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Leadless Cardiac Pacemakers

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Disclaimer

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Coverage

Ventricular Pacing
The Micra™ VR or Aveir™ VR (see Policy Guidelines) single-chamber transcatheter pacing system **may be considered medically necessary** in individuals when **BOTH** conditions below are met:

- The individual has high-grade arteriovenous (AV) block in the presence of atrial fibrillation or has significant bradycardia and:
    - Normal sinus rhythm with rate episodes of 2nd degree or 3rd degree AV block or sinus arrest; or
    - Chronic atrial fibrillation; or
    - Severe physical disability; AND
- 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; or

- 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 arteriovenous (AV) fistula for hemodialysis; or
- Presence of a bioprosthetic tricuspid valve.

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

- The individual has a high-grade AV block (see Policy Guidelines) in the presence of atrial fibrillation or has significant bradycardia and:
  - Normal sinus rhythm with rate episodes of 2nd degree or 3rd degree AV block or sinus arrest; or
  - Chronic atrial fibrillation; or
  - Severe physical disability; or
  - There is an indication for AV synchronous (VDD) pacing and the individual may benefit from maintenance of AV synchronous ventricular pacing (see Policy Guidelines); AND
- The individual has a significant contraindication precluding placement of convention 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 (See Policy Guidelines); or
  - 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 arteriovenous fistula (AV) fistula for hemodialysis; or
  - Presence of a bioprosthetic tricuspid valve.

The Micra™ and Aveir™ single-chamber transcatheter pacing systems **are considered experimental, investigational and/or unproven** in all other situations in which the above criteria are not met.

Atrial Pacing

Atrial leadless pacing systems (e.g., Abbott Aveir™ AR) **are considered experimental, investigational and/or unproven** for all indications.

Dual Chamber Pacing

Dual-chamber transcatheter pacing systems (Aveir™ DR) **are considered experimental, investigational and/or unproven** for all indications.

Policy Guidelines

Device Contraindications

Aveir™ Leadless Pacemaker

As per the FDA label, the Aveir™ Leadless Pacemaker Model LSP112V (right ventricular), LSP201A (right atrial) and LSP202V (right ventricular) are contraindicated in the following situations:

- Use of any pacemaker is contraindicated in individuals with a co-implanted implantable cardioverter-defibrillator because high-voltage shocks could damage the pacemaker and the pacemaker could reduce shock effectiveness.
- Single-chamber ventricular demand pacing is relatively contraindicated in individuals who have demonstrated pacemaker syndrome, have retrograde ventriculoatrial conduction, or suffer a drop in arterial blood pressure with the onset of ventricular pacing.
- Programming of rate-responsive pacing is contraindicated in individuals with intolerance of high sensor-driven rates.
- Use is contraindicated in individuals with an implanted vena cava filter or mechanical tricuspid valve because of interference between these devices and the delivery system during implantation.
- Individuals with known history of allergies to any of the components of this device may suffer an allergic reaction to this device. Prior to use, the recipient should be counseled on the materials contained in the device and a thorough history of allergies must be discussed.

The Aveir™ Leadless Pacemaker is conditionally safe for use in the magnetic resonance imaging (MRI) environment when used according to the instructions in the MRI-Ready Leadless System Manual (which includes equipment settings, scanning procedures, and a listing of conditionally approved components). Scanning under different conditions may result in severe patient injury, death, or device malfunction.

<u>Aveir DR Leadless System (dual-chamber)</u>
Contraindications for the Aveir™ DR are the same as the Aveir™ Leadless Pacemaker (single chamber) (Listed above).

<u>Micra™ Leadless Pacemakers</u>
As per the U.S. Food and Drug Administration (FDA) label, the Micra Model MC1VR01 (Micra VR) and Model MC1AVR1 (Micra AV) pacemakers are contraindicated for individuals 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 and Model MC1AVR1 pacemakers are also contraindicated for individuals 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™ pacemaker should not be used in individuals 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.

For the MRI contraindications for individuals with a Micra MRI device, refer to the Medtronic MRI Technical Manual.

As per the FDA label, some individuals will not benefit from the AV synchronous (VDD) mode supported by the Micra Model MC1AVR1 pacemaker. Individuals with the following conditions should instead be considered for a dual-chamber transvenous pacing system:
- Sinus node dysfunction;
- High sinus rates requiring atrial tracking;
- Weak atrial contraction;
- Symptoms during loss of atrioventricular (AV) synchrony;
- Frequent premature atrial or ventricular contractions.

Description

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 two components: a pulse generator (i.e., battery component) and electrodes (i.e., leads). The pulse generator consists of 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 one lead is placed, typically in the right ventricle. In dual-chamber pacemakers, two 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. (1) Implantable pacemakers are considered life-sustaining, life-supporting class III devices for patients with a variety of bradyarrhythmias. Pacemaker systems have matured over the years with well-established, acceptable performance standards. As per the 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 (PCT) 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. These data are summarized in Table 1. 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 two decades. (2) 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. (3) Cohen et al. (2001) reported outcomes from a retrospective analysis of 123 patients who underwent 207 epicardial lead implantations. (4) 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).

Doll et al. (2008) reported results of a randomized controlled trial comparing epicardial implantation vs. conventional pacemaker implantation in 80 patients with indications for cardiac resynchronization therapy. (5) 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 two groups at discharge but longer in the epicardial group during follow-up. Adverse events were also similar in the two groups. The following events were experienced by one (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). (6) Pacing indications included AV block in three patients and sinus node dysfunction in two. 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 six months after implant with only partial resolution of pacing-induced cardiomyopathy. Tsutsumi et al. (2010) reported 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. (7)

Table 1. Reported Complication Rates with Conventional Pacemakers

Complications	**Rates, % (8-10)[a]**
Traumatic complications	
RV perforation	0.2-0.8
RV perforation with tamponade	0.07-0.4
Pneumo(hemo)thorax	0.7-2.2
Pocket Complications	
Including all hematomas, difficult to control bleeding, infection, discomfort, skin erosion	4.75
Including only those requiring invasive correction or reoperation	0.66-1.0
Lead-related complications	
Including lead fracture, dislodgement, insulation problem, infection, stimulation threshold problem, diaphragm or pocket stimulation, other	1.6-3.8
All system-related infections requiring reoperation or extraction	0.5-0.7

Adapted from Food and Drug Administration executive summary memorandum. (2016) (11)

[a] Rates are for new implants only and ventricular single-chamber devices when data were available. Some rates listed in this column are for single-and dual-chamber devices when data were not separated in the publication. Note that Micra™ transcatheter pacing system is a single-chamber device.
RV: right ventricle.

Potential Advantages of Leadless Cardiac Pacemakers over Conventional Pacemakers
The potential advantages of leadless pacemakers fall into three 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. (12)

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.

Atrioventricular Synchrony
The Micra AV device supports maintenance of atrioventricular (AV) synchrony by sensing atrial mechanical contraction (A4 signal). Several small-cohort studies have investigated the relationship between parameters (e.g., clinical and echocardiographic) and A4 signal amplitude. Briongos-Figuero et al. (2023) investigated clinical and echocardiographic predictors of optimal AV synchrony, defined as ≥85% of total cardiac cycles being synchronous, in individuals with successful Micra AV implant (N=43). The authors performed univariate analyses followed by multivariate analysis. They found diabetes and chronic obstructive pulmonary disease to be associated with A4 signal amplitude, however no echocardiographic parameters were associated with A4 signal amplitude. (13) Troisi et al. (2024) studied the relationship between echocardiographic parameters and A4 signal amplitude in individuals implanted with Micra AV (N=21). The authors concluded echocardiographic parameters, particularly related to left atrial function, may be related to successful AV synchrony. (14) Kawatani et al. (2024) et al studied predictors of AV synchrony in individuals with Micra AV implants (N=50). Participants were stratified into 2 groups, high and low A4 amplitude. In a multivariate analysis, maximum deflection index was the only parameter associated with low A4 amplitude. (15) These studies were exploratory and results among the studies were inclusive. More research is in larger

cohort studies is needed to produce more conclusive evidence on parameters that are predictive of AV synchrony.

Battery Life and Device Retrieval

Currently, real-world evidence of long-term battery life for leadless pacemakers is limited. Breeman et al. (2023) studied the battery life of the Micra VR after implantation (N=153). The manufacturer's predicted battery life for the Micra VR is 12 years. Using mixed models to assess changes in electrical parameters over time, the authors concluded that for a majority of individuals the expected batter longevity is >8 years. (16) Due to the limited lifespan of leadless pacemakers, they are designed to be retrievable (e.g., the helix fixation design of the Aveir devices). However, evidence on the safety and success of device retrieval is limited to case reports. (17-19)

Anatomical Placement

Li et al. (2023) studied different anatomical placements in the ventricular septum of the Micra VR (N=15) and found no impact on safety or electrical characteristics of the device. (20) In a large cohort study in individuals with Micra AV or Micra VR implants (N=358) by Shantha et al. (2023), the authors found apical septum placement was associated with a higher risk of pacing-induced cardiomyopathy compared to mid/high septum placement. (21) Larger randomized studies are needed to confirm how anatomical placement of the device impacts safety and effectiveness.

Leadless Cardiac Pacemakers in Clinical Development

Leadless pacemakers are self-contained in a hermetically sealed capsule. The capsule houses the 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 ten years, depending on the programmed parameters. (11)

Four systems are currently being evaluated in clinical trials: 1) the Micra™ Transcatheter Pacing System (Medtronic), 2) the Aveir VR Leadless Pacemaker (Abbott; formerly Nanostim, St. Jude Medical); 3) the Aveir DR Dual Chamber Leadless Pacemaker System (Abbott); and 4) the WiCS Wireless Cardiac Stimulation System (EBR Systems). The first three 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 Micra and Aveir 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 devices, there is a screw-in helix that penetrates into the myocardium. In the Micra and Aveir devices, the cathode is steroid eluting and delivers pacing current; the anode is located in a titanium case. The fourth 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. (11)

Of these four, only the Micra and Aveir VR single-chamber transcatheter pacing systems and the Aveir dual-chamber transcatheter pacing system are approved by the FDA and commercially available in the U.S. Multiple clinical studies of the Aveir predecessor device, Nanostim, have been published (1, 22-26) 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. (27)

The Micra™ is about 25.9 mm in length and introduced using a 23 French catheter via the femoral vein to the right ventricle. It weighs about 1.75 grams and has an accelerometer-based rate response. (28)

The Aveir VR (ventricular) 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. (29)

The atrial Aveir DR is 32.3 mm in length and weighs about 2.1 grams. The ventricular Aveir DR is about 38.0 mm in length and weighs about 2.4 grams. Both are introduced using a 25 French catheter. The system used a temperature-based rate response. (30)

Regulatory Status

In April 2016, the Micra™ transcatheter pacing system (Medtronic) was approved by the FDA through the premarket approval process (PMA number: P150033) for use in patients who have experienced one or more of the following conditions:

- Symptomatic paroxysmal or permanent high-grade arteriovenous block in the presence of atrial fibrillation;
- Paroxysmal or permanent high-grade arteriovenous 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 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. (31) 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.

In June 2023, a premarket approval application supplement with expanded indications to include dual-chamber pacing with the Aveir DR Leadless System was approved by the FDA (PMA number: P150035) for use in individuals with 1 or more of the following permanent conditions:

- Syncope;
- Pre-syncope;
- Fatigue;
- Disorientation.

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

Dual-Chamber Pacing is indicated for individuals exhibiting:

- Sick sinus syndrome;
- Chronic, symptomatic second-and third-degree atrioventricular block;
- Recurrent Adams-Stokes syndrome;
- Symptomatic bilateral bundle branch block when tachyarrhythmia and other causes have been rules out.

In June 2023, the Aveir AR Leadless pacemaker received coverage with evidence development (CED). This CED study utilizes a real-world evidence (RWE) method merging multiple real-world datasets from Abbott and the Center for Medicare Services to assess Aveir AR LP health outcomes among Medicare beneficiaries. The study will enroll all Medicare patients with continuous claims data implanted with the Aveir AR LP or a single-chamber atrial transvenous pacemaker system from any manufacturer.

Rationale

This policy was created in December 2015 with searches of the PubMed database. The most recent literature update was completed through March 14, 2024.

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients, and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Conventional pacemaker systems have been in use for over 50 years and current technology has matured with significant similarities in designs across models. Extensive bench testing data with conventional pacemakers and a good understanding of operative and early postimplant safety and effectiveness are available, which limits the need for clinical data collection to understand their safety and effectiveness with regard to implantation, tip fixation, electrical measures, and rate response. As such, an RCT comparing the leadless pacemakers with conventional pacemakers was not required by the Food and Drug Administration (FDA).

Ventricular Pacing for Individuals Who are Medically Eligible for a 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.

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

Populations

The relevant populations of interest is individuals 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. (32)

Comparators
The following therapy is currently being used to make decisions about managing individuals 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.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies on the currently marketed version of the technology were sought.
- Studies with duplicative or overlapping populations were excluded.

Systemic Reviews

Wu et al. (2023) conducted a systematic review and meta-analysis on the efficacy and safety of leadless pacemakers with atrioventricular synchronous pacing (Tables 2 to 4). (33) Eight prospective and retrospective single-arm observational studies were included in the meta-analyses. In 8 studies atrioventricular (AV) synchrony (AVS) proportion had a pooled mean of 78.9% (95% confidence interval [CI]: 71.9% to 86.0%, N=303). In 4 studies manually optimized reprogramming of AVS was studied. The mean difference between baseline and post-programming AVS was 11.3% (95% CI: 7.0% to 15.7%, p<.01, N=112). In 3 studies left ventricular outflow tract velocity time integral (LVOT-VTI) was compared with the algorithm programmed to VVI and VDD modes. The mean difference was 1.9 cm (95% CI: 1.2 to 2.6 cm, p<.01, N=137). Seven studies (N=351) reported safety endpoints with a total of 22 complications related to the AV algorithm or procedures reported (6.3%). The authors noted several limitations of the meta-analysis: 1) there were no RCTs, 2) the approach to measuring AVS varied among the studies, 3) there was high heterogeneity for the pooled AVS proportion, 4) the studies represented data differently, so data needed to be estimated and transformed to combine, and 5) there were few studies with small cohorts included. The authors concluded the results demonstrated leadless pacemakers with AVS are effective and safe.

Table 2. Trial Included in Systematic Review and Meta-analyses

Trials	Systematic Reviews/Meta-analyses
	Wu et al. (2023) (33)
Neugebauer et al. (2022) (34)	•
Mechulan et al. (2022) (35)	•
Kowlgi et al. (2022) (36)	•
Chinitz et al. (2022) (37); AccelAV	•
Briongos-Figuero et al. (2022) (38)	•
Arps et al. (2021) (39)	•
Steinwender et al. (2020) (40); MARVEL 2	•
Chinitz et al. (2018) (41); MARVEL	•

AccelAV: Accelerometer Sensing for Micra AV; CED: coverage with evidence development; MARVEL: Micra Atrial tRacking using a Ventricular accELerometer.

Table 3. Systematic Review and Meta-analyses Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Wu et al. (2023) (33)	To September 2022	8	Patients implanted with Micra AV Leadless Pacemaker	464 (20 to 152)	Prospective and retrospective observational studies	NR

NR, not reported.

Table 4. Systematic Review and Meta-analyses Results

Study	AVS proportion (%)	Optimized AVS proportion (%)	Change in LVOT-VTI between VVI and

			VDD pacing modes (cm)
Wu et al. (2023) (33)			
Total N	303	112	137
Pooled effect (95% CI)	MRAW, 78.93 (71.87 to 85.98)	MD, 11.33 (6.96 to 15.71)	MD, 1.93 (1.24 to 2.61)
I^2(p)	90% (<.01)	13% (.33)	0% (.85)

AVS: atrioventricular synchrony; CI: confidence interval; LVOT-VTI: left ventricular outflow tract velocity time integral; MD: mean difference; MRAW: raw mean.

Randomized Controlled Trials

Micra Leadless Pacemaker

Garweg et al. (2023) conducted a prospective, un-blinded, randomized, noninferiority, single center study (N=51) comparing outcomes in individuals implanted with a single-chamber Micra leadless pacemaker (n=27) or a conventional single-chamber ventricular pacemaker (n=24). (42) The primary endpoints were related to mechanical outcomes, including change in left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) during a 12-month follow up period. At 12 months, both groups showed similar worsening in left ventricular function. The change in LVEF was -10 ± 7.3% in the Micra group and -13.4 ± 9.9% in the conventional group (p=.218). The change in GLS was 5.7 ± 6.4 in the Micra group and 5.2 ± 3.2 in the conventional group (p=.778). For the secondary endpoints, the Micra group had no significant change in tricuspid (p=.195) and mitral (p=.460) valve function and the conventional group had significant worsening in tricuspid (p=.001) and mitral (p=.017) valve function over 12 months. Change in valve function over 12 months between the groups was significantly different for the tricuspid valve (p=.009) and not significantly different for the mitral valve (p=.304). Median N-terminal-pro hormone B-type natriuretic peptide levels at 12 months was lower in the Micra group (970 pg/dL) compared to the conventional group (1394 pg/dL) (p=.041). For electrical performance, over 12 months the Micra group had higher impedance (p<.001) and lower pacing threshold (p<.001) compared to the conventional group, however there was no interaction between time and intervention. All implant procedures for both groups were successful, with no acute major complications. The authors conclude that Micra is non inferior to conventional pacemakers, with comparable impacts on ventricular function and less valvular dysfunction. Study characteristics and key results are summarized in Tables 5 and 6.

Table 5. Summary of Key RCT Characteristics

Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**	**Interventions**	
					Micra Leadless Pacemaker	*Conventional Singe-Chamber Ventricular Pacemaker*

Garweg et al. (2023) (42)	NR	1	2018-2020	Patients ≥18 years old with a Class I or II indication for a single-chamber ventricular pacemaker	n=27	n=24

NR: not reported; RCT: randomized controlled trial.

Table 6. Summary of Key RCT Results

Study	**LVEF(%)**	**GLS(%)**
Barweg at el. (2023) (42)	*Change from baseline at 12 months*	*Change from baseline at 12 months*
N	51	51
Micra Leadless Pacemaker (n=27)	−10.3 ± 7.3	5.7 ± 6.4
Conventional Single-Chamber Ventricular Pacemaker (n=24)	−13.4 ± 9.9	5.2 ± 3.2
p-value	.218	.778

GLS: global longitudinal strain; LVEF: left ventricular ejection fraction; RCT: randomized controlled trial.

Nonrandomized Controlled Trials

Micra Leadless Pacemaker

Pivotal Trial

The pivotal investigational device exemption (IDE) trial was a prospective single cohort study that enrolled 744 patients with class I or II indications for implantation of a single-chamber ventricular pacemaker based on national guidelines. Details on the design (43) and results of the IDE trial have been published. (44-46) Trial characteristics and results at six months are summarized in Tables 2 and 3, respectively. System performance from the pivotal trial has been published, (47) 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 the average age was 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 the 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. (46)

The IDE trial had two 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. (28) 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." (28)

Safety and efficacy results of the IDE trial are summarized in Table 8. 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%. (46)

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. (45) 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; $p < 0.001$) and a mean Mental Component Scale score of 50.7 (SD=12.2; $p < 0.001$) 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=0.001). (46) Because there were differences in baseline patient characteristics between the two 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=0.288). (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. (11)

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. (48) 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 only 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. (48) 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. (49) 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). (50) 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%) actual 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 three percutaneous retrievals and one 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 two 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 (actual 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<0.001).

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. (28) 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. (48)

Study characteristics and results at one year (reported in the FDA documents and published) are summarized in Table 7 and 8, 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 8 summarize the data at 30 days published by Roberts et al. (2017) (51) and El-Chami et al. (2018) (52, 53) 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. (51) 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. (54) 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. (55)

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). (52) The reduction in major complications compared to historical controls was primarily driven by a significant 74% (95% CI, 54 to 85; p=0.0001) relative risk reduction in system revisions and 71% (95% CI, 51 to 83; p=0.0001) 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.

El-Chami et al. (2024) reported results on a 5-year follow-up of the Micra PAR study. (56) Major complication rates for individuals with an attempted Micra VR implant procedure (n=1809) was 4.47% (95% CI, 3.6% to 5.5%) at 60 months and there were no Micra removals due to infection reported during follow-up. The authors concluded that low rates of major complications, low incidence of infection, and low rates of system revisions have been reported in long-term follow-up. Study characteristics and results are summarized in Tables 7 and 8.

Roberts et al. (2023) conducted a prospective, single-arm study of the Micra Acute Performance European and Middle Eastern (MAP EMEA) registry and compared results to the IDE and PAR studies. (57) The primary endpoint was 30-day major complication rate. For the MAP EMEA individuals (N=928) at 30 days there were 24 major complications in 24 individuals (2.59%; 95% CI, 1.66% to 3.82%). Of these events, 10 were at the groin and puncture site, 6 cardiac effusion/perforation events, 4 device pacing issues, 3 infection events (2 resulting in system revisions), and 1 event of hemodynamic instability. Through study follow-up after 30 days (mean duration, 9.7 ± 6.5 months), there were 11 more major complications in 9 individuals adjudicated as related to the Micra VR device or procedure. The MAP EMEA cohort, compared to the IDE (N=726) and PAR (N=1811) study cohorts, had less heart failure (8.3% vs. 18.0% vs. 13.0%, p<.001) and coronary artery disease (19.9% vs. 28.2% vs. 22.0%, p<.001) and were more likely to have renal dysfunction (28.9% vs. 20.5% vs. 21.5%, p<.001) and be on dialysis (10.2% vs. 3.9% vs. 7.9%, p<.001). However, a limitation of this comparison is the median duration of follow-up varied among the MAP EMEA, IDE, and PAR study cohorts (9.6, 19.6, and 34.2 months, respectively). Study characteristics and results are summarized in Tables 7 and 8.

Piccini et al. (2021) published initial data from the ongoing Longitudinal Coverage with Evidence Development Study on Micra Leadless Pacemakers (Micra CED). (58) 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 7 and 8.

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. (59) 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 7 and 8.

Boveda et al. (2023) reported 2-year outcomes from the Micra CED study in a subgroup of individuals at higher risk of pacemaker complications. (60) Participants were considered high-risk if they had a diagnosis of chronic kidney disease Stages 4 to 5, end-stage renal disease, malignancy, diabetes, tricuspid valve disease (TVD), or chronic obstructive pulmonary disease (COPD) 12 months prior to implant. They compared outcomes between high-risk individuals with leadless-VVI pacemakers (n=9858) and transvenous-VVI pacemakers (n=12157). The leadless-VVI group had fewer complications compared to the transvenous-VVI group in those with malignancy (HR, 0.68; adjusted CI, 0.48 to 0.95), diabetes (HR, 0.69; adjusted CI, 0.53 to 0.89), TVD (HR, 0.60; adjusted CI, 0.44 to 0.82), and COPD (HR, 0.73; adjusted CI, 0.55 to 0.98), had fewer reinterventions in those with diabetes (HR, 0.58; adjusted CI, 0.37 to 0.89), TVD (HR, 0.46; adjusted CI, 0.28 to 0.76), and COPD (HR, 0.51; adjusted CI, 0.29 to 0.90), and lower rates of combined outcome of device complications and select reinterventions in those with malignancy (HR, 0.52; adjusted CI, 0.32 to 0.83), diabetes (HR, 0.52; adjusted CI, 0.35 to 0.77), TVD (HR, 0.44; adjusted CI, 0.28 to 0.70), and COPD (HR, 0.55; adjusted CI, 0.34 to 0.89). The authors conclude that in this real-world study, individuals with leadless pacemakers had lower 2-year complications and reinterventions rates than individuals with transvenous pacemakers in several high-risk subgroups.

Three-year outcomes from the Micra Coverage with Evidence Development study were published by Crossley et al. in 2023. (61) Patients implanted with leadless pacemakers had a 32% lower rate of chronic complications (HR, 0.68; 95% CI, 0.59 to 0.78; p<.001) and a 41%

lower rate of any reinterventions compared to patients receiving a transvenous pacemaker (HR, 0.59; 95% CI, 0.44 to 0.78; p=.0002). Use of a leadless system was also associated with a 49% lower rate (p=.01) of upgrades to a dual-chamber system and a 35% lower rate (p=.002) of upgrades to cardiac resynchronization therapy. Heart failure hospitalizations at 3 years were slightly, but significantly lower in adjusted time-to-event models (HR, 0.90; 95% CI, 0.83 to 0.97; p=.005) in patients receiving a leadless system. All-cause mortality rates at 3 years between leadless and transvenous systems were not significantly different after accounting for differences in baseline characteristics (HR, 0.97; 95% CI, 0.92 to 1.03; p=.32). No significant differences in the composite endpoint of time to heart failure hospitalization or death were observed for the original full cohort (p=.28) or in a subgroup of patients without a history of heart failure (p=.98). Study characteristics and results are summarized in Tables 7 and 8.

Crossley et al. (2024) reported outcomes from the Micra AV Coverage with Evidence Development study comparing individuals implanted with Micra AV (n=7471) to a comparator cohort (n=107,800) of individuals implanted with a dual-chamber transvenous pacemaker regardless of pacing indication. (62) At 30 days, the adjusted overall complications were 8.6% for Micra AV group and 11.0% for dual chamber transvenous group (p<.0001) and the adjusted all-cause mortality was 6.0% for the Micra AV group and 3.5% for the dual chamber transvenous group (p<.0001). At 6 months, the Micra AV group had significantly lower rates of complications (adjusted HR, 0.50; 95% CI, 0.43 to 0.57; p<.0001), lower reinterventions (adjusted HR, 0.46; 95% CI, 0.36 to 0.58; p<.0001), and higher all-cause mortality (adjusted HR, 1.69; 95% CI, 1.57 to 1.83; p<.0001) compared to the dual chamber transvenous group. The authors concluded that leadless pacemakers with AV synchronous pacing demonstrated safety and efficacy. The authors noted limitations to the study. First, Medicare claims data was used, which is a secondary database without traditional clinical adjudication. Second, the comparator cohort included all individuals regardless of pacing indications, because it could not be reliably determined from the data. Study characteristics and results are summarized in Tables 7 and 8.

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. (63) 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%). (64) 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.

Maclean et al. (2023) conducted a retrospective study of data from the MAUDE database for events related to Micra tine fracture and damage. (65) Of the 4241 medical device reports, these included 2104 Micra VR and 2167 Micra AV reports. After duplicates were excluded, there were 230 reports including terms "fracture" and "tine." There were 7 reports of tine fracture and 19 reports of tine damage. Clinical signs and symptoms were reported in 2 of the 7 (29%) tine fracture cases and 4 of 19 (21%) of the tine damage cases. The authors concluded there is a low frequency of tine fracture and tine damage reports with the tine-based fixation mechanism of the Micra leadless pacing system.

Multiple studies have analyzed data from the International Leadless Pacemaker Registry (i-LEAPER), a European, multicenter, open-label, independent, and physician-initiated observational registry of the Micra leadless pacemaker devices. Mitacchione et al. (2023) used i-LEAPER data to investigate outcomes of leadless pacemaker implantation following transvenous lead extraction at a median follow-up of 33 months. (66) The study cohort (N=1179) was grouped by those with leadless pacemaker implantation after transvenous lead extraction (TLE) (n=184) or de novo (n=995). There was no difference in leadless pacemaker-related major complications between TLE (1.6%) and de novo (2.2%) (p=.785) or all-cause mortality between TLE (5.4%) and de novo (7.8%) (p=.288). Pacing threshold was higher in the TLE group compared to the de novo group at implantation and follow-up. The authors noted that when the leadless pacemaker was deployed at a different right ventricular location than were the previous transvenous right ventricular lead was extracted, there was a lower proportion of individuals with high pacing threshold at implantation through 12-months follow-up. In another study by Mitacchione et al. (2023) using the i-LEAPER database, they assessed sex differences in leadless pacemaker implantation. (67) The authors noted that of the overall population (N=1179), 64.3% were male. At median follow-up (25 months), female sex was not associated with leadless pacemaker-related major complications (HR, 2.03; 95% CI, 0.70 to 5.84; p=.190) or all-cause mortality (HR, 0.98; 95% CI, 0.40 to 2.42; p=.960). The authors conclude that females underrepresented in the study, but had comparable safety and efficacy outcomes to males.

Lenormand et al. (2023) conducted a retrospective observational study on the efficacy and safety of leadless cardiac pacing. (68) Individuals (N=400) implanted with Micra VR (n=328) and Micra AV (n=72) were included in the analysis. The pacing threshold was similar between groups and remained stable through follow-up. There was no difference between median chronic pacing threshold between Micra VR (0.5 V) and Micra AV (0.5 V) (p=.87). In the overall population there were 14 individuals (3.5%) with major perioperative complications, 93% of which were in the Micra VR group. There were 116 deaths (29%) during follow-up, with mortality rates of 18% and 55% at 1 and 5 years, respectively. Pacemaker syndrome occurred in 6 (1.8%) individuals in the Micra VR group and no cases in the Micra AV group (p=.60). Pacing-induced cardiomyopathy occurred in 4 (1.2%) individuals in the Micra VR group and 2 (2.8%) individuals in the Micra AV group (p=.30). Overall, the authors conclude leadless pacing is safe. However, this study is limited as a retrospective observational study and it did not have a comparison conventional transvenous cardiac pacing group.

Strik et al. (2023) evaluated the safety and efficacy of Micra VR in young adults between 18 and 40 years (N=35) in a multicenter, retrospective, observational study. (69) The primary safety endpoint was freedom from system-related or procedure-related major complications at 6 months. All patients met the primary safety endpoint at 6 months. During follow-up (26 ± 15 months), there were 3 deaths. The authors note these were not related to device implantation or malfunction. The authors conclude the results demonstrated favorable safety for the Micra VR. However, this study is limited by its small sample size and retrospective design.

Shah et al. (2023) conducted a retrospective study reporting results from the Pediatric and Congenital Electrophysiology Society (PACES) Transcatheter Leadless Pacemakers (TLP) registry. (70) Individuals (N=63) were ≤21 years of age and met a class I or II indication for pacemaker implantation for a Micra device. Implantation was successful in 62 (98%) of the participants. During the follow-up period (mean, 9.5 ± 5.3 months), there were 10 (16%) complications including 1 cardiac perforation/pericardial effusion, 1 nonocclusive femoral venous thrombus, and 1 retrieval and replacement of TLP due to high thresholds. There were no deaths or device-related infections reported during the study period.

Ando et al. (2023) studied the safety and performance of the Micra VR in the Micra Acute Performance (MAP) Japan cohort (N=300). (71) Within 30 days of implantation, there were 11 major complications in 10 individuals (3.33%; 95% CI, 1.61 to 6.04). These included 3 cardiac effusions/perforations, 2 events at the groin puncture site, 2 cases of deep vein thrombosis, and 4 pacing issues leading to system modifications. There were 2 deaths within 30 days of implantation, and a total of 22 deaths during the 12-month study period. The author concluded the safety and performance observed in this cohort was comparable to other global Micra trials. Study characteristics and results are summarized in Tables 7 and 8.

Racine et al. (2023) conducted a single center, retrospective study of individuals implanted with a Micra only (n=72) or a Micra and concomitant or delayed AVNA (n=12). (72) Two patients in the Micra with AVNA group had acute pacing threshold, requiring device retrieval. This was a

single center study with a small sample size, so further evidence is needed to investigate the safety of implantation of Micra with AVNA.

Two retrospective studies have investigated implantation of Micra devices after cardiac surgery and valve interventions. Kassab et al. (2024) studied individuals (N=9) who underwent Micra AV implantation within 30 days post-transcatheter aortic valve replacement. (73) There were no procedural complications and at follow-up (mean, 353 days) capture threshold and lead impedance remained stable. Huang et al (2023) studied individuals (N=78) who received Micra VR (n=40) or Micra AV (n=38) implants who had undergone cardiac surgery (n=50) or transcatheter structural valve interventions (n=28). (74) During 1-year follow up, there was 1 (1.3%) femoral access site hematoma requiring evacuation. Within 30 days, 4 (5.1%) patients were rehospitalized and 3 (3.8%) patients died. More evidence is needed to determine the safety of leadless pacemaker implantation after cardiac surgery and valve interventions. The authors of both papers noted several clinical characteristics and age contributed to the decision to implant leadless pacemakers instead of transvenous pacemakers. However, it is unclear whether these individuals were considered medically eligible for a conventional transvenous pacemaker.

Atrioventricular Synchrony

Chinitz et al. (2022) conducted a prospective, single-arm study (AccelAV) at 20 sites in the United States and Hong Kong to assess the efficacy of the Micra AV leadless pacemaker in promoting atrioventricular synchrony (AVS) in adults with a history of atrioventricular (AV) block (n=157). (37) This device uses an accelerometer and detection algorithm to mechanically sense atrial contractions to facilitate VDD pacing and AVS in individuals with normal sinus function. Based on a preliminary feasibility study (MARVEL 2), (40) a sample size of 150 individuals was expected to provide at least 50 individuals with complete AV block and normal sinus function to permit estimation of AVS. Micra AV implantation and completion of the 1-month study visit was achieved by 139 individuals, of which 54 (mean age, 77 years; 55.6% female) comprised the intended use population with a predominant heart rhythm of complete AV block with normal sinus rhythm. The primary endpoint was the rate of AVS during a 20-minute resting period at 1-month postimplant in these patients. Atrioventricular synchronous pacing was defined as a ventricular marker preceding a P wave within 300 ms, regardless of the underlying cardiac rhythm. Secondary endpoints included stability of AVS during rest between 1 and 3 months, percent AVS during a 24-hr ambulatory period at 1 months and change in stroke volume. Quality of life was also measured with the EQ-5D-3L health status assessment. At 1 month, AVS percentage at rest was 85.4% (95% CI, 81.1% to 88.9%; median, 90.0%) during VDD pacing, with 85.2% of patients achieving >70% resting AVS. At the 3-month visit, 37/54 remained in the same rhythm. Among these subjects, no significant change in AVS synchrony was detected (p=.43) between the 3-month (mean, 84.1%; 95% CI, 78.3% to 88.6%) and 1-month visits (mean, 84.1%; 95% CI, 81.2% to 89.9%). At the 1-month visit, average 24-hour ambulatory AVS was 74.5% (95% CI, 70.4% to 78.2%). EQ-5D-3L health status scores significantly improved by 0.07 points between baseline and 3 months (p=.031) among patients with complete AV block and normal sinus function. Ambulatory AVS percentage significantly increased from 71.9% to 82.6% (p<.001) in twenty patients who participated in a substudy at a

mean follow-up of 9.5 months designed to characterize the impact of optimized device programming. Improvement in AVS was most evident during elevated sinus rates between 80 and 110 bpm. In the safety cohort (n=152), there were 14 major complications, including 4 pericardial effusions and 2 heart failure events. One pericardial effusion resulted in perforation and death in a 92-year-old woman with high baseline risk. A second death was reported in an 83-year-old man at 127 days postimplant but was not considered system- or procedure-related. No device upgrades and 1 device explantation and replacement was reported during follow-up. Study interpretation is limited by lack of a comparator group and short duration of follow-up. The ongoing Micra AV Post-Approval Registry (NCT04253184) has follow-up planned through 3 years. The investigators also noted that the AVS percentage required to maintain a clinical benefit over time is unknown, but likely is not 100%.

Garweg et al. (2023) conducted a real-world assessment of AV synchrony in leadless pacemakers. (75) They first conducted a retrospective analysis of participants from the MARVEL 2 study with persistent third-degree AV block and normal sinus rhythm (n=40). The median atrial mechanical sensed-ventricular pacing (%AM-VP) was 79.1%, with a range of 21.6% to 95.0%, and was highly correlated with AVS measured from surface electrocardiogram (R^2 = 0.764, p<.001). The authors also conducted a large real-world analysis of individuals with Micra AV implants enrolled in the CareLink database with devices programmed to VDD mode (n=4384). They found that ventricular pacing exceeded 90% in 37.9% (n=1662) of these participants and was near 100% in 15.7% (n=689) of these participants. Overall, the authors concluded the results demonstrated stable AVS over time.

Lenormand et al. (2023) conducted a retrospective study comparing the Micra VR and AV devices in individuals with sinus rhythm and complete atrioventricular block (N=93). (76) Between the VR (n=45) and AV (n=48) groups mean ventricular pacing burden was comparable (77% vs. 82%; p=.38), and there were more cases of pacemaker syndrome in the VR compared to AV group (5 patients vs. 0 patients; p=.02). Atrioventricular synchrony was assessed in the AV group. Median total AVS was 79% and there was poor A4 sensing in 7 (15%) of patients. The authors conclude that the Micra AV was able to provide AVS in most patients and was associated with no cases of pacemaker syndrome. However, this study is limited by it's retrospective design and small sample size. More evidence is needed to compare the effectiveness and safety of the Micra VR and AV devices.

<u>Aveir Leadless Pacemaker</u>

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. (29) Primary results from the IDE trial have been summarized in a published research correspondence (27) and FDA documents. (29) Trial characteristics and results through 6 and 12 months are summarized in Tables 7 and 8, 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 8. 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. (28) 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%.

Reddy et al. (2023) reported 1-year outcomes from the LEADLESS II IDE trial. (77) Confirmatory safety and efficacy endpoints at 1 year were both met for European regulatory approval, including freedom from device-or-procedure-related complications in 93.2% of patients (95% CI, 88.7% to 95.9%), compared with a performance goal of 83%, and a composite success rate of 95.1% (95% CI, 91.2% to 97.6%), compared with a performance goal of 80%. Most complications (11 of 15) were reported within the first 3 days post-implantation, including 4 cardiac tamponade events, 3 premature deployments with or without device migration, 2 access site bleeding events, 1 pulmonary embolism, and 1 case of deep vein thrombosis. Four long-term complications were reported between 3.8- and 9.5-months post-implantation, including 2 cases of heart failure and 2 cases of pacemaker-induced cardiomyopathy. Based on the device-use conditions in this analysis cohort, the investigators estimate that mean device battery longevity is 17.6 ± 6.6 years (95% CI, 16.6 to 18.6).

Santobuono et al. (2023) presented a case report of a Micra AV with a sudden battery malfunction, which resulted in successful extraction and replacement with a new device in the

right ventricle. (78) The authors noted, to their knowledge, this is the first case of a sudden battery failure not related to elevated pacing threshold.

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 7. Summary of Key Nonrandomized Trial Characteristics

Study; Trial	Study Type	Country	Dates	Participants	Treatment	Follow-Up, months
Micra						
Reynolds et al. (2016) (46); 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) (51); El-Chami et al. (2018) (52, 53); NCT02536118; El-Chami et al. (2024) (56); 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] and 1809[c])	1.8[a] 6.8[b] 60[c]
Piccinni et al. (2021) (58)	Prospective Medicare registry	United States	2017-2018	All Medicare patients implanted with a leadless single-	Micra pacemaker (n=5746); Transvenous pacemaker (n=9662)	6

				chamber pacemaker or transvenous single-chamber pacemaker with at least 12 months of continuous Medicare enrollment prior to implantation		
El-Chami et al. (2022) (59)	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
Crossley et al. (2023) (61)	Prospective Medicare registry	United States	2017-2018	All Medicare patients implanted with a leadless single-chamber pacemaker	Micra pacemaker (n=6219); Transvenous pacemaker (n=10,212)	36

				or transvenous single-chamber pacemaker with at least 12 months of continuous Medicare enrollment prior to implantation		
Chinitz et al. (2022) (37)	Prospective single cohort	United States and Hong Kong	2020-2021	Adults with a history of AV block or complete AV block and normal sinus rhythm implanted with the Micra AV leadless pacemaker	Micra AV pacemaker (N=157) Micra AV pacemaker in adult with complete AV block and normal sinus rhythm (n=54)	3
Roberts et al. (2023) (57)	Prospective single arm	14 countries in Europe and the Middle East	2018-2020	Patients intended to be implanted with a market approved Micra VR device (MC1VR01)	Micra VR pacemaker (N=928)	12
Ando et al. (2023) (71)	Prospective single cohort	Japan	2019-2022	Patients implanted with a Micra VR device	Micra VR (N=300)	6
Crossley et al. (2024) (62)	Prospective Medicare registry	United States	2020-2021	Patients implanted with a Micra AV or dual	Micra AV (n=7471); Transvenous	6

				chamber transvenous pacemaker	pacemaker (n=107,800)	
Aveir						
FDA SSED (2022); PMA P150035 (29); Reddy et al. (2022) (27)	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
Reddy et al. (2023) (77)	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=210)	12

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

[a] 30-day results reported by Roberts et al. (2017) (51)

[b] Results after a mean follow-up of 6.8 months reported by El-Chami et al. (2018) (52, 53)

[c] Results from 5-year follow-up reported by El-Chami et al. (2024) (56)

Table 8. 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) (46)				
N	719[a]; 300[b]	719	725	725
Micra	96.0%	98.3% (≤2.0 V)	Death: 1 (0.1) Loss of device function: 1 (0.1) Hospitalization: 13 (2.3	TMSs: 28 in 25 patients (3.5%) DVT: 1 (0.1) Pulmonary TE: 1 (0.1) Events at groin puncture site: 5: 0.7)

			Prolonged hospitalization (≥48hr); 16 (2.6) System revision[c]:3 (0.4	Cardiac perforation: 11 (1.6) Pacing issues: 2 (0.3) 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) (79)				
N	726	NA	726	726
Micra	96.0%	NR (93%)	Death: NR (0.1) Loss of device function: NR (0.3) Hospitalization : NR (2.3) Prolonged hospitalization (≥48 hrs): NR (2.2) System revision[c]: NR (0.7)	TMC: 32 in 29 patients (4.0) DVT: 1 (0.1) Pulmonary TE: 1 (0.1) Events at groin puncture site: 5 (0.7) Cardiac perforation: 11 (1.6) Pacing issues: 2 (0.3) Others: 11 (1.7)
95% CI	94.2% to 97.2%	NA	NA	NA
Micra™ Post-Approval Study				
	30 Days	30 Days	30 Days	30 Days
Roberts et al. (2017) (51)				
N	795	NA	795	795
Micra	97.3%[d]	87.2% (≤1.0 V) 97.0% (≤2.0 V)	Death: 1 (0.13%) Hospitalization : 4 (0.50) Prolonged hospitalization (≥48 hrs): 9 (1.01) System revision[c]: 2 (0.25)	TMCs: 13 in 12 patients (1.51% [95% CI, 0.78% to 2.62%]) DVT: 1 (0.13) Events at groin puncture site: 6 (0.75) Cardiac effusion/perforation: 1 (0.13) Device dislodgement: 1 (0.13) Pacing issues: 1 (0.13) 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) (53)				
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%]) Pericardial effusion: 8 (0.44) Dislodgement: 1 (0.06) Procedure-related infections: 3 (0.17) Procedure-related deaths: 5 (0.28) As per FDA: Complicaations[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] 0.37 (0.27 to 0.52)[g]	NA	NA	NA
El-Chami et al. (2024) (56)			60 months	60 months
N	NA	NA	1809	1809
Micra	NA	NA	Death: 676 (5-year mortality rate: 39.5%)	4.47% (95% CI, 3.6% to 5.5%)
Micra CED Study				
	30 days and 6 months	NA	NA	30 days and 6 months
Piccini et al. (2021) (58)				
N	5746	NA	NA	5746
Micra complicatio n rate, HR (95% CI)	30-d, unadjusted: NR 30-d, adjusted: 0.3 (-0.6 to 1.3) 6-mo, unadjusted: 0.84 (0.68 to 1.03)	NA	NA	Acute (30 days), n (%): • Overall: 484 in 5746 patients (8.4) • Embolism and thrombosis, 202 (3.5) • Events at puncture site, 78 (1.4)

	6-mo, adjusted: 0.77 (0.62 to 0.96)			• Cardiac effusion and/or perforation, 47 (0.8) • Device-related complication, 81 (1.4) • Other complications, 136 (2.4) 6-Month CIF Estimates, % (95% CI) Overall: 3.2 (2.9 to 3.6) • Embolism and thrombosis: <10 events • Device-related complications: 1.7 (1.5 to 1.9) • Other complications: 1.6 (1.3 to 1.8)
	24 months[h]	NA	NA	24 months[i]
El-Chami et al. (2022) (59)				
N	6,219 (Micra) 10, 212 (transvenous)	NA	NA	6,219 (Micra) 10, 212 (transvenous)
Micra	Adjusted, 3.1%	NA	NA	Chronic complications CIF Estimates, % (95% CI) • Overall: 4.6 (4.2 to 4.9) • Embolism and thrombosis:<10 events • Device-related complications: 2.4 (2.2 to 2.5) • Other complications: 2.1 (2.0 to 2.3) ○ Pericarditis: 1.6 (1.4 to 1.9)

Transvenous	Adjusted, 4.9%	NA	NA	Chronic complications CIF Estimates, % (95% CI) • Overall: 6.5 (6.1 to 6.9) • Embolism and thrombosis: 0.2 (0.2 to 0.2) • Device-related complications: 4.8 (4.7 to 5.0) • Other complications: 1.4 (1.3 to 1.6) ○ 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) • Overall: 31 (19 to 40) • Embolism and thrombosis: 46 (-17 to 75) • Device-related complications: 52 (42 to 60) • Other complications: -48 (-91 to -15) ○ Pericarditis: -105 (-180 to -50)
Crossley et al. (2023) (61)				
N	6219 (Micra) 10,212 (transvenous)	NA	NA	6219 (Micra) 10,212 (transvenous)
Micra	Adjusted, 3.6%	NA	NA	Chronic complications CIF Estimates, % (95% CI) • Overall: 4.9 (4.6 to 5.2) • Embolism and thrombosis: <11 events

				• Device-related complications: 2.6 (2.5 to 2.7)
				• Other complications: 2.1 (2.0 to 2.2)
				  ○ Pericarditis: 1.7 (1.4 to 1.9)
				  ○ Hemothorax: 0.7 (0.6 to 0.8)

Trans-venous	Adjusted, 6.0%	NA	NA	Chronic complications CIF Estimates, % (95% CI)
				• Overall: 7.1 (6.7 to 7.6)
				• Embolism and thrombosis: 0.3 (0.3 to 0.3)
				• Device-related complications: 5.2 (5.1 to 5.3)
				• Other complications: 1.5 (1.4 to 1.6)
				  ○ Pericarditis: 0.9 (0.8 to 1.0)
				  ○ Hemothorax: 0.9 (0.7 to 1.0)

RR or HR (95% CI)	Adjusted, 0.41 (0.22 to 0.56)	NA	NA	Relative risk reduction (95% CI) • Overall: 32 (22 to 41) • Embolism and thrombosis: 56 (6 to 79) • Device-related complications: 51 (41 to 59)

				• Other complications: -39 (-76 to -9)
				  ○ Pericarditis: -93 (-161 to -42)
				  ○ Hemothorax: 22 (-18 to 48)

Micra AV AccelAV Study				
	3 months	NA	NA	3 months
Chinitz et al. (2022) (37)				
N	54;152[j]	NA	NA	54;152[j]
Micra AV	Overall (n=152): 90.8% Intended Use (n=54): 90.7%	NA	NA	Events, n (%) – Overall • Total events: 14/152 (9.2) • Cardiac effusion/perforation: 4 (2.6) • Elevated threshold: 1 (0.7) • Cardiac rhythm disorder: 4 (2.6) • Other: 5 (3.3) Events, n (%) – Intended Use • Total events: 5/54 (9.3) • Cardiac effusion/perforation: 0 (0) • Elevated threshold: 1 (1.9) • Cardiac rhythm disorder: 1 (1.9) • Other: 3 (5.6)
Micra AV Coverage with Evidence Development				
	NA	NA	NA	30 days and 6 months

Crossley et al. (2024) (62)				
N	NA	NA	NA	Micra AV (n=7471); Dual chamber transvenous pacemaker (n=107,800)
Micra AV	NA	NA	NA	30-day acute complications adjusted rates (%): • Overall complications: 8.6 • Embolism and thrombosis: 4.0 • Events at the puncture site: 0.9 • Cardiac effusion/perforation: 1.4 • Device-related complication: 1.4 • Other complications: 2.1 • All-cause mortality: 6.0 6-month chronic complications weighted CIF estimates (95% CI): • Overall complications: 3.5% (3.4% to 3.7%) • Embolism and thrombosis: 0.2% (0.2% to 0.2%) • Device-related complications: 2.2% (2.2% to 2.3%) • Other complications: 1.7% (1.6% to 1.7%) o Pericarditis: 1.2% (1.1% to 1.3%)

				○ Hemothorax: 0.4% (0.4% to 0.5%)
Dual chamber transvenous pacemaker	NA	NA	NA	30-day acute complications adjusted rates (%): • Overall complications: 11.0 • Embolism and thrombosis: 3.7 • Events at the puncture site: 0.5 • Cardiac effusion/perforation: 0.8 • Device-related complication: 4.1 • Other complications: 3.0 • All-cause mortality: 3.5 6-month chronic complications weighted CIF estimates (95% CI): • Overall complications: 7.0% (6.7% to 7.3%) • Embolism and thrombosis: 0.2% (0.2% to 0.2%) • Device-related complications: 5.9% (5.8% to 5.9%) • Other complications: 1.7% (1.6% to 1.7%) ○ Pericarditis: 1.2%

				(1.1% to 1.3%) o Hemothorax: 0.5% (0.4% to 0.6%)
RR or HR (95% CI)	NA	NA	NA	6-month relative risk reduction (95% CI): • Overall complications: 50% (43% to 57%) • Embolism and thrombosis: -6% (-86% to 40%) • Device-related complications: 62% (56% to 68%) • Other complications: 1% (-20% to 18%) o Pericarditis: 4% (-23% to 26%) o Hemothorax: 15% (-24% to 42%)
MAP EMEA Registry				
	NA	NA	12 months	30 days and 12 months
Roberts et al. (2023) (57)				
N	NA	NA	928	928
Micra VR	NA	NA	• Death: 127 • Permanent loss of device function due to mechanical or electrical dysfunctio	30 days: • Total events: 24 (2.69%; 95% CI: 1.66 to 3.82%) • Events at the groin and puncture site: 10 • Cardiac effusion/perforation events: 6

			n of the device: NR • Hospitalization: NR • Prolonged hospitalization by 48 hours or more: NR • System revision: 11	• Device pacing issues: 4 • Infection events: 3 • hemodynamic instability: 1 12 months: • Events after 30 days: 11
MAP Japan				
	NA	NA	6 months	30 days and 6 months
Ando et al. (2023) (71)				
N	NA	NA	300	300
Micra VR	NA	NA	• Death: 22 • Permanent loss of device function due to mechanical or electrical dysfunction of the device: NR • Hospitalization: NR • Hospitalization ≥48 hours: NR • System revision: NR	30 days, n (number of patients, %): • Total major complications: 11 (10, 3.33%) • Thrombosis: 2 (2, 0.67%) • Events at groin puncture site: 2 (1, 0.33%) • Cardiac effusion/perforation: 3 (3, 1.00%) • Pacing issues: 4 (4, 1.33%) 6 months, n (%): • Total major complications: 11 (10, 3.33%) • Thrombosis: 2 (2, 0.67%) • Events at groin puncture site: 2 (1, 0.33%) • Cardiac effusion/perforation: 3 (3, 1.00%)

				• Pacing issues: 4 (4, 1.33%)
Aveir LEADLESS II IDE Trial				
	6 weeks 6 months	6 weeks 6 months	NR	6 weeks
FDA SSED (2022); PMA P150035 (29); Reddy et al. (2021) (27)				
N	200	200	NR	200
Aveir	0.960 (0.922 to 0.982); 0.933 (0.898 to 0.956)	0.959 (0.921 to 0.982); 0.934 (0.899 to 0.960)	NR	SADEs: 9 in 8 patients (4.0% [95% CI, NR]) • Cardiac perforation/tamponade: 3 (1.5) • Premature deployment with migration: 2 (1.0) • Premature deployment without migration: 1 (0.5) • Vascular access site complication - bleeding: 1 (0.5) • Embolism: 1 (0.5) • Thrombosis (0.5)
	1 year	1 year	NR	1 year
Reddy et al. (2023) (77)				
N	210	210	NR	210
Aveir	0.832 (0.887 to 0.959)	0.915 (0.912 to 0.976)	NR	SADEs: 15 in 14 patients (6.7% [95% CI, NR]) • Cardiac perforation/tamponade/pericardial effusion: 4 (1.9) • Premature deployment with or without migration: 3 (1.5) • Vascular access site bleeding event: 2 (1.0)

				• Heart failure: 2 (1.0) • Pacemaker-induced cardiomyopathy: 2 (1.0) • Pulmonary embolism: 1 (0.5) • DVT: 1 (0.5)

CI: confidence interval; DVT: deep vein thrombosis; FDA: Food and Drug Administration; HR: hazard ratio: IDE: investigational device exemption: OR: odds ratio; NA: not available; NR: not reported; TE: thromboembolism: TMC: Total major complication, CED: coverage with evidence development; SADE: serious adverse device effects; SSED: Summary of Safety and Effectiveness Data; PMA: premarket approval; CIF: cumulative incidence function, IDE: investigational device exemption; MAP EMEA: Micra Acute Performance European and Middle Eastern;

[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 Blue Cross Blue Shield Association (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.

[j] Overall safety and intended use (n=54) subpopulation.

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. (80) 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 but have not yet been published as of March 2023. Ten-year reports are due in March 2032.

Garg et al. (2023) analyzed data from the FDA MAUDE database to capture adverse events associated with the Aveir VR device. (81) The database was queried on January 20, 2023 and there were a total of 98 medical device reports for the Aveir VR. They excluded duplicate, programmer-related, and introducer-sheath-related entries (n=34), so 64 entries were included in the final analysis. The most common reported events were high threshold/noncapture (28.1%, n=18), stretched helix (17.2%, n=11), device dislodgement (15.6%, n=10), and device separation failure (14.1%, n=9). Other reported events included high impedance (14.1%, n=9), sensing issues (12.5%, n=8), bent/broken helix (7.8%, n=5), premature separation (4.7%, n=3),

interrogation problem (3.1%, n=2), low impedance (3.1%, n=2), premature battery depletion (1.6%, n=1), and inadvertent magnetic resonance imaging mode switch (1.6%, n=1). There were 10 miscellaneous events (15.6%). There were 8 serious patient injury events, including pericardial effusion requiring pericardiocentesis (7.8%, n=5) due to cardiac perforation, resulting in 2 deaths (3.1%), and sustained ventricular arrhythmias (4.6%, n=3). Overall, this study demonstrated that serious adverse events occurred, including life-threatening ventricular arrhythmias, pericardial effusion, device explantation/reimplantation, and death.

Tables 9 And 10 display notable limitations identified for key studies.

Table 9. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-up[e]
Micra					
Reynolds et al. (2016) (46); Duray et al. (2017) (79)			2. This was a single cohort study; there was no comparator.		1-2. Insufficient duration for harms.
Roberts et al. (2017) (51); El-Chami et al. (2018) (53)			2. This was a single cohort study; there was no comparator.		1-2. Insufficient duration for harms.
Piccini et al. (2021) (58)	1. It is unclear whether all patients were considered medically eligible for a transvenous device.				1-2. Insufficient duration for harms.
El-Chami et al. (2022) (59)	1. It is unclear whether all patients were considered medically eligible for a transvenous device.				1-2. Insufficient duration for harms.
Crossley et al. (2023) (61)	1. It is unclear whether all patients were				1-2. Insufficient

	considered medically eligible for a transvenous device.				duration for harms
Chinitz et al. (2022) (37)	1. Approximately 25% of patients were not considered medically eligible for a transvenous device		2. This was a single cohort study; there was no comparator.	1. Outcomes not stratified by medical eligibility; 5. Clinically significant difference for atrioventricular synchrony not known	1-2. Insufficient duration for harms
El-Chami et al. (2024) (56)			2. This was a single cohort study; there was no comparator		
Garweg et al. (2023) (42)					1-2. Insufficient duration for benefit and harms
Roberts et al. (2023) (57)			2. This was a single cohort study; there was no comparator		1-2. Insufficient duration for benefit and harms
Ando et al. (2023) (71)			2. This was a single cohort study; there was no comparator		1-2. Insufficient duration for benefit and harms
Crossley et al. (2024) (62)			2. Not standard or optimal; comparator from Medicare claims data		1-2. Insufficient duration for benefit and harms
Aveir					

FDA SSED (2022); PMA P150035 (29); Reddy et al. (2022) (27)			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 harms.
Reddy et al. (2023) (77)			2. This was a single cohort study; there was no comparator	1. Survival data and quality of life outcomes not reported	1-2. Insufficient duration for harms

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive limitations 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 clear1y defined; 2. Version used unclear: 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

[c] Comparator key: 1. Not clear1y 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 10. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Complete-ness[d]	Power[e]	Statistical[f]
Micra						
Reynolds et al. (2016 (46); Duray et al. (2017) (79)	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) (51); El-Chami et al. (2018) (53)	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) (58)	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) (59)	1. Participants not randomly allocated; design was prospective registry	1. Not blinded to treatment assignment; 2. Outcome assessment not described.				
Crossley et al. (2023) (61)	1. Participants not randomly allocated; design was prospective registry	1. Not blinded to treatment assignment; 2. Outcome assessment not described.				
Chinitz et al. (2022) (37)	1. Participants not randomly	1. Not blinded to treatment assignment;				

	allocated; design was prospective registry	2. Blinding of outcome assessment unclear.				
El-Chami et al. (2024) (56)	1. Participants no randomly allocated; design was prospective single cohort study	1. Not blinded to treatment assignment; 2. Blinding of outcome assessment no described.				
Garweg et al. (2023) (42)		1. Not blinded to treatment assignment; 2. Blinding of outcome assessment no described.				
Roberts et al. (2023) (57)	1. Participants not randomly allocated; design was prospective single-arm study	1. Not blinded to treatment assignment; 2. Blinding of outcome assessment no described.				
Ando et al. (2023) (57)	1. Participants not randomly allocated; design was prospective single-arm study	1. Not blinded to treatment assignment; 2. Blinding of outcome assessment no described.				
Crossley et al. (2024) (62)	1. Participants not randomly	1. Not blinded to treatment assignment;				

	allocated; design was prospective registry	2. Blinding of outcome assessment no described.				
Aveir						
FDA SSED (2022); PMA P150035) (29); Reddy et al. (2022) (27)	1. Participants not randomly allocated; design was prospective single cohort study	1. Not blinded to treatment assignment; 2-3. Blinding of outcome assessment not described				
Reddy et al. (2023) (77)	1. Participants not randomly allocated; design was prospective single cohort study	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 literature review; this is not a comprehensive limitations 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

<u>Comparison of Micra and Aveir Devices</u>

Tam et al. (2024) conducted a non-randomized retrospective analysis of pacing threshold performance on the Aveir VR (n=123) compared to the Micra VR (n=139). (82) The primary

endpoint was pacing threshold at various time points before, during, and through 3 months after the procedure. High pacing threshold was defined as ≥1.5 V at 0.4 ms for the Aveir VR and ≥1.5 V at 0.24 ms for the Micra VR. At the end of the procedure, more individuals in the Aveir VR group had a high pacing threshold (11.5%) compared to in the Micra VR group (2.2%) (p=.004). At 3 months, there was no difference in the probability of a high pacing threshold between the Aveir VR group (2.3%) and the Micra VR group (3.1%) (p=1.000). The authors note the Aveir VR demonstrated satisfactory performance, however the study was limited by its small sample size and lack of randomization.

Section Summary: Ventricular Pacing for Individuals Who Are Medically Eligible for a Conventional Pacing System

The evidence for use of the Micra™ transcatheter pacing system consists of a pivotal 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% patients). Most of the system- or procedural-related complications occur within 30 days. At one year, the incidence of major complications did not increase substantially from six months (3.5% at six months vs. 4% at one 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 six studies of conventional pacemakers used as a historical comparator. While the Micra™ transcatheter pacing system eliminates adverse events associated with lead and pocket issue, 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 41% lower adjusted rate of reinterventions and a 32% lower adjusted rate of chronic complications compared with transvenous pacing, with no significant difference in adjusted all-cause mortality at 3 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. No significant differences were noted in the composite endpoint of time to heart failure hospitalization or death for the full cohort (p=.28) or the subgroup without a history of heart failure (p=.98). 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. A single-arm study of the Micra AV device reported that 85.2% of individuals with complete AV block and normal sinus rhythm successfully achieved a >70% resting AV synchrony (AVS) rate at 1-month postimplant and that AVS rates could be further enhanced with additional device programming. However,

clinically meaningful rates of AVS are unknown. Longer-term device characterization is planned in the Micra AV Post-Approval Registry through 3 years. The evidence for the use of the Aveir transcatheter 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 and at 1 year were 93.2% and 91.5%, respectively. Incidence of major complications at 1 year was 6.7% compared to 4.0% at 6 months. 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 device and end-of-life device issues. Early and limited experience has suggested that retrieval of these devices is unlikely because in due course of time, the devices 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 is limited to case reports.

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 system 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.

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

Populations

The relevant populations 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.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies on the currently marketed version of the technology were sought.
- Studies with duplicative or overlapping populations were excluded.

Nonrandomized Controlled Trials

No studies that exclusively enrolled individuals 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 published paper (46) or the FDA documents. (11, 83, 28, 48)

In the postapproval registry as an abstract, the authors reported stratified results for 105 of 1820 patients who had previous cardiac implantable electronic device (CIED) infection. (84) 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 11 and 12, 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. (85) 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 11. Summary of Key Nonrandomized Trial Characteristics in Patients Ineligible for a Conventional Pacing System and/or Previous Cardiac Implantable Electronic Device (CIED) Infection

Study; Trial	Study Type	Country	Dates	Participants	Treatment	Follow-up; months
El-Chami et al. (2018) (84); NCT 02536118	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) (85)	Post hoc analysis of prospectively collected data from	Multinational	NR	Any patient in a Micra study considered ineligible for a	Micra pacemaker (N=546)	23.5 ± 14.7

	Micra studies			conventional pacing system		

CIED: cardiac implantable electronic device; NCT: national clinical trial; NR: not reported.

Table 12. Summary of Key Nonrandomized Trial Results in Patients Ineligible for a Conventional Pacing System and/or Previous Cardiac Implantable Electronic Device

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) (84)			
N	105	82	105
Micra™	4 (4/105)	0.6 V	Total major complications: 6 in 4 patients. (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) (85)			
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: in cava filter

[a]Outcome reported at 36 months.

Tables 13 and 14 display notable limitations identified in selected studies.

Table 13. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-up[e]
El-Chami et al. (2018) (84)			2. This was a single cohort study; there		1. Insufficient duration for benefit.

			was no comparator.		2. Insufficient duration for harms.
Garg et al. (2020 (85)					1. Insufficient duration for benefit. 2. Insufficient duration for harms.

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive limitations 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 14. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[e]	Power[e]	Statistical[f]
El-Chami et al. (2018) (84)	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.				
Garg et al. (2020 (85)	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 literature review; this is not a comprehensive limitations 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 e vent; 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: Ventricular Pacing for Individuals Who Are Medically Ineligible for a Conventional Pacing System

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 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 patients ineligible for conventional pacing systems.

Dual-Chamber Transcatheter Pacing for Individuals Who are Medically Eligible for a Conventional Pacing System

Clinical Context and Therapy Purpose

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

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

Populations

The relevant populations of interest is individuals with a class I or II guidelines-based indication for implantation of a dual-chamber ventricular pacemaker who are medically eligible to receive conventional pacing system.

Interventions
The therapy being considered is a dual-chamber pacing system (e.g., Aveir).

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies on the currently marketed version of the technology were sought.
- Studies with duplicative or overlapping populations were excluded.

Nonrandomized Controlled Trials
Aveir Leadless Pacemaker
Pivotal Trial
The pivotal trial was a prospective, multicenter, single-group study enrolling 300 individuals to evaluate the safety and performance of the dual-chamber leadless pacemaker system. (86) Inclusion criteria for the study population included having at least 1 clinical indication for device implant based on evidence-based dual chamber pacing guidelines and at least 18 years of age. Results through 3 months post implantation were reported. The primary safety endpoint was freedom from complications and the primary performance endpoint was a combination of adequate atrial capture threshold and sensing amplitude at 3 months. Within 90 days post

implantation, there were 35 complications in 29 individuals, of which 28 complications occurred within 2 days post implantation. There were 271 individuals (90.3%; 95% CI, 87.0% to 93.7%) free from complications. Adequate atrial capture threshold and sensing amplitude were met in 90.2% of patients (95% CI, 86.8% to 93.6%). There were 4 deaths reported during follow-up. Study characteristics and results are summarized in Tables 15 and 16. Study limitations are summarized in Tables 17 and 18.

Results from the pivotal trial through 6 months were reported in the Summary of Safety and Effectiveness submitted in the FDA Premarket Approval. (30) At 6 months, 89.1% (95% CI, 85.6% to 92.7%) of individuals were free from complications and adequate atrial capture threshold was met in 90.8% (95% CI, 87.4% to 94.2%) of individuals. Through 6 months there were 4 deaths reported. Study characteristics and results are summarized in Tables 15 and 16. Study limitations are summarized in Tables 17 and 18.

Table 15. Summary of Key Nonrandomized Trial Characteristics

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up, mo
Knops et al. (2023) (86); FDA SSED (2023); PMA P150035 (30)	Prospective single cohort	55 centers in United States, Canada, and Europe	2022	Patients who met a guidelines based indication.	Aveir DR dual chamber leadless pacemaker (N=300)	3[a] 6[b]

[a]Results from 3-month follow-up reported by Knop et al (2023) (86),
[b]Results from 6-month follow-up reported in the FDA SSED (2023) (30),
FDA: Food and Drug Administration; PMA: premarket approval; SSED: Summary of Safety and Effectiveness Data.

Table 16. Summary of Key Nonrandomized Trial Results

Study	Freedom from complications, % of patients (95% CI)	Adequate atrial capture threshold and sensing amplitude, % of patients (95% ci)	Complications
	3 months	*3 months*	*3 months*
Knops et al. (2023) (86)			
N	300	300	300
Aveir DR	90.3% (87.0% to 93.7%)	90.2% (86.8% to 93.6%)	Complications, n (number of patients, %): • Total: 35 (29, 9.7) • Cardiac arrhythmia: 10 (10, 3.3)

			• Intermittent or complete loss of implant-to-implant communication: 1 (1, 0.3) • Intraprocedural dislodgement: 6 (5, 1.7) • Postprocedural dislodgement[a]: 5 (5, 1.7) • Urinary retention: 3 (3, 1.0) • Pericardial effusion: 2 (2, 0.7) • Capture threshold issues: 2 (2, 0.7) • Access site bleeding: 1 (1, 0.3) • Retroperitoneal hematoma: 1 (1, 0.3) • Syncope[b]: 1 (1, 0.3) • Heart failure: 1 (1, 0.3) • Oral pain[c]: 1 (1, 0.3) • Pleural effusion: 1 (1, 0.3)
	6 months	*6 months*	*6 months*
FDA SSED (2023); PMA P150035 (30)			
N	294	297	300
Aveir DR	89.1% (85.6% to 92.7%)	90.8% (87.4% to 94.2%)	Serious adverse device effects, n (number of patients, %): • Cardiac Arrhythmia - Atrial Fibrillation: 9 (9, 3.0) • Device Dislodgement: 5 (5, 1.7) • Inadequate Fixation During Implant Without LP Migration: 3 (2, 0.7) • Urinary Retention: 3 (3, 1.0) • Threshold Elevation: 2 (2, 0.7)

			• Pericardial Effusion or Rub: 2 (2, 0.7) • Inadequate Fixation During Implant With LP Migration: 2 (2, 0.7) • False Magnet Mode: 1 (1, 0.3) • Syncope: 1 (1, 0.3) • Intermittent Capture: 1 (1, 0.3) • Intermittent or Loss of i2i Communication: 1 (1, 0.3) • Oversensing: 1 (1, 0.3) • Pre-Syncope: 1 (1, 0.3) • Access Site Bleeding Event: 1 (1, 0.3) • Heart Failure: 1 (1, 0.3) • Hematoma Formation, Including Retroperitoneal Hematoma/Hemorrhage: 1 (1, 0.3) • Pain: 1 (1, 0.3) • Pleural Effusion: 1 (1, 0.3) • Pulmonary Embolism: 1 (1, 0.3) • Mechanical Device Dislodgement: 1 (1, 0.3) • Complete AV Block: 1 (1, 0.3)

AV: atrioventricular; CI: confidence interval; FDA: Food and Drug Administration; LP: leadless pacemaker; PMA: premarket approval; SSED: Summary of Safety and Effectiveness Data.

[a]All dislodgements after the implantation procedure were dislodgements of atrial leadless pacemakers. The count excludes 1 additional atrial leadless pacemaker mechanical dislodgement that occurred during a coronary artery bypass surgery that was not related to the study. The device was successfully retrieved, and the event was not considered to be device- or procedure-related by the clinical events committee.

[b]Syncope resulted in fracture of the patient's right distal phalanx.

[b]Oral pain after the procedure, possibly a result of oral instrumentation associated with anesthesia, led to tooth extraction

Table 17 and 18 display notable limitations identified in selected studies.

Table 17. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Knops et al. (2023) (86); FDA SSED (2023); PMA P150035 (30)			2. This was a single cohort study; there was no comparator		1-2. Insufficient duration for benefit and harms

FDA: Food and Drug Administration; PMA: premarket approval; SSED: Summary of Safety and Effectiveness Data.
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. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b]Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c]Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d]Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e]Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 18. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Knops et al. (2023) (86); FDA SSED (2023); PMA P150035 (30)	1. Participants not randomized; single cohort study	1-3. Blinding and outcome assessment not described.				

FDA: Food and Drug Administration; PMA: premarket approval; SSED: Summary of Safety and Effectiveness Data.
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; 5. Other.

[b]Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c]Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[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); 7. Other.
[e]Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[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; 5. Other.

Section Summary: Dual-Chamber Pacing for Individuals Who Are Medically Eligible for a Conventional Pacing System

The evidence for the use of the Aveir DR leadless pacemaker system consists of a pivotal prospective single cohort study. Results from 3 months and 6 months or the pivotal study reported freedom from complications in 90.3% and 89.1% of individuals, respectively, and adequate atrial capture threshold and sensing amplitude in 90.2% and 90.8% of individuals, respectively. Acute and long-term events will be captured in a post approval study through 9 years.

Dual-Chamber Pacing for Individuals Who are Medically Ineligible for a Conventional Pacing System

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

The therapy being considered is a dual-chamber pacing system (e.g., 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 surgical epicardial dual-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.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies on the currently marketed version of the technology were sought.
- Studies with duplicative or overlapping populations were excluded.

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

Section Summary: Dual-Chamber Pacing for Individuals Who are Medically Ineligible for a Conventional Pacing System

No studies that exclusively enrolled individuals who were medically ineligible for a conventional pacing system were identified.

Atrial Pacing

In January 2024, the Aveir AR coverage with evidence development (CED) study (ARRIVE) was started. This CED study utilizes a real-world evidence (RWE) method merging multiple real-world datasets from Abbott and the Center for Medicare Services to assess Aveir AR LP health outcomes among Medicare beneficiaries. The study will enroll all Medicare patients with continuous claims data implanted with the Aveir AR LP or a single-chamber atrial transvenous pacemaker system from any manufacturer. Due to the RWE data collection methods used in this study, a central institutional review board (IRB)approved informed consent waiver has been granted. Due to this waiver and the sponsor's use of the central IRB, individual hospitals are not required to consent patients or complete local IRB submissions for this RWE study.

Primary completion of the observational ARRIVE study is estimated to be January 2030. Enrollment is estimated at 586.

No RCT's or other studies on atrial pacing have been identified.

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 Food and Drug Administration (FDA) database analysis. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. 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% patients). Most of the system- or procedural-related complications occurred within 30 days. At one year, the incidence of major complication did not increase substantially from six months (3.5% at six months vs 4% at one year). Results of the Micra postapproval study were consistent with a 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 six 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 41% lower adjusted rate of reinterventions and a 32% lower adjusted rate of chronic complications compared with transvenous pacing, with no significant difference in adjusted all-cause mortality at 3 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. No significant differences were noted in the composite endpoint of time to heart failure hospitalization or death for the full cohort (p=.28) or the subgroup without a history of heart failure (p=.98). It is also unclear whether all patients were considered medically eligible for a conventional pacing system. A single-arm study of the Micra AV device reported that 85.2% of individuals with complete AV block and normal sinus rhythm successfully achieved a >70% resting AV synchrony (AVS) rate at 1-month postimplant and that AVS rates could be further enhanced with additional device programming. However, clinically meaningful rates of AVS are unknown. Longer-term device characterization is planned in the Micra AV Post-Approval Registry through 3 years. 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 and at 1 year were 93.2% and 91.5%, respectively. Incidence of major complications at 1 year was 6.7% compared to 4.0% in the Micra pivotal trial. 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, limited data are available on retrieval outcomes. 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 guidelines-based indication for a ventricular pacing system who are medically ineligible for a conventional pacing system who receive a single-chamber transcatheter pacing system, the evidence includes subgroup analysis of a pivotal prospective cohort study and a postapproval prospective cohort study for the Micra device. It is unclear whether the Aveir pivotal study enrolled patients medically ineligible for a conventional pacing system. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Information on the outcomes in the subgroup of patients from the postapproval study showed that the Micra device 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 for patients 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%. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a guidelines-based indication for a dual-chamber pacing system who are medically eligible for a conventional pacing system who receive a dual-chamber leadless pacing system, the evidence includes a pivotal prospective single cohort study. Relevant outcomes are freedom from complications and adequate atrial capture threshold and sensing amplitude. Results from 3 months and 6 months or the pivotal study reported freedom from complications in 90.3% and 89.1% of individuals, respectively, and adequate atrial capture threshold and

sensing amplitude in 90.2% and 90.8% of individuals, respectively. Acute and long-term events will be captured in a post approval study through 9 years. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a guidelines-based indication for a dual-chamber pacing system who are medically ineligible for a conventional pacing system who receive a dual-chamber leadless pacing system, no evidence was identified that exclusively enrolled individuals who were medically ineligible for a conventional pacing system. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who receive an atrial pacing system, no studies were identified, only a coverage with evidence development study. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Clinical Input from Physician Specialty Societies and Academic Medical Centers
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 AV or Aveir 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 bradycardia and:
    - Normal sinus rhythm with rare episodes of 2° or 3° atrioventricular (AV) block or sinus arrest and severe physical disability or short expected lifespan; OR
    - Chronic atrial fibrillation.
- 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 cardiovascular implantable electronic device 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.

For individuals with a guidelines-based indication for a ventricular pacing system who are medically eligible for a conventional pacing system who receive a Micra AV or Aveir transcatheter pacing system, clinical input indicates this use is consistent with generally accepted medical practice but reports mixed support that this use provides a clinically meaningful improvement in net health outcomes.

Practice Guidelines and Position Statements
American College of Cardiology Foundation et al.

In 2012, The American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and the Heart Rhythm Society (HRS) issued a focused update of the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. (87) These guidelines included recommendations regarding permanent pacemaker implantation in individuals with class I or II indications.

Hearth 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. (88) 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

In 2018, the National Institute for Health and Care Excellence (NICE) issued evidence-based recommendations on leadless cardiac pacemaker implantation for adults with bradyarrhythmias. (89) The guidance states that the evidence "on the safety of leadless cardiac pacemaker implantation for bradyarrhythmias shows that there are serious but well-recognised 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."

The guidance is awaiting development as of April 2023 with expected publication in June 2024.

Medicare National Coverage

The Centers for Medicare & Medicaid (CMS) cover leadless pacemakers under coverage with evidence development criteria when procedures are performed in prospective longitudinal studies approved the Food and Drug Administration (FDA) using "leadless pacemakers ... in accordance with the FDA approved label for devices that have either:

- An associated ongoing FDA approved postapproval study; or
- Completed an FDA post-approval study.

Each study must be approved by CMS and as a fully-described, written part of its protocol, must address the following research questions:

- What are the peri-procedural and post-procedural complications of leadless pacemakers?
- What are the long term outcomes of leadless pacemakers?
- What are the effects of patient characteristics (age, gender, comorbidities) on the use and health effects of leadless pacemakers?" (90)

The following 6 studies are currently approved by CMS: (91)

1. Aveir AR Coverage With Evidence Development (CED) Study (ARRIVE) (NCT06100770); CMS approval date: 01/18/24;
2. Aveir DR CED Study (NCT05932602); CMS approval date: 10/31/23;
3. Aveir VR Coverage With Evidence Development Post-Approval Study (NCT05336877); CMS approval date: 6/2/22;
4. Effectiveness of the EMPOWER™ Modular Pacing System and EMBLEM™ Subcutaneous ICD to Communicate Antitachycardia Pacing (NCT04798768); CMS approval date: 1/20/22;
5. The LEADLESS II IDE Study (Phase II): A Safety and Effectiveness Trial for a Leadless Pacemaker System (NCT04559945); CMS approval date: 3/16/21;
6. Longitudinal Coverage with Evidence Development Study on Micra AV Leadless Pacemakers (Micra AV CED) (NCT04235491); CMS approval date: 2/5/2020;
7. The Micra CED Study (NCT03039712); CMS approval date: 03/09/17; and
8. Micra Transcatheter Pacing System Post-Approval Registry (NCT02536118); CMS approval date: 02/09/17.

See table 19 for additional details.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 19.

Table 19. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT06100770[a, b]	Aveir AR Coverage With Evidence Development (CED) Study	586	Jan 2031 (ongoing)
NCT05932602[a,b]	The AVEIR DR Coverage With Evidence Development (DRIVE) Study	2812	Oct 2025 (ongoing)
NCT05935007[a]	Aveir Dual-Chamber Leadless Pacemaker Real-World Evidence Post-Approval Study	1805	Jan 2030 (ongoing)
NCT05856799	Danish Randomized Trial on VDD Leadless Atrial Tracking With MicraTM AV Transcatheter Pacing	80	Aug 2025 (ongoing)

	System vs Transvenous DDD Pacing in Elderly Patients With AV-block		
NCT05817695	Effect of Different Pacing Sites on Cardiac Synchronization and Tricuspid Regurgitation After Leadless Pacemaker Implantation	40	May 2023 (ongoing)
NCT04559945[a, b]	The LEADLESS II IDE Study (Phase II): A Safety and Effectiveness Trial for a Leadless Pacemaker System	326	Aug 2023 (ongoing)
NCT05528029	International Leadless Pacemaker Registry (i-LEAPER)	2000	Dec 2024 (recruiting)
NCT04253184[a]	Micra AV Transcatheter Pacing System Post-Approval Registry (Micra AV PAS)	802	Apr. 2025 (ongoing)
NCT05498376	The Leadless AV Versus DDD Pacing Study: A Randomized Controlled Single-center Trial on Leadless Versus Conventional Cardiac Dual-chamber Pacing (LEAVE DDD)	100	Feb 2026 (recruiting)
NCT04236491[a, b]	Longitudinal Coverage With Evidence Development Study on Micra AV Leadless Pacemakers (Micra AV CED)	37,000	Jun 2027 (ongoing)
NCT04051814	A Retrospective Trial to Evaluate the Micra Pacemaker	500	May 2025 (recruiting)
NCT03039712[a, b]	Longitudinal Coverage with Evidence Development Study on Micra Leadless Pacemakers (Micra CED)	37,000	June 2027 (ongoing)
NCT04926792	Taiwan Registry for Leadless Pacemaker	300	Jun 2025 (not yet recruiting)
NCT05252702[a]	Aveir Dual-Chamber Leadless i2i IDE Study	550	Nov 2025 (recruiting)
NCT02536118[a, b]	Micra Transcatheter Pacing System Post-Approval Registry	3100	Aug 2026 (ongoing)
NCT05336877[a, b]	Aveir Single-Chamber Leadless Pacemaker Coverage With Evidence Development (ACED) Post-Approval Study	8744	Jan 2028 (recruiting)
NCT04798768[a, b]	Effectiveness of the EMPOWER™ Modular Pacing System and EMBLEM™ Subcutaneous ICD to Communicate Antitachycardia Pacing (MODULAR ATP)	300	Dec 2030 (recruiting)

NCT: national clinical trial
[a] Denotes industry-sponsored or cosponsored trial.
[b] Denotes CMS-approved study.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	33274, 33275, 0795T, 0796T, 0797T, 0798T, 0799T, 0800T, 0801T, 0802T, 0803T, 0804T, 0823T, 0824T, 0825T, 0826T
HCPCS Codes	C1605

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

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A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
12/01/2024	Document updated with literature review. The following change was made in Coverage: Added "The Aveir™ DR dual-chamber pacing system is considered experimental, investigational and/or unproven." References 13-21, 30, 33-36, 38-39, 41-42, 56-57, 60, 62, 65-76, 78, 81-82, and 87 added; others updated, and some removed.
10/15/2023	Document updated with literature review. The following change was made in Coverage: 1) Added medically necessary statements for Aveir single-chamber systems and Micra AV transcatheter pacing systems with criteria based on FDA labeled indications for use and 2) Added experimental, investigational, and/or unproven statement for dual-chamber leadless transcatheter pacing systems. References 39, 42-44, 49-50, and 56-57 added; others updated.
12/01/2022	Document updated with literature review. The following change was made in Coverage: Added the "Aveir™ single-chamber transcatheter pacing system is consider experimental, investigational and/or unproven for all indications." References 18, 20-22, 35-40, 42, 44-46 and 48 added; others removed.
07/15/2021	Reviewed. No changes.
05/01/2020	Document updated with literature review. Coverage revised to state: The Micra™ transcatheter pacing system may be considered medically necessary in 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); AND 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 cardiovascular implantable electronic device (CIED) infection or who are at high risk for infection; or, 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; or, presence of a bioprosthetic tricuspid valve. The Micra™ transcatheter pacing system is considered experimental, investigational and/or unproven in all other situations in which the above criteria are not met. References revised and renumbered; 2-13, 15-20, 22, 24-35 and 37 added. Some references removed.

11/15/2018	Reviewed. No changes.
11/15/2017	Document updated with literature review. Coverage unchanged.
05/15/2016	Reviewed. No changes.
12/15/2015	New medical document. Leadless cardiac pacemakers are considered experimental, investigational and/or unproven for all indications.