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Long-term Performance of a Transcatheter Pacing System: 12 month results from the Micra Transcatheter Pacing Study

ShortTitle: Micra Transcatheter Pacemaker Long-Term Performance

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Abstract

Background

Early performance of the Micra transcatheter pacemaker from the global clinical trial reported a 99.2% implant success rate, low and stable pacing capture thresholds, and a low (4.0%) rate of major complications up to 6 months.

Objective

The pre-specified long-term safety objective of Micra at 12 months and electrical performance through 24 months are reported.

Methods

The Micra Transcatheter Pacing Study was a prospective single-arm study designed to assess the safety and efficacy of the Micra VVIR leadless/intracardiac pacemaker. Enrolled patients met Class I or II guideline indications for de novo ventricular pacing. The long-term safety objective was freedom from a system or procedure related major complication at 12 months. A pre-defined historical control group of 2667 patients with transvenous pacemakers was used to compare major complication rates.

Results

The long-term safety objective was met with a freedom from major complication rate of 96.0% at 12 months (95% CI: 94.2%-97.2%, $P<0.0001$ versus performance goal). The risk of major complications for Micra patients (N=726) was 48% lower than for transvenous patients through 12-months post-implant (HR: 0.52, 95% CI: 0.35-0.77, $P=0.001$). Across subgroups of age, sex, and comorbidities, Micra reduced the risk of major complications compared to transvenous systems. Electrical performance was excellent through 24 months, with projected battery longevity of 12.1 years.

Conclusions

Long-term performance of the Micra transcatheter pacemaker remains consistent with previously reported data. Few patients experienced major complications through 12 months follow-up, and all patient subgroups benefited as compared to a transvenous pacemaker historical control group.

Keywords: Transcatheter pacemaker, leadless pacing, long-term results

Introduction

The source for the majority of short- and long-term complications associated with traditional pacing systems can be attributed to the pocket and lead. Within months from the implant procedure, as many as 1 in 8 patients may experience a complication such as infection, hematoma, loose header connection, lead dislodgement, or pneumothorax.[1, 2] Chronically, complications with traditional systems include infection, Twiddler's Syndrome, lead fracture and insulation breach, venous thrombosis/obstruction, and tricuspid valve injury.[2] Advances in battery chemistry and component design have enabled cardiac pacemakers to be dramatically reduced in size and placed entirely in the heart, eliminating the need for a subcutaneous "pocket" and a transvenous lead and the related complications.

To date, only the early performance of transcatheter pacing systems have been reported.[3, 4] The Micra Transcatheter Pacing Study was a global clinical trial evaluating the safety and efficacy of the Micra Transcatheter Pacemaker System (Medtronic plc, Minneapolis, MN). The trial enrolled 745 patients from 56 centers in 19 counties, where 99.2% of patients were successfully implanted by 94 physicians. Both the primary safety and efficacy objectives were met at 6 months of follow-up.[4] In this report, we describe the long-term electrical performance and safety objective of patients followed for up to 24 months from the Micra Transcatheter Pacing Study.

Methods

Study Design

The design of the pivotal study has been described previously.[5] Briefly, the aim of the prospective, non-randomized, worldwide clinical trial was to evaluate the short-term and long-term safety and efficacy of the Micra Transcatheter Pacemaker System. The protocol was

approved by the ethics committee at each of the 56 participating centers. Adverse events were adjudicated by a Clinical Events Committee (CEC) comprised of independent physicians. Safety oversight was provided by an independent data monitoring committee (DMC).

Patients and Procedures

Detailed inclusion/exclusion criteria have been previously described.[5] Enrolled patients met Class I or II guideline recommendations[6, 7] for *de novo* ventricular pacing and were not restricted by comorbidities. All patients provided written and informed consent.

The Micra transcatheter pacemaker is a single-chamber ventricular pacemaker, is 90% smaller than a transvenous system, and is self-contained in a hermetically enclosed capsule (0.8 cubic centimeter, 2.0 grams). Functionality and features of the device are similar to existing single chamber pacemakers and include rate adaptive pacing, remote monitoring capabilities, and automated pacing capture threshold management to maximize battery longevity. Micra is inherently MRI conditionally safe for full body scans in both 1.5 and 3.0 Tesla scanners due to its small size and low amount of ferrous material.[8]

The device is implanted using a 23 French internal diameter/27 French outer diameter introducer through a femoral vein and the delivery catheter is advanced into the right ventricle. The device is fixated in the myocardium via 4 flexible nitinol tines. After verifying device fixation and obtaining adequate electrical measurements, a tether is cut and the delivery system is removed.

Enrolled patients underwent implant attempt and were followed, including adverse event and device evaluation at 1, 3, and 6 months and then bi-annually for at least 12 months until all successfully implanted patients had the opportunity to complete their 12-month visit at which time the study was closed.

Endpoints

As reported previously, the two primary endpoints assessed the system's early performance: a safety endpoint to evaluate freedom from major complications at 6 months and an efficacy endpoint to evaluate the proportion of patients with low and stable pacing thresholds at 6 months. Both primary objectives were met.[4] With respect to the safety objective, major complications were defined as events resulting in death, permanent loss of device function due to mechanical or electrical dysfunction, hospitalization, prolonged hospitalization by at least 48 hours, or system revision. The diagnoses of all adverse events were reported by site investigators. An independent CEC reviewed and adjudicated at minimum all procedure or system related events to determine relatedness and seriousness.

The subject of this report is of the long-term safety and electrical performance. The trial had a pre-specified long-term safety performance objective to be assessed after all implanted patients had the opportunity to complete at least 12-months of follow-up. The objective was to demonstrate that the freedom from major complications related to the Micra system or procedure was significantly greater than 82% at 12 months post implant (assumed performance, 89%). For a comparison of safety performance relative to conventional pacemaker systems with transvenous leads, an individual patient level dataset of 2667 *de novo* pacemaker patients from 6 recent Medtronic trials of dual chamber pacing was assembled.[4] A single chamber dataset was approximated by excluding events related only to the right atrial lead. Rates of major complications (using the major complication criteria from the Micra trial) were compared between Micra and the transvenous control group. Finally, electrical performance was assessed in patients followed up to 24 months.

Statistical Analysis

The study sample size of 720 patients successfully implanted with the Micra system provided >90% power to test the study's two primary objectives.[4, 5] The long-term safety performance goal of 82% was based on the major complication freedom rates at 12-months from the 6 trials in the reference dataset and set to 1% below the 6-month performance goal used for the primary objective to reflect the expectation that few major complications would be anticipated beyond 6-months post-implant. The 12-month Kaplan-Meier estimate of the freedom from major complications was evaluated against the performance goal of 82% using a one-sample Wald test implying that the long-term safety objective would be met if the lower two-sided 95% confidence limit of the Kaplan-Meier estimate exceeded 82%. Simulation analyses confirmed the power to test the long-term safety objective exceeded 90% when the 6-month major complication freedom rate (primary objective) exceeded 90%.

The Fine-Gray[9] competing risk model was used to compare the risk of major complication through 12-months between the 2667 patients in the transvenous control group and the 726 Micra patients with an attempted implant. Similarly, this model was used to compare the Micra patients and transvenous control group with respect to each component of the major complication endpoint and within subgroups. Finally, the primary comparison was repeated with a 1:1 propensity matched subgroup of transvenous control patients to adjust for differences in patient characteristics, including age, sex, coronary artery disease history, congestive heart failure history, atrial fibrillation history, hypertension history, valvular disease history, and all pairwise interactions. All analyses were conducted with SAS software, version 9.4 (SAS Institute), or the R statistical package (R Project for Statistical Computing).

Electrical parameters were summarized at each study visit using means and standard deviations. Battery longevity was projected using Monte Carlo methods by combining bench measured static current drain distributions combined with actual use conditions obtained via 12-month device interrogation files, plus six 30-minute telemetry sessions per year.

Results

Study Patients

Enrollment began December 2013 and concluded May 2015 with a total of 745 patients at 56 centers in 19 countries worldwide. There were 726 patients who underwent attempted Micra implant by 94 physicians, of which, 720 (99.2%) patients were successfully implanted. Detailed patient characteristics have previously been described;[4] (the original 6 month primary endpoints report was on 725 attempted and 719 successfully implanted; one additional successful implant occurred after database closure of the early performance analysis). Average follow-up duration was 16.4 ± 4.9 months. Compliance to protocol-required study visits was >99%.

Long-Term Safety

There were a total of 32 major complications in 29 patients adjudicated as related to the Micra system or procedure. The long-term safety objective was met with 96.0% freedom from major complications related to the Micra system or procedure at 12-months post-implant (95% CI: 94.2% - 97.2%, $P<0.0001$ versus performance goal). Major complications are shown in Table 1. Four new major complications occurred since the primary results analysis, which occurred when the first 300 patients had been followed for 6 months:[4] 3 were associated with cardiac failure events and 1 was associated with pacemaker syndrome. There were no radiographically visible device dislodgements and no telemetry failures. Also, there were no infections related to the Micra device during the entire follow up duration.

Of the 32 major complications, 24 (75%) occurred within 30 days of a Micra implant attempt, and 6 (19%) occurred between 30 days and 6-months of implant attempt. Only two of the major complications occurred after 6 months of the implant attempt. The two events involving hospitalizations for heart failure at 300 and 343 days post implant, respectively, occurred in two patients paced 87% and 99% of the time.

Major complication criteria were not mutually exclusive, and of the 32 major complications: 18 were associated with prolonged hospitalization, 17 with new hospitalization, 5 with system revision, 2 with loss of device function though neither were caused by technical failure of the device (elevated pacing threshold and pacemaker syndrome leading to the device programmed off to OOO mode), and 1 death following the procedure (Table 2).

Of the 5 system revisions that met the criteria for a major complication, percutaneous retrieval was attempted in 3 patients: 1 attempt was successful 16 days post implant, 1 attempt was unsuccessful due to inability to extract the device 259 days post implant, and 1 attempt was aborted due to fluoroscopy failure 229 days post implant. In the remaining 2 patients, the Micra device was turned to Device Off mode without a retrieval attempt 32 and 44 days post implant.

Pacemaker Syndrome and Heart Failure

The 2 patients with a major complication related to pacemaker syndrome, as expected, were among the 36% of patients who had no persistent atrial arrhythmias at baseline. Both patients were upgraded – one to dual chamber pacing and one to CRT.

All 6 patients with a major complication related to heart failure had persistent atrial arrhythmias at baseline. Only 1 of these patients was upgraded to CRT. The remainder were managed with medication.

Infections

There were no major infectious complications related to the Micra device or procedure. There were 26 patients with 33 systemic infectious events during the trial; including septic shock (16), endocarditis (2), bacteremia (3), and other septic events (12). In all instances, these events were determined to be unrelated to the Micra device or procedure by the investigator, and these determinations were confirmed by the CEC. Micra removal was not required in 25 of 26 patients. In 1 patient, Micra was removed 430 days after implant during surgical replacement of an infected prosthetic aortic valve.

Deaths

There were 77 deaths among the 745 enrolled subjects, 29 were previously reported[4] and there were 48 new deaths since the primary results analysis. Of the 77 deaths, 10 were due to sudden cardiac death, 22 were due to non-sudden cardiac death, 43 were due to non-cardiac death, and 2 were for unknown reasons. None of the deaths were considered related to the Micra system; 1 death was considered related to the implant procedure and was previously described.[4]

Comparison to Historical Control

The risk of major complication through 12-months post-implant was 48% lower in Micra patients relative to transvenous control patients (HR: 0.52, 95% CI: 0.35-0.77, P=0.001, Figure 1). To account for differences in baseline characteristics, propensity scores for each patient were derived and each of the 726 Micra patients was matched to a historical control patient. Absolute standardized differences were all less than 0.2, indicating successful matching. After propensity matching, a similar reduction in major complications was observed (HR: 0.46, 95% CI: 0.30 – 0.72, P<0.001). The reduction in major complications was primarily driven by a 47% relative risk reduction in hospitalizations and 82% relative risk reduction in system revisions (Table 2).

Across age, sex, and comorbidities, Micra was associated with a lower risk of major complications through 12 months compared to transvenous pacemakers, and there were no subgroups where Micra showed a higher risk (Figure 2).

Electrical Performance

Of the 630 subjects with available pacing threshold data at 12 months, 93% had a pacing threshold ≤1V (mean 0.60 ± 0.38V) at 0.24 ms pulse duration, and of the 58 subjects with available pacing threshold data at 24 months, 97% had a pacing threshold ≤1V (mean 0.53 ± 0.23V) also at 0.24 ms. Pacing thresholds tended to decrease after implant and remained stable thereafter (Figure 3A). The estimated battery longevity based upon use conditions at 12 months was 12.1 years with 89% of patients having a projected longevity >10 years. The average pacing impedance decreased from implant to 12-months (724 Ohms compared to 596 Ohms, Figure 3B) and was stable through 24 months. Following successful implant, the mean R-wave amplitude was 11.2 mV compared to a mean R-wave amplitude of 15.1 mV at 12-months post-implant and was 15.5 mV at 24 months.

Discussion

In a prospective, non-randomized, worldwide trial of 726 patients, the Micra transcatheter pacemaker met its long-term safety performance objective with 96.0% freedom from major complications through 12 months post-implant. To our knowledge, this is the largest report of transcatheter pacing patients with the longest follow-up. As previously reported in the 6 month follow-up dataset, electrical performance remains stable through 12 months with 93% of patients having a pacing threshold ≤1 V at 0.24 ms. Micra patients experienced a 48% reduction in the risk of major complication compared to transvenous control patients, driven by reductions in hospitalizations and system revisions. Throughout the duration of the trial, Micra met all pre-

specified objectives, beginning with the early performance objectives at 3 months,[10] the primary objectives at 6 months,[4] and continuing through 12 months as outlined in this report.

Major complications occurred in 4% of patients in this first-in-man trial, which is in-line with published reports for transvenous systems.[1, 2] Among 94 implanters from 56 centers in 19 countries, the implant success rate was 99.2%. Remarkably, there were no device dislodgements or infections related to the device.

The advantage of leadless pacemakers lies in the absence of a lead and pocket, the primary sources of complications with transvenous systems. Specifically, lead related complications (2.4-5.5%), pocket related complications (0.4-4.8%), pneumothorax (0.9-2.2%), and infection (0.3-0.8%) are well-characterized in the transvenous peri-procedural setting.[1, 2] Use of Micra avoided all of these complications. These data highlight that this advantage is observed very early in follow-up and sustained in the longer-term. As with transvenous systems, the majority of complications occurred early, but Micra patients experienced 82% fewer system revisions and 47% fewer hospitalizations. These reductions were despite Micra patients being older and having more co-morbidities than the transvenous control group patients.

While these long-term data demonstrate that the beneficial effects of Micra versus transvenous systems are sustained to 2 years, we anticipate continued benefit chronically with Micra. Long-term data suggest that transvenous systems remain prone to infections and are associated with complications related to venous obstruction, lead fracture and insulation breach, injury to the tricuspid valve, and Twiddler's Syndrome. Data of transcatheter pacemakers is needed to shed light on the benefits of eliminating these chronic device complications.

The electrical performance of Micra remains stable up to 24 months follow-up. Based on the actual use conditions of patients followed through 12 months, the mean longevity is projected

to be >12 years which compares favorably to traditional systems.[11, 12] Given the typical patient profile indicated for VVI pacing (e.g. average age 76 years, comorbidities), this longevity projection suggests that a single Micra will serve the total pacing needs of at least 75% of patients (Rys et al, unpublished data). Though experience was limited, Micra was able to be retrieved percutaneously or turned off and left in place with a concomitant device placed, thus allowing for options when device upgrade or replacement is required.

Although 36% of patients receiving Micra VVI pacing therapy were without persistent atrial arrhythmia at baseline, only 1.1% of patients experienced major complications related to this pacing mode – 6 were associated with heart failure and 2 with pacemaker syndrome. While careful pacing mode selection is advised, it appears that in this trial the low rate of heart failure and pacemaker syndrome reflects reasonable use of this new technology.

Published literature indicates that cardiac implantable electronic device related infections occur with traditional transvenous systems in 0.3-0.8% of implants.[13] Currently, experts recommend complete hardware removal in virtually all of these situations as infections typically involve the device pocket and/or the lead.[14, 15] Micra's small size, reduced surface area, and lack of polymer insulated lead exposed to the bloodstream appear to substantially mitigate the risk of early device infection. Over the long-term, these features will also promote complete device encapsulation, which may significantly reduce the risk of chronic infection. The absence of obvious device infections in this trial is encouraging.

Results from a differently designed leadless pacemaker (Nanostim, St. Jude Medical) have also been reported. Primary efficacy and safety objectives were met in 300 patients, with 90% receiving adequate pacemaker function to 6 months.[3] In the total cohort of 526 patients, device-related serious adverse events occurred in 6.5% of patients, including cardiac perforation

in 8 (1.5%) patients, device dislodgement in 6 (1.1%) patients, device migration in 2 (0.4%) patients, and infection in 0 patients. Long-term safety data have not yet been reported.

Limitations

A limitation of the trial is the absence of a randomized control group for comparison. In order to derive a relative comparison to transvenous systems, a historical control comprised of 6 transvenous pacemaker trials was assembled and major complications were estimated. The safety analyses, as pre-specified, are restricted to the events meeting major complication criteria, and events not leading to death, hospitalization, prolonged hospitalization by at least 48 hours, or loss of device function are outside the scope of the present analysis. In addition, there are limited data on system revisions, and no patients were followed beyond 2 years. Data from the Micra Post-Approval Registry (refer to https://clinicaltrials.gov/ct2/show/NCT02536118) is aimed to address these questions.

Conclusion

The Micra Transcatheter Pacing Study met its prespecified long-term safety objective with 96% freedom from major complications. Micra patients experienced a 48% reduction in the risk of major complication at 12 months compared to transvenous patients from a historical control group, resulting in 82% fewer system revisions and 47% fewer hospitalizations. Pacing thresholds remained low and stable through 24 months follow-up.

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378 **Table 1: Major Complications (Patients with Micra Implant Attempt, N=726)**

	No. Events (No. Subjects, %)			
Adverse Event Keyterm	**Within 30 Days**	**30 Days - 6-Months**	**>6-Months**	**Total Major Complications**
TOTAL MAJOR COMPLICATIONS	**24 (21, 2.89%)**	**6 (6, 0.83%)**	**2 (2, 0.28%)**	**32 (29, 3.99%)**
EMBOLISM AND THROMBOSIS	**2 (2, 0.28%)**	**0 (0, 0%)**	**0 (0, 0%)**	**2 (2, 0.28%)**
DEEP VEIN THROMBOSIS	1 (1, 0.14%)	0 (0, 0%)	0 (0, 0%)	1 (1, 0.14%)
PULMONARY EMBOLISM	1 (1, 0.14%)	0 (0, 0%)	0 (0, 0%)	1 (1, 0.14%)
EVENTS AT GROIN PUNCTURE SITE	**5 (5, 0.69%)**	**0 (0, 0%)**	**0 (0, 0%)**	**5 (5, 0.69%)**
ARTERIOVENOUS FISTULA	4 (4, 0.55%)	0 (0, 0%)	0 (0, 0%)	4 (4, 0.55%)
VASCULAR PSEUDOANEURYSM	1 (1, 0.14%)	0 (0, 0%)	0 (0, 0%)	1 (1, 0.14%)
CARDIAC EFFUSION/PERFORATION	**10 (10, 1.38%)**	**1 (1, 0.14%)**	**0 (0, 0%)**	**11 (11, 1.52%)**
PACING ISSUES: ELEVATED THRESHOLDS	**2 (2, 0.28%)**	**0 (0, 0%)**	**0 (0, 0%)**	**2 (2, 0.28%)**
OTHER	**5 (5, 0.69%)**	**5 (5, 0.69%)**	**2 (2, 0.28%)**	**12 (12, 1.65%)**
ACUTE MYOCARDIAL INFARCTION	1 (1, 0.14%)	0 (0, 0%)	0 (0, 0%)	1 (1, 0.14%)
CARDIAC FAILURE	0 (0, 0%)	4 (4, 0.55%)	2 (2, 0.28%)	6 (6, 0.83%)
METABOLIC ACIDOSIS	1 (1, 0.14%)*	0 (0, 0%)	0 (0, 0%)	1 (1, 0.14%)
PACEMAKER SYNDROME	1 (1, 0.14%)	1 (1, 0.14%)	0 (0, 0%)	2 (2, 0.28%)
PRESYNCOPE	1 (1, 0.14%)	0 (0, 0%)	0 (0, 0%)	1 (1, 0.14%)
SYNCOPE	1 (1, 0.14%)	0 (0, 0%)	0 (0, 0%)	1 (1, 0.14%)

*Led to procedure-related death in patient with end-stage renal disease

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380 **Table 2: Components of Major Complication for Micra and Transvenous Control Patients**

	12-Month Kaplan-Meier Event Rate (95% CI)		Relative Risk Reduction (95% CI)
Major Complication Criterion	**Micra (n=726)**	**Historical Control (n=2667)**	
Total Major Complications	4.0% (2.8% - 5.8%)	7.6% (6.6% - 8.7%)	48% (23% - 65%)**
Death	0.1% (0% - 1.0%)	0.0% (NE)	NE
Hospitalization	2.3% (1.4% - 3.7%)	4.1% (3.4% - 5.0%)	47% (11% - 69%)*
Prolonged Hospitalization	2.2% (1.4% - 3.6%)	2.4% (1.9% - 3.1%)	9% (-57% - 47%)
System Revision	0.7% (0.3% - 1.7%)	3.8% (3.1% - 4.6%)	82% (55% - 93%)**
Loss of device function	0.3% (0.1% - 1.1%)	0.0% (NE)	NE

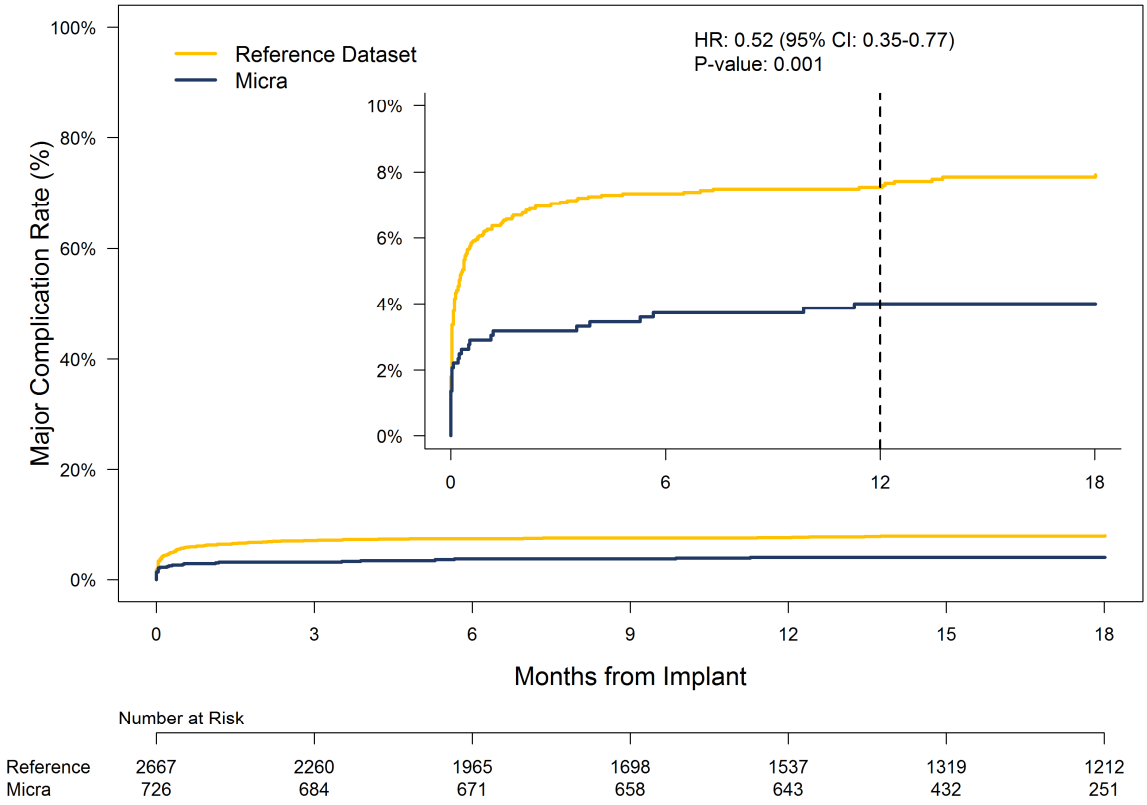
381 Not mutually exclusive as a single event may meet more than one major complication criteria.
382 NE = Not estimable
383 *P<0.05
384 **$P\leq$0.001
385

Figure Legends

Figure 1: Major Complication Rate through 18-months Post-Implant for Micra and Transvenous Control Cohort. Subdistributional hazard ratio derived from data through 365 days post implant for each cohort by comparing the cumulative incidence functions to the left of the dashed line.

Figure 2: Risk of Major Complications through 12 Months Post-Implant Comparing Micra to Reference Dataset in Subgroups. Vertical solid line corresponds to equal risk. Vertical dashed line is the subdistributional hazard ratio from the full comparison. Horizontal solid lines are the 95% confidence intervals for the hazard ratios.

Figure 3: Micra Electrical Parameters by Study Visit. Data in the graphs are mean values. Vertical solid lines represent the standard deviation. N values are the numbers of patients for whom data were available at each study visit.



Number at Risk

Reference	2667	2260	1965	1698	1537	1319	1212
Micra	726	684	671	658	643	432	251