implanted with dual-chamber pacemakers. While we have excluded complications related to the atrial lead, a comparison to a cohort implanted with VVI pacemakers may have provided a more fair assessment. Furthermore, only a randomized controlled study would allow a direct comparison and would clearly define the benefits and drawbacks of leadless pacing compared to TV-PPMs. Nevertheless, this registry presents prospective data on the largest cohort of patients implanted with the Micra TPS.

Conclusion

The updated results of the Micra PAR highlight the major advantages of a leadless pacing system in reducing complications associated with the pocket and lead of TV-PPMs. Furthermore, low rates of infections and dislodgments

were observed. These results also alleviate some of the early concerns about perforation rates, showing >50% reduction in the rate of pericardial effusions compared to the IDE study.

Acknowledgments

We thank Kurt Stromberg, MS, of Medtronic for statistical support and Nicky Zuniga, BA, of Medtronic for study management. In addition, the authors thank the site physicians, coordinators, and patients that participated in the study.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2018.08.005.

References

1. Udo EO, Zuithoff NP, van Hemel NM, de Cock CC, Hendriks T, Doevendans PA, Moons KG. Incidence and predictors of short- and long-term complications in pacemaker therapy: the FOLLOWPACE study. Heart Rhythm 2012;9:728–735.
2. Kirkfeldt RE, Johansen JB, Nohr EA, Jorgensen OD, Nielsen JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. Eur Heart J 2014;35:1186–1194.
3. Reddy VY, Exner DV, Cantillon DJ, et al. Percutaneous implantation of an entirely intracardiac leadless pacemaker. N Engl J Med 2015;373:1125–1135.
4. Reynolds D, Duray GZ, Omar R, et al. A leadless intracardiac transcatheter pacing system. N Engl J Med 2016;374:533–541.
5. Duray GZ, Ritter P, El-Chami M, et al. Long-term performance of a transcatheter pacing system: 12-month results from the Micra Transcatheter Pacing Study. Heart Rhythm 2017;14:702–709.
6. Roberts PR, Clementy N, Al Samadi F, et al. A leadless pacemaker in the real-world setting: the Micra Transcatheter Pacing System Post-Approval Registry. Heart Rhythm 2017;14:1375–1379.
7. Soejima K, Edmonson J, Ellingson ML, Herberg B, Wiklund C, Zhao J. Safety evaluation of a leadless transcatheter pacemaker for magnetic resonance imaging use. Heart Rhythm 2016;13:2056–2063.
8. El-Chami MF, Roberts PR, Kypta A, Omdahl P, Bonner MD, Kowal RC, Duray GZ. How to implant a leadless pacemaker with a tine-based fixation. J Cardiovasc Electrophysiol 2016;27:1495–1501.
9. Lloyd MS, El-Chami MF, Nilsson KR Jr, Cantillon DJ. Transcatheter/leadless pacing. Heart Rhythm 2018;15:624–628.
10. Mont L, Cunnane R, El-Chami MF, Roberts PR, Steffel J, Soejima K, Liu F, Hudnall JH, Piccini JP. Risk factors for cardiac perforation/effusion in leadless pacemaker patients: experience with the Micra transcatheter pacemaker [abstract]. Heart Rhythm 2018;18:S119.
11. Kypta A, Blessberger H, Lichtenauer M, Steinwender C. Complete encapsulation of a leadless cardiac pacemaker. Clin Res Cardiol 2016;105:94.
12. Vamos M, Erath JW, Benz AP, Bari Z, Duray GZ, Hohnloser SH. Incidence of cardiac perforation with conventional and with leadless pacemaker systems: a systematic review and meta-analysis. J Cardiovasc Electrophysiol 2017;28:336–346.
13. Pyatt JR, Somauroo JD, Jackson M, Grayson AD, Osula S, Aggarwal RK, Charles RG, Connelly DT. Long-term survival after permanent pacemaker implantation: analysis of predictors for increased mortality. Europace 2002;4:113–119.