SYSTEMATIC REVIEW AND META-ANALYSIS

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

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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...
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. Nevertheless, the initial evidence supporting the use of these devices was limited and came from mostly small observational studies 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, 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 and limited reviews of LP-associated cardiac perforation and dislodgement. 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. 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.
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, 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]

**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,
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%) |
| Atroventricular 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.

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%; R=0.00%) and the pooled incidence of complications at 90 days (0.50%; 95% CI, 0.00%–1.78%; R=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%; R=55.10%).

**DISCUSSION**

In this systematic review and meta-analysis, we found that a LP, especially the Micra, is associated with a high...
| Author (y) | Study Design | Study Population | Device | Sample Size | Follow-Up Time, mo | Major Complications | Dislodgment | Tamponade | Infection | Vascular Injury |
|-----------|--------------|------------------|--------|-------------|-------------------|---------------------|-------------|-----------|----------|----------------|
| Reddy (2014) | Prospective, single-arm, multicenter cohort study | Consecutive patients undergoing LP implantations | Nanostim | 33 | 3 | 2 | 1 | 1 | 0 | 0 |
| Cantillon (2018) | Prospective, 2-arm, multicenter cohort study | Patients implanted with Nanostim were propensity-score matched in a 1:2 ratio with 1436 patients implanted with TVP. | Nanostim | 718 | 1 | 42 | 7 | 7 | 0 | 8 |
| Vaidya (2019) | Retrospective, 2-arm, single-center cohort study | Consecutive patients undergoing LP implantations | Nanostim | 17 | 2.1 | 4 | 0 | 0 | 0 | 0 |
| Ritter (2015) | Prospective, single-arm, multicenter cohort study | Consecutive patients undergoing LP implantations | Micra | 140 | 3 | 2 | 0 | 1 | 0 | 1 |
| Pachón (2016) | Single-arm, single-center cohort study | Consecutive patients undergoing LP implantations | Micra | 10 | 1.8 | 0 | 0 | 0 | 0 | 0 |
| da Costa (2017) | 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) | Prospective, single-arm, multicenter cohort study | Consecutive patients undergoing LP implantations | Micra | 795 | 1 | 12 | 1 | 1 | 1 | 6 |
| Vaidya (2019) | Retrospective, 2-arm, single-center cohort study | Consecutive patients undergoing LP implantations | Micra | 73 | 2.1 | 0 | 0 | 0 | 0 | 0 |
| Kiani (2019) | 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) | Prospective, single-arm, single-center cohort study | Consecutive patients undergoing LP implantations | Micra | 10 | 0 | 1 | 0 | 0 | 0 | 1 |
| Mohammed (2020) | 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) | 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) | 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)        | Prospective, single-arm, multicenter cohort study | Consecutive patients undergoing LP implantations       | Nanostim   | 300         | 6                  | 20                  |
| Knops (2015)        | Prospective, single-arm, multicenter cohort study | Consecutive patients undergoing LP implantations       | Nanostim   | 33          | 12                 | 2                   |
| Sperzel (2018)      | Prospective, single-arm, multicenter cohort study | Consecutive patients undergoing LP implantations       | Nanostim   | 300         | 6                  | 16                  |
| Reynolds (2016)     | Prospective, single-arm, multicenter cohort study | Consecutive patients undergoing LP implantations       | Nanostim   | 20          | 6                  | 25                  |
| Martínez-Sande (2017) | Prospective, single-arm, single-center cohort study | Consecutive patients undergoing LP implantations       | Micra      | 725         | 6                  | 25                  |
| El-Chami (2018)     | Prospective, single-arm, multicenter cohort study | Consecutive patients undergoing LP implantations       | Micra      | 30          | 5.3                | 0                   |
| Bongiorni (2018)    | Prospective, single-arm, single-center cohort study | Consecutive patients undergoing LP implantations       | Micra      | 1817        | 12                 | 41                  |
| Kazczmarek (2019)   | Prospective, single-arm, single-center cohort study | Consecutive patients undergoing LP implantations       | Micra      | 52          | 13                 | 0                   |
| Valton (2019)       | Retrospective, single-arm, multicenter cohort study | Consecutive patients undergoing LP implantations       | Micra      | 133         | 13.9               | 0                   |
| Roberts (2019)      | Retrospective, single-arm, multicenter cohort study | Patients implanted with Micra LP for cardioinhibitory vasovagal syncope | Micra      | 92          | 12                 | 8                   |
| Garweg (2019)       | Prospective, single-arm, single-center cohort study | Consecutive patients undergoing LP implantations       | Micra      | 32          | 13.5               | 1                   |
| Denman (2019)       | Prospective, single-arm, single-center cohort study | Consecutive patients undergoing LP implantations       | Micra      | 10          | 13                 | 1                   |
| Hai (2019)          | Prospective, single-arm, single-center cohort study | Consecutive patients undergoing LP implantations       | Micra      | 79          | 11.8               | 1                   |
| Haeberlin (2020)    | Prospective, single-arm, 2-center cohort study | Consecutive patients undergoing LP implantations       | Micra      | 51          | 7.3                | 1                   |
| Turagam (2020)      | Retrospective, 2-arm, multicenter cohort study | Patients with cardio inhibitory vasovagal syncope implanted with LP | Micra      | 111         | 13                 | 3                   |
| Tachibana (2020)    | 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 trial9, LEADLESS Observational study9, or LEADLESS II9. • TVP group was identified using the prospective FOLLOWPACE nationwide cohort study1. | 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 MCRATA TPS11. • 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)
| 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) | Retrospective, 2-arm, single-center cohort study | • LP group: consecutive patients ≥85 y underwent LP implantation<br>• 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)    | Retrospective, 2-arm, multicenter cohort study | • LP group: patients ≥85 y implanted with a Micra<br>• 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)  | Retrospective, 2-arm, multicenter cohort study | • LP group: patients with cardioinhibitory vasovagal syncope implanted with LP<br>• 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. reported complications for both Nanostim (17 patients) and Micra LPs (73 patients) compared with those associated with TVPs (90 patients).
| Author (Y) | Study Design | Study Population | Device | No. of Patients at Follow-Up | No. of Patients With Acceptable Capture Threshold |
|------------|--------------|------------------|--------|-----------------------------|---------------------------------------------|
| Knops (2015) | Prospective, single-arm, multicenter cohort study | Consecutive patients undergoing LP implantations | Nanostim | 12 | 31 |
| Reddy (2015) | Prospective, single-arm, multicenter cohort study | Consecutive patients implanted with LP | Nanostim | 6 | 300 |
| Spiering (2018) | Prospective, single-arm, multicenter cohort study | Consecutive patients implanted with LP | Nanostim | 6 | 390 |
| Reynolds (2018) | Prospective, single-arm, multicenter cohort study | Consecutive patients implanted with LP | Nanostim | 6 | 390 |
| Pachón (2016) | Single-arm, single-center cohort study | Consecutive patients underwent LP implantation attempts | Micra | 6 | 292 |
| Da Costa (2017) | Single-arm, single-center cohort study | Consecutive patients implanted with LP | Micra | 1.8 | 10 |
| El-Chami (2018) | Prospective, single-arm, multicenter cohort study | Consecutive patients with full or relative contraindications of TVP implantation | Micra | 12 | 566 |
| Kiani (2019) | Retrospective, single-arm, multicenter cohort study | Patients with an attempted LP implantation attempt | Micra | 1.5 | 125 |
| Demian (2019) | Retrospective, single-arm, multicenter cohort study | Patients undergoing LP implantation attempts | Micra | 11.8 | 74 |
| Kaczmarek (2019) | Retrospective, single-arm, multicenter cohort study | Patients with an attempted LP implantation attempt | Micra | 13.9 | 23 |
| Valiton (2019) | Retrospective, single-arm, multicenter cohort study | Patients with an attempted LP implantation attempt | Micra | 12 | 30 |
| Garweg (2019) | Retrospective, single-arm, multicenter cohort study | Patients with an attempted LP implantation attempt | Micra | 10.4 | 66 |
| Hai (2019) | Retrospective, 2-arm, multicenter cohort study | Patients with an attempted LP implantation attempt | Micra | 7.3 | 45 |
| Tachibana (2020) | Retrospective, 2-arm, multicenter cohort study | Patients with an attempted LP implantation attempt | Micra | 6 | 23 |

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) | 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) | 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, 661, 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) | 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) | 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.
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

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**Table**

| Author (year)         | Estimate (95% CI)                  |
|-----------------------|-----------------------------------|
| **Nanostim**          |                                   |
| Reddy (2014)¹⁸        | 96.97% (84.24% - 99.92%)          |
| Reddy (2015)³⁹        | 95.82% (93.74% - 97.36%)          |
| Sperzel (2018)³⁶      | 96.57% (94.50% - 98.03%)          |
| Vaidya (2019)⁴⁴       | 100% (80.49% - 100%)              |
| **Sub total (I²=0.0%, p=0.910)** | 97.12% (95.86% - 98.20%) |
| **Micra**             |                                   |
| Reynolds (2016)¹¹     | 99.17% (98.21% - 99.70%)          |
| Pachon (2016)³³       | 100% (69.15% - 100%)              |
| Martinez-Sande (2016)³⁵ | 100% (88.43% - 100%)             |
| Da Costa (2017)³⁴     | 100% (76.84% - 100%)              |
| El-Chami (2018)²⁰     | 99.12% (98.57% - 99.50%)          |
| Bongiorni (2018)³⁷    | 100% (93.15% - 100%)              |
| Hal (2019)⁴⁰         | 100% (93.02% - 100%)              |
| Garweg (2019)⁴⁹      | 100% (97.26% - 100%)              |
| Denman (2019)³⁸       | 96.20% (89.30% - 99.21%)          |
| Kaczmarek (2019)⁴¹    | 100% (85.75% - 100%)              |
| Valiton (2019)⁴⁵      | 97.83% (92.37% - 99.74%)          |
| Roberts (2019)³³      | 100% (89.11% - 100%)              |
| Vaidya (2019)⁴⁴       | 100% (95.07% - 100%)              |
| Turagram (2020)⁵³     | 100% (83.89% - 100%)              |
| Pagan (2020)⁵⁰       | 98.36% (95.28% - 99.66%)          |
| El Amrani (2020)⁴⁶    | 98.45% (94.51% - 99.81%)          |
| Grabowski (2020)⁴⁷    | 100% (69.15% - 100%)              |
| Tachibana (2020)⁵¹    | 100% (87.23% - 100%)              |
| Tolosana (2020)⁵²     | 98.18% (93.59% - 99.78%)          |
| Haeberlin (2020)⁴⁸    | 95.50% (89.80% - 98.52%)          |
| **Sub total (I²=0.0%, p=0.536)** | 99.85% (99.59% - 99.99%) |

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**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)³⁰ study (Micra Post-Approval Registry), and therefore were not included in this meta-analysis.

**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 al⁴⁴ 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.
### Table A: Incidence of complications

| Author (year) | Estimate (95% CI) |
|---------------|-------------------|
| **Nanostim**  |                   |
| Reddy (2014)  | 6.06% (0.74% - 20.23%) |
| Cantillon (2018) | 5.85% (4.25% - 7.82%) |
| Vaidya (2019) | 23.53% (6.81% - 49.90%) |
| **Micra**     |                   |
| Ritter (2015) | 1.43% (0.17% - 5.07%) |
| Pachon (2016) | 0.00% (0.00% - 30.85%) |
| Roberts (2017) | 1.51% (0.78% - 2.62%) |
| Da Costa (2017) | 0.00% (0.00% - 23.16%) |
| Kiani (2019) | 1.18% (0.14% - 4.19%) |
| Vaidya (2019) | 0.00% (0.00% - 4.93%) |
| El Amrani (2020) | 2.33% (0.48% - 6.65%) |
| Pagan (2020) | 1.09% (0.13% - 3.89%) |
| Mohammed (2020) | 2.38% (0.29% - 8.34%) |
| Grabowski (2020) | 10.0% (0.25% - 44.50%) |
| **Sub total (I²=0.0%, p=0.791)** | **0.46% (0.08% - 1.05%)** |

### Table B: Incidence of complications

| Author (year) | Estimate (95% CI) |
|---------------|-------------------|
| **Nanostim**  |                   |
| Reddy (2015)  | 6.67% (4.12% - 10.11%) |
| Knops (2015) | 6.06% (0.74% - 20.23%) |
| Sperzel (2018) | 5.33% (3.08% - 8.52%) |
| **Micra**     |                   |
| Reynolds (2016) | 3.45% (2.24% - 5.05%) |
| Martinez-Sande (2016) | 0.00% (0.00% - 11.57%) |
| El-Chami (2018) | 2.26% (1.62% - 3.05%) |
| Bongiorni (2018) | 0.00% (0.00% - 6.85%) |
| Hai (2019) | 1.96% (0.05% - 10.45%) |
| Kaczmarek (2019) | 0.00% (0.00% - 14.25%) |
| Vaitlon (2019) | 8.70% (3.83% - 16.42%) |
| Roberts (2019) | 3.13% (0.08% - 16.22%) |
| Garweg (2019) | 0.00% (0.00% - 2.74%) |
| Denman (2019) | 1.27% (0.03% - 6.85%) |
| Tachibana (2020) | 7.41% (0.91% - 24.29%) |
| Haeberlin (2020) | 2.70% (0.56% - 7.70%) |
| Turagam (2020) | 4.76% (0.12% - 23.82%) |
| **Sub total (I²=51.2%, p=0.017)** | **1.77% (0.76% - 3.07%)** |

### Table C: Odds of complications associated with LP vs. TVP

| Author (year) | Estimate OR (95% CI) | Events/Sample size (LP) | Events/Sample size (TVP) |
|---------------|----------------------|-------------------------|--------------------------|
| **Nanostim**  |                      |                         |                          |
| Cantillon (2018) | 0.48 (0.34 – 0.68) | 42/718                  | 165/1436                 |
| *Vaidya (2019)* | 2.23 (1.24 – 4.04) | 4/17                    | 5/90                     |
| **Micra**     |                      |                         |                          |
| Duray (2017) | 0.51 (0.34 – 0.76) | 29/726                  | 202/2667                 |
| *Vaidya (2019)* | 0.11 (0.01 – 1.94) | 0/73                    | 5/90                     |
| Turagam (2020) | 0.43 (0.05 – 3.93) | 1/21                    | 5/45                     |
| Pagan (2020) | 0.32 (0.06 – 1.76) | 2/183                   | 4/119                    |
| Tachibana (2020) | 0.62 (0.10 – 3.67) | 2/27                    | 4/35                     |
| **Sub total (I²=0.0%, p=0.536)** | **0.49 (0.34 – 0.80)** | **34/1030** | **220/2959** |
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 and device dislodgement, 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 (within 3 months) or the 15% to 16% incidence of long-term complications 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. Although no such concern has been reported with the Micra LP, the only LP currently approved by the Food and Drug

| Author (year) | Estimate (95% CI) |
|---------------|-------------------|
| Nanostim | |
| Reddy (2015)⁹ | 90.0% (86.03% - 93.15%) |
| Knops (2015)¹⁹ | 100% (88.78% - 100%) |
| Sperzel (2018)³⁶ | 100% (99.06% - 100%) |
| Micra | |
| Pachon (2016)³³ | 100% (69.15% - 100%) |
| Da Costa (2017)³⁴ | 100% (76.84% - 100%) |
| Roberts (2017)²⁸ | 97.0% (95.46% - 98.14%) |
| El-Chami (2018)²⁰ | 97.0% (95.23% - 98.24%) |
| Hai (2019)⁴⁰ | 100% (92.13% - 100%) |
| Valiton (2019)⁴⁵ | 90.0% (73.47% - 97.89%) |
| Garweg (2019)³⁹ | 100% (94.56% - 100%) |
| Denman (2019)³⁸ | 100% (95.14% - 100%) |
| Kiani (2019)⁸¹ | 100% (97.09% - 100%) |
| Tachibana (2020)⁵¹ | 86.96% (66.41% - 97.22%) |
| Turagam (2020)⁵³ | 90.48% (69.62% - 97.22%) |
| Tolosana (2020)⁵² | 97.14% (91.88% - 99.41%) |
| Sub total (I²=58.76%, p=0.005) | 98.96% (97.26% - 99.94%) |

![Figure 4](image-url) Pooled proportion of patients having a pacing capture threshold ≤2 V at 1 year after implantation.
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.

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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

REFERENCES
1. Kusumoto Fred M, Schoenfeld Mark H, Barrett C, Edgerton James R, Ellenbogen Kenneth A, Gold Michael R, Goldschlager NF, Hamilton RM, Joglar JA, Kim RJ, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2019;140:e382–e482.

2. Ranasinghe I, Labrosciano C, Horton D, Ganesan A, Curtis JP, Krumholz HM, McGavigan A, Hossain S, Air T, Hanhuraparthan S, et al. Institutional variation in quality of cardiovascular implantable electronic device implantation: a cohort study. Ann Intern Med. 2019;171:309–317. DOI: 10.7326/M18-2810.

3. Udo EO, Zulthoff NPA, van Hemel NM, de Cock CC, Hendriks T, Doevendans PA, Moons KGM. Incidence and predictors of short- and long-term complications in pacemaker therapy: the
FOLLOWPACE study, Heart Rhythm. 2012;5:728–735. DOI: 10.1016/j.hrthm.2011.12.014.

4. Cantillon DJ, Exner DV, Badie N, Davis K, Gu NY, Nabutovsky Y, Doshi R. Complications and health care costs associated with transcatheter pacemakers in a nationwide assessment. JACC Clin Electrophysiol. 2017;3:1296–1305. DOI: 10.1016/j.jcpace.2017.05.007.

5. Ludwig S, Theis C, Wolf C, Nicole E, Witthohn A, Götte A. Complications and associated healthcare costs of transcatheter cardiac pacemakers in Germany. J Comp Eff Res. 2019;8:589–597. DOI: 10.1007/s12967-018-0114-0.

6. Chintiz L, Ritter P, Khelia SK, Iacopino S, Garweg C, Grazia-Bongiorni M, Neuzil P, Johansen JB, Mont L, Gonzalez E, et al. Accelerometer-based atrioventricular synchronous pacing with a ventricular leadless pacemaker: results from the Micra atrioventricular feasibility studies. Heart Rhythm. 2018;15:1363–1371. DOI: 10.1016/j.hrthm.2018.05.004.

7. Steinwender C, Khelai SK, Garweg C, Chan JYS, Ritter P, Johansen JB, Sagi V, Epstein LM, Piccini JP, Pasqual M, et al. Atrioventricular synchronous pacing using a leadless ventricular pacemaker: results from the MARVEL 2 study. JACC Clin Electrophysiol. 2020;6:94–1016. DOI: 10.1016/j.jciecep.2019.10.017.

8. Reddy YY, Knops RE, Sperzel J, Miller MA, Petru J, Simon J, Sediva L, de Groot JR, Crossley GH, Hummel JD, Narasimhan C, Omar R, et al. Patient selection, pacing indications, and subsequent outcomes with de novo leadless ventricular pacemakers in the real-world setting: a comparison to the investigational study and a transvenous historical control. Heart Rhythm. 2018;15:1800–1807. DOI: 10.1016/j.hrthm.2018.08.005.

9. Nyaga VN, Arbyn M, Aerts M. Metapop: a Stata command to perform meta-analysis of binomial data. Arch Public Health. 2014;72:3258–3729. DOI: 10.1186/2049-3258-72-39.

10. Harris R, Bradburn M, Deeks J, Harbord R, Altman D, Sterne J. Meta-analysis of fixed- and random-effects meta-analysis. Stata J. 2008;8:3–28. DOI: 10.1177/153687270800800102.

11. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–188. DOI: 10.1016/0197-2456(86)90046-2.

12. Cabanas-Grandio P, Garcia Campo E, Bisbal F, Garcia-Seara J, Pachón M, Juan-Salvadores P, Paredes E, Molinero A, Martínez-Sande JL, Arias MA, et al. Quality of life of patients undergoing conventional vs leadless pacemaker implantation: a multicenter observational study. J Cardiovasc Electrophysiol. 2020;31:330–336. DOI: 10.1111/jce.14322.

13. Beurskens NEG, Tjong FY, Du Bruin-Bon RA, Dassaëlaer KJ, Kuitj WJ, Wilde AAM, Knops RE. Impact of leadless pacemaker therapy on cardiac and atrioventricular valve function through 12 months of follow-up. Circ Arrhythm Electrophysiol. 2019;12:e007124.

14. Salama E, Tommassian L, Simonetti B, Giorgi R, Franceschi F, Koubli- Franchi JL, Houdrain J, Habib G, Deharo J-C. Right ventricular and tricuspid valve function in patients chronically implanted with leadless pacemakers. Europace. 2019;20;823–828. DOI: 10.1093/europace/eux101.

15. Duray GZ, Ritter P, El-Chami M, Narasimchan C, Omar R, Tosloa JM, Zheng S, Soejima K, Steinhoven C, Cappolinii L, et al. Long-term performance of an entirely intracardiac leadless pacemaker: results from the Micra Transcatheter Pacemaker Study. Heart Rhythm. 2017;14:702–709. DOI: 10.1016/j.hrthm.2017.01.035.

16. Roberts PR, Clementy N, Al Samadhi F, Garweg C, Martinez-Sande JL, Iacopino S, Johansen JB, Vinolas Prat X, Kowal RC, Klug D, et al. A leadless pacemaker in the real-world setting: the Micra Transcatheter Pacing System Post-Approval Registry. Heart Rhythm. 2017;14:1375–1379. DOI: 10.1016/j.hrthm.2017.05.017.

17. Cantillon DJ, Dukkipati SR, Ip JH, Exner DV, Niazi IK, Banker RS, Rajathin M, Puchol A, Akerström F, Rodrigues M, et al. Permanent leadless cardiac pacemakers. Heart Rhythm. 2018;15:1023–1030. DOI: 10.1016/j.hrthm.2018.04.022.

18. Tjong FY, Knops RE, Udo EO, Brouwer TF, Dukkipati SR, Koruth JS, Petru J, Sediva L, van Hemel NM, Neuzil P, et al. Leadless pacemaker versus transvenous single-chamber pacemaker therapy: a propensity score-matched analysis. Heart Rhythm. 2018;15:1387–1393. DOI: 10.1016/j.hrthm.2018.04.027.

19. Kiani S, Black GB, Rao B, Thakkar N, Massad C, Patel AV, Lu MLR, Merchant FM, Hoskins MH, Lurio DB, et al. The safety and feasibility of a one-day discharge after implantation of MIgRA transcatheter leadless pacemaker system. J Arrhythm. 2019;12:2153. DOI: 10.4022/jarrh.2153.

20. Tjong FY, Beurskens NEG, Groot J, Wauerw, Liu S, Ritter P, Reynolds D, Wilde AAM, Knops RE. Health-related quality of life impact of a transcatheter pacing system. J Cardiovasc Electrophysiol. 2018;29:1697–1704. DOI: 10.1111/jce.13726.

21. Pachón M, Puchol A, Akerström F, Rodríguez-Padial L, Arias MA. Implantation of the Micra transcatheter pacing system: initial experience in a single Spanish center. Rev Esp Cardiol (Engl Ed). 2016;69:346–349. DOI: 10.1016/j.rec.2015.11.020.

22. Da Costa A, Axiots A, Romeyer-Bouchard C, Abdelouafi L, Atif Z, Guichard JB, Gerbay A, Isaa K. Transcatheter leadless cardiac pacing: the new alternative solution. Int J Cardiol. 2017;227:122–126. DOI: 10.1016/j.ijcard.2016.11.196.

23. Martínez-Sande JL, García-Seara J, Rodríguez-Mañero M, Fernández- López XA, González-Melchor L, Redondo-Díezguez A, González- Ferrerro R, González-Juanatey JR. The Micra leadless transcatheter pacemaker. Implantation and mid-term follow-up results in a single center. Rev Esp Cardiol. 2017;70:275–281.

24. Sperzel J, Delafaye P, Dechauro JC, García-Guerrero JJ, Knops RE, Tondo C, Deharo J-C, Wong T, Neuzil P. Primary safety results from the LEADLESS Observational Study, Europace. 2018;20:1491–1497. DOI: 10.1093/eurheartj/eux359.

25. Bongiorni MG, Della Tommasina V, Barletta V, Di Cori A, Rogani S, Viani S, Segregi L, Paperni L, Soldati E, De Lucia R, et al. Feasibility and long-term effectiveness of a non-apical Micra pacemaker implantation.
in a referral centre for lead extraction. Europace. 2019;21:114–120. DOI: 10.1093/europace/euy116.

38. Denman RA, Lee AC, Mengei C, Townsend S, Betts J, Bovey N, Wright D, Davison O, Haqgani HM. Leadless permanent pacing: a single centre Australian experience. Heart Lung Circ. 2019;28:1677–1682. DOI: 10.1016/j.hlc.2018.09.014.

39. Garweg C, Vandenberk B, Foulon S, Haemers P, Ector J, Willems R. Leadless pacing with Micra TPS: a comparison between right ventricular outflow tract, mid-septal, and apical implant sites. J Cardiovasc Electrophysiol. 2019;30:2002–2011. DOI: 10.1111/jce.14083.

40. Hai J-J, Fang J, Tam C-C, Wong C-K, Lau C-P, Tse H-F. Safety and feasibility of a midseptal implantation technique of a leadless pacemaker. Heart Rhythm. 2019;16:896–902. DOI: 10.1016/j.hrthm.2018.12.007.

41. Kaczmarek K, Cygankiewicz I, Czarniak B, Jakubowski P, Strzelecki A, Wranicz JK, Ptaszyniski P. Septal implantation of the Micra transcatheter pacing system guided by intraprocedural transophageal echocardiography. Kardiol Pol. 2019;77:1190–1192. DOI: 10.33963/kp.15043.

42. Kiani S, Black GB, Rao B, Thakkar N, Massad C, Patel AV, Merchant FM, Hoskins MH, Lurgio DB, Patel AM, et al. Outcomes of Micra leadless pacemaker implantation with uninterrupted anticoagulation. J Cardiovasc Electrophysiol. 2019;30:1313–1318. DOI: 10.1111/jce.13965.

43. Roberts PR, Pepper C, Rinaldi CA, Bates MGD, Thornley A, Somani R, Abozguia K, Harris S, Rao A, Pedersen M, et al. The use of a single chamber leadless pacemaker for the treatment of cardioinhibitory vasovagal syncope. Int J Cardiol Heart Vasc. 2019;23:100349. DOI: 10.1016/j.ijchv.2019.100349.

44. Vaidya VR, Dai M, Asirvatham SJ, Rea RF, Thorne TM, Srivathsan K, Mulpuru SK, Kusumoto F, Venkatachalam KL, Ryan JD, et al. Real-world experience with leadless cardiac pacing. Pacing Clin Electrophysiol. 2019;42:366–373. DOI: 10.1111/pace.13601.

45. Vaiton V, Graf D, Pruvot C, Carroz P, Froner M, Bischof L, Tran VN, Cook S, Scharf C, Burri H, et al. Leadless pacing using the transcatheter pacing system (Micra TPS) in the real world: initial Swiss experience from the Romandie region. Europace. 2019;21:275–280. DOI: 10.1093/europace/euy195.

46. El Amrani A, Campos B, Alonso-Martín C, Guerra-Ramos JM, Rodríguez-Font E, Moreno-Weidmann Z, Alcalde-Rodriguez O, Méndez-Zurita FJ, Santaló M, Espinosa-Viamonte H, et al. Performance of the Micra cardiac pacemaker in nonagenarians. Rev Esp Cardiol (Engl Ed). 2020;73:307–312.

47. Grabowski M, Michalak M, Gawalko M, Gajda S, Cacko A, Januszkiewicz Ł, Kolodzińska A, Mitkowski PP, Duray GZ, Opolski G, et al. Implantation of the Micra transcatheter pacing system: Single Polish center experience with the real costs of hospitalization analysis. Cardiol J. 2020;27:47–53. DOI: 10.5603/CJ.Ja2018.0075.

48. Haeberlin A, Kozhuharov N, Knecht S, Tanner H, Schaer B, Noti F, Osswald S, Servatius H, Baidinger S, Seiler J, et al. Leadless pacemaker implantation quality: importance of the operator’s experience. Europace. 2020;22:939–946. DOI: 10.1093/europace/euaa097.

49. Mohammed M, Arshi J, Ramza BM, Wimmer AP, Steinhaus DA, Giocoando MJ, Gupta SK, Youssif SK. Outcomes using a single tapered dilator for Micra leadless pacemaker implant. Indian Pacing Electrophysiol J. 2020;20:105–111. DOI: 10.1016/j.ipej.2020.03.001.

50. Pagan E, Gabriels J, Khodak A, Chang D, Beldner S, Epstein LM, Willner J. Safety of leadless pacemaker implantation in the very elderly. Heart Rhythm. 2020;17:2023–2028. DOI: 10.1016/j.hrthm.2020.05.022.

51. Tachibana M, Banba K, Matsumoto K, Ohara M. The feasibility of leadless pacemaker implantation for superelderly patients. Pacing Clin Electrophysiol. 2020;43:374–381. DOI: 10.1111/pace.13894.

52. Tolosana JM, Guasch E, San Antonio R, Apolo J, Pujol-López M, Chipasani F, Trucco E, Roca-Luque I, Brugada J, Mont L, et al. Very high pacing thresholds during long-term follow-up predicted by a combination of implant pacing threshold and impedance in leadless transcatheter pacemakers. J Cardiovasc Electrophysiol. 2020;31:868–874. DOI: 10.1111/jce.14360.

53. Turagam MK, Gopinathannair R, Park PH, Tummala RV, Vasanreddy C, Shah A, Koerber S, Krauthammer Y, Di Blase L, Murtaza G, et al. Safety and efficacy of leadless pacemaker for cardio inhibitory vasovagal syncope. Heart Rhythm. 2020;17:1575–1581. DOI: 10.1016/j.hrthm.2020.05.006.

54. Al-bawardy R, Krishnaswamy A, Rajeswaran J, Bhargava M, Wazni O, Wilkoff B, Tuzcu EM, Martin D, Thomas J, Blackstone E, et al. Tricuspid regurgitation and implantable devices. Pacing Clin Electrophysiol. 2015;38:259–266. DOI: 10.1111/pace.12530.

55. Lee RC, Friedman SE, Kono AT, Greenberg ML, Palac RT. Tricuspid regurgitation following implantation of endocardial leads: incidence and predictors. Pacing Clin Electrophysiol. 2015;38:1267–1274. DOI: 10.1111/pace.12701.

56. Chang JD, Manning WJ, Ebrille E, Zimetbaum PJ. Tricuspid valve dysfunction following pacemaker or cardioverter-defibrillator implantation. J Am Coll Cardiol. 2017;69:2331. DOI: 10.1016/j.jacc.2017.02.055.
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)  | Prospective, single-arm, multi-center cohort study | Consecutive patients undergoing LP implantations | Nanostim | 33 | 32 |
| Reddy (2015)  | Prospective, single-arm, multi-center cohort study | Consecutive patients undergoing LP implantations | Nanostim | 300 | 289 |
| Sperzel (2018) | Prospective, single-arm, multi-center cohort study | Consecutive patients undergoing LP implantations | Nanostim | 467 | 451 |
| Vaidya (2019) | Retrospective, two-arm, single-center cohort study | Consecutive patients undergoing LP implantations | Nanostim | 17 | 17 |
| Reynolds (2016) | Prospective, single-arm, multi-center cohort study | Consecutive patients undergoing LP implantations | Micra | 725 | 719 |
| Pachon (2016) | Single-arm, single-center cohort study | Consecutive patients undergoing LP implantations | Micra | 10 | 10 |
| Martinez-Sande (2017) | Prospective, single-arm, single-center cohort study | Consecutive patients undergoing LP implantations | Micra | 30 | 30 |
| Da Costa (2016) | Prospective, single-arm, single-center cohort study | Consecutive patients with full or relative contraindications of traditional TVP | Micra | 14 | 14 |
| Bongiorni (2018) | Prospective, single-arm, single-center cohort study | Consecutive patients undergoing LP implantations | Micra | 52 | 52 |
| El-Chami (2018) | Prospective, single-arm, single-center cohort study | Consecutive patients implanted with Micra devices after approval | Micra | 1817 | 1801 |
| Deman (2019)  | Prospective, single-arm, single-center cohort study | Consecutive patients undergoing LP implantations | Micra | 79 | 76 |
| Kaczmarek (2019) | Prospective, single-arm, single-center cohort study | Consecutive patients undergoing LP implantations | Micra | 24 | 24 |
| Roberts (2019) | Retrospective, single-arm, multi-center cohort study | Patients implanted with Micra LP for cardioinhibitory vasovagal syncope | Micra | 32 | 32 |
| Vaidya (2019) | Retrospective, two-arm, single-center cohort study | Consecutive patients undergoing LP implantations | Micra | 73 | 73 |
| Valiton (2019) | Retrospective, single-arm, multi-center cohort study | Consecutive patients undergoing LP implantations | Micra | 92 | 90 |
| Garweg (2019) | Prospective, single-arm, single-center cohort study | Patients implanted with Micra LP for cardioinhibitory vasovagal syncope | Micra | 133 | 133 |
| Hai (2019)    | Prospective, single-arm, single-center cohort study | Consecutive patients undergoing LP implantations | Micra | 51 | 51 |
| Turagam (2020) | Retrospective, two-arm, multi-center cohort study | Patients with cardio inhibitory vasovagal syncope implanted with LP. | Micra | 24 | 24 |
| Tachibana (2020) | Retrospective, two-arm, single-center cohort study | Consecutive patients ≥85 years underwent LP implantation | Micra | 27 | 27 |
| Haebelin (2020) | Prospective, single-arm, two-center cohort study | Consecutive patients undergoing LP implantations | Micra | 111 | 106 |
| Grabowski (2020) | Prospective, single-arm, single-center cohort study | Consecutive patients undergoing LP implantations | Micra | 10 | 10 |
| El Amrani (2012) | Prospective, single-arm, single-center cohort study | Consecutive patients >70 years with an attempted LP implant | Micra | 129 | 127 |
| Pagan (2020)  | Retrospective, two-arm, multi-center cohort study | Patients ≥85 years implanted with a Micra LP | Micra | 183 | 180 |
| Tolosana (2020) | 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)           | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y  |     |    |    |    | GOOD    |
| Knops (2015)          | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y  |     |    |    |    | GOOD    |
| Reddy (2015)          | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y  |     |    |    |    | GOOD    |
| Ritter (2015)         | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y  |     |    |    |    | GOOD    |
| Pachon (2016)         | Y | Y | Y | Y | Y | Y | Y | Y | Y | X  |     |    |    |    | GOOD    |
| Reynolds (2016)       | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y  |     |    |    |    | GOOD    |
| Da Costa (2017)       | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y  |     |    |    |    | GOOD    |
| Duray (2017)          | Y | Y | NA | Y | NA | NA | NA | NA | Y | NA | N | N | Y | NA | FAIR    |
| Martinez-Sande (2017) | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y  | N  |    |    |    | FAIR    |
| Roberts (2017)        | Y | Y | Y | Y | Y | Y | Y | N | Y | N  |    |    |    |    | FAIR    |
| Cantillon (2018)      | Y | Y | Y | Y | Y | Y | Y | N | Y | Y  |    |    |    |    | FAIR    |
| El-Chami (2018)       | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y  |    |    |    |    | GOOD    |
| Sperzel (2018)        | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y  |    |    |    |    | GOOD    |
| Tjong (2018)          | Y | Y | NA | N | NA | NA | NA | NA | Y | NA | Y | N | Y | NA | FAIR    |
| Bongiorni (2018)      | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y  |    |    |    |    | GOOD    |
| Denman (2019)         | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y  |    |    |    |    | GOOD    |
| Garweg (2019)         | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y  | N  |    |    |    | FAIR    |
| Hai (2019)            | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y  |    |    |    |    | GOOD    |
| Kaczemarek (2019)     | Y | Y | Y | Y | Y | N | Y | Y | N | Y  |    |    |    |    | FAIR    |
| Kiani (2019)          | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y  |    |    |    |    | GOOD    |
| Researcher                | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Evaluation   |
|--------------------------|---|---|---|---|---|---|---|---|---|---|--------------|
| Kiani (2019)             | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | GOOD        |
| Roberts (2019)           | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | FAIR        |
| Vaidya (2019)            | Y | Y | NA| N | Y | Y | Y | Y | Y | Y | FAIR        |
| Valiton (2019)           | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | GOOD        |
| El Amrani (2020)         | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | GOOD        |
| Grabowski (2020)         | Y | Y | Y | Y | Y | N | N | Y | N | Y | FAIR        |
| Haeberlin (2020)         | Y | Y | Y | Y | Y | Y | N | Y | N | N | FAIR        |
| Mohammed (2020)          | Y | Y | Y | Y | Y | N | N | Y | Y | Y | FAIR        |
| Pagan (2020)             | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | FAIR        |
| Tachibana (2020)         | Y | Y | NA| Y | NA| NA| NA| NA| Y | NA| N | N | Y | NA| FAIR        |
| Tolosana (2020)          | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | GOOD        |
| Turagam (2020)           | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | GOOD        |
| Salaun (2018)            | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | FAIR        |
| Tjong (2018)             | Y | Y | NA| N | NA| NA| NA| NA| Y | NA| Y | N | Y | Y | FAIR        |
| Beurskens (2019)         | Y | Y | NA| Y | NA| NA| NA| NA| Y | NA| Y | N | Y | Y | GOOD        |
| Cabanas-Grandio (2019)   | Y | Y | NA| Y | NA| NA| NA| NA| Y | NA| Y | N | Y | Y | GOOD        |

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