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SYSTEMATIC REVIEW AND META-ANALYSIS

Safety and Efficacy of Leadless Pacemakers: A Systematic Review and Meta-Analysis

Linh Ngo, MD; Daniel Nour, MBBS; Russell A. Denman, MBBS; Tomos E. Walters, MBBS, PhD; Haris M. Haqqani, MBBS, PhD; Richard J. Woodman, PhD; Isuru Ranasinghe, MBChB, MMed (Clin Epi), PhD

BACKGROUND: Leadless pacemaker is a novel technology, and evidence supporting its use is uncertain. We performed a systematic review and meta-analysis to examine the safety and efficacy of leadless pacemakers implanted in the right ventricle.

METHODS AND RESULTS: We searched PubMed and Embase for studies published before June 6, 2020. The primary safety outcome was major complications, whereas the primary efficacy end point was acceptable pacing capture threshold (≤2 V). Pooled estimates were calculated using the Freedman-Tukey double arcsine transformation. Of 1281 records screened, we identified 36 observational studies of Nanostim and Micra leadless pacemakers, with most (69.4%) reporting outcomes for the Micra. For Micra, the pooled incidence of complications at 90 days (n=1608) was 0.46% (95% CI, 0.08%–1.05%) and at 1 year (n=3194) was 1.77% (95% CI, 0.76%–3.07%). In 5 studies with up to 1-year follow-up, Micra was associated with 51% lower odds of complications compared with transvenous pacemakers (3.30% versus 7.43%; odds ratio [OR], 0.49; 95% CI, 0.34–0.70). At 1 year, 98.96% (95% CI, 97.26%–99.94%) of 1376 patients implanted with Micra had good pacing capture thresholds. For Nanostim, the reported complication incidence ranged from 6.06% to 23.54% at 90 days and 5.33% to 6.67% at 1 year, with 90% to 100% having good pacing capture thresholds at 1 year (pooled result not estimated because of the low number of studies).

CONCLUSIONS: Most studies report outcomes for the Micra, which is associated with a low risk of complications and good electrical performance up to 1-year after implantation. Further data from randomized controlled trials are needed to support the widespread adoption of these devices in clinical practice.

Key Words: efficacy ■ leadless pacemaker ■ meta-analysis ■ safety ■ systematic review

Transvenous pacemakers (TVPs), consisting of a subcutaneously implanted pulse generator and one or more transvenous electrodes extending to the heart chamber(s), are a well-established treatment for bradyarrhythmias.[1] Nevertheless, implantation of these devices is not devoid of substantial complications.[2–5] Studies have shown that TVPs are consistently associated with a 7.76% to 12.4% risk of serious complications at 90 days, with nearly half of these attributable to lead- and generator-related complications.[2–4] In the longer term, TVPs have a 1% to 2% risk of complications per year, mainly attributable to lead failure and infection.[3] About 1 in 6 patients with a TVP experiences a serious complication by 3 years,[3,4] and these complications are exceedingly costly to treat.[4,5] Strategies to minimize harm and costs associated with permanent pacemakers are therefore highly desirable.

The leadless pacemaker (LP) is a novel alternative consisting of a capsule-like device containing a generator and electrode system that is implanted into the right ventricle via a percutaneously inserted femoral venous catheter. By omitting the need for a generator

Correspondence to: Linh Ngo, MD, The University of Queensland Northside Clinical Unit, The Prince Charles Hospital, 627 Rode Road, Chermside, QLD 4032, Australia. E-mail: linh.ngo@uq.edu.au

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CLINICAL PERSPECTIVE

What Is New?

- We performed the first systematic review and meta-analysis that comprehensively examines the safety and efficacy of the Micra and Nanostim leadless pacemakers implanted in the right ventricle.
- Our results showed leadless pacemakers are associated with a low incidence of complications (0.46% at 90 days and 1.77% at 1 year for Micra) and good electrical performance at 1 year after implantation, with >90% of devices having an acceptable capture threshold.
- Micra is associated with 51% lower odds of complications compared with a transvenous pacemaker.

What Are the Clinical Implications?

- Based on observational data, leadless pacemakers appear to have a markedly lower incidence of early complications compared with transvenous pacemakers.
- Nevertheless, data on battery longevity (beyond 2 years) and clinical outcomes, such as incidence of new-onset heart failure, are currently lacking.
- Robust randomized trials that directly compare the safety and efficacy of leadless and transvenous pacemakers are needed to provide more rigorous data to support the widespread adoption of this novel technology.

Nonstandard Abbreviations and Acronyms

LP	leadless pacemaker
TV	tricuspid valve
TVP	transvenous pacemaker

pocket and transvenous leads, a LP may avoid many of the lead- and generator pocket–related complications typically associated with a TVP. Although the LP was first solely indicated for right ventricular pacing, the emergence of LPs capable of atrioventricular synchronous pacing promises expanding indications for these novel devices.[6,7] Nevertheless, the initial evidence supporting the use of these devices was limited and came from mostly small observational studies,[8–11] with no randomized control trials that have directly compared safety and efficacy of LPs versus TVPs. Furthermore, despite initial promising data, the Nanostim (Abbott Medical, Abbott Park, IL) LP was withdrawn from premarket testing because of premature battery failure,[12] raising concerns about the long-term performance of LPs.

To date, there has been no systematic review and meta-analysis of LPs beyond narrative reviews[13,14] and limited reviews of LP-associated cardiac perforation[15] and dislodgement.[16] Accordingly, we sought to perform a systematic review and meta-analysis of published studies to evaluate the safety and efficacy of LPs. Specifically, we examined the pooled incidence of early complications up to 3 months after implant as well as the incidence of complications beyond the early postimplantation period. The pooled odds ratio (OR) was drawn from studies that compared complications associated with LPs versus TVPs. We also evaluated the proportion of patients with a successful implant, and the efficacy of LPs focusing on electrical performance and clinical outcomes.

METHODS

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocol.[17] All data used in this study were extracted from individual studies. The authors declare that all supporting data are available within the article and the supplementary documents.

Literature Search

Two independent reviewers (L.N. and D.N.) performed a comprehensive systematic search across PubMed and Embase databases and included all studies published up to the June 6, 2020. The keyword search terms were leadless, pacemaker, Micra, and Nanostim. Studies were included if they explored either the primary safety or efficacy end point of LP implantation in the right ventricle. The exclusion criteria were (1) sample size of <10 patients; (2) review, survey, abstracts, or conference proceedings without full text, editorial comments, or responses (to ensure reliable data could be extracted); (3) studies with concurrent atrioventricular nodal ablation, defibrillator or resynchronization device implantations, or those conducted on patients with heart block requiring pacemaker implantation after transcatheter aortic valve replacement, because complications could be attributable to these additional interventions; (4) studies that reported different results from the same population or outcomes not relevant to LP safety and efficacy; (5) studies in which an LP was implanted through the jugular vein instead of the conventional femoral vein; (6) studies not conducted on live humans; and (7) studies published in languages other than English.

Included studies were agreed on by both reviewers, with discrepancies resolved by a third reviewer (I.R.). All search keywords used are described in Table S1.

Data Extraction

Data were extracted using a data extraction form with a standard set of variables collected for each publication.

Quality Assessment

We used the National Institute of Health Quality Assessment Tool to evaluate the quality of each included study.[18] This tool includes a set of questions (14 for cohort studies and 9 for case-series studies), with overall quality of the study graded as good, fair, or poor. The first reviewer (L.N.) assessed the quality of included studies, and results were confirmed by the second reviewer (D.N.), with conflicts resolved by consensus.

Primary End Points

The primary safety end point was the occurrence of any major device and procedure-related complications, defined as events that resulted in death, required intervention, or prolonged the hospital stay, or led to a readmission. For example, a pericardial effusion not requiring drainage or surgery or a groin hematoma not requiring blood transfusion are not considered major complications. Secondary safety end points included the proportion of patients with a successful implant and the incidences of specific complications that could be extracted from each study. We examined the pooled incidence of complications at up to 90 days including those that occurred during implantation, and ≈1 year after implant. These time points were selected because they are the timeframes most commonly used by the studies reporting complications following cardiac device implantation.[2,8,10,19,20] The proportion of patients with a successful implant was calculated as the percentage of patients received a LP among those with an attempted implant.

The primary efficacy end point was good electrical performance indicated by a pacing capture threshold of ≤2 V at 1 year after device implantation. The secondary efficacy endpoints were other clinical outcomes including quality of life and cardiac function.

Statistical Analysis

All analysis was performed using Stata version 16.0 statistical software (StataCorp, College Station, TX).

To calculate the pooled proportion (for implant success and efficacy) and pooled incidence of complications, we used the Stata user-written command Metaprop, with the Freedman-Tukey double arcsine transformation that allows inclusion of studies with an incidence or proportion of 0% and 100%.[21] The meta-analysis of studies comparing LP with TVP was performed using Stata's in-built Metan command, with results being reported as OR and 95% CI.[22] We chose to report OR because of the lack of reporting of either hazard ratio or statistics to estimate hazard ratio in individual studies. The heterogeneity among studies was evaluated using the I^2 statistic,[23] and the sensitivity of the pooled estimates was examined by subgroup analyses of different types of study design or quality. Results were reported for Micra and Nanostim separately because of the stark differences in design and fixation mechanism of these 2 devices. A 2-tailed P value of <0.05 was considered statistically significant.

RESULTS

Characteristics of Included Studies

A total of 1281 studies were screened, and 36 were included for our analysis[8–11,19,20,24–53] (Figure 1). Table 1 summarizes the characteristics of the included studies, all of which were observational (details of the 36 studies are provided in Tables 2 through 6, and Table S2). Eight studies[8,10,27–32] used the same cohort as other included studies but reported outcomes at a different follow-up interval, leaving 28 studies with unique patient cohorts (n=4748 patients; mean age, 83.3 years [95% CI, 80.9–85.6], 61.0% [95% CI, 59.6%–62.4%] were men). Most of the patients had comorbid hypertension (69.7%; 95% CI, 64.2%–75.0%) and atrial fibrillation (66.7%; 95% CI, 59.7%–73.5%). Only 24.3% (95% CI, 18.0%–31.3%) of patients had a history of heart failure at implantation. Median sample size was 66 patients (range, 10–1817 patients), with 64.3% having a sample size <100 patients. Median follow-up time was 6 months (range, 0–24 months). Among the 36 studies included, 10 were retrospective (27.8%), 22 were prospective (61.1%), and 4 (11.1%) did not clearly state the design. Five studies (13.9%) analyzed the Nanostim LP, whereas 25 (69.4%) explored the Micra LP (Medtronic, Minneapolis, MN), 5 (13.9%) analyzed both, and 1 study did not clearly report the type of LP used.[24] Seven studies compared LPs with TVPs, 3 of which used propensity score–matched controls[29,30,44] and 1 used a historical control group.[27]

Quality Assessment

Of the 36 studies, most (n=20, 55.6%) were evaluated as having good quality, whereas 15 (41.7%) and 1 (2.8%) were graded as fair and poor, respectively. Detailed assessments are provided in Table S3.

Proportion of Patients With a Successful Implant

A total of 23 studies (n=4769 patients) reported the proportion of patients with a successful implant. The pooled proportion was 99.85% (95% CI,

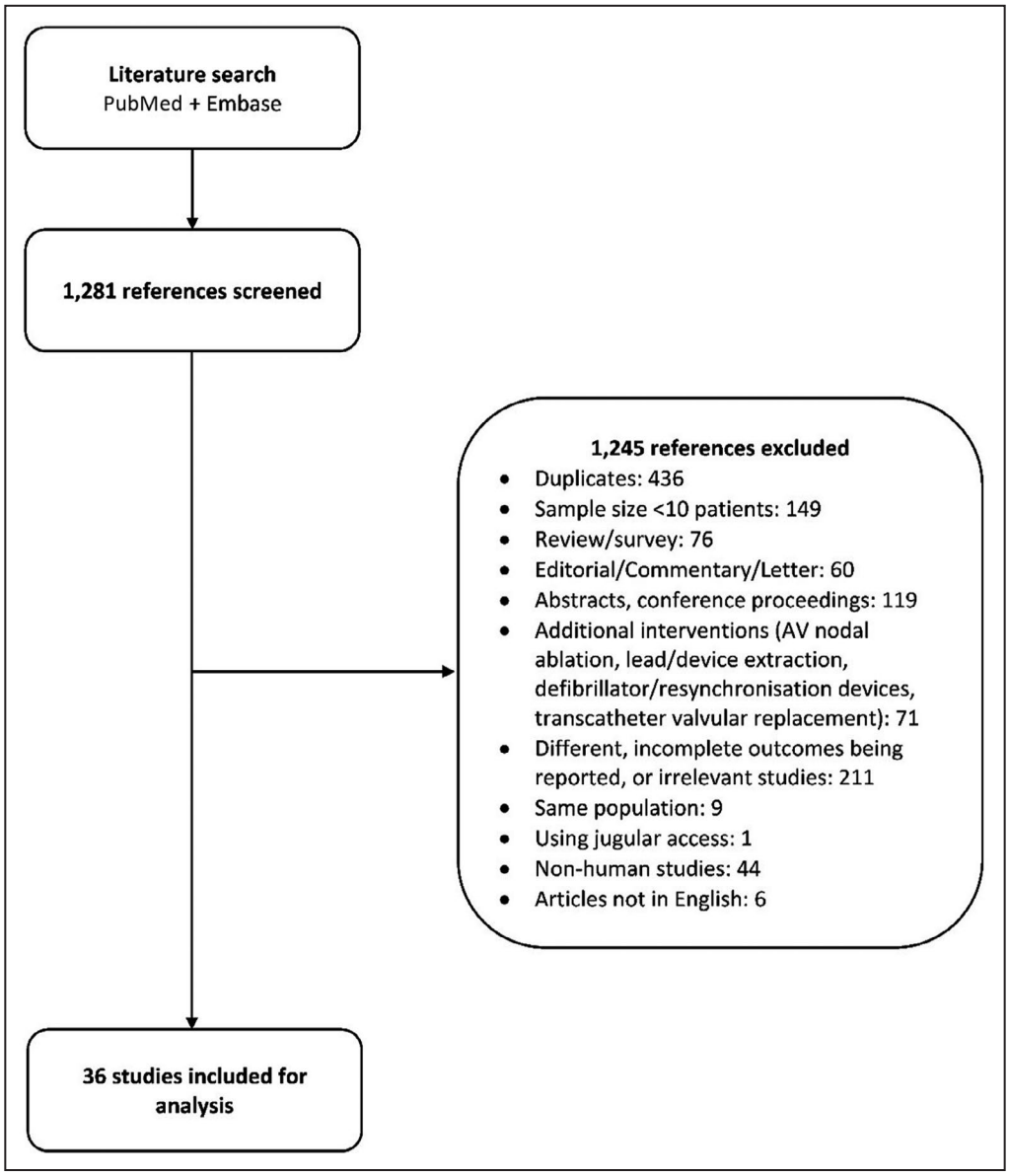


Figure 1. Study selection flow diagram.
AV indicates atrioventricular.

99.59%–99.99%; I^2=0.00%) for Micra and 97.12% (95% CI, 95.86%–98.20%; I^2=0.00%) for Nanostim (Table S2 and Figure 2).

Safety of LPs

Overall, 12 studies (n=2376 patients) reported safety end points at up to 90 days after implant (Table 2 and Figure 3A). Three (n=768 patients) used the Nanostim LP and reported a 90-day complication incidence of 5.85% to 23.5%, with pooled estimates not drawn because of the small number of studies. The pooled incidence of complications of the Micra LP (n=1608 patients) was 0.46% (95% CI, 0.08%–1.05%; I^2=0.00%). When individual complications associated with Micra devices were considered, incidences of device dislodgement (0.00%; 95% CI, 0.00%–0.00%; I^2=0.00%), tamponade/cardiac perforation (0.00%; 95% CI, 0.00%–0.26%; I^2=0.00%), infection (0.00%; 95% CI, 0.00%–0.00%; I^2=0.00%), and vascular injury (0.05%; 95% CI, 0.00%–0.77%; I^2=0.00%) at 90 days were low. Incidences of other complications, such as minor vascular injury or pericardial effusion that did not require intervention, could not be reliably extracted from the included studies.

Sixteen studies (n=3827 patients) with follow-up times beyond 90 days reported safety endpoints at ≈12 months after implantation (Table 3 and Figure 3B). A pooled estimate for Nanostim was also not drawn

Table 1. Characteristics of Included Studies

Characteristics	No. of Studies (No. of Patients)	Summary Estimate
Patient demographics		
Age, y, pooled mean (95% CI)	24 (4335 patients)	83.3 (80.9–85.6)
Men*	28 (4748 patients)	61.0% (59.6%–62.4%)
Comorbidities		
Heart failure	18 (4580 patients)	24.3% (18.0%–31.3%)
Hypertension	23 (4881 patients)	69.7% (64.2%–75.0%)
Coronary artery disease	20 (4556 patients)	28.5% (23.1%–34.2%)
Atrial fibrillation	20 (4611 patients)	66.7% (59.7%–73.5%)
Diabetes mellitus	21 (4695 patients)	23.3% (20.5%–26.3%)
Atrioventricular block	18 (3786 patients)	43.5% (28.2%–59.5%)
Study design		
Prospective	22	61.1%
Retrospective	10	27.8%
Not reported	4	11.1%
Quality assessment		
Good	20	55.6%
Fair	15	41.7%
Poor	1	2.8%
Device used		
Nanostim	5	13.9%
Micra	25	69.4%
Both devices	5	13.9%
Not reported	1	2.8%

*Eight studies used the same cohort as another included study but reported outcomes at a different follow-up interval, leaving 28 studies with unique patient cohorts, 24 of which reported mean and standard deviation for age, and all 28 studies reported the percentage of male patients. CI indicates confidence interval; and y, years.

because of the low number of studies that reported a complication incidence ranging from 5.33% to 6.67%. The pooled incidence of complications for the Micra LP (n=3194 patients) was 1.77% (95% CI, 0.76%–3.07%; I^2=51.2%). There was a lack of safety data beyond 2 years, with only 1 report of a complication incidence of 1.82% at 24 months after implantation.[52]

Seven studies compared outcomes of patients implanted with a LP versus TVP (Table 4 and Figure 3C). The follow-up period in these studies varied from 0 to 26.7 months. In 5 studies with follow-up time of up to 1 year, Micra was associated with 51% lower odds of complications compared with a TVP (3.30% versus 7.43%; OR, 0.49 [95% CI, 0.34–0.70; I^2=0.00%]) (Figure 3C). Only 2 studies compared the safety of Nanostim versus TVP, and therefore, the pooled OR for this comparison was not estimated. One study did not report the numbers for Nanostim and Micra separately.[30]

Efficacy of LPs

The proportion of patients having a pacing capture threshold ≤2 V at 1 year reported for the Nanostim LP ranged from 90% to 100% in 3 studies (Table 5 and Figure 4, pooled estimate not drawn). For the Micra LP, among 12 studies (n=1376 patients), the pooled proportion of patients with a pacing capture threshold ≤2 V at 1 year was 98.96% (95% CI, 97.26%–99.94%) (Figure 4). Only 2 studies, all with Micra implantation, reported an efficacy endpoint beyond 1 year, with 100% (41) and 91.53% (52) of patients having pacing threshold ≤2 V at 13 and 24 months, respectively. Examination of electrical performance beyond 2 years was lacking.

Four studies reported clinical outcomes as their efficacy end point, among which 2 showed improved quality of life and good patient satisfaction (Table 6). The other 2 examined right ventricular and tricuspid valve (TV) function, with 1 reporting that 43% of 53 patients experienced worsening TV regurgitation, whereas the other found 1 out of 23 patients (4.35%) experienced significantly deteriorated TV function.

Sensitivity Analysis

Given the low number of studies investigating the Nanostim system, all sensitivity analyses were performed using studies that reported data for the Micra LP. When we examined good-quality studies only (12 studies, n=3270 patients), the pooled proportion of patients with a successful implant (99.85%; 95% CI, 99.56%–99.99%; I^2=0.00%) and the pooled incidence of complications at 90 days (0.50%; 95% CI, 0.00%–1.78%; I^2=0.00%) were comparable to the overall results. However, the complication incidence at 1 year was higher, with an estimated incidence of 2.39% (95% CI, 1.14%–3.99%; I^2=55.10%). The proportion of patients meeting the efficacy end point of adequate capture threshold at 1 year was 98.77% (95% CI, 97.16%–99.81%; I^2=37.96%), similar to the overall results. We also compared results when only prospective or retrospective studies were included in the meta-analysis. Results from analysis of prospective studies showed pooled estimates of patients experiencing complications and meeting the efficacy end point at 1 year after implant were 1.77% (95% CI, 0.76%–3.07%; I^2=51.20%) and 98.98% (95% CI, 97.66%–99.83%; I^2=26.37%), respectively. On the other hand, retrospective studies reported a slightly lower proportion of patients meeting the efficacy end point of 94.36% (95% CI, 80.54%–100%; I^2=83.86%) and higher incidence of complications at 1 year of 6.52% (95% CI, 2.97%–11.06%; I^2=0.00%).

DISCUSSION

In this systematic review and meta-analysis, we found that a LP, especially the Micra, is associated with a high

Table 2. Studies Included for Meta-Analysis of Incidence of Complications at Up to 90 Days

Author (y)	Study Design	Study Population	Device	Sample Size	Follow-Up Time, mo	Major Complications	Dislodgment	Tamponade	Infection	Vascular Injury
Reddy (2014)[8]	Prospective, single-arm, multicenter cohort study	Consecutive patients undergoing LP implantations	Nanostim	33	3	2	1	1	0	0
Cantillon (2018)[29]	Prospective, 2-arm, multicenter cohort study	Patients implanted with Nanostim were propensity-score matched in 1:2 ratio with 1436 patients implanted with TVP.	Nanostim	718	1	42	7	7	0	8
Vaidya (2019)[44]	Retrospective, 2-arm, single-center cohort study	Consecutive patients undergoing LP implantations	Nanostim	17	2.1	4	0	0	0	0
Ritter (2015)[10]	Prospective, single-arm, multicenter cohort study	Consecutive patients undergoing LP implantations	Micra	140	3	2	0	1	0	1
Pachón (2016)[33]	Single-arm, single-center cohort study	Consecutive patients undergoing LP implantations	Micra	10	1.8	0	0	0	0	0
Da Costa (2017)[34]	Prospective, single-arm, single-center cohort study	Consecutive patients with full or relative contraindications of traditional TVP	Micra	14	3	0	0	0	0	0
Roberts (2017)[28]	Prospective, single-arm, multicenter cohort study	Consecutive patients undergoing LP implantations	Micra	795	1	12	1	1	1	6
Vaidya (2019)[44]	Retrospective, 2-arm, single-center cohort study	Consecutive patients undergoing LP implantations	Micra	73	2.1	0	0	0	0	0
Kiani (2019)[42]	Retrospective, single-arm, multicenter cohort study	Patients underwent LP implantations, among which 26 continued oral anticoagulation during implantation and 144 patients did not.	Micra	170	0	2	0	1	0	1
Grabowski (2020)[47]	Prospective, single-arm, single-center cohort study	Consecutive patients undergoing LP implantations	Micra	10	0	1	0	0	0	1
Mohammed (2020)[49]	Retrospective, single-arm, single-center cohort study	Patients underwent LP implantations using different types of dilators.	Micra	84	0	2	0	0	0	0
El Amrani (2020)[46]	Prospective, single-arm, single-center cohort study	Consecutive patients >70 y with an attempted LP implant, among which 41 were aged ≥90 y	Micra	129	1	3	0	0	0	1
Pagan (2020)[50]	Retrospective, 2-arm, multicenter cohort study	Patients ≥85 y implanted with a Micra	Micra	183	0	2	0	1	0	0

LP indicates leadless pacemaker; and TVP, transvenous pacemaker.

Table 3. Studies Included for Meta-Analysis of Incidence of Complications at ≈1 Year After Implant

Author (y)	Study Design	Study Population	Device	Sample Size	Follow-Up Time, mo	Major Complications
Reddy (2015)[9]	Prospective, single-arm, multicenter cohort study	Consecutive patients undergoing LP implantations	Nanostim	300	6	20
Knops (2015)[19]	Prospective, single-arm, multicenter cohort study	Consecutive patients undergoing LP implantations	Nanostim	33	12	2
Sperzel (2018)[36]	Prospective, single-arm, multicenter cohort study	Consecutive patients undergoing LP implantations	Nanostim	300	6	16
Reynolds (2016)[11]	Prospective, single-arm, multicenter cohort study	Consecutive patients undergoing LP implantations	Micra	725	6	25
Martínez-Sande (2017)[35]	Prospective, single-arm, single-center cohort study	Consecutive patients undergoing LP implantations	Micra	30	5.3	0
El-Chami (2018)[20]	Prospective, single-arm, multicenter cohort study	Consecutive patients implanted with Micra devices after approval	Micra	1817	12	41
Bongiorni (2018)[37]	Prospective, single-arm, single-center cohort study	Consecutive patients undergoing LP implantations	Micra	52	13	0
Kaczmarek (2019)[41]	Prospective, single-arm, single-center cohort study	Consecutive patients undergoing LP implantations	Micra	133	13.9	0
Valiton (2019)[45]	Retrospective, single-arm, multicenter cohort study	Consecutive patients undergoing LP implantations	Micra	92	12	8
Roberts (2019)[43]	Retrospective, single-arm, multicenter cohort study	Patients implanted with Micra LP for cardioinhibitory vasovagal syncope	Micra	32	13.5	1
Garweg (2019)[39]	Prospective, single-arm, single-center cohort study	Consecutive patients undergoing LP implantations	Micra	10	13	1
Denman (2019)[38]	Prospective, single-arm, single-center cohort study	Consecutive patients undergoing LP implantations	Micra	79	11.8	1
Hai (2019)[40]	Prospective, single-arm, single-center cohort study	Consecutive patients undergoing LP implantations	Micra	51	7.3	1
Haeberlin (2020)[48]	Prospective, single-arm, 2-center cohort study	Consecutive patients undergoing LP implantations	Micra	111	13	3
Turagam (2020)[53]	Retrospective, 2-arm, multicenter cohort study	Patients with cardio inhibitory vasovagal syncope implanted with LP	Micra	21	12	1
Tachibana (2020)[51]	Retrospective, 2-arm, single-center cohort study	Consecutive patients ≥85 y underwent LP implantation	Micra	27	6	2

LP indicates leadless pacemaker.

Table 4. Studies Comparing Incidence of Complications Between Leadless Pacemakers and Transvenous Pacemakers

Author (y)	Study Design	Study Population	Device	Sample Size of the LP Group	Follow-Up Time, mo	Major Complications in the LP Group	Sample Size of the TVP Group	Major Complications in the TVP Group	Reported Hazard Ratio
Tjong (2018)[30]	Retrospective, 2-arm, multicenter cohort study	• LP group included 220 among 254 consecutive patients undergoing LP implantation, most of whom participated in 1 or more of LEADLESS trial[8], LEADLESS Observational study[36], or LEADLESS II[9] • TVP group was identified using the prospective FOLLOWPACE nationwide cohort study[3].	Both	220	26.7	9	220	21	HR, 0.20 (0.04–0.89; *P*=0.02) excluding PM advisory-related events* HR, 2.09 (0.94–4.62; *P*=0.06) including PM advisory-related events
Cantillon (2018)[29]	Prospective, 2-arm, multicenter cohort study	• LP group: 718 patients implanted with Nanostim were propensity score–matched in 1:2 ratio with 1436 patients implanted with TVP • TVP group: matched control patients were selected among 9376 patients implanted with single-chamber pacemakers identified in the MarketScan database	Nanostim	718	1	42	1436	165	Adjusted HR, 0.44 (0.32–0.60); *P*<0.001
Vaidya (2019)[44†]	Retrospective, 2-arm, single-center cohort study	• LP group: consecutive patients underwent LP implantation • TVP group: age- and sex-matched patients who underwent single-chamber TVP implantation using billing databases	Nanostim	17	2.1	4	90	5	Not reported
Vaidya (2019)[44†]	Retrospective, 2-arm, single-center cohort study	• LP group: consecutive patients underwent LP implantation • TVP group: age- and sex-matched patients who underwent single-chamber TVP implantation using billing databases	Micra	73	2.1	0	90	5	Not reported
Duray (2017)[27]	Prospective, 2-arm, multicenter cohort study	• LP group: patients recruited in the MICRA TPS[11] • TVP group: derived from individual patient level data set of 2667 patients with de novo pacemakers from 6 recent Medtronic trials of dual-chamber pacing	Micra	726	12	29	2667	209	HR, 0.52 (0.35–0.77); *P*=0.001

(*Continued*)

Table 4. Continued

Author (y)	Study Design	Study Population	Device	Sample Size of the LP Group	Follow-Up Time, mo	Major Complications in the LP Group	Sample Size of the TVP Group	Major Complications in the TVP Group	Reported Hazard Ratio
Tachibana (2020)[51]	Retrospective, 2-arm, single-center cohort study	• LP group: consecutive patients ≥85 y underwent LP implantation • TVP group: consecutive patients ≥85 y implanted with single-chamber TVP during the same study period at the same institute	Micra	27	6	1	35	4	Not reported
Pagan (2020)[50]	Retrospective, 2-arm, multicenter cohort study	• LP group: patients ≥85 y implanted with a Micra • TVP group: patients ≥85 y implanted with single-chamber TVP during the same study period by the same electrophysiologists	Micra	183	0	2	119	4	Not reported
Turagam (2020)[53]	Retrospective, 2-arm, multicenter cohort study	• LP group: patients with cardioinhibitory vasovagal syncope implanted with LP • TVP group: patients implanted with dual-chamber TVP during the same study period	Micra	21	12	1	48	5	Not reported

HR indicates hazard ratio; LP, leadless pacemaker; MICRA TPS, Micra transcatheter pacing study; and TVP, transvenous pacemaker.

*During the study, a pacemaker advisory was issued for the Nanostim LP on the occurrence of device failures because of abrupt battery failure. The authors performed separate analyses including and excluding pacemaker advisory-related complications to examine the differences in performance with and without the effects of this advisory.

†Vaidya et al[44] reported complications for both Nanostim (17 patients) and Micra LPs (73 patients) compared with those associated with TVPs (90 patients).

Table 5. Studies Reporting Efficacy Outcome of Acceptable Capture Threshold

Author (y)	Study Design	Study Population	Device	Follow-Up Time, mo	No. of Patients at Follow-Up	No. of Patients With Acceptable Capture Threshold
Knops (2015)[19]	Prospective, single-arm, multicenter cohort study	Consecutive patients undergoing LP implantations	Nanostim	12	31	31
Reddy (2015)[9]	Prospective, single-arm, multicenter cohort study	Consecutive patients implanted with LP	Nanostim	6	300	270
Sperzel (2018)[36]	Prospective, single-arm, multicenter cohort study	Consecutive patients with an attempted implantation	Nanostim	6	390	390
Reynolds (2016)[11]	Prospective, single-arm, multicenter cohort study	Consecutive patients implanted with LP	Micra	6	297	292
Pachón (2016)[33]	Single-arm, single-center cohort study	Consecutive patients underwent LP implantation attempts	Micra	1.8	10	10
Da Costa (2017)[34]	Prospective, single-arm, single-center cohort study	Consecutive patients with full or relative contraindications of traditional TVP	Micra	3	14	14
El-Chami (2018)[20]	Prospective, single-arm, multicenter cohort study	Consecutive patients implanted with Micra devices after approval	Micra	12	566	549
Kiani (2019)[31]	Retrospective, single-arm, multicenter cohort study	Patients underwent LP implantations, among which 25 patients were discharged on the same day of implantation	Micra	125	1.5	125
Deman (2019)[38]	Prospective, single-arm, single-center cohort study	Consecutive patients underwent LP implantations	Micra	11.8	74	74
Kaczmarek (2019)[41]	Prospective, single-arm, single-center cohort study	Consecutive patients underwent LP implantation	Micra	13.9	23	23
Valiton (2019)[45]	Retrospective, single-arm, multicenter cohort study	Patients with an attempted LP implantation	Micra	12	30	27
Garweg (2019)[39]	Prospective, single-arm, single-center cohort study	Consecutive patients underwent LP implantations	Micra	10.4	66	66
Hai (2019)[40]	Prospective, single-arm, single-center cohort study	Consecutive patients underwent LP implantation	Micra	7.3	45	45
Turagam (2020)[53]	Retrospective, 2-arm, multicenter cohort study	Consecutive patients with an attempted implantation	Micra	12	24	21
Tachibana (2020)[51]	Retrospective, 2-arm, single-center cohort study	Consecutive patients ≥85 y underwent LP implantation	Micra	6	23	20

LP indicates leadless pacemaker; and TVP, transvenous pacemaker.

Table 6. Studies Reporting Clinical Outcomes as Efficacy End Points

Author (y)	Study Design	Study Population	Follow-Up Time	Efficacy End Point	Results
Cabanas-Grandío (2020)[24]	2-arm, multicenter cohort study	One hundred six patients (64 patients implanted with TVP and 42 patients implanted with LP). The choice of TVP or LP was based on clinical criteria and operator availability.	6 mo	Quality of life evaluated by the SF-36 questionnaire	LP is associated with significantly higher scores on physical function (63 vs 42; $P<0.001$), physical role (64 vs 36; $P=0.004$), and mental health (75 vs 65; $P=0.017$) compared with TVP. LP is also associated with lower discomfort and physical restrictions compared with TVP. Hazard/odds ratio not reported.
Tjong (2018)[32]	Prospective, multicenter, single-arm cohort study	Seven hundred twenty patients. Number of patients who completed the SF-36 questionnaire at baseline, 3, and 12 mo was 702, 681, and 635, respectively.	3 and 12 mo	Health-related quality of life evaluated using the SF-36 questionnaire	Health-related quality of life was improved at 3 and 12 mo after LP implantation (mental component score improved by 28.4% at 3 mo and 26.9% at 12 mo; increases in physical component score were 26.8% and 25.3%, respectively). At 3 mo, most patient were satisfied with the treatment.
Beurskens (2019)[25]	Retrospective, 2-arm, single-center cohort study	Fifty-six consecutive patients underwent LP implantations, but only 53 patients (28 Nanostim and 25 Micra) with quality echocardiography images were included.	12 mo	Tricuspid valve regurgitation grade evaluated by echocardiography	Tricuspid valve regurgitation worsened in 23 (43%) patients but comparable to that (38%) in those with TVP ($P=0.39$) and was unrelated to pacing rates. Hazard/odds ratio not reported.
Salaun (2018)[26]	Single-arm, single-center cohort study	Twenty-nine consecutive patients implanted with LP, but only 23 were included for analysis (14 with Nanostim and 9 with Micra). Three patients were excluded because of lack of echocardiography images, and 3 refused to participate.	2 mo	Right ventricular and tricuspid valve function evaluated by echocardiography	No significant change in right ventricular function was observed. One patient experienced significantly deteriorating tricuspid valve regurgitation that was related to pulmonary hypertension caused by chronic obstructive lung disease.

LP indicates leadless pacemaker; SF-36, Short Form-36; and TVP, transvenous pacemaker.

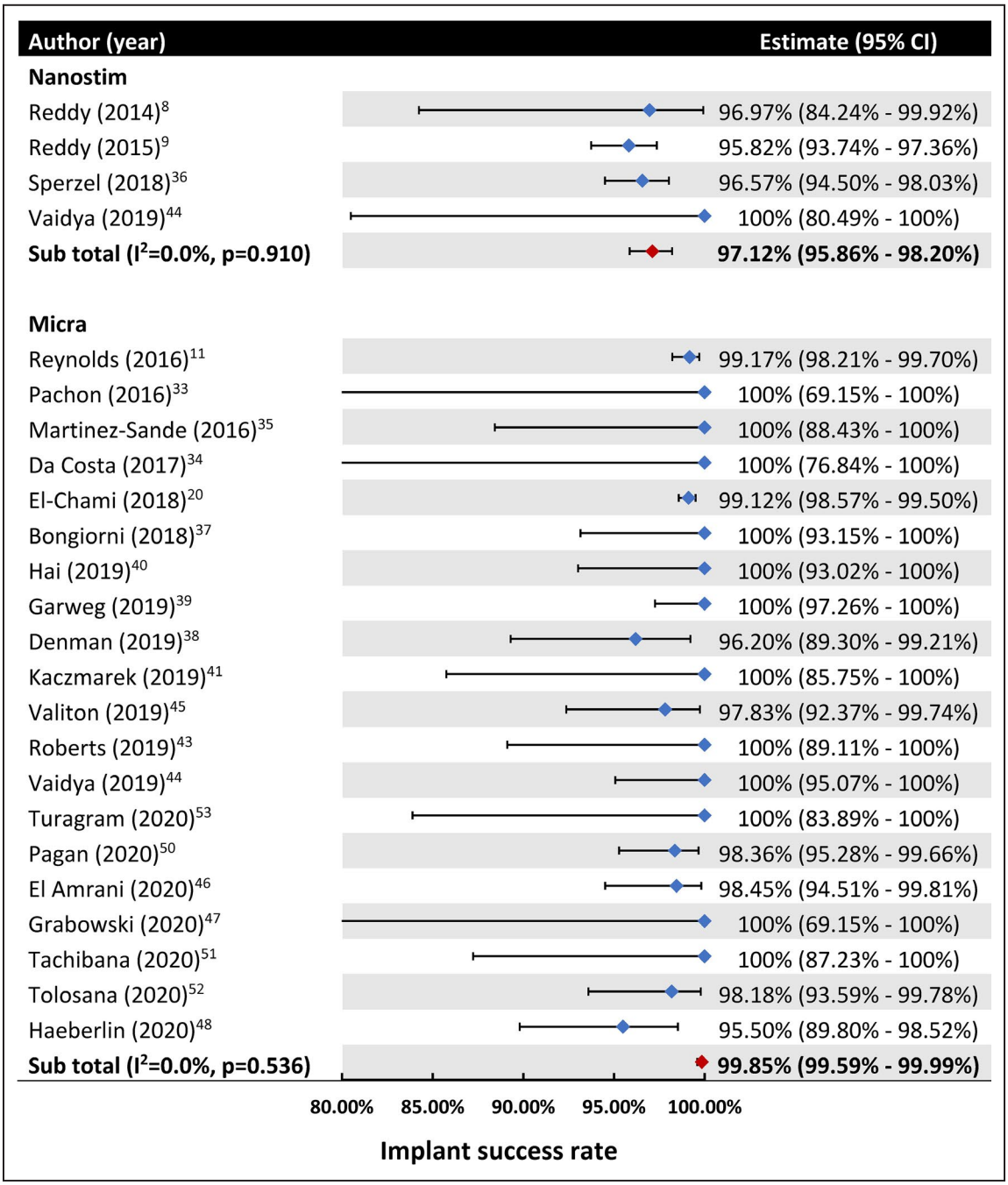
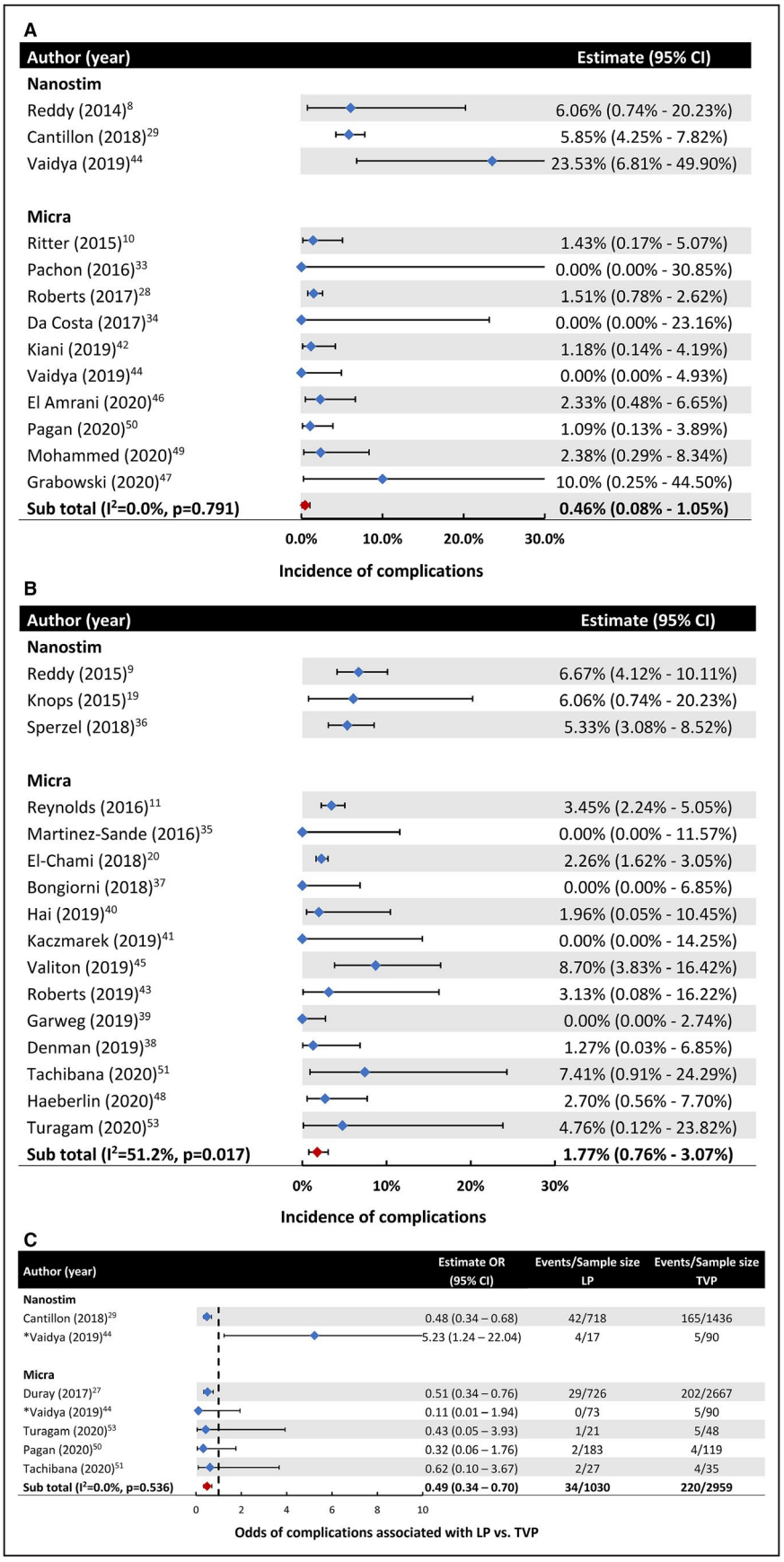


Figure 2. Pooled proportion of patients with a successful implant.
Catillon et al (2018)[29] and Roberts et al (2017)[28] both reported the proportion of patients with a successful implant, but they used the same population as the Reddy et al (2015)[9] study (LEADLESS II trial) and El-Chami et al (2018)[20] study (Micra Post-Approval Registry), and therefore were not included in this meta-analysis.

proportion of patients having a successful implant and a low incidence of complications at 90 days and 1 year after implantation. In the few studies that compared LPs with TVPs, Micra devices were associated with 51% lower odds of complications. Furthermore, the combined data suggested that LPs have good

Figure 3. Meta-analysis of the safety of the leadless pacemaker (LP).
A, Pooled incidence of overall complications at up to 90 days after LP implantation. **B**, Pooled incidence of overall complications at ≈1 year after LP implantation in studies that reported safety outcomes beyond 90 days. **C**, Incidence of overall complications in studies that compared the LP with the transvenous pacemaker (TVP) implantation. *Vaidya et al[44] reported complications for both Nanostim (17 patients) and Micra LPs (73 patients) compared with those associated with a TVP (90 patients). OR indicates odds ratio.


A
Author (year)
Estimate (95% CI)
Nanostim
Reddy (2014)[8]
6.06% (0.74% - 20.23%)
Cantillon (2018)[29]
5.85% (4.25% - 7.82%)
Vaidya (2019)[44]
23.53% (6.81% - 49.90%)
Micra
Ritter (2015)[10]
1.43% (0.17% - 5.07%)
Pachon (2016)[33]
0.00% (0.00% - 30.85%)
Roberts (2017)[28]
1.51% (0.78% - 2.62%)
Da Costa (2017)[34]
0.00% (0.00% - 23.16%)
Kiani (2019)[42]
1.18% (0.14% - 4.19%)
Vaidya (2019)[44]
0.00% (0.00% - 4.93%)
El Amrani (2020)[46]
2.33% (0.48% - 6.65%)
Pagan (2020)[50]
1.09% (0.13% - 3.89%)
Mohammed (2020)[49]
2.38% (0.29% - 8.34%)
Grabowski (2020)[47]
10.0% (0.25% - 44.50%)
Sub total (I²=0.0%, p=0.791)
0.46% (0.08% - 1.05%)
0.0% 10.0% 20.0% 30.0%
Incidence of complications
B
Author (year)
Estimate (95% CI)
Nanostim
Reddy (2015)[9]
6.67% (4.12% - 10.11%)
Knops (2015)[19]
6.06% (0.74% - 20.23%)
Sperzel (2018)[36]
5.33% (3.08% - 8.52%)
Micra
Reynolds (2016)[11]
3.45% (2.24% - 5.05%)
Martinez-Sande (2016)[35]
0.00% (0.00% - 11.57%)
El-Chami (2018)[20]
2.26% (1.62% - 3.05%)
Bongiorni (2018)[37]
0.00% (0.00% - 6.85%)
Hai (2019)[40]
1.96% (0.05% - 10.45%)
Kaczmarek (2019)[41]
0.00% (0.00% - 14.25%)
Valiton (2019)[45]
8.70% (3.83% - 16.42%)
Roberts (2019)[43]
3.13% (0.08% - 16.22%)
Garweg (2019)[39]
0.00% (0.00% - 2.74%)
Denman (2019)[38]
1.27% (0.03% - 6.85%)
Tachibana (2020)[51]
7.41% (0.91% - 24.29%)
Haeberlin (2020)[48]
2.70% (0.56% - 7.70%)
Turagam (2020)[53]
4.76% (0.12% - 23.82%)
Sub total (I²=51.2%, p=0.017)
1.77% (0.76% - 3.07%)
0% 10% 20% 30%
Incidence of complications
C
Author (year)
Estimate OR (95% CI)
Events/Sample size LP
Events/Sample size TVP
Nanostim
Cantillon (2018)[29]
0.48 (0.34 – 0.68)
42/718
165/1436
*Vaidya (2019)[44]
5.23 (1.24 – 22.04)
4/17
5/90
Micra
Duray (2017)[27]
0.51 (0.34 – 0.76)
29/726
202/2667
*Vaidya (2019)[44]
0.11 (0.01 – 1.94)
0/73
5/90
Turagam (2020)[53]
0.43 (0.05 – 3.93)
1/21
5/48
Pagan (2020)[50]
0.32 (0.06 – 1.76)
2/183
4/119
Tachibana (2020)[51]
0.62 (0.10 – 3.67)
2/27
4/35
Sub total (I²=0.0%, p=0.536)
0.49 (0.34 – 0.70)
34/1030
220/2959
0 2 4 6 8 10
Odds of complications associated with LP vs. TVP

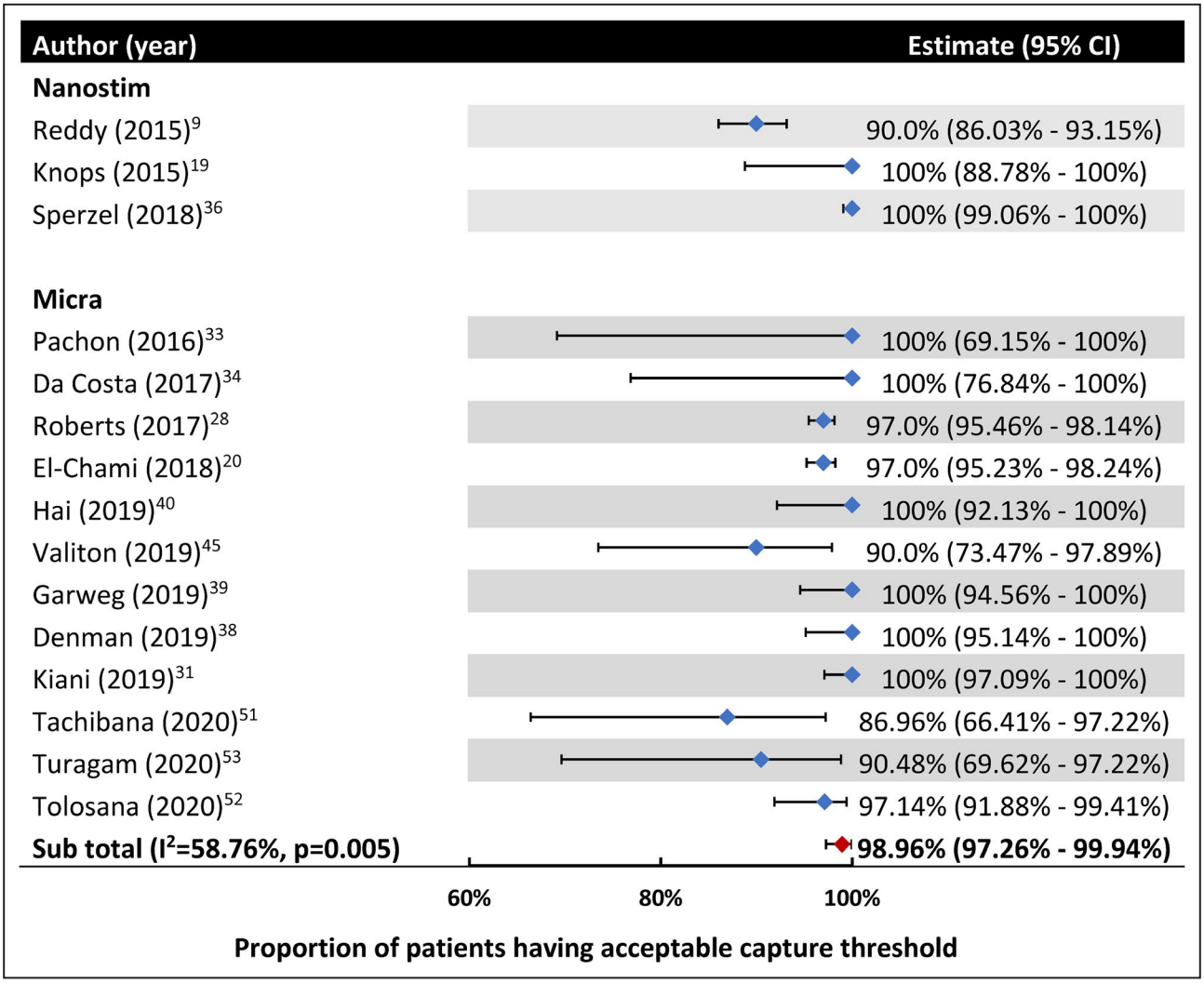


Figure 4. **Pooled proportion of patients having a pacing capture threshold ≤2 V at 1 year after implantation.**

electrical performance up to 1 year after implantation, with >90% of devices having an adequate pacing capture threshold. However, the current literature is predominantly based on the Micra LP and includes only observational data with limited follow-up time, with electrical performance and clinical outcomes rarely being reported beyond the second year. Although the available data are promising, robust randomized trials with longer-term clinical outcome data are required to confirm these findings.

This study represents the first systematic evaluation of the safety and efficacy of LPs implanted in the right ventricle. There are 2 systematic reviews related to LPs that examined the incidences of cardiac perforation[15] and device dislodgement,[16] respectively, although neither reported pooled estimates because they included only 2 and 3 LP studies, respectively. We extend the literature by providing pooled estimates of overall as well as specific complications. Notably, the pooled complication incidence associated with Micra is considerably lower than the 7.76% to 12.4% incidence of early complications[2–4] (within 3 months) or the 15% to 16% incidence of long-term complications[3,4] that are typically associated with TVPs. Our meta-analysis of studies comparing LPs and TVPs confirmed this observation, with the Micra LP having half the odds of TVPs. Collectively, these findings suggest that LP implantation is safe and associated with less harm than TVPs.

Besides the good safety profile, the implant success and the short-term efficacy of LPs were high. However, there was a lack of efficacy data beyond 2 years, which leaves uncertainty about the longevity of the device performance. The unexpected premature battery failure of the Nanostim LP occurred at 2.3 to 4.0 years after implantation.[12] Although no such concern has been reported with the Micra LP, the only LP currently approved by the Food and Drug

Administration, whether it can match the battery life of contemporary TVPs remains uncertain. More data are also needed about the long-term management of these devices such as pacemaker retrieval and how additional devices are implanted when LPs reach the end of battery life.

Uncertainties also exist about the clinical outcomes associated with LPs, because most studies only report acceptable pacing capture threshold as the primary efficacy end point. Although the electrical performance is easy to measure, clinical outcomes like mortality, syncope, heart failure, TV function and quality of life are equally relevant to patients and clinicians. Only a few studies have evaluated quality of life, all of which reported improved quality of life,[24,32] and 1 showed better physical activity, physical role, and mental health associated with LP compared with conventional devices.[24] On the other hand, TV function was evaluated in 2 small studies, with 1 study suggesting worsening TV regurgitation in up to 45% of patients, which is comparable to the 38% incidence associated with TVPs (P=0.39).[25] The other recorded only 1 out of 23 patients experiencing increased TV regurgitation,[26] which was thought to result from pulmonary hypertension rather than pacing. Nevertheless, neither studies reported new onset of heart failure as a clinical endpoint. Theoretically, without a lead crossing the valve, TV regurgitation should occur less frequently with LPs, because studies have shown that worsening TV function associated with traditional cardiac devices are likely attributable to lead-related damages to TV leaflets or subvalvular structures, or impairment of leaflet mobility and coaptation.[54–56] Future investigations are needed to examine the underlying mechanisms of this phenomenon as well as evaluate other clinical outcomes.

Several limitations should be considered when interpreting our results. Although our findings are promising, the data were entirely observational, and most studies had a small sample size and short follow-up time of <1 year. Because there are essential differences in sizes, fixation and pacing mechanisms between the Nanostim and Micra devices, a meta-analysis was performed separately for each device. However, because of the low number of studies that used the Nanostim LP, pooled estimates for this device were not drawn, and most of the pooled estimates reflect the performance of the Micra LP only. The inconsistency about which complications are reported makes estimating pooled incidences for specific complications challenging. Similarly, efficacy endpoints about pacing capture threshold were defined differently among studies, with some considering ≤2 V acceptable, whereas others used the 1.5-V threshold. The exclusion of abstracts and conference proceedings may increase the risk of publication bias, although data using only fully published articles are considered more reliable and generally necessarily provide all required information.

CONCLUSIONS

Based on pooled observational data, leadless pacemakers have a low incidence of complications (0.46% at 3 months and 1.77% at 1 year for the Micra LP) and good short-term electrical performance, with >90% of LPs having acceptable pacing threshold at 1 year. A Micra is also associated with 51% lower odds of complications when compared with a TVP. Further data from well-designed randomized controlled trials with longer follow-up time are still required to determine longer-term safety and efficacy of LPs to support the widespread adoption of these novel devices in clinical practice.

ARTICLE INFORMATION

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Affiliations

School of Clinical Medicine, The University of Queensland, Brisbane, QLD, Australia (L.N., T.E.W., H.M.H., I.R.); Department of Cardiology, The Prince Charles Hospital, Brisbane, QLD, Australia (L.N., D.N., R.A.D., H.M.H., I.R.); Cardiovascular Centre, E Hospital, Hanoi, Vietnam (L.N.); St Vincent's Private Hospital Northside, Brisbane, QLD, Australia (T.E.W.); and Flinders Centre for Epidemiology and Biostatistics, Flinders University, Adelaide, SA, Australia (R.J.W.).

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Disclosures

Dr Denman has delivered talks for Medtronic on LPs, has run 4 training courses for Medtronic at The Prince Charles Hospital to train other physicians in how to implant the Micra LP. Dr Denman is also a local principal investigator for the St Jude Nanostim study. Dr Haqqani has received speaking and proctoring honoraria from Medtronic and has served on the scientific advisory board of Medtronic. Dr Haqqani has also received speaking honoraria from Abbott. The remaining authors have no disclosures to report.

Supplementary Material

Tables S1–S3
References 8–11, 20, 24–53

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SUPPLEMENTAL MATERIAL

Table S1. Search strategy and keywords.

DATABASE	SEARCH KEYWORDS
Pubmed	(Micra[tiab] OR Nanostim[tiab] OR Leadless[tiab]) AND (pacemaker*[tiab] OR pacemaker[mh])
Embase	(‘micra’:ti,ab OR ‘nanostim’:ti,ab OR ‘leadless’:ti,ab) AND (‘pacemaker’/exp OR ‘pacemaker’:ti,ab)

Table S2. Studies included for meta-analysis of proportion of patients with a successful implant.

Author (year)	Study design	Study population	Device	Number of patients with implant attempt(s)	Number of patients with successful implant
Reddy (2014)[8]	Prospective, single-arm, multi-center cohort study	Consecutive patients undergoing LP implantations	Nanostim	33	32
Reddy (2015)[9]	Prospective, single-arm, multi-center cohort study	Consecutive patients undergoing LP implantations	Nanostim	300	289
Sperzel (2018)[36]	Prospective, single-arm, multi-center cohort study	Consecutive patients undergoing LP implantations	Nanostim	467	451
Vaidya (2019)[44]	Retrospective, two-arm, single-center cohort study	Consecutive patients undergoing LP implantations	Nanostim	17	17
Reynolds (2016)[11]	Prospective, single-arm, multi-center cohort study	Consecutive patients undergoing LP implantations	Micra	725	719
Pachon (2016)[33]	Single-arm, single-center cohort study	Consecutive patients undergoing LP implantations	Micra	10	10
Martinez-Sande (2017)[35]	Prospective, single-arm, single-center cohort study	Consecutive patients undergoing LP implantations	Micra	30	30
Da Costa (2016)[34]	Prospective, single-arm, single-center cohort study	Consecutive patients with full or relative contraindications of traditional TVP	Micra	14	14
Bongiorni (2018)[37]	Prospective, single-arm, single-center cohort study	Consecutive patients undergoing LP implantations	Micra	52	52
El-Chami (2018)[20]	Prospective, single-arm, multi-center cohort study	Consecutive patients implanted with Micra devices after approval	Micra	1817	1801
Deman (2019)[38]	Prospective, single-arm, single-center cohort study	Consecutive patients undergoing LP implantations	Micra	79	76
Kaczmarek (2019)[41]	Prospective, single-arm, single-center cohort study	Consecutive patients undergoing LP implantations	Micra	24	24
Roberts (2019)[43]	Retrospective, single-arm, multi-center cohort study	Patients implanted with Micra LP for cardioinhibitory vasovagal syncope	Micra	32	32
Vaidya (2019)[44]	Retrospective, two-arm, single-center cohort study	Consecutive patients undergoing LP implantations	Micra	73	73
Valiton (2019)[45]	Retrospective, single-arm, multi-center cohort study	Consecutive patients undergoing LP implantations	Micra	92	90
Garweg (2019)[39]	Prospective, single-arm, single-center cohort study	Patients implanted with Micra LP for cardioinhibitory vasovagal syncope	Micra	133	133
Hai (2019)[40]	Prospective, single-arm, single-center cohort study	Consecutive patients undergoing LP implantations	Micra	51	51
Turagam (2020)[53]	Retrospective, two-arm, multi-center cohort study	Patients with cardio inhibitory vasovagal syncope implanted with LP.	Micra	24	24
Tachibana (2020)[51]	Retrospective, two-arm, single-center cohort study	Consecutive patients ≥85 years underwent LP implantation	Micra	27	27
Haeberlin (2020)[48]	Prospective, single-arm, two-center cohort study	Consecutive patients undergoing LP implantations	Micra	111	106
Grabowski (2020)[47]	Prospective, single-arm, single-center cohort study	Consecutive patients undergoing LP implantations	Micra	10	10
El Amrani (20120)[46]	Prospective, single-arm, single-center cohort study	Consecutive patients >70 years with an attempted LP implant	Micra	129	127
Pagan (2020)[50]	Retrospective, two-arm, multi-center cohort study	Patients ≥85 years implanted with a Micra	Micra	183	180
Tolosana (2020)[52]	Single-arm, single-center v	Consecutive patients undergoing LP implantations	Micra	110	108

LP=leadless pacemaker

Table S3. Study quality assessment results.

Author (Year)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quality
Reddy (2014)[8]	Y	Y	Y	Y	Y	Y	Y	Y	Y						GOOD
Knops (2015)[19]	Y	Y	Y	Y	Y	Y	Y	Y	Y						GOOD
Reddy (2015)[9]	Y	Y	Y	Y	Y	Y	Y	Y	Y						GOOD
Ritter (2015)[10]	Y	Y	Y	Y	Y	Y	Y	Y	Y						GOOD
Pachon (2016)[33]	Y	Y	Y	Y	Y	Y	Y	Y	Y						GOOD
Reynolds (2016)[11]	Y	Y	Y	Y	Y	Y	Y	Y	Y						GOOD
Da Costa (2017)[34]	Y	Y	Y	Y	Y	Y	Y	Y	Y						GOOD
Duray (2017)[27]	Y	Y	NA	Y	NA	NA	NA	NA	Y	NA	N	N	Y	NA	FAIR
Martinez-Sande (2017)[35]	Y	Y	Y	Y	Y	Y	Y	Y	N						FAIR
Roberts (2017)[28]	Y	Y	Y	Y	Y	Y	N	Y	N						FAIR
Cantillon (2018)[29]	Y	Y	Y	Y	Y	Y	N	Y	Y						FAIR
El-Chami (2018)[20]	Y	Y	Y	Y	Y	Y	Y	Y	Y						GOOD
Sperzel (2018)[36]	Y	Y	Y	Y	Y	Y	Y	Y	Y						GOOD
Tjong (2018)[30]	Y	Y	NA	N	NA	NA	NA	NA	Y	NA	Y	N	Y	NA	FAIR
Bongiorni (2018)[37]	Y	Y	Y	Y	Y	Y	Y	Y	Y						GOOD
Denman (2019)[38]	Y	Y	Y	Y	Y	Y	Y	Y	Y						GOOD
Garweg (2019)[39]	Y	Y	Y	Y	Y	Y	Y	Y	N						FAIR
Hai (2019)[40]	Y	Y	Y	Y	Y	Y	Y	Y	Y						GOOD
Kaczemarek (2019)[41]	Y	Y	Y	Y	Y	N	Y	Y	N						FAIR
Kiani (2019)[31]	Y	Y	Y	Y	Y	Y	Y	Y	Y						GOOD

Kiani (2019)[42]	Y	Y	Y	Y	Y	Y	Y	Y	Y						GOOD
Roberts (2019)[43]	Y	Y	N	Y	Y	Y	Y	Y	Y						FAIR
Vaidya (2019)[44]	Y	Y	NA	N	NA	NA	NA	NA	Y	NA	Y	N	Y	NA	FAIR
Valiton (2019)[45]	Y	Y	Y	Y	Y	Y	Y	Y	Y						GOOD
El Amrani (2020)[46]	Y	Y	Y	Y	Y	Y	Y	Y	Y						GOOD
Grabowski (2020)[47]	Y	Y	Y	Y	Y	N	N	Y	N						POOR
Haeberlin (2020)[48]	Y	Y	Y	Y	Y	Y	N	Y	N						FAIR
Mohammed (2020)[49]	Y	Y	Y	Y	Y	N	N	Y	Y						FAIR
Pagan (2020)[50]	Y	Y	Y	Y	Y	Y	N	Y	Y						FAIR
Tachibana (2020)[51]	Y	Y	NA	Y	NA	NA	NA	NA	Y	NA	N	N	Y	NA	FAIR
Tolosana (2020)[52]	Y	Y	Y	Y	Y	Y	Y	Y	Y						GOOD
Turagam (2020)[53]	Y	Y	Y	Y	Y	Y	Y	Y	Y						GOOD
Salaun (2018)[26]	Y	Y	Y	Y	Y	Y	N	Y	Y						FAIR
Tjong (2018)[32]	Y	Y	NA	N	NA	NA	NA	NA	Y	NA	Y	N	Y	Y	FAIR
Beurskens (2019)[25]	Y	Y	NA	Y	NA	NA	NA	NA	Y	NA	Y	N	Y	Y	GOOD
Cabanas-Grandio (2019)[24]	Y	Y	NA	Y	NA	NA	NA	NA	Y	NA	Y	N	Y	Y	GOOD

NA=Not applicable, N=No, Y=Yes.