***Current Policy Effective Date: 3/1/24**
(See policy history boxes for previous effective dates)

Title: Leadless Cardiac Pacemakers

Description/Background

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

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

Annually, approximately 200,000 pacemakers are implanted in the United States 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 has usually demonstrated acceptable pacing capture thresholds and sensing. Intermediate performance (90 days through more than 5 years) has usually demonstrated the reliability of the pulse generator and lead technology. Chronic performance (5-10 years) includes a predictable decline in battery life and mechanical reliability but a vast majority of patients receive excellent pacing and sensing free of operative or mechanical reliability failures.

Even though the safety profile of conventional pacemakers is excellent, they are associated with complications particularly related to leads. Most safety data on the use of conventional pacemakers comes 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 2 decades.[2] As such, the following data are contemporary and limited to single-chamber systems when reported separately.

In many cases when conventional pectoral approach is not possible, alternate 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 an RCT comparing epicardial implantation versus conventional pacemaker implantation.[5] In 80 patients with indications for cardiac resynchronization therapy, the authors reported that the conventional pacemaker group had significantly shorter ICU 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 1 (3%) patient each in the epicardial group: pleural puncture, pneumothorax, wound infection, Acute Respiratory Distress Syndrome, and hospital mortality.

As a less invasive alternate to epicardial approach, 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 3 patients and sinus node dysfunction in 2. After a median follow-up of 4.1 years (range 1.0-16.7 years), outcomes were reported for 4 patients. One patient underwent device revision for lead position-related groin discomfort; a second patient developed atrial lead failure following a Maze operation and underwent lead replacement by the iliac approach. One patient underwent heart transplantation 6 months after implant with only partial resolution of pacing-induced cardiomyopathy. 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 authors concluded iliac vein approach was satisfactory and less invasive alternative to epicardial lead implantation. However, the authors reported that 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 require special expertise and long term performance is suboptimal.[7]

Table 1. Reported Complication Rates with Conventional Pacemakers

Complications	Rates, %[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).[6]
[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.

Potential Advantages of Leadless Cardiac Pacemakers Over Conventional Pacemakers
The potential advantages of leadless pacemakers fall into 3 categories: avoidance of risks associated with intravascular leads in conventional pacemakers, avoidance of risks associated with pocket creation for placement of conventional pacemakers, and an additional option for patients who require a single-chamber pacer.[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 tricuspid valve. In addition, there are risks of venous thrombosis and occlusion of the subclavian system from the leads. Use of a leadless system eliminates such risks with the added advantage that a patient has vascular access preserved for other medical conditions (e.g., dialysis, chemotherapy).

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

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

Leadless Cardiac Pacemakers
Leadless pacemakers are self-contained in a hermetically sealed capsule. The capsule houses a 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 glucocorticosteroid to reduce acute inflammation at the implantation site. Leadless pacemakers have rate-responsive functionality, and current device longevity estimates are based on bench data. Estimates have suggested that these devices may last over 10 years, depending on the programmed parameters.[11]

Three 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); and (3) the WiCS Wireless Cardiac Stimulation System (EBR Systems). The first 2 devices are free-standing capsule-sized devices that are delivered via femoral venous access using a steerable delivery sheath. However, the fixing mechanism differs between the 2 devices. In the Micra Transcatheter Pacing System, the fixation system consists of 4 self-expanding nitinol tines, which anchor into the myocardium; for the Aveir device, there is a screw-in helix that penetrates into the myocardium. In both devices, the cathode is steroid eluting and delivers pacing current; the anode is located in a titanium case. The third device, WiCS system differs from the other devices; this system requires implanting a pulse generator subcutaneously near the heart, which then wirelessly transmits ultrasound energy to a receiver electrode implanted in the left ventricle. The receiver electrode converts the ultrasound energy and delivers electrical stimulation to the heart sufficient to pace the left ventricle synchronously with the right.[11]

Of these 3, only the Micra systems and Aveir single-chamber and dual-chamber transcatheter pacing system are approved by FDA and commercially available in the United States. Multiple clinical studies of Aveir predecessor device, Nanostim, have been published but trials have been halted due to the migration of the docking button in the device and premature battery depletion. These issues have since been addressed with the Aveir device.[1,13,14,15,16,17,18]

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

The Aveir single-chamber is about 38 mm in length and introduced using an 25 French catheter via the femoral vein to the right ventricle. It also weighs about 3 grams and uses a temperature-based rate response sensor.[20]

The Aveir dual-chamber leadless pacemaker system is capable of pacing and sensing in both chambers through the combination of an atrial leadless pacemaker (AVEIR™ AR LP) and a ventricular leadless pacemaker (AVEIR™ VR LP).[37] Dual chamber, leadless synchronous pacing between the atrium and the ventricle is made possible with proprietary implant-to-implant (i2i™) communication technology capable of providing true dual-chamber rate-modulated (DDDR) pacing for continuous, atrioventricular (AV) synchrony, regardless of patient posture. Patient therapy can be tailored by implanting an atrial or ventricular device alone, or both combined for dual chamber support. The option to upgrade over time allows for the ability to meet the individual's immediate needs and adapt to common disease progression later.

Regulatory Status

In April 2016, the Micra™ Transcatheter Pacing System (Micra™ VR Single Chamber System, Model MC1VR01) (Medtronic) was approved by FDA through the premarket approval process 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 Dual Chamber Transcatheter Pacing System Model MC1AVR1 and Application Software Model SW044 were approved as a (premarket approval) PMA supplement (S061) to the Micra system described above. The Micra AV includes an enhanced algorithm to provide AV synchronous pacing (dual chamber).

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.[21,] 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 Single Chamber 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 would benefit from increased stimulation rates concurrent with physical activity.

On July 5, 2023, Abbott announced that the U.S. FDA has approved the AVEIR™ dual chamber (DR) leadless pacemaker system that treats people with abnormal or slow heart rhythms.

Medical Policy Statement

The safety and effectiveness of leadless cardiac pacemakers have been established. It may be considered a useful therapeutic option when indicated.

Inclusionary and Exclusionary Guidelines

For axillary transvenous pacemakers, there is a concern that leads or the generator could be impacted by the recoil of using a firearm (e.g., rifles or shotguns). Thus leadless cardiac pacemakers can provide an alternative for patients who suffer lead fracture or malfunction from mechanical stress and may be considered when axillary venous access is present only on a side of the body that would not allow use of equipment producing such mechanical stress (e.g., a firearm).

The Micra™ VR or Aveir™ single-chamber transcatheter pacing system may be considered established in individuals when **BOTH** conditions below are met:

1. The individual has high-grade atrioventricular (AV) block[a] in the presence of atrial fibrillation or has significant bradycardia and:
   - Normal sinus rhythm with rare episodes of 2° or 3° AV block or sinus arrest[a] ; OR
   - Chronic atrial fibrillation; OR
   - Severe physical disability[b]

2. The individual has a significant contraindication precluding placement of conventional single-chamber ventricular pacemaker leads such as any of the following:
   - History of an endovascular or cardiovascular implantable electronic device (CIED) infection or who are at high risk for infection[c];
   - 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;
   - Presence of a bioprosthetic tricuspid valve.

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

1. The individual has high-grade AV block[a] in the presence of atrial fibrillation or has significant bradycardia and:
   - Normal sinus rhythm with rare episodes of 2° or 3° AV block or sinus arrest[a] OR
   - Chronic atrial fibrillation; OR
   - Severe physical disability[b] OR
   - There is an indication for VDD pacing and the individual may benefit from maintenance of AV synchronous ventricular pacing.
2. The individual has a significant contraindication precluding placement of conventional single-chamber ventricular pacemaker leads such as any of the following:
   - History of an endovascular or cardiovascular implantable electronic device (CIED) infection or who are at high risk for infection[c];
   - 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 for hemodialysis;
   - Presence of a bioprosthetic tricuspid valve.

The Aveir™ DR Dual Chamber leadless pacemaker system may be considered established in individuals when **both** criteria are met:

1. The individual exhibits any of the following:
    - Sick sinus syndrome,
    - Chronic, symptomatic second- and third-degree AV block,
    - Recurrent Adams-Stokes syndrome,
    - Symptomatic bilateral bundle-branch block when tachyarrhythmia and other causes have been ruled out.
2. The individual has 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[c];
    - 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 for hemodialysis;
    - Presence of a bioprosthetic tricuspid valve.

[a] Atrioventricular block occurs when there is interference of the electrical signals from the atrium to the ventricle. AV block is categorized based on severity. First degree AV block occurs when signals are transferred more slowly than normal. Second-degree AV block is divided into Type I and Type II. Type I is also called Mobitz Type I or Wenckebach's AV block. There is gradually slower activity which may produce skipped heartbeats. Second-degree Type II is also called Mobitz Type II where more signals fail to reach the ventricles, resulting in a slower and more abnormal heart rhythm. Second-degree AV block can be paroxysmal (not persistent) or permanent. Additionally, high-degree AV block is a form of second-degree AV block in which the conduction ratio is high representing multiple atrial contractions that are not conducting to the ventricle; however, there is still some AV conduction and as such is not a third-degree AV block. Third-degree AV block is a complete block of the electrical signals; while the ventricles contract on their own, the consequences are reduced and irregular heart rate and reduced cardiac output. Individuals with rare episodes of AV block or sinus arrest generally do not require pacing intervention, although symptomatic individuals might have significant need for pacing. The Micra™ VR and Aveir™ devices are indicated when there is infrequent AV block. The Micra™ AV device is indicated with infrequent or chronic AV block. These definitions come from the intended use definitions of the devices and clinical input. Note that there is no strict definition of the frequency of episodes or the degree of symptoms.
[b] Clinical input suggests that severe physical disability encompasses a variety of comorbidities where conventional pacemaker placement would confer undue short- or long-term risk or further compromise a limited ability to meet activities of daily living, including compliance with postoperative care instructions.
[c] The 2019 European Heart Rhythm Association (EHRA) international consensus paper on the prevention, diagnosis, and treatment of cardiac implantable electronic device (CIED) infections has been endorsed by the Heart Rhythm Society (HRS) and lists the following non-modifiable patient-related risk factors for CIED infections:

- End-stage renal disease;
- Corticosteroid use;
- Renal failure;
- History of device infection;
- Chronic obstructive pulmonary disease;
- Heart failure (New York Heart Association [NYHA] Class ≥II);
- Malignancy;
- Diabetes mellitus.

Exclusions:

<u>Micra™ Leadless Pacemakers</u>

- As per the FDA label, the Micra™ pacemaker is contraindicated for patients who have the following types of devices implanted:
    - An implanted device that would interfere with the implant of the Micra device in the judgment of the implanting physician
    - An implanted inferior vena cava filter
    - A mechanical tricuspid valve

    - An implanted cardiac device providing active cardiac therapy which may interfere with the sensing performance of the Micra device
- As per the FDA label, the Micra™ pacemaker is also contraindicated for patients who have the following conditions:
    - Femoral venous anatomy unable to accommodate a 7.8 mm (23 French) introducer sheath or implant on the right side of the heart (for example, due to obstructions or severe tortuosity)
    - Morbid obesity that prevents the implanted device to obtain telemetry communication within <12.5 cm (4.9 in)
    - Known intolerance to titanium, titanium nitride, parylene C, primer for parylene C, polyether ether ketone, siloxane, nitinol, platinum, iridium, liquid silicone rubber, silicone medical adhesive, and heparin or sensitivity to contrast medical dye which cannot be adequately premedicated
- As per the FDA label, the Micra™ pacemaker should not be used in patients for whom a single dose of 1.0 mg dexamethasone acetate cannot be tolerated because the device contains a molded and cured mixture of dexamethasone acetate with the target dosage of 272 µg dexamethasone acetate. It is intended to deliver the steroid to reduce inflammation and fibrosis.
- The Micra™ transcatheter pacing system is considered investigational in all other situations in which the above criteria are not met.

<u>Aveir Leadless Pacemakers</u>
The Aveir Leadless Pacemaker should not be used in patients with:
- An implanted cardioverter/defibrillator (ICD) that detects life-threatening rapid heartbeats and sends an electrical shock to correct the rhythm
- An implanted filter to catch blood clots in one of the primary veins that carries blood to the heart (vena cava) or a mechanical valve between the heart's right lower chamber (ventricle) and the right upper chamber (atrium), called the tricuspid valve
- A known history of allergies to any of the parts or components of this device

Some features of the Aveir Leadless Pacemaker should not be used under certain conditions.
- Single-chamber ventricular demand pacing should not be used for most patients who have shown worsening symptoms after the pacemaker is implanted (pacemaker syndrome), a heart condition known as retrograde (ventriculo-atrial) conduction, or who experience a drop blood pressure in the arteries when pacing starts.
- Rate-responsive pacing should not be used for patients who are not able to tolerate high sensor-driven rates.

The Aveir™ single or dual chamber transcatheter pacing systems are considered investigational in all other situation in which the above criteria are not met.

Please see appendix for policy guidelines according to the U.S. FDA labeled indications for use and clinical input.

CPT/HCPCS Level II Codes ***(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)***

Established codes:

33274	33275	0795T	0796T	0797T	0798T
0799T	0800T	0801T	0802T	0803T	0804T

Other codes (investigational, not medically necessary, etc.):

0823T	0824T	0825T	0826T

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 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 pace makers systems have been in use for over 50 years and the current available technology has matured with significant similarities of device design across models. Extensive bench testing experience with conventional pacemakers and a good understanding of operative and early post-implant safety and effectiveness is available which limits the need for collection of clinical data to understand their safety and effectiveness with regard to implant, tip fixation, electrical measures, and rate response. As such, a randomized trial comparing the leadless pacemakers with conventional pacemakers was not required by the Food and Drug Administration (FDA).

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

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

The following **PICOs** were used to select literature to inform this review.

Populations

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

Interventions

The therapy being considered is the single or dual-chamber transcatheter pacing Systems. The Micra and Aveir devices are 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 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.[22]

Comparators

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

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

Nonrandomized Controlled Trials

Micra Leadless Pacemaker

Pivotal Trial
The pivotal investigational device exemption (IDE) trial was a prospective single cohort study in which 744 patients with class I or II indication for implantation of a single chamber ventricular pacemaker according to ACC/AHA/HRS 2008 guidelines and any national guidelines were enrolled. The details on the design[23] and results of the IDE trial have been published.[24-26] Trial characteristics and results at 6 months are summarized in Table 2 and 3, respectively. System performance from the pivotal trial has been published[27] but results are not discussed further.

Of the 744 patients, the implantation of the Micra Transcatheter Pacing System was attempted in 725 patients of whom 719 (99.2%) were successfully implanted. The demographics of the trial population were typical for a single chamber pacemaker study performed in the United States with 42% being female and 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 those 27.4% (n=199) without atrial fibrillation, 16.1% (n=32) had a primary indication of sinus bradycardia and 3.5% (n=7) had a primary indication of tachycardiabradycardia.[26]

The IDE trial had 2 primary end points related to safety and efficacy. The trial would have met the safety end point if the lower bound of the 95% confidence interval (CI) for the rate of freedom from major complications related to the Micra Transcatheter Pacing System or implantation procedure exceeded 83% at 6 months. Major complications were defined as those resulting in any of the following; death, permanent loss of device function due to mechanical or electrical dysfunction of the device (e.g., pacing function disabled, leaving device abandoned electrically), hospitalization, prolonged Hospitalization by at least 48 hours or system revision (reposition, replacement, explant). The trial would have met the efficacy end point if the lower bound of the 95% CI for the proportion of patients with adequate pacing capture thresholds (PCT) exceeded 80% at 6 months. PCT as an effectiveness objective is a common electrical measure of pacing efficacy and is consistent with recent studies. Pacing capture threshold measured in volts is defined as the minimum amount of energy needed to capture the myocardial tissue electrically. Unnecessary high pacing output adversely shortens the battery life of the pacemaker and is Influenced by physiologic and pharmacologic factors. As per FDA, demonstrating that "PCT is less than 2 Volts for the vast majority of subjects will imply that the Micra Transcatheter Pacing System will have a 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 3. At 6 months, the trial met both the efficacy and safety primary end points including freedom from major complications related to the system or procedure in 96.0% of the patients (95% CI, 93.9% to 97.3%), compared with a performance goal of 83%, and an adequate pacing capture threshold in 98.3% of the patients (95% CI, 96.1% to 99.5%), compared with a performance goal of 80%.[26]

Quality of life results of the IDE trial were published in 2018. At baseline and 12 months, 702 (98%) and 635 (88%) participants completed the SF-36 questionnaire, respectively.[25] The mean SF-36 Physical Component Scale at baseline was 36.3 (SD=9.0) and the mean SF-36 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 the six previous pacemaker studies conducted between 2005 and 2012 by Medtronic that evaluated performance requirement at 6 months post-implant of right ventricle pacing leads (single-chamber rates obtained by excluding any adverse events that were only related to the right atrial lead from the analysis). Micra Transcatheter Pacing System was associated with fewer complication than the historical control (4.0% vs. 7.4%; hazard ratio [HR], 0.49; 95% CI, 0.33 to 0.75; p=0.001).[26] Because there were differences in the baseline patient characteristics between the 2 cohorts (patients in the historical cohort were younger and with lower prevalence of coexisting conditions vs the IDE trial), an additional propensity matched analysis was also conducted that showed similar result (HR=0.46; 95% CI, 0.28 to 0.74). As per FDA, lower rate of major complication with Micra Transcatheter Pacing System were 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 were no device/lead dislodgements in the Micra IDE trial).[11]

While the overall rate of complication 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). Thus, there appears to be a trade-off between types of adverse events with Micra Transcatheter Pacing System and conventional pacemakers. While adverse events related to leads and pocket are eliminated or minimized with Micra Transcatheter Pacing System, certain adverse events such as groin vascular complications and vascular/cardiac bleeding occur at a higher frequency or are additive (new events) than conventional pacemakers. Of these, procedural complications such as acute cardiac perforations that were severe enough to resulting 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 possibility of device-device interactions.[29] 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. Even though, there have only been few device retrievals and very limited experience with time course of encapsulation of these devices in humans, it is highly likely that these devices will be fully encapsulated by the end of its typical battery life, and therefore device retrieval is unlikely. Current recommendations for end-of-device life care for a Micra device may include the addition of a replacement device with or without explantation of the Micra device, which should be turned off.[30] 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).[31] 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 FDA approval. The mean follow-up duration was 13 months (16 months in the IDE patients and 2 months in the continued access patients). There were 11 system revisions in 10 patients, corresponding to a 1.4% (95% CI, 0.7% to 2.6%) actutimes rate of revisions through 24 months. Micra was disabled and left in situ in 7 of 11 revisions including 5 patients in which there was no retrieval attempt, 1 patient in which retrieval was aborted because of fluoroscopy failure, and 1 patient in which retrieval was unsuccessful because of inability to dislodge the device. There were 3 percutaneous retrievals and 1 retrieval during surgical valve replacement. There were no complications associated with retrievals. The report indicates that there when a transvenous system was implanted with a deactivated Micra, there were no reported interactions between the 2 systems, although it is not clear how often this occurred. In the historical controls from the IDE study, there were 123 revisions in 117 patients through 24 months (actutimes rate 5.3%; 95% CI, 4.4% to 6.4%).Using propensity score matching, the reduction in system revisions for Micra compared to historical controls was significant (Hazard Ratio=0.27; 95% CI, 0.14 to 0.54; p<0.001).

Micra Post-Approval Experience

The FDA approval of the Micra Transcatheter Pacing System is contingent on multiple post-approval studies to ensure reasonable assurance of continued safety and effectiveness of the device. Among these, the Micra Transcatheter Pacing System Post-Approval Study, a global, prospective, observational, multi-center study, enrolled 1830 patients to ensure that data is available for 1741 patients to estimate acute complication rate within 30 day of the implant, 500 patients to estimate 9-year complication free survival rate, and a minimum of 200 patients with a Micra Transcatheter Pacing System revision for characterizing end of device 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 surrounding 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.[29]

Study characteristics and results at 1 year (reported in FDA documents and published) are summarized in Table 2 and 3, respectively. The post-approval study completed enrollment in early March 2018. The definition of major complication in the post-approval study was same as the Micra IDE trial. Although some patients who participated in the IDE study consented to also participate in the PAR study, the publication excludes those patients from analysis and therefore includes an independent population. Results summarized in Table 3 report the data at 30 days published by Roberts et al (2017)[32] and Chami et al (2018)[33,34] with a mean follow-up of 6.8 months of 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 post-approval study compared with IDE trial (odds ratio [OR], 0.58; 95% CI, 0.27 to 1.25) although this did not reach statistical difference. The lower major complications was associated with a decrease in events that led to hospitalization, prolonged hospitalization, or loss of device function in the post-approval study compared to the IDE trial.[32] 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.[35,] 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% versus 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.[36,]

After a mean follow-up of 6.8 months, the 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 Micra Transcatheter Pacing System relative to conventional pacemakers (HR=0.37; 95% CI, 0.27 to 0.52). Additionally, the risk for major complication was lower in the Micra post-approval study than in the IDE trial but it was statistically significant different (HR= 0.71, 95% CI, 0.44 to 1.1).[33] 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.

Piccini et al (2021) published initial data from the ongoing Longitudinal Coverage with Evidence Development Study on Micra Leadless Pacemakers (Micra CED).[37,] 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 versus 4.6; p<.001). The unadjusted acute 30-day complication rate was higher in the Micra subgroup (8.4% versus 7.3%; p=.02), but no significant difference was found following adjustment for patient characteristics (p=.49).

Pericardial effusion and/or perforation within 30 days of implantation was significantly higher in the Micra population in the adjusted model (0.8% versus 0.4%; P=.004). Patients with Micra pacemakers had a 23% lower risk of complications at 6 months compared to patients receiving a transvenous pacemaker (HR, 0.77; 95% CI, 0.62 to 0.96; p=.02) and a 37% reduction In rates of device revision after adjustment for patient baseline characteristics. The 30-day all-cause mortality rate was not significantly different between groups in both unadjusted (p=.14) and adjusted analyses (p=.61). The study is ongoing with an estimated study completion data of June 2025 (see Table 10). Study characteristics and results are summarized in Tables 2 and 3.

El-Chami et al (2022) subsequently compared reinterventions, chronic complications, and all-cause mortality at 2 years in patients implanted with the Micra leadless pacemaker or a transvenous pacemaker in the Micra Coverage with Evidence Development study.[38,] Patients implanted with leadless (n=6219) or transvenous pacemakers (n=10212) were identified from Medicare claims data and compared contemporaneously. Patients receiving leadless pacemakers had higher rates of end-stage renal disease (12.0% versus 2.3%) and a higher Charlson comorbidity index (5.1 versus 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% versus 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% versus 0.8%; p<.0001). Adjusted all-cause mortality at 2 years was not significantly different between groups (adjusted HR 0.97; 95% CI, 0.91 to 1.04; p=.37) despite the higher comorbidity index in patients implanted with a Micra device. Study interpretation is limited by reliance on claims data. It is unclear whether all patients receiving leadless devices were considered medically eligible for transvenous devices. Study characteristics and results are summarized in Tables 2 and 3.

Three year outcomes from the Micra Coverage with Evidence Development study were published by Crossley et al in 2023.[39] 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 2 and 3.

Hauser et al (2021) analyzed the Food and Drug Administration's Manufacturers and User Facility Device Experience (MAUDE) database to capture major adverse clinical events (MACE) associated with the Micra device compared to the Medtronic CapSureFix transvenous pacing system.[40] 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% versus 2.4%; p<.001)), cardiac tamponade (79.1% versus 23.4%; p<.001), and rescue thoracotomy (27.3% versus 5.2%; p<.001) were reported. Micra patients were more likely to require cardiopulmonary resuscitation (21.8% versus 1.1%) and to suffer hypotension or shock (22.0% versus 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). In 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%).[41] Emergency surgery was required in 146 patients (26%). Half 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 health care 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.

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).[42] 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),[43] 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%.

Aveir Leadless Pacemaker

Pivotal Trial

The pivotal investigational device exemption (IDE) trial of the Aveir leadless pacemaker (LEADLESS II – Phase 2; NCT04559945) was a multicenter, prospective single cohort study enrolling 200 patients with a guidelines-based indication for single-chamber pacing.[20] Primary results from the IDE trial have been summarized in a published research correspondence[18] and FDA documents.[20] Trial characteristics and results through 6 months and 12 months are summarized in Tables 2 and 3, respectively.

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

Safety and efficacy results of the Aveir IDE trial are summarized in Table 3. At 6 weeks, the trial met both of its confirmatory safety and efficacy endpoints, including freedom from device-or-procedure-related complications in 96% of patients (95% CI, 92.2% to 98.2%), compared with a performance goal of 86%, and a composite success rate of 95.9% of patients (95% CI, 92.1% to 98.2%), compared with a performance goal of 85%. The 6-month complication-free rate was 94.9% (95% CI, 90.0% to 97.4%). The most frequent complications included 3 cardiac tamponade events and 3 premature deployment events. The rates 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.[44] 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).

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 direct evidence on battery longevity. While the device is designed to be retrieved when therapy needs evolve or the device needs to be replaced, there is currently inadequate clinical experience with issues related to devices that have reached end-of-life. Survival data for the currently marketed version of the Aveir device has not been reported.

Table 2. Summary of Key Nonrandomized Trial Characteristics

Study; Trial	Study Type	Country	Dates	Participants	Treatment	Follow-Up, mo
Micra						
Reynolds et al (2016)[26]; 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)[32]; El-Chami et al (2018)[33,34]; NCT02536118	Prospective single cohort (Micra Post-Approval Study)	23 countries in North America, Europe, Asia, Australia, and Africa	2016-2018	Any patient to be implanted with a Micra device	Micra pacemaker (n=795[a] and 1830[b])	1.8[a] 6.8[b]
Piccinni et al (2021)[37]	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	Micra pacemaker (n=5746); Transvenous pacemaker (n=9662)	6

Study; Trial	Study Type	Country	Dates	Participants	Treatment	Follow-Up, mo
				months of continuous Medicare enrollment prior to implantation		
El-Chami et al (2022)[38]	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)[39]	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)	36
Chinitz et al (2022)[42]	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
Aveir						
FDA SSED (2022); PMA P150035[20]; Reddy et al (2021)[18]	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)[44]	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

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

[a] 30-day results reported by Roberts et al (2017).
[b] Results after a mean follow-up of 6.8 months reported by El-Chami et al (2018)

Table 3. Summary of Key Nonrandomized Trial Results

Study	Freedom From System- or Procedure-Related Major Complications	Percentage of Patients With Adequate Pacing Capture Thresholds	Major Complications Criteria, n (%)	Major Complications, n (%)
Micra IDE Trial				
	6 Months	6 Months	6 Months	6 Months
Reynolds et al (2016)[26]				
N	719[a]; 300[b]	719	725	725
Micra	96.0%	98.3% (≤2.0 V)	• Death: 1 (0.1) • Loss of device function: 1 (0.1) • Hospitalization: 13 (2.3) • Prolonged hospitalization (≥48 h): 16 (2.6) • System revision[c]: 3 (0.4)	TMCs: 28 in 25 patients (3.5%) • 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: 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)[45]				
N	726	NA	726	726
Micra	96.0%	NR (93%)	• Death: NR (0.1) • Loss of device function: NR (0.1) • Hospitalization: NR (2.3) • Prolonged hospitalization (≥48 h): NR (2.2) • System revision[c]: NR (0.7) • Loss of device function: NR (0.3)	TMCs: 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		
Micra Post-Approval Study				
	30 Days	30 Days	30 Days	30 Days
Roberts et al (2017)[32]				
N	795	NA	795	795

Micra	97.3%[d]	87.2% (≤1.0 V) 97.0% (≤2.0 V)	• Death: 1 (0.13%) • Hospitalization: 4 (0.50) • Prolonged hospitalization (≥48 h): 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)[34]				
N	1817	NA	NA	1817
Micra	97.3%[d]	NA	NA	TMCs: 46 in 41 patients (2.7% [95% CI, 2.0% to 3.6%]) • Pericardial effusions: 8 (0.44) • Dislodgement: 1 (0.06) • Procedure-related infections: 3 (0.17) • Procedure-related deaths: 5 (0.28) As per FDA: Complications[f]: 61 in 53 (deaths: 4 procedure-related; 3 unknown relatedness; 3 pending adjudication)
HR (95% CI)	0.71 (0.44 to 1.1)[e] 0.37 (0.27 to 0.52)[g]	NA	NA	NA
Micra CED Study				
	30 days and 6 months	NA	NA	30 days and 6 months
Piccini et al (2021)[37]				
N	5746	NA	NA	5746
Micra complication rate, RR or HR (95% CI)	30-d, unadjusted: NR 30-d, adjusted: 0.3 (-0.6 to 1.3) 6-mo, unadjusted: 0.84 (0.68 to 1.03) 6-mo, adjusted: 0.77 (0.62 to 0.96)	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) • 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)[38]				
N	6219 (Micra) 10,212 (tranvenoustransvenous)	NA	NA	6219 (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)
○	36 months[h]	NA	NA	36 months[i]
Crossley et al (2023)[39]				
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)

Transvenous	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)[42]				
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)
Aveir LEADLESS II IDE Trial				
	6 Weeks 6 Months	6 Weeks 6 Months	NR	6 Weeks
FDA SSED (2022); PMA P150035 [20]; Reddy et al (2021)[18]				
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)[44]				
N	210	210	NR	210
Aveir	0.932 (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.
[a] Total number of patients who received the implant successfully.
[b] Number of patients for whom data were available for 6-month evaluation.
[c] Device explant, reposition, or replacement.
[d] Calculations performed by BCBSA based on the major complication rate (2.7%; 95% CI 2.0 to 3.6%) reported by El-Chami et al (2018).
[e] Major complication vs IDE trial.
[f] Unclear if the complications met the definition of a major complication as events leading to death, hospitalization, prolonged hospitalization by 48 hours, system revision, or loss of device therapy.
[g] Major complication vs historical controls.
[h] Device reintervention rate.
[i] Chronic complications.
[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.[46] 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 data were submitted to the FDA in September 2022 but have not yet been published as of July 2023. Ten year reports are due in March 2032.

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

Table 4. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Micra					
Reynolds et al (2016)[26,]; Duray et al (2017)[45,]			2. This was a single cohort study; there was no comparator		1-2. Insufficient duration for benefit and harms
Roberts et al (2017)[32,];El-Chami et al (2018)[34,]			2. This was a single cohort study; there was no comparator		1-2. Insufficient duration for benefit and harms
Piccini et al (2021)[37,]	1. It is unclear whether all patients were considered medically eligible for a transvenous device.				1-2: Insufficient duration for benefit and harms
El-Chami et al (2022)[38,]	1. It is unclear whether all patients were considered medically eligible for a transvenous device.				1-2. Insufficient duration for benefit and harms
Crossley et al (2023)[39,]	1. It is unclear whether all patients were considered medically eligible for a transvenous device.				1-2. Insufficient duration for benefit and harms
Chinitz et al (2022)[42,]	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 benefit and harms

Aveir					
FDA SSED (2022); PMA P150035[20]; Reddy et al (2021)[18]			2. This was a single cohort study; there was no comparator	1. Survival data not based on currently marketed device; quality of life outcomes are not available	1-2. Insufficient duration for benefit and harms
Reddy et al (2023)[44]			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 benefit and harms

The evidence limitations stated in this table are those notable in the current 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 5. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
Micra						
Reynolds et al (2016)[26]; Duray et al (2017)[41]	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)[32]; El-Chami et al (2018)[34]	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)[37]	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)[38]	1. Participants not randomly allocated; design was prospective registry	1. Not blinded to treatment assignment; 2. Outcome assessment not described.				
Crossley et al (2023)[39,]	1. Participants not randomly allocated; design was prospective registry	1. Not blinded to treatment assignment; 2. Outcome assessment not described.				
Chinitz et al (2022)[42,]	1. Participants not randomly allocated; design was prospective single cohort study	1. Not blinded to treatment assignment; 2. Blinding of outcome assessment unclear.				
Aveir						
FDA SSED (2022); PMA P150035[20] Reddy et al (2021)[18]	1. Participants not randomly allocated; design was prospective single cohort	1. Not blinded to treatment assignment; 2-3. Blinding of outcome assessment not described				
Reddy et al (2023)[44,]	1. Participants not randomly allocated; design was prospective single cohort	1. Not blinded to treatment assignment; 2-3. Blinding of outcome assessment not described				

The evidence limitations stated in this table are those notable in the current 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.

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 and a post-approval prospective cohort study. A postapproval prospective cohort study, A Medicare registry, and a retrospective FDA database analysis. Results at 6 months and 1 year for the pivotal study reported high procedural success (>99%) and device effectiveness (pacing capture threshold met in 98% patients). Most of the system- or procedural-related complications occur within 30 days. At 1 year, the incidence of major complications did not increase substantially from 6 months (3.5% at 6 months vs 4% at 1 year). Results of the post-approval study were consistent with pivotal study and showed a lower incidence of major complications up to 30 days post-implantation and 1 year (1.5% and 2.7%, respectively). In both studies, the point estimates of major complication were lower than the pooled estimates from 6 studies of conventional pacemakers used as a historical comparator. While the Micra transcatheter pacing system eliminates adverse events associated with lead and pocket 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 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 rate of reinterventions and a 32% lower 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 device 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 durability of device and end-of-life device issues. Early and limited experience with the Micra device has suggested that retrieval is unlikely because, in due course of time, the 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 has not yet been reported.

VENTRICULAR PACING for Individuals WHO ARE MEDICALLY INELIGIBLE FOR A CONVENTIONAL PACING SYSTEM

Clinical Context and Therapy Purpose

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

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest is patients with a class I or II guidelines-based indication for implantation of a single-chamber ventricular pacemaker who are medically 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 patients 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 issues related to device end-of-life, follow-up to 9 to 12 years post-implant with an adequate sample size are required to characterize device durability and complications with sufficient certainty.

Nonrandomized Controlled Trials

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

Micra Leadless Pacemaker

In the IDE trial, 6.2% or 45 patients received the Micra Transcatheter Pacing System because they were medically ineligible for a conventional pacing system due to compromised venous access, the need to preserve veins for hemodialysis, thrombosis, a history of infection, or the need for an indwelling venous catheter. A stratified analysis of these 45 patients was not presented in the published paper[26] or the FDA documents.[11,19,28,29]

In the post-approval registry, the authors reported stratified results for 105 of 1820 patients who had previous cardiac implantable electronic device (CIED) infection.[47] Of these 105, 83 patients (79%) were classified as medically ineligible to receive a conventional pacemaker in the opinion of the physician. A stratified analysis of these 83 patients was not presented in the publication. Trial characteristics and results are summarized in Tables 6 and 7, respectively. In this cohort of patients with CIED infection, the Micra device was implanted successfully in 104 patients and the previous CIED was explanted the same day as the Micra device was implanted in 37% of patients. Major complications were reported in 3.8% of patients with an average follow-up of 8.5 months. Ten deaths were reported (14% at 12 months) but none were related to the Micra transcatheter pacing system or the implantation procedure.

Garg et al (2020) conducted a post-hoc analysis on safety and all-cause mortality outcomes for 546 patients enrolled in the Micra IDE study, the Micra Continued Access (CA) study, and the Micra Post-Approval Registry who were deemed ineligible for conventional pacing system implantation.[48] 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% versus 1.32%; p=.022) and total mortality at 36 months (38.1% versus 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% versus 23.2%). The rate of acute major complications (2.93% versus 2.47%; p=.55) and total major complications through 36 months (4.30% versus 3.81%; p=.40) was not significantly different between the medically ineligible and nonprecluded Micra groups, respectively. The authors emphasized that the elevated rate of all-cause mortality may be related to a higher incidence of chronic comorbidities in the medically ineligible population, such as diabetes, renal dysfunction, and current dialysis treatment, which may have increased overall mortality risk during follow-up. The majority of medically ineligible patients were enrolled in the CA and Post-Approval Registry studies, which unlike the IDE study, did not exclude patients with a life expectancy <12 months.

Table 6. Summary of Key Nonrandomized Trial Characteristics in Patients Ineligible for a Conventional Pacing System and/or Previous CIED Infection

Study; Trial	Study Type	Country	Dates	Participants	Treatment	Follow-up, mo
El-Chami et al (2018)[47]	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)[48]	Post hoc analysis of prospectively collected data from Micra studies	Multinational	NR	Any patient in a Micra study considered ineligible for a conventional pacing system	Micra pacemaker (N=546)	23.5 ± 14.7

CIED: cardiac implantable electronic device.

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

Study	No. of Patients with System- or Procedure-Related Major Complications at 1 Year, % (n/N)	Average Pacing Threshold at 1 Year	Major Complications at 1 Year
El-Chami et al (2018)[47]			
N	105	82	105
Micra	4 (4/105)	0.6 V	Total major complications: 6 in 4 patients (patient 1: effusion requiring pericardiocentesis; patient2: elevated thresholds, complication of device removal [IVC filter entanglement], and subsequent abdominal wall infection, patients 3 and 4: pacemaker syndrome)
Garg et al (2020)[48]			
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. NR: not reported.
[a] Outcome reported at 36 months.

Table 8 and 9 display notable gaps identified in selected studies.

Table 8. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up [e]
El-Chami et al (2018)[47]			2.This was a single cohort study; there has no comparator		1.Insufficient duration for benefit 2.Insufficient duration for harms
Garg et al (2020)[48]					1. Insufficient duration for benefit;

					2. Insufficient duration for harms

The evidence limitations stated in this table are those notable in the current 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 9. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
El-Chami et al (2018)[47]	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)[48]	1. Participants not randomly allocated; post-hoc analysis	1-3. Blinding and outcome assessment not described.				

The evidence limitations stated in this table are those notable in the current 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.

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 use of conventional pacemakers was precluded was enrolled in the pivotal and the post-approval trials. Information on the outcomes in these subgroups of patients from the post-approval study showed that Micra was successfully implanted in 98% 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.

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 Micra transcatheter pacing system, the evidence includes a pivotal prospective cohort study and a post-approval prospective cohort study. 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 1 year, the incidence of major complication did not increase substantially from 6 months (3.5% at 6 months vs 4% at 1 year). Results of the post-approval study were consistent with pivotal study and showed a lower incidence of major complications up to 30 days post-implantation as well as 1 year (1.5% and 2.7%, respectively). In both studies, the point estimates of major complications were lower than the pooled estimates from 6 studies of conventional pacemakers used as a historical comparator. While Micra device eliminates lead- and surgical pocket-related complications, its use can result in potentially more serious complications related to implantation and release of the device (traumatic cardiac injury) and less serious complications related to the femoral access site (groin hematomas, access site bleeding). Initial data from a Medicare registry found a significantly higher rate of pericardial effusion and/or perforation within 30 days in patients with the leadless Micra pacemaker compared to patients who received a transvenous device; however, overall 6-month 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 rate of reinterventions and a 32% lower 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 device 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 63.% 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 durability of device and device end-of-life issues. Early and limited experience has suggested that retrieval of these devices is unlikely because, in due course, the devices 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. Althought the Aveir device is specifically designed to be retrieved when therapy needs evalve or the device needs to be replaced. Limited data are available on retrieval outcomes. The evidence is sufficient to determine the effects of technology on health outcomes.

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 post-approval prospective cohort study. 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 post-approval study showed that the Micra device was successfully implanted in 98% 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 for patients, ineligible for conventional pacing systems. Clinical input supplements and informs the interpretation of the published evidence. Clinical input supports the use of leadless pacemakers in individuals who are ineligible for conventional pacing. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

2023 Input

Clinical input was sought to help determine whether the use of an Aveir or Micra AV transcatheter pacing system for an individual with a guidelines-based indication for a ventricular pacing system would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice depending on individual medical eligibility for a conventional pacing system. In response to requests, clinical input was received from 2 respondents, including 1 specialty society-level response including physicians with academic medical center affiliation and 1 physician-level response with academic affiliation identified through a specialty society.

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 significant 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 at 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 arteriovenous 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.

2019

In response to requests while this policy was under review in 2018/2019, clinical input on use of leadless cardiac pacemakers was received from two respondents, including one specialty society-level response and one physician-level responses identified through specialty societies including physicians with academic medical center affiliations.

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

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

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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.[33] The guidance states that the evidence “on the safety of leadless cardiac pacemaker implantation for bradyarrhythmias shows that there are serious but well-recognized complications. The evidence on efficacy is inadequate in quantity and quality:

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

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

Heart Rhythm Society

In 2020, the Heart Rhythm Society (HRS), along with the International Society for Cardiovascular Infectious Diseases (ISCVID) and several other Asian, European and Latin American societies, endorsed the European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections.[34] 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 CIED infection and after extraction of infected leads.'

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 10.

Table 10. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03039712	Longitudinal coverage with evidence development study on Micra Leadless pacemakers (Micra CED)	37,000	Jun 2027
NCT02051972[a]	Nanostim study for a leadless cardiac pacemaker system	1000	Mar 2024
NCT02536118[a]	Micra Transcatheter Pacing System Post-Approval Registry	3100	Aug 2026
NCT04559945[a,b]	The LEADLESS II IDE Study (Phase II): A Safety and Effectiveness Trial for a Leadless Pacemaker System	326	Aug 2023
NCT05528029	Nternational Leadless Pacemaker Registry (i-LEAPER)	2000	Dec 2024
NCT04253184[a]	Micra AV Transcatheter Pacing System Post-Approval Registry	750	Apr 2025
NCT04235491[a,b]	Longitudinal Coverage With Evidence Development Study on Micra AV Leadless Pacemakers (Micra AV CED)	37,000	Jun 2027
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
NCT04926792	Taiwan Registry for Leadless Pacemaker	300	Jun 2025
NCT04051814	A Retrospective Trial to Evaluate the Micra Pacemaker	500	May 2025
NCT05336877[a,b]	Aveir Single-Chamber Leadless Pacemaker Coverage With Evidence Development (ACED) Post-Approval Study	8744	Jan 2028
NCT04798768[a,b]	Effectiveness of the EMPOWER™ Modular Pacing System and EMBLEM™ Subcutaneous ICD to Communicate Antitachycardia Pacing (MODULAR ATP)	300	Dec 2030
NCT05252702	Prospective, nonrandomized multicenter study to evaluate the safety and effectiveness of the Aveir™ dual chamber leadless pacemaker system	550	Nov 2025

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

Government Regulations

National:

National Coverage Determination for Leadless Pacemakers (20.8.4), effective 8/29/17.

Indications and Limitations of Coverage

B. Nationally Covered Indications

Effective January 18, 2017, the Centers for Medicare & Medicaid Services (CMS) covers leadless pacemakers through Coverage with Evidence Development (CED). CMS covers leadless pacemakers when procedures are performed in Food and Drug Administration (FDA) approved studies. CMS also covers, in prospective longitudinal studies, leadless pacemakers that are used in accordance with the FDA approved label for devices that have either:

- an associated ongoing FDA approved post-approval 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?

Leadless cardiac pacemakers are currently approved for the following six studies per CMS:

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

Local:

No local coverage decision available.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through July 2023, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/15	7/16/15	7/16/15	Joint policy established. E/I status.
9/1/16	6/21/16	6/21/16	Routine policy maintenance. Added current clinical trials in progress. FDA approval of Micra TPS added.
9/1/17	6/20/17	6/20/17	Updated CMS and clinical trials sections.
9/1/18	6/19/18	6/19/18	Routine policy maintenance. Added references 9m 14-17. No change in policy status.
11/1/19	9/5/19		Coverage now established with criteria. Rationale updated and reformatted.
11/1/20	8/18/20		Routine policy maintenance, one reference replaced and one old reference removed (#25 and #24).
11/1/21	8/17/21		Routine policy maintenance, policy statements unchanged.
11/1/22	8/16/22		Clarify the language on Micra devices Add exclusion of aveir per BCBSA Add axillary pacemaker to inclusion section from BCBSA Routine policy maintenance, no change in policy status.
11/1/23	8/29/23		• Added codes 0795T-0804T as established to policy effective 7/1/23 • Coverage added for Aveir • Added Appendix with policy guideline information • Updated rationale section, references 39, and 42-44 added Vendor managed: Carelon. (ds)
3/1/24	12/19/23		• Codes 0823T-0826T added to policy as E/I, these codes represent only atrial pacing. Codes effective 1/1/24 Vendor managed: Carelon. (ds)

Next Review Date: 3rd Qtr. 2024

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: LEADLESS CARDIAC PACEMAKERS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered per policy
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member’s contract must be active at the time the service is rendered.
- Coverage is based on each member’s certificate and is not guaranteed. Please consult the individual member’s certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member’s PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT – HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- Duplicate (back-up) equipment is not a covered benefit.