# Leadless Cardiac Pacemaker

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## DESCRIPTION

Pacemakers are intended to be used as a substitute for the heart's intrinsic pacing system to correct cardiac rhythm disorders. Conventional pacemakers consist of 2 components: a pulse generator and electrodes (or leads). Pacemakers are considered life-sustaining, life-supporting class III devices for patients with a variety of brady arrhythmias. Even though the efficacy and safety profile of conventional pacemakers are excellent, in a small proportion of patients, they may result in lead complications and the requirement for a surgical pocket. Further, some patients are medically ineligible for conventional pacemakers due to lack of venous access and recurrent infection. Leadless pacemakers are single-unit devices that are implanted in the heart via femoral access, thereby eliminating the potential for complications as a result of leads and surgical pocket. The Micra and Aveir single chamber transcatheter pacing systems (TPS) are the only commercially available leadless pacemaker in the U.S. approved by the U.S. Food and Drug Administration.

**Conventional Pacemakers**

Pacemakers are intended to be used as a substitute for the heart's intrinsic pacing system to correct cardiac rhythm disorders. By providing an appropriate heart rate and heart rate response, cardiac pacemakers can reestablish effective circulation and more normal hemodynamics that are compromised by a slow heart rate. Pacemakers vary in system complexity and can have multiple functions as a result of the ability to sense and/or stimulate both the atria and the ventricles.

Transvenous pacemakers or pacemakers with leads (hereinafter referred to as conventional pacemakers) consist of 2 components: a pulse generator (ie, battery component) and electrodes (i.e., leads). The pulse generator consists of a power supply and electronics that can provide periodic electrical pulses to stimulate the heart. The generator is commonly implanted in the infraclavicular region of the anterior chest wall and placed in a pre-pectoral position; in some cases, a subpectoral position is advantageous. The unit generates an electrical impulse, which is transmitted to the myocardium via the electrodes affixed to the myocardium to sense and pace the heart as needed.

Conventional pacemakers are also referred to as single-chamber or dual-chamber systems. In single-chamber systems, only 1 lead is placed, typically in the right ventricle. In dual-chamber pacemakers, 2 leads are placed-one in the right atrium and the other in the right ventricle. Single-chamber ventricular pacemakers are more common.

Annually, approximately 200,000 pacemakers are implanted in the U.S. and 1 million worldwide. Pacemaker systems have matured over the years with well-established, acceptable performance standards. As per the U.S. Food and Drug Administration (FDA), the early performance of conventional pacemaker systems from implantation through 60 to 90 days have usually demonstrated acceptable pacing capture thresholds and sensing. Intermediate performance (90 days through more than 5 years) has usually demonstrated the reliability of the pulse generator and lead technology. Chronic performance (5-10 years) includes a predictable decline in battery life and mechanical reliability, but a vast majority of patients receive excellent pacing and sensing free of operative or mechanical reliability failures.

Even though the safety profile of conventional pacemakers is excellent, they are associated with complications particularly related to leads. Most safety data on the use of conventional pacemakers come from registries from Europe, particularly from Denmark where all pacemaker implants are recorded in a national registry. It is important to recognize that valid comparison of complication rates is limited by differences in definitions of complications, which results in a wide variance of outcomes, as well as by the large variance in follow-up times, use of single-chamber or dual-chamber systems, and data reported over more than 2 decades. As such, the following data are contemporary and limited to single-chamber systems when reported separately.

In many cases when a conventional pectoral approach is not possible, alternative approaches such as epicardial pacemaker implantation and trans-iliac approaches have been used. From a retrospective analysis of 123 patients who underwent 207 epicardial lead implantations. Congenital heart disease was present in 103 (84%) of the patients. Epicardial leads were followed for 29 months (range 1 to 207 months). Lead failure was defined as the need for replacement or abandonment due to pacing or sensing problems, lead fracture, or phrenic/muscle stimulation. The 1-, 2-, and 5-year lead survival was 96%, 90%, and 74%, respectively. Epicardial lead survival in those placed by a subxiphoid approach was 100% at 1 year and at 10 years, by the sternotomy approach (93.9% at 1 year and 75.9% at 10 years) and lateral thoracotomy approach (94.1% at 1 year and 62.4% at 10 years).

A randomized controlled trial comparing epicardial implantation versus conventional pacemaker implantation in 80 patients with indications for cardiac resynchronization therapy. The authors reported that the conventional pacemaker group had a significantly shorter intensive care unit stay, less blood loss, and shorter ventilation times while the epicardial group had less exposure to radiation and less use of contrast medium. The left ventricular pacing threshold was similar in the 2 groups at discharge but longer in the epicardial group during follow-up. Adverse events were also similar in the 2 groups. The following events were experienced by 1 (3%) patient each in the epicardial group: pleural puncture, pneumothorax, wound infection, acute respiratory distress syndrome, and hospital mortality.

As a less invasive alternative to the epicardial approach, the trans-iliac approach has also been utilized. Data using trans-iliac approach is limited. Multiple other studies with smaller sample size report a wide range of lead longevity.

Harake et al (2018) reported a retrospective analysis of 5 patients who underwent a transvenous iliac approach (median age 26.9 years). Pacing indications included AV block in 3 patients and sinus node dysfunction in 2. After a median follow-up of 4.1 years (range 1.0-16.7 years), outcomes were reported for 4 patients. One patient underwent device revision for lead position-related groin discomfort; a second patient developed atrial lead failure following a Maze operation and underwent lead replacement by the iliac approach. One patient underwent heart transplantation 6 months after implant with only partial resolution of pacing-induced cardiomyopathy.

A case series of 4 patients from Japan in whom conventional pectoral approach was precluded due to recurrent lead infections (n=1), superior vena cava obstruction following cardiac surgery (n=2) and a postoperative dermal scar (n=1). The mean follow-up was 24 months, and the authors concluded the iliac vein approach was satisfactory and less invasive alternative to epicardial lead implantation. However, the authors reported that the incidence of atrial lead dislodgement using this approach in the literature ranged from 7 to 21%. Experts who provided clinical input reported that trans-iliac or surgical epicardial approach requires special expertise and long-term performance is suboptimal.

**Potential Advantages of Leadless Cardiac Pacemakers Over Conventional Pacemakers**

The potential advantages of leadless pacemakers fall into 3 categories: avoidance of risks associated with intravascular leads in conventional pacemakers, avoidance of risks associated with pocket creation for placement of conventional pacemakers, and an additional option for patients who require a single-chamber pacer.

Lead complications include lead failure, lead fracture, insulation defect, pneumothorax, infections requiring lead extractions and replacements that can result in a torn subclavian vein or the tricuspid valve. In addition, there are risks of venous thrombosis and occlusion of the subclavian system from the leads. Use of a leadless system eliminates such risks with the added advantage that a patient has vascular access preserved for other medical conditions (e.g., dialysis, chemotherapy).

Pocket complications include infections, erosions, and pain that can be eliminated with leadless pacemakers. Further, a leadless cardiac pacemaker may be more comfortable and appealing because unlike conventional pacemakers, patients are unable to see or feel the device or have an implant scar on the chest wall.

Leadless pacemakers may also be a better option than surgical endocardial pacemakers for patients with no vascular access due to renal failure or congenital heart disease.

**Leadless Cardiac Pacemakers in Clinical Development**

Leadless pacemakers are self-contained in a hermetically sealed capsule. The capsule houses battery and electronics to operate the system. Similar to most pacing leads, the tip of the capsule includes a fixation mechanism and a monolithic controlled-release device. The controlled-release device elutes a glucocorticosteroid to reduce acute inflammation at the implantation site. Leadless pacemakers have rate-responsive functionality, and current device longevity estimates are based on bench data. Estimates have suggested that these devices may last over 10 years, depending on the programmed parameters.

Three systems have been or are currently being evaluated in clinical trials:

1) The Micra Transcatheter Pacing Systems (TPS) (Medtronic)
2) The Aveir VR Leadless Pacemaker (Abbott; formerly Nanostim, St. Jude Medical0
3) The WiCS Wireless Cardiac Stimulation System (EBR Systems)

The first 2 devices are free-standing capsule-sized devices that are delivered via femoral venous access using a steerable delivery sheath. However, the fixing mechanism differs between the 2 devices. In the Micra Transcatheter Pacing System, the fixation system consists of 4 self-expanding nitinol tines, which anchor into the myocardium; for the Aveir device, there is a screw-in helix that penetrates into the myocardium. In both devices, the cathode is steroid eluting and delivers pacing current; the anode is located in a titanium case. The third device, WiCS system differs from the other devices; this

system requires implanting a pulse generator subcutaneously near the heart, which then wirelessly transmits ultrasound energy to a receiver electrode implanted in the left ventricle. The receiver electrode converts the ultrasound energy and delivers electrical stimulation to the heart sufficient to pace the left ventricle synchronously with the right.

Of these 3, only the Micra and Aveir single chamber transcatheter pacing systems are approved by the FDA and commercially available in the U.S. Multiple clinical studies of the Aveir predecessor device, Nanostim, have been published but trials have been halted due to the migration of the docking button in the device and premature battery depletion. These issues have since been addressed with the Aveir device.

The Micra is about 26 mm in length and introduced using a 23 French catheter via the femoral vein to the right ventricle. It weighs about 2 grams and has an accelerometer-based rate response.[19,]

The Aveir is about 42 mm in length and introduced using a 25 French catheter to the right ventricle. It also weighs about 3 grams and uses a temperature-based rate response sensor.

**Ventricular Pacing for Individuals who are Medically Eligible for Conventional Pacing System**

**Clinical Context and Therapy Purpose**
The purpose of single chamber transcatheter pacing systems in individuals with a class I or II guidelines-based indication for implantation of a single-chamber ventricular pacemaker is to provide a treatment option that is an alternative to or an improvement on conventional pacing systems.

**Populations**
The relevant population of interest is patients with a class I or II guidelines-based indication for implantation of a single-chamber ventricular pacemaker who are medically eligible to receive conventional pacing system.

**Interventions**
The therapy being considered is a single-chamber transcatheter pacing system. The Micra and Aveir devices are single-chamber, ventricular pacemakers implanted through a femoral vein by advancing a delivery catheter into the right ventricle and affixing the device in the myocardium.

Micra has a programmable mode to deactivate pacing and sensing at the end of the life of the device and may remain in the body indefinitely after deactivation. The device also has a retrieval feature at the proximal end for percutaneous snare retrieval and removal.

Aveir has a unique mapping capability to assess correct positioning prior to placement and is specifically designed to be retrieved when therapy needs evolve or the device needs to be replaced.

**Comparators**

The following therapy is currently being used to make decisions about managing patients requiring a pacemaker: a conventional single-chamber pacemaker.

**Outcomes**

The general outcomes of interest are treatment-related mortality and morbidity. Specifically, the short-term outcomes include acute complication-free survival rate, the electrical performance of the device, including the pacing capture threshold, and adverse events, including procedural and postprocedural complications. Long-term outcomes include chronic complication-free survival rate, the electrical performance of the device, including pacing impedance and pacing thresholds, and chronic complications, including any system explant, replacement (with and without system explant), and repositions. Further, analysis of summary statistics regarding battery length is important.

To assess short-term safety, the first 30 days postimplant is generally considered appropriate because most device and procedural complications occur within this time frame. To assess long-term efficacy and safety as well as issues related to device end-of-life, a follow-up to 9 to 12 years postimplant with an adequate sample size are required to characterize device durability and complications with sufficient certainty.

**Review of Evidence**

**Nonrandomized Controlled Trials**

**Micra Leadless Pacemaker**

The pivotal investigational device exemption (IDE) trial was a prospective single cohort study enrolling 744 patients with a class I or II indication for implantation of a single-chamber ventricular pacemaker based on national guidelines. Of the 744 patients enrolled, implantation of the Micra transcatheter pacing system was successful in 719 (99.2%) of the 725 patients who underwent the procedure. The demographics of the trial population were typical for a single-chamber pacemaker study performed in the U.S., with 42% being female and an average age of 76 years. Sixty-four percent had a pacing indication associated with persistent or permanent atrial arrhythmias, 72.6% had any atrial fibrillation at baseline, and 27.4% did not have a history of atrial fibrillation. Among those 27.4% (n=199) without atrial fibrillation, 16.1% (n=32) had a primary indication of sinus bradycardia and 3.5% (n=7) had a primary indication of tachycardia-bradycardia.

This trial had 2 primary endpoints related to safety and efficacy. The trial would meet its safety endpoint if the lower bound of the 95% confidence interval (CI) for the rate of freedom from major complications related to the Micra transcatheter pacing system or implantation procedure exceeded 83% at 6 months. Major complications were defined as

those resulting in any of the following: death, permanent loss of device function due to mechanical or electrical dysfunction of the device (e.g., pacing function disabled, leaving device abandoned electrically), hospitalization, prolonged hospitalization by at least 48 hours, or system revision (reposition, replacement, explant). The trial would meet its efficacy endpoint if the lower bound of the 95% CI for the proportion of patients with adequate pacing capture thresholds (PCT) exceeded 80% at 6 months. PCT as an effectiveness objective is a common electrical measure of pacing efficacy and is consistent with recent studies. Pacing capture threshold measured in volts is defined as the minimum amount of energy needed to capture the myocardial tissue electrically. Unnecessary high pacing output adversely shortens the battery life of the pacemaker and is influenced by physiologic and pharmacologic factors. As per the FDA, demonstrating that "PCT is less than 2 Volts for the vast majority of subjects will imply that the Micra system will have longevity similar to current pacing systems since Micra's capture management feature will nominally set the safety margin to 0.5 Volts above the PCT with hourly confirmation of the PCT.

Safety and efficacy results of the IDE trial are summarized in Table 3. At 6 months, the trial met both of its efficacy and safety primary endpoints including freedom from major complications related to the system or procedure in 96.0% of the patients (95% CI, 93.9% to 97.3%), compared with a performance goal of 83%, and an adequate pacing capture threshold in 98.3% of the patients (95% CI, 96.1% to 99.5%), compared with a performance goal of 80%.[26,]

Quality of life results of the IDE trial were published in 2018. At baseline and 12 months, 702 (98%) and 635 (88%) participants completed the 36-Item Short Form questionnaire, respectively. The mean 36-Item Short Form Physical Component Scale at baseline was 36.3 (standard deviation [SD]=9.0) and the mean 36-Item Short Form Mental Component Scale was 47.3 (SD=12.5); the general population mean for both scores is 50. Both the Physical Component Scale and Mental Component Scale improved at 12 months post-implant to a mean Physical Component Scale score of 38.6 (SD=9.4; p<.001) and a mean Mental Component Scale score of 50.7 (SD=12.2; p<.001) compared with baseline.

IDE trial results were compared post hoc with a historical cohort of 2667 patients generated from 6 previous pacemaker studies, conducted between 2005 and 2012 by Medtronic, that evaluated the performance requirement at 6 months postimplant of right ventricle pacing leads (single-chamber rates obtained by excluding any adverse events only related to the right atrial lead from the analysis). The Micra device was associated with fewer complications than the historical control (4.0% vs. 7.4%; hazard ratio [HR], 0.49; 95% CI, 0.33 to 0.75; p=.001). Because there were differences in baseline patient characteristics between the 2 cohorts (patients in the historical cohort were younger and had a lower prevalence of coexisting conditions vs. the IDE trial), an additional propensity-matched analysis was conducted. It showed similar results (HR=0.46; 95% CI, 0.28 to 0.74). As per the FDA, the lower rate of major complications with the Micra device was driven by reductions in access site events (primarily implant site hematoma and implant site infections), pacing issues (primarily device capture and device pacing

issues), and fixation events (there was no device or lead dislodgements in the Micra IDE trial).[11,]

While the overall rate of complications was low, the rate of major complications related to cardiac injury (i.e., pericardial effusion or perforation) was higher in the Micra IDE trial than in the 6 reference Medtronic pacemaker studies (1.6% vs. 1.1%, p=.288). Thus, there appears to be a trade-off between types of adverse events with the Micra transcatheter pacing system and conventional pacemakers. While adverse events related to leads and pocket are eliminated or minimized with the Micra device, certain adverse events (e.g., groin vascular complications, vascular or cardiac bleeding) occur at a higher frequency or are additive (new events) compared with conventional pacemakers. Of these, procedural complications (e.g., acute cardiac perforations) that were severe enough to result in tamponade and emergency surgery were most concerning.

In addition to lack of adequate data on long-term safety, effectiveness, reliability, and incidence of late device failures and battery longevity, there is also inadequate clinical experience with issues related to devices that have reached end-of-life, including whether to extract or leave the device in situ and possible device-device interactions.[29,] There are limited data on device-device interactions (both electrical and mechanical) that may occur when there is a deactivated Micra device alongside another leadless pacemaker or when a leadless pacemaker and transvenous device are both present. Even though there have been few device retrievals and very limited experience with the time course of encapsulation of these devices in humans, it is highly likely that these devices will be fully encapsulated by the end of its typical battery life, and therefore device retrieval is unlikely.[29,] Current recommendations for end-of-device-life care for a Micra device may include the addition of a replacement device with or without explantation of the Micra device, which should be turned off. Grubman et al (2017) reported on system revisions including patients from the IDE study (n=720) and the Micra Transcatheter Pacing System Continued Access Study (n= 269; NCT02488681). The Continued Access study was conducted to allow for continued access of the Micra in the same centers as the IDE study while the device was pending the FDA approval. The mean follow-up duration was 13 months (16 months in the IDE patients and 2 months in the continued access patients). There were 11 system revisions in 10 patients, corresponding to a 1.4% (95% CI, 0.7% to 2.6%) actutimes rate of revisions through 24 months. Micra was disabled and left in situ in 7 of 11 revisions including 5 patients in which there was no retrieval attempt, 1 patient in which retrieval was aborted because of fluoroscopy failure, and 1 patient in which retrieval was unsuccessful because of inability to dislodge the device. There were 3 percutaneous retrievals and 1 retrieval during surgical valve replacement. There were no complications associated with retrievals. The report indicates that when a transvenous system was implanted with a deactivated Micra, there were no reported interactions between the 2 systems, although it is not clear how often this occurred. In the historical controls from the IDE study, there were 123 revisions in 117 patients through 24 months (actutimes rate 5.3%; 95% CI, 4.4 to 6.4). Using propensity score matching, the reduction in system revisions for Micra compared to historical controls was significant (HR=0.27; 95% CI, 0.14 to 0.54; p<.001).

**Aveir Leadless Pacemaker**

**Pivotal Trial**

The pivotal investigational device exemption (IDE) trial of the Aveir leadless pacemaker (LEADLESS II - Phase 2; NCT04559945) was a multicenter, prospective single cohort study enrolling 200 patients with a guidelines-based indication for single-chamber pacing. Primary results from the IDE trial have been summarized in a published research correspondence. and FDA documents. Trial characteristics and results through 6 months are summarized in Tables 2 and 3, respectively.

Implantation of the Aveir leadless pacing system was successful in 196/200 (98%) trial subjects (mean age, 75.6 years; 37.5% female). The primary indication for pacing was chronic atrial fibrillation with 2nd or 3rd degree atrioventricular block (52.5%). The trial had 2 primary endpoints related to safety and efficacy. The trial would meet its safety endpoint if the lower bound of the 97.5% CI for the complication-free rate exceeded 86% at 6 weeks. A complication was defined as a device-or-procedure-related serious adverse event, including those that prevented initial implantation. The trial would meet its efficacy endpoint if the lower bound of the 97.5% CI for the composite success rate exceeded 85% at 6 weeks. The confirmatory effectiveness endpoint was considered met if the pacing threshold voltage is ≤ 2.0 V at 0.4 ms and the sensed R-wave amplitude is either ≥ 5.0 mV at the 6-week visit or ≥ the value at implant.

Safety and efficacy results of the Aveir IDE trial are summarized in Table 3. At 6 weeks, the trial met both of its confirmatory safety and efficacy endpoints, including freedom from device-or-procedure-related complications in 96% of patients (95% CI, 92.2 to 98.2), compared with a performance goal of 86%, and a composite success rate of 95.9% of patients (95% CI, 92.1 to 98.2), compared with a performance goal of 85%. The 6-month complication-free rate was 94.9% (95% CI, 90.0 to 97.4). The most frequent complications included 3 cardiac tamponade events and 3 premature deployment events. The rate of cardiac perforation/tamponade/pericardial effusion was 1.5%. No dislodgement events were reported in the Aveir cohort.

Confirmatory secondary endpoints included assessment of an appropriate and proportional rate-response during a Chronotropic Assessment Exercise Protocol (CAEP) exercise protocol and an estimated 2-year survival rate. The CAEP assessment was initiated in 23 subjects, of which 17 were considered analyzable. The rate-response slope was 0.93 (95% CI, 0.78 to 1.08), which fell within the prespecified range of 65% to 135%. The estimated 2-year survival rate based on the Nanostim Phase 1 cohort (N=917) was 85.3% (95% CI, 82.7 to 87.4), which exceeded the performance goal of 80%.

The current evidence on the use of the Aveir device is limited by a lack of adequate data on quality of life, long-term safety, effectiveness, reliability, and incidence of late device failures and battery longevity. While the device is designed to be retrieved when therapy needs evolve or the device needs to be replaced, there is currently inadequate clinical

experience with issues related to devices that have reached end-of-life. Survival data for the currently marketed version of the Aveir device has not been reported.

**Table 2. Summary of Key Nonrandomized Trial Characteristics**

| Study; Trial | Study Type | Country | Dates | Participants | Treatment | Follow-Up, mo |
|---|---|---|---|---|---|---|
| **Micra** | | | | | | |
| Reynolds et al (2016); NCT02004873 | Prospective single cohort | 19 countries in North America, Europe, Asia, Australia, and Africa | 2013-2015 | Patients who met a class I or II guidelines-based indication for pacing and suitable candidates for single-chamber ventricular demand pacing | Micra pacemaker (n=744) | 6 |
| Roberts et al (2017)<br><br>El-Chami et al (2018) NCT02536118 | Prospective single cohort (Micra Post-Approval Study) | 23 countries in North America, Europe, Asia, Australia, and Africa | 2016-2018 | Any patient to be implanted with a Micra device | Micra pacemaker (n=795[a] and 1830[b]) | 1.8[a]<br><br>6.8[b] |
| Piccinni et al (2021) | Prospective Medicare registry | United States | 2017-2018 | All Medicare patients implanted with a leadless single-chamber pacemaker or transvenous single-chamber pacemaker with at least 12 months of continuous Medicare enrollment prior to implantation | Micra pacemaker (n=5746); Transvenous pacemaker (n=9662) | 6 |
| El-Chami et al (2022) | Prospective Medicare registry | United States | 2017-2018 | All Medicare patients implanted with a leadless single-chamber pacemaker or transvenous single-chamber pacemaker with at least 12 months of continuous Medicare enrollment prior to implantation | Micra pacemaker (n=6219); Transvenous pacemaker (n=10,212) | 24 |
| **Aveir** | | | | | | |
| FDA SSED (2022); PMA P150035 | Prospective single cohort | 43 sites in the United States, Canada, and Europe | 2020-2021 | Patients with a guidelines-based indication for single-chamber pacing | Aveir pacemaker (n=200) | 6 |

FDA: U.S. Food and Drug Administration; NCT: national clinical trial; PMA: premarket approval; SSED: Summary of Safety and Effectiveness Data.

[a] 30-day results reported by Roberts et al (2017).[32,]

[b] Results after a mean follow-up of 6.8 months reported by El-Chami et al (2018)

## Table 3. Summary of Key Nonrandomized Trial Results

| Study | Freedom From System- or Procedure-Related Major Complications | Percentage of Patients With Adequate Pacing Capture Thresholds | Major Complications Criteria, n (%) | Major Complications, n (%) |
|---|---|---|---|---|
| **Micra IDE Trial** | | | | |
| | 6 Months | 6 Months | 6 Months | 6 Months |
| Reynolds et al (2016)[26,] | | | | |
| N | 719[a];300[b] | 719 | 725 | 725 |
| Micra | 96.0% | 98.3% (≤2.0 V) | • Death: 1 (0.1)<br>• Loss of device function: 1 (0.1)<br>• Hospitalization: 13 (2.3)<br>• Prolonged hospitalization (≥48 h): 16 (2.6)<br>• System revision[c]: 3 (0.4) | TMCs: 28 in 25 patients (3.5%)<br>• DVT: 1 (0.1)<br>• Pulmonary TE: 1 (0.1)<br>• Events at groin puncture site: 5 (0.7)<br>• Cardiac perforation: 11 (1.6)<br>• Pacing issues: 2 (0.3)<br>• Others: 8 (1.7) |
| 95% CI | 93.9% to 97.3% | 95.4% to 99.6% | NA | NA |
| | 12 Months | 12 Months | 12 Months | 12 Months |
| Duray et al (2017)[41,] | | | | |
| N | 726 | NA | 726 | 726 |
| Micra | 96.0% | NR (93%) | • Death: NR (0.1)<br>• Loss of device function: NR (0.1)<br>• Hospitalization: NR (2.3)<br>• Prolonged hospitalization | TMCs: 32 in 29 patients (4.0)<br>• DVT: 1 (0.1)<br>• Pulmonary TE: 1 (0.1)<br>• Events at groin puncture site: 5 (0.7)<br>• Cardiac perforation: 11 (1.6)<br>• Pacing issues: 2 (0.3)<br>• Others: 11 (1.7) |

| | | | | |
|---|---|---|---|---|
| | | | (≥48 h): NR (2.2)<br>• System revision[c]: NR (0.7)<br>• Loss of device function: NR (0.3) | |
| 95% CI | 94.2% to 97.2% | NA | | |
| **Micra Post-Approval Study** | | | | |
| | 30 Days | 30 Days | 30 Days | 30 Days |
| Roberts et al (2017)[32,] | | | | |
| N | 795 | NA | 795 | 795 |
| Micra | 97.3%[d] | 87.2% (≤1.0 V)<br>97.0% (≤2.0 V) | • Death: 1 (0.13%)<br>• Hospitalization: 4 (0.50)<br>• Prolonged hospitalization (≥48 h): 9 (1.01)<br>• System revision[c]: 2 (0.25) | TMCs: 13 in 12 patients (1.51% [95% CI, 0.78 to 2.62])<br>• DVT: 1 (0.13)<br>• Events at groin puncture site: 6 (0.75)<br>• Cardiac effusion/perforation: 1 (0.13)<br>• Device dislodgement: 1 (0.13)<br>• Pacing issues: 1 (0.13)<br>• Others: 3 (0.38) |
| OR (95% CI) | 0.58 (0.27 to 1.25)[e] | NA | NA | NA |
| | 1 Year | 1 Year | 1 Year | 1 Year |
| El-Chami et al (2018)[34,] | | | | |
| N | 1817 | NA | NA | 1817 |
| Micra | 97.3%[d] | NA | NA | TMCs: 46 in 41 patients (2.7% [95% CI, 2.0% to 3.6%])<br>• Pericardial effusions: 8 (0.44)<br>• Dislodgement: 1 (0.06)<br>• Procedure-related infections: 3 (0.17)<br>• Procedure-related deaths: 5 (0.28)<br>As per FDA: Complications[f]: 61 in 53 (deaths: 4 procedure-related; 3 unknown relatedness; 3 pending adjudication) |

| | | | | |
|---|---|---|---|---|
| HR (95% CI) | 0.71 (0.44 to 1.1)[e]<br>0.37 (0.27 to 0.52)[g] | NA | NA | NA |
| **Micra CED Study** | | | | |
| | 30 days and 6 months | NA | NA | 30 days and 6 months |
| Piccini et al (2021)[37,] | | | | |
| N | 5746 | NA | NA | 5746 |
| Micra complication rate, RR or HR (95% CI) | 30-d, unadjusted: NR<br>30-d, adjusted: 0.3 (-0.6 to 1.3)<br>6-mo, unadjusted: 0.84 (0.68 to 1.03)<br>6-mo, adjusted: 0.77 (0.62 to 0.96) | NA | NA | Acute (30 days), n (%):<br>• Overall: 484 in 5746 patients (8.4)<br>• Embolism and thrombosis, 202 (3.5)<br>• Events at puncture site, 78 (1.4)<br>• Cardiac effusion and/or perforation, 47 (0.8)<br>• Device-related complication, 81 (1.4)<br>• Other complications, 136 (2.4)<br>6-Month CIF Estimates, % (95% CI)<br>• Overall: 3.2 (2.9 to 3.6)<br>• Embolism and thrombosis: <10 events<br>• Device-related complications: 1.7 (1.5 to 1.9)<br>• Other complications: 1.6 (1.3 to 1.8) |
| • | 24 months[h] | NA | NA | 24 months[i] |
| El-Chami et al (2022)[38,] | | | | |
| N | 6219 (Micra)<br>10,212 (tranvenous) | NA | NA | 6219 (Micra)<br>10,212 (transvenous) |
| Micra | adjusted, 3.1% | NA | NA | Chronic complications CIF Estimates, % (95% CI)<br>• Overall: 4.6 (4.2 to 4.9)<br>• Embolism and thrombosis:<10 events<br>• Device-related complications: 2.4 (2.2 to 2.5) |

| | | | | |
|---|---|---|---|---|
| | | | | • Other complications: 2.1 (2.0 to 2.3)<br>  ○ Pericarditis: 1.6 (1.4 to 1.9) |
| Transvenous | adjusted, 4.9% | NA | NA | Chronic complications CIF Estimates, % (95% CI)<br>• Overall: 6.5 (6.1 to 6.9)<br>• Embolism and thrombosis: 0.2 (0.2 to 0.2)<br>• Device-related complications: 4.8 (4.7 to 5.0)<br>• Other complications: 1.4 (1.3 to 1.6)<br>  ○ Pericarditis: 0.8 (0.7 to 0.9) |
| RR or HR (95% CI) | adjusted, 0.62 (0.45 to 0.85) | NA | NA | Relative risk reduction (95% CI)<br>• Overall: 31 (19 to 40)<br>• Embolism and thrombosis: 46 (-17 to 75)<br>• Device-related complications: 52 (42 to 60)<br>• Other complications: -48 (-91 to -15)<br>  ○ Pericarditis: -105 (-180 to -50) |
| **Aveir IDE Trial** | | | | |
| | 6 Weeks<br>6 Months | 6 Weeks<br>6 Months | NR | 6 Weeks |
| FDA SSED (2022); PMA P150035 [20,] | | | | |
| N | 200 | 200 | NR | 200 |
| Aveir | 0.960 (0.922 to 0.982);<br>0.933 (0.898 to 0.956) | 0.959 (0.921 to 0.982);<br>0.934 (0.899 to 0.960) | NR | SADEs: 9 in 8 patients (4.0% [95% CI, NR])<br>• Cardiac perforation/tamponade: 3 (1.5)<br>• Premature deployment with migration: 2 (1.0)<br>• Premature deployment without migration: 1 (0.5)<br>• Vascular access site complication - bleeding: 1 (0.5)<br>• Embolism: 1 (0.5) |

| | | | | |
|---|---|---|---|---|
| | | | | • Thrombosis (0.5) |

CED: coverage with evidence development; CI: confidence interval; CIF: cumulative incidence function; DVT: deep vein thrombosis; FDA: U.S. Food and Drug Administration; HR: hazard ratio; IDE: investigational device exemption; OR: odds ratio; NA; not available; NR: not reported; PMA: premarket approval; RR: relative risk; SADE: serious adverse device effects; SSED: Summary of Safety and Effectiveness Data; TE: thromboembolism; TMC: Total major complication.
[a] Total number of patients who received the implant successfully.
[b] Number of patients for whom data were available for 6-month evaluation.
[c] Device explant, reposition, or replacement.
[d] Calculations performed by BCBSA based on the major complication rate (2.7%; 95% CI 2.0 to 3.6) reported by El-Chami et al (2018).
[e] Major complication vs. IDE trial.
[f] Unclear if the complications met the definition of a major complication as events leading to death, hospitalization, prolonged hospitalization by 48 hours, system revision, or loss of device therapy.
[g] Major complication vs. historical controls.
[h] Device reintervention rate.
[i] Chronic complications.

## Aveir Postapproval Experience

Continued FDA approval of the Aveir transcatheter pacing system is contingent on the results of the Aveir VR Real-World Evidence Study. This post-approval study is designed to evaluate the long-term safety of the Aveir device in a real-world sample of 2100 participants. Both acute and long-term safety will be evaluated as post implant complication-free rates at 30-days and 10-years. Six-month and 10-year reports are due in September 2022 and March 2032, respectively.

Tables 4 and 5 display notable limitations identified for key studies.

### Table 4. Study Relevance Limitations

| Study | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Follow-Up[e] |
|---|---|---|---|---|---|
| **Micra** | | | | | |
| Reynolds et al (2016);Duray et al (2017) | | | 2. This was a single cohort study; there was no comparator | | 1-2. Insufficient duration for benefit and harms |
| Roberts et al (2017);El-Chami et al (2018) | | | 2. This was a single cohort study; there was no comparator | | 1-2. Insufficient duration for benefit and harms |
| Piccini et al (2021) | 1. It is unclear whether all patients were considered medically eligible for a transvenous device. | | | | 1-2: Insufficient duration for benefit and harms |
| El-Chami et al (2022) | 1. It is unclear whether all patients were considered medically eligible | | | | 1-2. Insufficient duration for benefit and harms |

| | | | | | |
|---|---|---|---|---|---|
| | for a transvenous device. | | | | |
| **Aveir** | | | | | |
| FDA SSED (2022); PMA P150035 | | | 2. This was a single cohort study; there was no comparator | 1. Survival data not based on currently marketed device; quality of life outcomes are not available | 1-2. Insufficient duration for benefit and harms |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

## Table 5. Study Design and Conduct Limitations

| Study | Allocation[a] | Blinding[b] | Selective Reporting[c] | Data Completeness[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| **Micra** | | | | | | |
| Reynolds et al (2016); Duray et al (2017) | 1. Participants not randomly allocated; design was prospective single cohort study | 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment. However, adverse events analyzed by an independent clinical event committee. Trial oversight provided by an independent data and safety monitoring committee. | | | | |
| Roberts et al (2017); El-Chami et al (2018) | 1. Participants not randomly allocated; design was prospective registry | 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician | | | | |
| Piccini et al (2021) | 1. Participants not randomly allocated; design was prospective registry | 1. Not blinded to treatment assignment; 2. Outcome assessment not described. | | | | |
| El-Chami et al (2022) | 1. Participants not randomly allocated; design was | 1. Not blinded to treatment assignment; 2. Outcome assessment not described. | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | prospective registry | | | | | |
| **Aveir** | | | | | | |
| FDA SSED (2022); PMA P150035 | 1. Participants not randomly allocated; design was prospective single cohort | 1. Not blinded to treatment assignment; 2-3. Blinding of outcome assessment not described | | | | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

**Section Summary**

The evidence for use of the Micra transcatheter pacing system consists of a pivotal prospective cohort study a postapproval prospective cohort study, a Medicare registry, and a retrospective FDA database analysis. Results at 6 months and 1 year for the pivotal study reported high procedural success (>99%) and device effectiveness (pacing capture threshold met in 98% of patients). Most of the system- or procedural-related complications occur within 30 days. At 1 year, the incidence of major complications did not increase substantially from 6 months (3.5% at 6 months vs. 4% at 1 year). Results of the postapproval study were consistent with a pivotal study and showed a lower incidence of major complications up to 30 days post implantation and 1 year (1.5% and 2.7%, respectively). In both studies, the point estimates of major complication were lower than the pooled estimates from 6 studies of conventional pacemakers used as a historical comparator. While the Micra transcatheter pacing system eliminates adverse events associated with lead and pocket issues, its use results in additional complications related to the femoral access site (groin hematomas, access site bleeding) and implantation and release of the device (traumatic cardiac injury). Initial data from a Medicare registry found a significantly higher rate of pericardial effusion and/or perforation within 30 days in patients with the leadless Micra pacemaker compared to patients who received a transvenous device; overall 6-month complication rates were significantly lower in the Micra group in the adjusted analysis (p=.02). In a real-world study of Medicare patients, the Micra device was associated with a 38% lower adjusted rate of reinterventions and a 31% lower adjusted rate of chronic complications compared with transvenous pacing, with no significant difference in adjusted all-cause mortality at 2 years despite the higher comorbidity index for patients implanted with a Micra device. However, patients receiving the Micra leadless pacemaker experienced significantly more other complications, driven by higher rates of pericarditis (adjusted, 1.6% vs. 0.8%; p<.0001). It is also unclear whether all patients were considered medically eligible for a

conventional pacing system. A 2021 analysis of the FDA Manufacturer's and User Facility Device Experience (MAUDE) database revealed significantly higher rates of death, cardiac tamponade, and rescue thoracotomy in Micra recipients compared to patients implanted with a transvenous pacemaker ($p<.001$), although this study is limited by potential risk of ascertainment bias. The evidence for the use of the Aveir transcather pacing system consists of a pivotal prospective cohort study. Primary safety and efficacy outcomes at 6 weeks exceeded performance goals for complication-free rate and composite success rate (96.0% and 95.9%, respectively). Results at 6 months were similar. Incidence of major complications was comparable to rates observed in the Micra pivotal trial (4.0%). The 2-year survival estimate of 85.3% is based on Phase 1 performance with the predecessor Nanostim device.

Considerable uncertainties and unknowns remain in terms of the durability of the devices and end-of-life device issues. Early and limited experience with the Micra device has suggested that retrieval is unlikely because in due course of time, the device will be encapsulated. There are limited data on device-device interactions (both electrical and mechanical), which might occur when there is a deactivated Micra device alongside another leadless pacemaker or when a leadless pacemaker and transvenous device are both present. While the Aveir device is specifically designed to be retrieved when therapy needs evolve or the device needs to be replaced, clinical experience with device retrieval has not yet been reported.

**Ventricular Pacing for Individuals who are Medically Ineligible for a Conventional Pacing System**

**Clinical Content and Therapy Purpose**
The purpose of single-chamber transcatheter pacing systems in individuals with a class I or II guidelines-based indication for implantation of a single-chamber ventricular pacemaker is to provide a treatment option that is an alternative to or an improvement on conventional pacing systems.

**Populations**
The relevant population of interest is individuals with a class I or II guidelines-based indication for implantation of a single-chamber ventricular pacemaker who are medically ineligible for a conventional pacing system.

**Interventions**
The therapy being considered a single chamber transcatheter pacing system (e.g., Micra, Aveir).

**Comparators**
The following therapy and practice are currently being used to make decisions about managing individual’s ineligible for a conventional pacemaker: medical management and/or conventional single-chamber pacemakers placed via trans-iliac venous lead placement or surgical epicardial pacemaker.

**Outcomes**
The general outcomes of interest are treatment-related mortality and morbidity. Specifically, the short-term outcomes include acute complication-free survival rate, the electrical performance of the device, including the pacing capture threshold, and adverse events, including procedural and postprocedural complications. Long-term outcomes include chronic complication-free survival rate, the electrical performance of the device, including pacing impedance, and pacing thresholds and chronic complications, including any system explant, replacement (with and without system explant), and repositions. Further, analysis of summary statistics regarding battery length is important.

To assess short-term safety, the first 30 days postimplant is generally considered appropriate because most device and procedural complications occur within this time frame. To assess long-term efficacy and safety as well as issues related to device end-of-life, a follow-up to 9 to 12 years postimplant with an adequate sample size are required to characterize device durability and complications with sufficient certainty.

**Review of Evidence**

**Nonrandomized Controlled Trials**

**Micra Leadless Pacemaker**

**Pivotal Trial**
The pivotal investigational device exemption (IDE) trial was a prospective single cohort study enrolling 744 patients with a class I or II indication for implantation of a single-chamber ventricular pacemaker based on national guidelines. Details on the design and results of the IDE trial have been published. Trial characteristics and results at 6 months are summarized in Tables 2 and 3, respectively. System performance from the pivotal trial has been published, but results are not discussed further.

Of the 744 patients enrolled, implantation of the Micra transcatheter pacing system was successful in 719 (99.2%) of the 725 patients who underwent the procedure. The demographics of the trial population were typical for a single-chamber pacemaker study performed in the U.S., with 42% being female and an average age of 76 years. Sixty-four percent had a pacing indication associated with persistent or permanent atrial arrhythmias, 72.6% had any atrial fibrillation at baseline, and 27.4% did not have a history of atrial fibrillation. Among those 27.4% (n=199) without atrial fibrillation, 16.1% (n=32) had a primary indication of sinus bradycardia and 3.5% (n=7) had a primary indication of tachycardia-bradycardia.

The IDE trial had 2 primary endpoints related to safety and efficacy. The trial would meet its safety endpoint if the lower bound of the 95% confidence interval (CI) for the rate of freedom from major complications related to the Micra transcatheter pacing system or implantation procedure exceeded 83% at 6 months. Major complications were defined as

those resulting in any of the following: death, permanent loss of device function due to mechanical or electrical dysfunction of the device (e.g., pacing function disabled, leaving device abandoned electrically), hospitalization, prolonged hospitalization by at least 48 hours, or system revision (reposition, replacement, explant).[28,] The trial would meet its efficacy endpoint if the lower bound of the 95% CI for the proportion of patients with adequate pacing capture thresholds (PCT) exceeded 80% at 6 months. PCT as an effectiveness objective is a common electrical measure of pacing efficacy and is consistent with recent studies. Pacing capture threshold measured in volts is defined as the minimum amount of energy needed to capture the myocardial tissue electrically. Unnecessary high pacing output adversely shortens the battery life of the pacemaker and is influenced by physiologic and pharmacologic factors. As per the FDA, demonstrating that "PCT is less than 2 Volts for the vast majority of subjects will imply that the Micra system will have longevity similar to current pacing systems since Micra's capture management feature will nominally set the safety margin to 0.5 Volts above the PCT with hourly confirmation of the PCT.

Safety and efficacy results of the IDE trial are summarized in Table 3. At 6 months, the trial met both of its efficacy and safety primary endpoints including freedom from major complications related to the system or procedure in 96.0% of the patients (95% CI, 93.9% to 97.3%), compared with a performance goal of 83%, and an adequate pacing capture threshold in 98.3% of the patients (95% CI, 96.1% to 99.5%), compared with a performance goal of 80%.

Quality of life results of the IDE trial were published in 2018. At baseline and 12 months, 702 (98%) and 635 (88%) participants completed the 36-Item Short Form questionnaire, respectively. The mean 36-Item Short Form Physical Component Scale at baseline was 36.3 (standard deviation [SD]=9.0) and the mean 36-Item Short Form Mental Component Scale was 47.3 (SD=12.5); the general population mean for both scores is 50. Both the Physical Component Scale and Mental Component Scale improved at 12 months post-implant to a mean Physical Component Scale score of 38.6 (SD=9.4; p<.001) and a mean Mental Component Scale score of 50.7 (SD=12.2; p<.001) compared with baseline.
IDE trial results were compared post hoc with a historical cohort of 2667 patients generated from 6 previous pacemaker studies, conducted between 2005 and 2012 by Medtronic, that evaluated the performance requirement at 6 months postimplant of right ventricle pacing leads (single-chamber rates obtained by excluding any adverse events only related to the right atrial lead from the analysis). The Micra device was associated with fewer complications than the historical control (4.0% vs. 7.4%; hazard ratio [HR], 0.49; 95% CI, 0.33 to 0.75; p=.001). Because there were differences in baseline patient characteristics between the 2 cohorts (patients in the historical cohort were younger and had a lower prevalence of coexisting conditions vs. the IDE trial), an additional propensity-matched analysis was conducted. It showed similar results (HR=0.46; 95% CI, 0.28 to 0.74). As per the FDA, the lower rate of major complications with the Micra device was driven by reductions in access site events (primarily implant site hematoma and implant site infections), pacing issues (primarily device capture and device pacing

issues), and fixation events (there was no device or lead dislodgements in the Micra IDE trial).[11,]

While the overall rate of complications was low, the rate of major complications related to cardiac injury (i.e., pericardial effusion or perforation) was higher in the Micra IDE trial than in the 6 reference Medtronic pacemaker studies (1.6% vs. 1.1%, p=.288).[11,] Thus, there appears to be a trade-off between types of adverse events with the Micra transcatheter pacing system and conventional pacemakers. While adverse events related to leads and pocket are eliminated or minimized with the Micra device, certain adverse events (e.g., groin vascular complications, vascular or cardiac bleeding) occur at a higher frequency or are additive (new events) compared with conventional pacemakers. Of these, procedural complications (e.g., acute cardiac perforations) that were severe enough to result in tamponade and emergency surgery were most concerning.

In addition to lack of adequate data on long-term safety, effectiveness, reliability, and incidence of late device failures and battery longevity, there is also inadequate clinical experience with issues related to devices that have reached end-of-life, including whether to extract or leave the device in situ and possible device-device interactions. There are limited data on device-device interactions (both electrical and mechanical) that may occur when there is a deactivated Micra device alongside another leadless pacemaker or when a leadless pacemaker and transvenous device are both present. Even though there have been few device retrievals and very limited experience with the time course of encapsulation of these devices in humans, it is highly likely that these devices will be fully encapsulated by the end of its typical battery life, and therefore device retrieval is unlikely. Current recommendations for end-of-device-life care for a Micra device may include the addition of a replacement device with or without explantation of the Micra device, which should be turned off. Grubman et al (2017) reported on system revisions including patients from the IDE study (n=720) and the Micra Transcatheter Pacing System Continued Access Study (n= 269; NCT02488681). The Continued Access study was conducted to allow for continued access of the Micra in the same centers as the IDE study while the device was pending the FDA approval. The mean follow-up duration was 13 months (16 months in the IDE patients and 2 months in the continued access patients). There were 11 system revisions in 10 patients, corresponding to a 1.4% (95% CI, 0.7% to 2.6%) actutimes rate of revisions through 24 months. Micra was disabled and left in situ in 7 of 11 revisions including 5 patients in which there was no retrieval attempt, 1 patient in which retrieval was aborted because of fluoroscopy failure, and 1 patient in which retrieval was unsuccessful because of inability to dislodge the device. There were 3 percutaneous retrievals and 1 retrieval during surgical valve replacement. There were no complications associated with retrievals. The report indicates that when a transvenous system was implanted with a deactivated Micra, there were no reported interactions between the 2 systems, although it is not clear how often this occurred. In the historical controls from the IDE study, there were 123 revisions in 117 patients through 24 months (actutimes rate 5.3%; 95% CI, 4.4 to 6.4). Using propensity score matching, the reduction in system revisions for Micra compared to historical controls was significant (HR=0.27; 95% CI, 0.14 to 0.54; p<.001).

**Micra Postapproval Experience**

The FDA approval of the Micra transcatheter pacing system was contingent on multiple postapproval studies to provide reasonable assurance of continued safety and effectiveness of the device. Among these, the Micra Transcatheter Pacing System Post-Approval Study, a global, prospective, observational, multicenter study, enrolled 1830 patients to collect data on 1741 patients to estimate the acute complication rate within 30 days of the implant, 500 patients to estimate the 9-year complication-free survival rate, and a minimum of 200 patients with a Micra device revision for characterizing device end of service. As per the protocol, if a subsequent device is placed and the Micra is deactivated or explanted, Medtronic would contact the implanting center and request the patient's clinical data concerning the revision. All such data would be summarized, including the type of system revision, how the extraction was attempted, success rate, and any associated complications.

Study characteristics and results at 1 year (reported in the FDA documents and published) are summarized in Table 2 and 3, respectively. The postapproval study completed enrollment in early March 2018. The definition of a major complication in the postapproval study was the same as the Micra IDE trial. Although some patients who participated in the IDE study consented to also participate in the PAR study, the publication excludes those patients from analysis and therefore includes an independent population. Results summarized in Table 3 summarize the data at 30 days published by Roberts et al (2017)[32,] and El-Chami et al (2018) with a mean follow-up of 6.8 months for 1817 patients, of whom 465 patients had a follow-up for more than 1 year.

At 30 days, the major complication rate was 1.51% (95% CI, 0.78 to 2.62). The major complication rate was lower in the postapproval study than in the IDE trial (odds ratio, 0.58; 95% CI, 0.27 to 1.25) although this did not reach statistical difference. The lower rate of major complications was associated with a decrease in events that led to hospitalization, prolonged hospitalization, or loss of device function in the postapproval study compared with the IDE trial. A subsequent subgroup analysis of patients who did not receive perioperative anticoagulation treatment, who received interrupted anticoagulation treatment, or who received continuous anticoagulation treatment did not find a significant difference in rates of acute major complications according to anticoagulation strategy (3.1%, 2.6%, and 1.5%, respectively; p=.29). The most common major complication was pacing problems, including elevated threshold and device capturing issues. A subgroup analysis of patients treated with and without atrioventricular node ablation (AVNA) at the time of Micra implantation identified a significantly higher risk of major complications at both 30 days (7.3% vs. 2.0%; p<.001) and 36 months (HR 3.81; 95% CI, 2.33 to 6.23; p<.001) in the AVNA group versus those without AVNA.

After a mean follow-up of 6.8 months, the estimated major complication rate at 12 months was 2.7% (95% CI, 2.0 to 3.7), corresponding to 46 major complications in 41 patients, the majority of which (89%) occurred within 30 days of implantation. The major complications included 14 device pacing issue events, 11 events at the groin puncture

site, 8 cardiac effusion/perforation events, 3 infections, 1 cardiac failure event, 1 cardiomyopathy event, and 1 pacemaker syndrome event. Authors compared these results with the same historical cohort of 2667 patients used in the IDE trial and reported a 63% reduction in the risk for major complications through 12 months with the Micra transcatheter pacing system relative to conventional pacemakers (HR=0.37; 95% CI, 0.27 to 0.52). Additionally, the risk for major complications was lower in the Micra postapproval study than in the IDE trial, but it was a statistically significant difference (HR=0.71, 95% CI, 0.44 to 1.1). The reduction in major complications compared to historical controls was primarily driven by a significant 74% (95% CI, 54 to 85; p=.0001) relative risk reduction in system revisions and 71% (95% CI, 51 to 83; p=.0001) relative risk reduction in hospitalizations. The reduction in risk compared to the IDE trial was driven by significantly lower pericardial effusion rates in the post-approval study.

Piccini et al (2021) published initial data from the ongoing Longitudinal Coverage with Evidence Development Study on Micra Leadless Pacemakers (Micra CED). Patients implanted between March 2017 and December 2018 were identified and included from a fee-for-service population with at least 12 continuous months of Medicare enrollment prior to device implantation. A total of 5746 patients with single-chamber leadless Micra pacemakers and 9662 patients with transvenous pacemakers were analyzed. Patients with a Micra pacemaker were more likely to have end-stage kidney disease (p<.001) and a higher mean Charlson Comorbidity Index score (5.1 vs. 4.6; p<.001). The unadjusted acute 30-day complication rate was higher in the Micra subgroup (8.4% vs. 7.3%; p=.02), but no significant difference was found following adjustment for patient characteristics (p=.49). Pericardial effusion and/or perforation within 30 days of implantation was significantly higher in the Micra population in the adjusted model (0.8% versus 0.4%; p=.004). Patients with Micra pacemakers had a 23% lower risk of complications at 6 months compared to patients receiving a transvenous pacemaker (HR, 0.77; 95% CI, 0.62 to 0.96; p=.02) and a 37% reduction in rates of device revision after adjustment for patient baseline characteristics. The 30-day all-cause mortality rate was not significantly different between groups in both unadjusted (p=.14) and adjusted analyses (p=.61). The study is ongoing with an estimated study completion data of June 2025 (see Table 10). Study characteristics and results are summarized in Tables 2 and 3.

El-Chami et al (2022) subsequently compared reinterventions, chronic complications, and all-cause mortality at 2 years in patients implanted with the Micra leadless pacemaker or a transvenous pacemaker in the Micra Coverage with Evidence Development study. Patients implanted with leadless (n=6219) or transvenous pacemakers (n=10,212) were identified from Medicare claims data and compared contemporaneously. Patients receiving leadless pacemakers had higher rates of end-stage renal disease (12.0% vs. 2.3%) and a higher Charlson comorbidity index (5.1 vs. 4.6). Patients with leadless pacemakers received 37% fewer reinterventions (adjusted HR 0.62; 95% CI, 0.45 to 0.85; p =.003), defined as system revision lead revision or replacement, system replacement, system removal, or system switch or upgrade to an alternative device. Patients implanted with leadless pacemakers also experienced fewer chronic complications (2.4% vs. 4.8%; adjusted HR 0.69; 95% CI, 0.60 to 0.81; p<.0001). However, patients receiving leadless

pacemakers experienced significantly more other complications, driven by higher rates of pericarditis (adjusted, 1.6% vs. 0.8%; p<.0001). Adjusted all-cause mortality at 2 years was not significantly different between groups (adjusted HR 0.97; 95% CI, 0.91 to 1.04; p=.37) despite the higher comorbidity index in patients implanted with a Micra device. Study interpretation is limited by reliance on claims data. It is unclear whether all patients receiving leadless devices were considered medically eligible for transvenous devices. Study characteristics and results are summarized in Tables 2 and 3.

Hauser et al (2021) analyzed the Food and Drug Administration's Manufacturers and User Facility Device Experience (MAUDE) database to capture major adverse clinical events (MACE) associated with the Micra device compared to the Medtronic CapSureFix transvenous pacing system. In a search of reports from 2016 through 2020, 363 MACE and 960 MACE were identified for the Micra and CapSureFix devices, respectively. For the Micra device, significantly higher rates of death (26.4% vs. 2.4%; p<.001), cardiac tamponade (79.1% vs. 23.4%; p<.001), and rescue thoracotomy (27.3% vs. 5.2%; p<.001) were reported. Micra patients were more likely to require cardiopulmonary resuscitation (21.8% vs. 1.1%) and to suffer hypotension or shock (22.0% vs. 5.8%) compared to CapSureFix recipients (p<.001). While the overall incidence of myocardial and vascular perforations and tears that may result in cardiac tamponade and death in Micra recipients is estimated to be low (<1%), the authors note that Micra patients were more likely to survive these events if they received surgical repair (p=.014). A subsequent analysis of the MAUDE database focused on rates of Micra perforations from 2016 to 2021. Hauser et al (2022) identified 563 perforations reported within 30 days of implant, resulting in 150 deaths (27%), 499 cardiac tamponades (89%), and 64 pericardial effusions (11%).[40,] Emergency surgery was required in 146 patients (26%). Half of all perforations were associated with 139 device problems (25%), 78 operator use problems (14%), and 62 combined device and operator use problems (11%). The most common device problem leading to redeployment were non-capture or inadequate electrical values that required implantable pulse generator recapture and reimplantation or replacement. No device or operator use problems were identified for the remaining 282 perforations (50%), but these were associated with 78 deaths, 245 tamponades, and 57 emergency surgeries. The authors concluded that Micra implantation should be confined to specialized centers capable of managing emergency complications and that a risk score for perforation should be developed and validated. Importantly, these analyses are limited by the passive nature of the FDA's post-market device surveillance system, which may not capture all voluntary reports from healthcare professionals, consumers, and patients. Such analyses carry a high risk of ascertainment bias which may lead to overestimation of the true prevalence of adverse events.

**Aveir Leadless Pacemaker**

**Pivotal Trial**

The pivotal investigational device exemption (IDE) trial of the Aveir leadless pacemaker (LEADLESS II - Phase 2; NCT04559945) was a multicenter, prospective single cohort study enrolling 200 patients with a guidelines-based indication for single-chamber

pacing. Primary results from the IDE trial have been summarized in a published research correspondence and FDA documents. Trial characteristics and results through 6 months are summarized in Tables 2 and 3, respectively.

Implantation of the Aveir leadless pacing system was successful in 196/200 (98%) trial subjects (mean age, 75.6 years; 37.5% female). The primary indication for pacing was chronic atrial fibrillation with 2nd or 3rd degree atrioventricular block (52.5%). The trial had 2 primary endpoints related to safety and efficacy. The trial would meet its safety endpoint if the lower bound of the 97.5% CI for the complication-free rate exceeded 86% at 6 weeks. A complication was defined as a device-or-procedure-related serious adverse event, including those that prevented initial implantation. The trial would meet its efficacy endpoint if the lower bound of the 97.5% CI for the composite success rate exceeded 85% at 6 weeks. The confirmatory effectiveness endpoint was considered met if the pacing threshold voltage is ≤ 2.0 V at 0.4 ms and the sensed R-wave amplitude is either ≥ 5.0 mV at the 6-week visit or ≥ the value at implant.

Safety and efficacy results of the Aveir IDE trial are summarized in Table 3. At 6 weeks, the trial met both of its confirmatory safety and efficacy endpoints, including freedom from device-or-procedure-related complications in 96% of patients (95% CI, 92.2 to 98.2), compared with a performance goal of 86%, and a composite success rate of 95.9% of patients (95% CI, 92.1 to 98.2), compared with a performance goal of 85%. The 6-month complication-free rate was 94.9% (95% CI, 90.0 to 97.4). The most frequent complications included 3 cardiac tamponade events and 3 premature deployment events. The rate of cardiac perforation/tamponade/pericardial effusion was 1.5%. No dislodgement events were reported in the Aveir cohort.

Confirmatory secondary endpoints included assessment of an appropriate and proportional rate-response during a Chronotropic Assessment Exercise Protocol (CAEP) exercise protocol and an estimated 2-year survival rate. The CAEP assessment was initiated in 23 subjects, of which 17 were considered analyzable. The rate-response slope was 0.93 (95% CI, 0.78 to 1.08), which fell within the prespecified range of 65% to 135%. The estimated 2-year survival rate based on the Nanostim Phase 1 cohort (N=917) was 85.3% (95% CI, 82.7 to 87.4), which exceeded the performance goal of 80%.
The current evidence on the use of the Aveir device is limited by a lack of adequate data on quality of life, long-term safety, effectiveness, reliability, and incidence of late device failures and battery longevity. While the device is designed to be retrieved when therapy needs evolve or the device needs to be replaced, there is currently inadequate clinical experience with issues related to devices that have reached end-of-life. Survival data for the currently marketed version of the Aveir device has not been reported.

**Table 2. Summary of Key Nonrandomized Trail Characteristics**

| Study; Trial | Study Type | Country | Dates | Participants | Treatment | Follow-Up, mo |
|---|---|---|---|---|---|---|
| **Micra** | | | | | | |

| Study; Trial | Study Type | Country | Dates | Participants | Treatment | Follow-Up, mo |
|---|---|---|---|---|---|---|
| Reynolds et al (2016); NCT02004873 | Prospective single cohort | 19 countries in North America, Europe, Asia, Australia, and Africa | 2013-2015 | Patients who met a class I or II guidelines-based indication for pacing and suitable candidates for single-chamber ventricular demand pacing | Micra pacemaker (n=744) | 6 |
| Roberts et al (2017)<br><br>El-Chami et al (2018) NCT02536118 | Prospective single cohort (Micra Post-Approval Study) | 23 countries in North America, Europe, Asia, Australia, and Africa | 2016-2018 | Any patient to be implanted with a Micra device | Micra pacemaker (n=795[a] and 1830[b]) | 1.8[a]<br><br>6.8[b] |
| Piccinni et al (2021) | Prospective Medicare registry | United States | 2017-2018 | All Medicare patients implanted with a leadless single-chamber pacemaker or transvenous single-chamber pacemaker with at least 12 months of continuous Medicare enrollment prior to implantation | Micra pacemaker (n=5746); Transvenous pacemaker (n=9662) | 6 |
| El-Chami et al (2022) | Prospective Medicare registry | United States | 2017-2018 | All Medicare patients implanted with a leadless single-chamber pacemaker or transvenous single-chamber pacemaker with at least 12 months of continuous Medicare enrollment prior to implantation | Micra pacemaker (n=6219); Transvenous pacemaker (n=10,212) | 24 |
| **Aveir** | | | | | | |
| FDA SSED (2022); PMA P150035 | Prospective single cohort | 43 sites in the United States, Canada, and Europe | 2020-2021 | Patients with a guidelines-based indication for single-chamber pacing | Aveir pacemaker (n=200) | 6 |

FDA: U.S. Food and Drug Administration; NCT: national clinical trial; PMA: premarket approval; SSED: Summary of Safety and Effectiveness Data.

[a] 30-day results reported by Roberts et al (2017).[32,]

[b] Results after a mean follow-up of 6.8 months reported by El-Chami et al (2018)

## Table 3. Summary of Key Nonrandomized Trial Results

| Study | Freedom From System- or Procedure-Related Major Complications | Percentage of Patients With Adequate Pacing | Major Complications Criteria, n (%) | Major Complications, n (%) |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| | | **Capture Thresholds** | | |
| **Micra IDE Trial** | | | | |
| | 6 Months | 6 Months | 6 Months | 6 Months |
| Reynolds et al (2016)[26,] | | | | |
| N | 719[a];300[b] | 719 | 725 | 725 |
| Micra | 96.0% | 98.3% (≤2.0 V) | • Death: 1 (0.1)<br>• Loss of device function: 1 (0.1)<br>• Hospitalization: 13 (2.3)<br>• Prolonged hospitalization (≥48 h): 16 (2.6)<br>• System revision[c]: 3 (0.4) | TMCs: 28 in 25 patients (3.5%)<br>• DVT: 1 (0.1)<br>• Pulmonary TE: 1 (0.1)<br>• Events at groin puncture site: 5 (0.7)<br>• Cardiac perforation: 11 (1.6)<br>• Pacing issues: 2 (0.3)<br>• Others: 8 (1.7) |
| 95% CI | 93.9% to 97.3% | 95.4% to 99.6% | NA | NA |
| | 12 Months | 12 Months | 12 Months | 12 Months |
| Duray et al (2017)[41,] | | | | |
| N | 726 | NA | 726 | 726 |
| Micra | 96.0% | NR (93%) | • Death: NR (0.1)<br>• Loss of device function: NR (0.1)<br>• Hospitalization: NR (2.3)<br>• Prolonged hospitalization (≥48 h): NR (2.2)<br>• System revision[c]: NR (0.7) | TMCs: 32 in 29 patients (4.0)<br>• DVT: 1 (0.1)<br>• Pulmonary TE: 1 (0.1)<br>• Events at groin puncture site: 5 (0.7)<br>• Cardiac perforation: 11 (1.6)<br>• Pacing issues: 2 (0.3)<br>• Others: 11 (1.7) |

| | | | | |
|---|---|---|---|---|
| | | | • Loss of device function: NR (0.3) | |
| 95% CI | 94.2% to 97.2% | NA | | |
| **Micra Post-Approval Study** | | | | |
| | 30 Days | 30 Days | 30 Days | 30 Days |
| Roberts et al (2017)[32,] | | | | |
| N | 795 | NA | 795 | 795 |
| Micra | 97.3%[d] | 87.2% (≤1.0 V)<br>97.0% (≤2.0 V) | • Death: 1 (0.13%)<br>• Hospitalization: 4 (0.50)<br>• Prolonged hospitalization (≥48 h): 9 (1.01)<br>• System revision[c]: 2 (0.25) | TMCs: 13 in 12 patients (1.51% [95% CI, 0.78 to 2.62])<br>• DVT: 1 (0.13)<br>• Events at groin puncture site: 6 (0.75)<br>• Cardiac effusion/perforation: 1 (0.13)<br>• Device dislodgement: 1 (0.13)<br>• Pacing issues: 1 (0.13)<br>• Others: 3 (0.38) |
| OR (95% CI) | 0.58 (0.27 to 1.25)[e] | NA | NA | NA |
| | 1 Year | 1 Year | 1 Year | 1 Year |
| El-Chami et al (2018)[34,] | | | | |
| N | 1817 | NA | NA | 1817 |
| Micra | 97.3%[d] | NA | NA | TMCs: 46 in 41 patients (2.7% [95% CI, 2.0% to 3.6%])<br>• Pericardial effusions: 8 (0.44)<br>• Dislodgement: 1 (0.06)<br>• Procedure-related infections: 3 (0.17)<br>• Procedure-related deaths: 5 (0.28)<br>As per FDA: Complications[f]: 61 in 53 (deaths: 4 procedure-related; 3 unknown relatedness; 3 pending adjudication) |
| HR (95% CI) | 0.71 (0.44 to 1.1)[e] | NA | NA | NA |

| | | | | |
|---|---|---|---|---|
| | 0.37 (0.27 to 0.52)[g] | | | |
| **Micra CED Study** | | | | |
| | 30 days and 6 months | NA | NA | 30 days and 6 months |
| Piccini et al (2021)[37,] | | | | |
| N | 5746 | NA | NA | 5746 |
| Micra complication rate, RR or HR (95% CI) | 30-d, unadjusted: NR<br>30-d, adjusted: 0.3 (-0.6 to 1.3)<br>6-mo, unadjusted: 0.84 (0.68 to 1.03)<br>6-mo, adjusted: 0.77 (0.62 to 0.96) | NA | NA | Acute (30 days), n (%):<br>• Overall: 484 in 5746 patients (8.4)<br>• Embolism and thrombosis, 202 (3.5)<br>• Events at puncture site, 78 (1.4)<br>• Cardiac effusion and/or perforation, 47 (0.8)<br>• Device-related complication, 81 (1.4)<br>• Other complications, 136 (2.4)<br>6-Month CIF Estimates, % (95% CI)<br>• Overall: 3.2 (2.9 to 3.6)<br>• Embolism and thrombosis: <10 events<br>• Device-related complications: 1.7 (1.5 to 1.9)<br>• Other complications: 1.6 (1.3 to 1.8) |
| • | 24 months[h] | NA | NA | 24 months[i] |
| El-Chami et al (2022)[38,] | | | | |
| N | 6219 (Micra)<br>10,212 (tranvenous) | NA | NA | 6219 (Micra)<br>10,212 (transvenous) |

| | | | | |
|---|---|---|---|---|
| Micra | adjusted, 3.1% | NA | NA | Chronic complications CIF Estimates, % (95% CI)<br>• Overall: 4.6 (4.2 to 4.9)<br>• Embolism and thrombosis:<10 events<br>• Device-related complications: 2.4 (2.2 to 2.5)<br>• Other complications: 2.1 (2.0 to 2.3)<br>  ○ Pericarditis: 1.6 (1.4 to 1.9) |
| Transvenous | adjusted, 4.9% | NA | NA | Chronic complications CIF Estimates, % (95% CI)<br>• Overall: 6.5 (6.1 to 6.9)<br>• Embolism and thrombosis: 0.2 (0.2 to 0.2)<br>• Device-related complications: 4.8 (4.7 to 5.0)<br>• Other complications: 1.4 (1.3 to 1.6)<br>  ○ Pericarditis: 0.8 (0.7 to 0.9) |
| RR or HR (95% CI) | adjusted, 0.62 (0.45 to 0.85) | NA | NA | Relative risk reduction (95% CI)<br>• Overall: 31 (19 to 40)<br>• Embolism and thrombosis: 46 (-17 to 75)<br>• Device-related complications: 52 (42 to 60)<br>• Other complications: -48 (-91 to -15)<br>  ○ Pericarditis: -105 (-180 to -50) |
| **Aveir IDE Trial** | | | | |

| | | | | |
|---|---|---|---|---|
| | 6 Weeks<br>6 Months | 6 Weeks<br>6 Months | NR | 6 Weeks |
| FDA SSED (2022); PMA P150035 [20,] | | | | |
| N | 200 | 200 | NR | 200 |
| Aveir | 0.960 (0.922 to 0.982);<br>0.933 (0.898 to 0.956) | 0.959 (0.921 to 0.982);<br>0.934 (0.899 to 0.960) | NR | SADEs: 9 in 8 patients (4.0% [95% CI, NR])<br>• Cardiac perforation/tamponade: 3 (1.5)<br>• Premature deployment with migration: 2 (1.0)<br>• Premature deployment without migration: 1 (0.5)<br>• Vascular access site complication - bleeding: 1 (0.5)<br>• Embolism: 1 (0.5)<br>• Thrombosis (0.5) |

CED: coverage with evidence development; CI: confidence interval; CIF: cumulative incidence function; DVT: deep vein thrombosis; FDA: U.S. Food and Drug Administration; HR: hazard ratio; IDE: investigational device exemption; OR: odds ratio; NA; not available; NR: not reported; PMA: premarket approval; RR: relative risk; SADE: serious adverse device effects; SSED: Summary of Safety and Effectiveness Data; TE: thromboembolism; TMC: Total major complication.
[a] Total number of patients who received the implant successfully.
[b] Number of patients for whom data were available for 6-month evaluation.
[c] Device explant, reposition, or replacement.
[d] Calculations performed by BCBSA based on the major complication rate (2.7%; 95% CI 2.0 to 3.6) reported by El-Chami et al (2018).
[e] Major complication vs. IDE trial.
[f] Unclear if the complications met the definition of a major complication as events leading to death, hospitalization, prolonged hospitalization by 48 hours, system revision, or loss of device therapy.
[g] Major complication vs. historical controls.
[h] Device reintervention rate.
[i] Chronic complications.

## Aveir Postapproval Experience

Continued FDA approval of the Aveir transcatheter pacing system is contingent on the results of the Aveir VR Real-World Evidence Study.[42,] This post-approval study is designed to evaluate the long-term safety of the Aveir device in a real-world sample of 2100 participants. Both acute and long-term safety will be evaluated as post implant complication-free rates at 30-days and 10-years. Six-month and 10-year reports are due in September 2022 and March 2032, respectively.

Tables 4 and 5 display notable limitations identified for key studies.

## Table 4. Study Relevance Limitations

| Study | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Follow-Up[e] |
|---|---|---|---|---|---|
| **Micra** | | | | | |
| Reynolds et al (2016);Duray et al (2017) | | | 2. This was a single cohort study; there was no comparator | | 1-2. Insufficient duration for benefit and harms |
| Roberts et al (2017);El-Chami et al (2018), | | | 2. This was a single cohort study; there was no comparator | | 1-2. Insufficient duration for benefit and harms |
| Piccini et al (2021) | 1. It is unclear whether all patients were considered medically eligible for a transvenous device. | | | | 1-2: Insufficient duration for benefit and harms |
| El-Chami et al (2022) | 1. It is unclear whether all patients were considered medically eligible for a transvenous device. | | | | 1-2. Insufficient duration for benefit and harms |
| **Aveir** | | | | | |
| FDA SSED (2022); PMA P150035, | | | 2. This was a single cohort study; there was no comparator | 1. Survival data not based on currently marketed device; quality of life outcomes are not available | 1-2. Insufficient duration for benefit and harms |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

## Table 5. Study Design and Conduct Limitations

| Study | Allocation[a] | Blinding[b] | Selective Reporting[c] | Data Completeness[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| **Micra** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Reynolds et al (2016); Duray et al (2017) | 1. Participants not randomly allocated; design was prospective single cohort study | 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment. However, adverse events analyzed by an independent clinical event committee. Trial oversight provided by an independent data and safety monitoring committee. | | | | |
| Roberts et al (2017); El-Chami et al (2018) | 1. Participants not randomly allocated; design was prospective registry | 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician | | | | |
| Piccini et al (2021) | 1. Participants not randomly allocated; design was prospective registry | 1. Not blinded to treatment assignment; 2. Outcome assessment not described. | | | | |
| El-Chami et al (2022) | 1. Participants not randomly allocated; design was prospective registry | 1. Not blinded to treatment assignment; 2. Outcome assessment not described. | | | | |
| **Aveir** | | | | | | |
| FDA SSED (2022); PMA P150035 | 1. Participants not randomly allocated; design was prospective single cohort | 1. Not blinded to treatment assignment; 2-3. Blinding of outcome assessment not described | | | | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

## Section Summary

The evidence for use of the Micra transcatheter pacing system consists of a pivotal prospective cohort study a postapproval prospective cohort study, a Medicare registry, and a retrospective FDA database analysis. Results at 6 months and 1 year for the pivotal study reported high procedural success (>99%) and device effectiveness (pacing capture

threshold met in 98% of patients). Most of the system- or procedural-related complications occur within 30 days. At 1 year, the incidence of major complications did not increase substantially from 6 months (3.5% at 6 months vs. 4% at 1 year). Results of the postapproval study were consistent with a pivotal study and showed a lower incidence of major complications up to 30 days postimplantation and 1 year (1.5% and 2.7%, respectively). In both studies, the point estimates of major complication were lower than the pooled estimates from 6 studies of conventional pacemakers used as a historical comparator. While the Micra transcatheter pacing system eliminates adverse events associated with lead and pocket issues, its use results in additional complications related to the femoral access site (groin hematomas, access site bleeding) and implantation and release of the device (traumatic cardiac injury). Initial data from a Medicare registry found a significantly higher rate of pericardial effusion and/or perforation within 30 days in patients with the leadless Micra pacemaker compared to patients who received a transvenous device; overall 6-month complication rates were significantly lower in the Micra group in the adjusted analysis (p=.02). In a real-world study of Medicare patients, the Micra device was associated with a 38% lower adjusted rate of reinterventions and a 31% lower adjusted rate of chronic complications compared with transvenous pacing, with no significant difference in adjusted all-cause mortality at 2 years despite the higher comorbidity index for patients implanted with a Micra device. However, patients receiving the Micra leadless pacemaker experienced significantly more other complications, driven by higher rates of pericarditis (adjusted, 1.6% vs. 0.8%; p<.0001). It is also unclear whether all patients were considered medically eligible for a conventional pacing system. A 2021 analysis of the FDA Manufacturer's and User Facility Device Experience (MAUDE) database revealed significantly higher rates of death, cardiac tamponade, and rescue thoracotomy in Micra recipients compared to patients implanted with a transvenous pacemaker (p<.001), although this study is limited by potential risk of ascertainment bias. The evidence for the use of the Aveir transcather pacing system consists of a pivotal prospective cohort study. Primary safety and efficacy outcomes at 6 weeks exceeded performance goals for complication-free rate and composite success rate (96.0% and 95.9%, respectively). Results at 6 months were similar. Incidence of major complications was comparable to rates observed in the Micra pivotal trial (4.0%). The 2-year survival estimate of 85.3% is based on Phase 1 performance with the predecessor Nanostim device.

Considerable uncertainties and unknowns remain in terms of the durability of the devices and end-of-life device issues. Early and limited experience with the Micra device has suggested that retrieval is unlikely because in due course of time, the device will be encapsulated. There are limited data on device-device interactions (both electrical and mechanical), which might occur when there is a deactivated Micra device alongside another leadless pacemaker or when a leadless pacemaker and transvenous device are both present. While the Aveir device is specifically designed to be retrieved when therapy needs evolve or the device needs to be replaced, clinical experience with device retrieval has not yet been reported.

## Ventricular Pacing for Individuals who are Medically Ineligible for a Conventional Pacing System

### Clinical Context and Therapy Purpose

The purpose of single-chamber transcatheter pacing systems in patients with a class I or II guidelines-based indication for implantation of a single-chamber ventricular pacemaker is to provide a treatment option that is an alternative to or an improvement on conventional pacing systems.

The question addressed in this evidence review is: Does use of single-chamber transcatheter pacing systems improve the net health outcome in patients with a class I or II guidelines-based indication for implantation of a single-chamber ventricular pacemaker who are medically ineligible for a conventional pacing system?

The following PICO was used to select literature to inform this review.

### Populations

The relevant population of interest is individuals with a class I or II guidelines-based indication for implantation of a single-chamber ventricular pacemaker who are medically ineligible for a conventional pacing system

### Interventions

The therapy being considered is a single chamber transcatheter pacing system (e.g., Micra, Aveir).

### Comparators

The following therapy and practice are currently being used to make decisions about managing individuals ineligible for a conventional pacemaker: medical management and/or conventional single-chamber pacemakers placed via trans-iliac venous lead placement or surgical epicardial pacemaker.

### Outcomes

The general outcomes of interest are treatment-related mortality and morbidity. Specifically, the short-term outcomes include acute complication-free survival rate, the electrical performance of the device, including the pacing capture threshold, and adverse events, including procedural and postprocedural complications. Long-term outcomes include chronic complication-free survival rate, the electrical performance of the device, including pacing impedance, and pacing thresholds and chronic complications, including any system explant, replacement (with and without system explant), and repositions. Further, analysis of summary statistics regarding battery length is important.

To assess short-term safety, the first 30 days postimplant is generally considered appropriate because most device and procedural complications occur within this time frame. To assess long-term efficacy and safety as well as issues related to device end-of-

life, a follow-up to 9 to 12 years postimplant with an adequate sample size are required to characterize device durability and complications with sufficient certainty.

## Review of Evidence

### Nonrandomized Controlled Trials

No studies that exclusively enrolled patients who were medically ineligible to receive a conventional pacing system were identified.

### Micra Leadless Pacemaker

In the IDE trial, 6.2% or 45 patients received the Micra Transcatheter Pacing System because they were medically ineligible for a conventional pacing system due to compromised venous access, the need to preserve veins for hemodialysis, thrombosis, a history of infection, or the need for an indwelling venous catheter. A stratified analysis of these 45 patients was not presented in the originally published paper or the FDA documents.

In the postapproval registry , the authors reported stratified results for 105 of 1820 patients who had previous cardiac implantable electronic device (CIED) infection. Of these 105, 83 patients (79%) were classified as medically ineligible to receive a conventional pacemaker in the opinion of the physician. A stratified analysis of these 83 patients was not presented in the publication. Trial characteristics and results are summarized in Tables 6 and 7, respectively. In this cohort of patients with CIED infection, the Micra device was implanted successfully in 104 patients and the previous CIED was explanted the same day as the Micra device was implanted in 37% of patients. Major complications were reported in 3.8% of patients with an average follow-up of 8.5 months. Ten deaths were reported (14% at 12 months) but none were related to the Micra transcatheter pacing system or the implantation procedure.

Garg et al (2020) conducted a post-hoc analysis on safety and all-cause mortality outcomes for 546 patients enrolled in the Micra IDE study, the Micra Continued Access (CA) study, and the Micra Post-Approval Registry who were deemed ineligible for conventional pacing system implantation. Most common reasons for conventional pacing system ineligibility included impaired venous access (42.5%) and history of device infection or bacteremia (38.8%). Implant success rates were >99% for both medically ineligible and nonprecluded subgroups implanted with Micra devices. Both acute mortality (2.75% vs. 1.32%; p=.022) and total mortality at 36 months (38.1% vs. 20.6%; p<.001) were significantly higher in the medically ineligible group compared to the nonprecluded Micra group. Mortality was also significantly higher in the medically ineligible group compared to a historical cohort implanted with a conventional transvenous pacing system (38.1% vs. 23.2%). The rate of acute major complications (2.93% vs. 2.47%; p=.55) and total major complications through 36 months (4.30% vs. 3.81%; p=.40) was not significantly different between the medically ineligible and nonprecluded Micra groups, respectively. The authors emphasized that the elevated rate of all-cause mortality may be related to a higher incidence of chronic comorbidities in the

medically ineligible population, such as diabetes, renal dysfunction, and current dialysis treatment, which may have increased overall mortality risk during follow-up. The majority of medically ineligible patients were enrolled in the CA and Post-Approval Registry studies, which unlike the IDE study, did not exclude patients with a life expectancy <12 months.

**Table 6. Summary of Key Nonrandomized Trial Characteristics in Patients Ineligible for Conventional Pacing System and/or Previous Cardiac Implantable Electronic Device Infection**

| Study; Trial | Study Type | Country | Dates | Participants | Treatment | Follow-Up, mo |
|---|---|---|---|---|---|---|
| El-Chami et al (2018); NCT02536118 | Prospective single cohort (Micra Post-Approval Registry) | 23 countries in North America, Europe, Asia, Australia, and Africa | 2016-2018 | Any patient to be implanted with a Micra with a CIED infection | Micra pacemaker (N=105) | 8.5 (range 0 to 28.5) |
| Garg et al (2020) | Post hoc analysis of prospectively collected data from Micra studies | Multinational | NR | Any patient in a Micra study considered ineligible for a conventional pacing system | Micra pacemaker (N=546) | 23.5 ± 14.7 |

CIED: cardiac implantable electronic device; NCT: national clinical trial.

**Table 7. Summary of Key Nonrandomized Trial Results in Patients Ineligible for a Conventional Pacing System and/or Previous Cardiac Implantable Electronic Device Infection**

| Study | No. of Patients with System- or Procedure-Related Major Complications at 1 Year, % (n/N) | Average Pacing Threshold at 1 Year | Major Complications at 1 Year |
|---|---|---|---|
| El-Chami et al (2018) | | | |
| N | 105 | 82 | 105 |
| Micra | 4 (4/105) | 0.6 V | Total major complications: 6 in 4 patients;<br>(patient 1: effusion requiring pericardiocentesis; patient 2: elevated thresholds, complication of device removal [IVC filter entanglement], and subsequent abdominal wall infection, patients 3 and 4: pacemaker syndrome) |
| Garg et al (2020) | | | |
| N | 546 | NR | 546 |
| Micra | 4 (22/546)[a] | NR | Total major complications: 24 in 22 patients; |

| | | | |
|---|---|---|---|
| | | | (4 cases cardiac effusion/perforation, 4 events at groin puncture site, 1 case of thrombosis, 4 cases of pacing issues, 1 case of cardiac rhythm disorder, 3 cases of infection, and 7 other) |

IVC: inferior vena cava filter; NR: not reported.
[a] Outcome reported at 36 months.

Tables 8 and 9 display notable limitations identified in selected studies.

## Table 8. Study Relevance Limitations

| Study | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Follow-Up[e] |
|---|---|---|---|---|---|
| El-Chami et al (2018) | | | 2. This was a single cohort study; there was no comparator | | 1. Insufficient duration for benefit;<br>2. Insufficient duration for harms |
| Garg et al (2020)[,] | | | | | 1. Insufficient duration for benefit;<br>2. Insufficient duration for harms |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

## Table 9. study Design and Conduct Limitations

| Study | Allocation[a] | Blinding[b] | Selective Reporting[c] | Data Completeness[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| El-Chami et al (2018) | 1. Participants not randomly allocated; design was prospective registry | 1. Not blinded to treatment assignment;<br>2. Not blinded outcome assessment;<br>3. Outcome assessed by treating physician | | | | |
| Garg et al (2020)[,] | 1. Participants not randomly allocated; post-hoc analysis | 1-3. Blinding and outcome assessment not described. | | | | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

**Section Summary**

No studies that exclusively enrolled patients who were medically ineligible for a conventional pacing system were identified. However, a subgroup of patients in whom the use of conventional pacemakers was precluded was enrolled in the pivotal and the postapproval trials of the Micra device. Information on the outcomes in these subgroups of patients from the post approval study showed that Micra was successfully implanted in 98% to 99% of cases and safety outcomes were similar to the original cohort. Even though the evidence is limited, and long-term effectiveness and safety are unknown, the short-term benefits may outweigh the risks because the complex trade-off of adverse events for these devices needs to be assessed in the context of the life-saving potential of pacing systems in patient's ineligible for conventional pacing systems.

**Clinical Input from Physician Specialty Societies and Academic Medical Centers**

In 2019, clinical input was sought by BCBS Association to help determine whether the use of leadless cardiac pacemakers for individuals with a guidelines-based indication for a ventricular pacing system would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 2 respondents, including 1 specialty society-level response and 1 physician-level response identified through specialty societies including physicians with academic medical center affiliations.

Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- Heart Rhythm Society (HRS)
- Kousik Krishnan, MD, Clinical Cardiac Electrophysiology, Rush University Identified by American College of Cardiology (ACC).

For individuals with a guidelines-based indication for a ventricular pacing system who are medically ineligible for a conventional pacing system who receive a Micra transcatheter pacing system, clinical input supports this use provides a clinically meaningful improvement in net health outcomes and indicates this use is consistent with generally accepted medical practice in a subgroup of appropriately selected patients when both conditions below are met:

- The patient has symptomatic paroxysmal or permanent high-grade arteriovenous block or symptomatic bradycardia-tachycardia syndrome or sinus node dysfunction (sinus bradycardia or sinus pauses).
- The patient has a significant contraindication precluding placement of conventional single-chamber ventricular pacemaker leads such as any of the following:

- History of an endovascular or CIED infection or who are very high-risk for infection
- Limited access for transvenous pacing given venous anomaly, occlusion of axillary veins or planned use of such veins for a semi-permanent catheter or current or planned use of an AV fistula for hemodialysis
- Presence of a bioprosthetic tricuspid valve

**Summary of Evidence**

For individuals with a guidelines-based indication for a ventricular pacing system who are medically eligible for a conventional pacing system who receive a single-chamber transcatheter pacing system, the evidence includes pivotal prospective cohort studies, a postapproval prospective cohort study, a Medicare registry, and a retrospective FDA database analysis. Results at 6 months and 1 year for the Micra pivotal study reported high procedural success (>99%) and device effectiveness (pacing capture threshold met in 98% of patients). Most of the system- or procedure-related complications occurred within 30 days. At 1 year, the incidence of major complications did not increase substantially from 6 months (3.5% at 6 months vs. 4% at 1 year). Results of the Micra postapproval study were consistent with the pivotal study and showed a lower incidence of major complications up to 30 days post implantation as well as 1 year (1.5% and 2.7%, respectively). In both studies, the point estimates of major complications were lower than the pooled estimates from 6 studies of conventional pacemakers used as a historical comparator. While Micra device eliminates lead- and surgical pocket-related complications, its use can result in potentially more serious complications related to implantation and release of the device (traumatic cardiac injury) and less serious complications related to the femoral access site (groin hematomas, access site bleeding). Initial data from a Medicare registry found a significantly higher rate of pericardial effusion and/or perforation within 30 days in patients with the leadless Micra pacemaker compared to patients who received a transvenous device; however, overall, 6-month complications rates were significantly lower in the Micra group in the adjusted analysis ($p=.02$). In a real-world study of Medicare patients, the Micra device was associated with a 38% lower adjusted rate of reinterventions and a 31% lower adjusted rate of chronic complications compared with transvenous pacing, with no significant difference in adjusted all-cause mortality at 2 years despite the higher comorbidity index for patients implanted with a Micra device. However, patients receiving the Micra leadless pacemaker experienced significantly more other complications, driven by higher rates of pericarditis (adjusted, 1.6% vs. 0.8%; $p<.0001$). It is also unclear whether all patients were considered medically eligible for a conventional pacing system. The Aveir pivotal prospective cohort study primary safety and efficacy outcomes at 6 weeks exceeded performance goals for complication-free rate and composite success rate (96.0% and 95.9%, respectively). Results at 6 months were similar. Incidence of major complications was comparable to rates observed in the Micra pivotal trial (4.0%). The 2-year survival estimate of 85.3% is based on Phase 1 performance with the predecessor Nanostim device. Considerable uncertainties and unknowns remain in terms of the durability of the devices and device end-of-life issues. Early and limited experience with the Micra device has suggested that retrieval of these devices is unlikely because in due course, the device

will be encapsulated. There are limited data on device-device interactions (both electrical and mechanical), which may occur when there is a deactivated Micra device alongside another leadless pacemaker or when a leadless pacemaker and transvenous device are both present. Although the Aveir device is specifically designed to be retrieved when therapy needs evolve or the device needs to be replaced, clinical experience with device retrieval has not yet been reported. While the current evidence is encouraging, overall benefit with the broad use of FDA-approved single-chamber transcatheter pacing systems compared with conventional pacemakers has not been shown. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a guideline-based indication for a ventricular pacing system who are medically ineligible for a conventional pacing system, the evidence includes subgroup analysis of pivotal prospective cohort study and a postapproval prospective cohort study for the Micra device.  trials. Information on the outcomes in these subgroups of patients from the postapproval study showed that Micra was successfully implanted in 98% to 99% of cases and safety outcomes were similar to the original cohort. Even though the evidence is limited, and long-term effectiveness and safety are unknown, the short-term benefits outweigh the risks because the complex trade-off of adverse events for these devices needs to be assessed in the context of the life-saving potential of pacing systems in patient's ineligible for conventional pacing systems. There are little data available regarding outcomes associated with other alternatives to conventional pacemaker systems such as epicardial leads or transiliac placement. Epicardial leads are most relevant for the patient who is already going to have a thoracotomy for treatment of their underlying condition (e.g., congenital heart disease). Epicardial leads are associated with a longer intensive care unit stay, more blood loss, and longer ventilation times compared to conventional pacemaker systems. The evidence for transiliac placement is limited to small case series and the incidence of atrial lead dislodgement using this approach in the literature ranged from 7% to 21%. While the evidence is insufficient to determine that the technology results in an improvement in net health outcomes, based on the clinical input obtained in 2019 by BCBS Association to help determine whether the use of leadless cardiac pacemakers for individuals with a guideline-based indication for a ventricular pacing system would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice; the clinical input received by the Heart Rhythm Society (HRS) and Kousik Krishnan, MD, Clinical Cardiac Electrophysiology, Rush University Identified by American College of Cardiology (ACC), clinical input supports the use of Micra transcatheter pacing system for individuals with a guidelines-based indication for a ventricular pacing system who are medically ineligible for a conventional pacing system as this use provides a clinically meaningful improvement in net health outcomes and indicates this use is consistent with generally accepted medical practice in a subgroup of appropriately selected patients when both conditions below are met:

- The patient has symptomatic paroxysmal or permanent high-grade arteriovenous block or symptomatic bradycardia-tachycardia syndrome or sinus node dysfunction (sinus bradycardia or sinus pauses).

- The patient has a significant contraindication precluding placement of conventional single-chamber ventricular pacemaker leads such as any of the following:
    - History of an endovascular or CIED infection or who are very high-risk for infection
    - Limited access for transvenous pacing given venous anomaly, occlusion of axillary veins or planned use of such veins for a semi-permanent catheter or current or planned use of an AV fistula for hemodialysis
    - Presence of a bioprosthetic tricuspid valve.

The current evidence on the use of the Aveir device is limited by a lack of adequate data on quality of life, long-term safety, effectiveness, reliability, and incidence of late device failures and battery longevity. While the device is designed to be retrieved when therapy needs evolve or the device needs to be replaced, there is currently inadequate clinical experience with issues related to devices that have reached end-of-life. Survival data for the currently marketed version of the Aveir device has not been reported. The continued FDA approval of the Aveir transcatheter pacing system is contingent on the results of the Aveir VR Real-World Evidence Study. This post-approval study is designed to evaluate the long-term safety of the Aveir device in a real-world sample of 2100 participants. Both acute and long-term safety will be evaluated as post implant complication-free rates at 30-days and 10-years. Six-month and 10-year reports are due in September 2022 (assessed for available data October 2022 not yet available) and March 2032, respectively. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Professional Guidelines and Position Statements**

**Heart Rhythm Society**

In 2020, the Heart Rhythm Society (HRS), along with the International Society for Cardiovascular Infectious Diseases (ISCVID) and several other Asian, European and Latin American societies, endorsed the European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections.[46,] The consensus states that for patients at high risk of device-related infections, avoiding a transvenous system, and implanting an epicardial system, may be preferential. It makes the following statements regarding leadless pacemakers:

- 'There is hope that ‘leadless’ pacemakers will be less prone to infection and can be used in a similar manner [as epicardial systems] in high-risk patients.'
- 'In selected high-risk patients, the risk of infection with leadless pacemakers appears low. The device also seems safe and feasible in patients with pre-existing [cardiovascular implantable electronic device] infection and after extraction of infected leads.'

**National Institute for Health and Care Excellence (NICE)**
In 2018, the National Institute for Health and Care Excellence (NICE) issued evidence-based recommendations on leadless cardiac pacemaker implantation for adults with brady arrhythmias.

**Recommendations**
Evidence on the safety of leadless cardiac pacemaker implantation for brady arrhythmias shows that there are serious but well-recognized complications. The evidence on efficacy is inadequate in quantity and quality:

- For people who can have conventional cardiac pacemaker implantation, leadless pacemakers should only be used in the context of research.
- For people in whom a conventional cardiac pacemaker implantation is contraindicated following a careful risk assessment by a multidisciplinary team, leadless cardiac pacemakers should only be used with special arrangements for clinical governance, consent and audit or research.

Clinicians wishing to do leadless cardiac pacemaker implantation for brady arrhythmias in people who cannot have conventional cardiac pacemaker implantation should:

- Inform the clinical governance leads in their NHS trusts.
- Ensure that patients and their caretakers understand the uncertainty about the procedure's safety and efficacy compared with conventional pacemaker implantation and provide them with clear written information. In addition, the use of NICE's information for the public is recommended.

**Regulatory Status**
In 2016, the U.S. Food and Drug Administration (FDA) approved the Micra™ Transcatheter Pacing System (Medtronic) for patients who have experienced one or more of the following conditions:

- Symptomatic paroxysmal or permanent high-grade atrioventricular block in the presence of atrial fibrillation.
- Symptomatic paroxysmal or permanent high-grade atrioventricular block in the absence of atrial fibrillation, as an alternative to dual-chamber pacing, when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy.
- Symptomatic bradycardia-tachycardia syndrome or sinus node dysfunction (sinus bradycardia or sinus pauses), as an alternative to atrial or dual-chamber pacing, when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy.

In 2017, the Nanostim (St. Jude Medical) was pulled from the market because of early battery depletion issues and, as of 2021, is still not available.

In January 2020, the Micra AV Transcatheter Pacing System Model MC1AVR1 and Application Software Model SW044.were approved as a PMA supplement (S061) to the

Micra system described above. The Micra AV includes an enhanced algorithm to provide AV synchronous pacing.

In November 2021, the U.S. FDA issued a letter to health care providers regarding the risk of major complications related to cardiac perforation during implantation of leadless pacing systems. Specifically, the FDA states that "real-world use suggests that cardiac perforations associated with Micra leadless pacemakers are more likely to be associated with serious complications, such as cardiac tamponade or death, than with traditional pacemakers."

In March 2022, the Aveir™ VR Leadless Pacemaker was approved by the U.S. FDA through the premarket approval process (PMA number: P150035) for use in patients with bradycardia and:

- normal sinus rhythm with only rare episodes of A-V block or sinus arrest
- chronic atrial fibrillation
- severe physical disability.

Rate-Modulated Pacing is indicated for patients with chronotropic incompetence, and for those who would benefit from increased stimulation rates concurrent with physical activity.

# PRIOR APPROVAL

Not applicable.

# POLICY

The Micra™ single chamber transcatheter pacing system may be considered **medically necessary** in individuals when both conditions below are met:

1. The individual has symptomatic paroxysmal or permanent high-grade arteriovenous block or symptomatic bradycardia-tachycardia syndrome or sinus node dysfunction (sinus bradycardia or sinus pauses); **and**

2. The individual has a significant contraindication precluding placement of conventional single-chamber ventricular pacemaker leads such as any of the following:
    - History of an endovascular or cardiovascular implantable electronic device (CIED) infection or who are at high risk for infection (individuals with immunosuppression caused by certain infections (HIV), some drugs (daily high dose corticosteroids >20mg/day, cytotoxic drugs [chemotherapy drugs], immunosuppressive drugs for transplantation [Cyclosporine, Imuran) and active radiation therapy.

- Limited access for transvenous pacing given venous anomaly, occlusion of axillary veins or planned use of such veins for a semi-permanent catheter or current or planned use of an AV fistula for hemodialysis
- Presence of a bioprosthetic tricuspid valve.

The Micra™ single chamber transcatheter pacing system is considered **investigational** when the criteria above are not met and all other situations (i.e., individual is eligible for placement of conventional single-chamber ventricular pacemaker leads) because the evidence is insufficient to determine the safety and effectiveness of the technology.

The Aveir™ single chamber transcatheter pacing system is considered **investigational** for all indications because the evidence is insufficient to determine the safety and effectiveness of the technology.

**Policy Guidelines**
As per the U.S. Food and Drug Administration (FDA) label, the Micra Model MC1VR01 pacemaker is contraindicated for patients who have the following types of devices implanted:

- An implanted device that would interfere with the implant of the Micra device in the judgment of the implanting physician
- An implanted inferior vena cava filter
- A mechanical tricuspid valve
- An implanted cardiac device providing active cardiac therapy which may interfere with the sensing performance of the Micra device

As per the FDA label, the Micra Model MC1VR01 pacemaker is also contraindicated for patients who have the following conditions:

- Femoral venous anatomy unable to accommodate a 7.8 mm (23 French) introducer sheath or implant on the right side of the heart (for example, due to obstructions or severe tortuosity)
- Morbid obesity that prevents the implanted device to obtain telemetry communication within <12.5 cm (4.9 in)
- Known intolerance to titanium, titanium nitride, parylene C, primer for parylene C, polyether ether ketone, siloxane, nitinol, platinum, iridium, liquid silicone rubber, silicone medical adhesive, and heparin or sensitivity to contrast medical which cannot be adequately premedicated

As per the FDA label, the Micra Model MC1VR01 pacemaker should not be used in patients for whom a single dose of 1.0 mg dexamethasone acetate cannot be tolerated because the device contains a molded and cured mixture of dexamethasone acetate with the target dosage of 272 µg dexamethasone acetate. It is intended to deliver the steroid to reduce inflammation and fibrosis.

# PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 33274 Transcatheter insertion or replacement of permanent leadless pacemaker, right ventricular, including imaging guidance (eg, fluoroscopy, venous ultrasound, ventriculography, femoral venography) and device evaluation (eg, interrogation or programming), when performed
- 33275 Transcatheter removal of permanent leadless pacemaker, right ventricular, including imaging guidance (eg, fluoroscopy, venous ultrasound, ventriculography, femoral venography), when performed

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# POLICY HISTORY

| Date | Reason | Action |
|---|---|---|
| November 2022 | Annual Review | Policy Revised |
| November 2021 | Annual Review | Policy Revised |
| November 2020 | Annual Review | Policy Revised |
| November 2019 | Annual Review | Policy Revised |
| November 2018 | Annual Review | Policy Revised |
| November 2017 | Annual Review | Policy Revised |
| November 2016 | Annual Review | Policy Revised |
| December 2015 | | New Policy |

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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