# Medical Policy

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## Title: Leadless Cardiac Pacemakers

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| Populations | Interventions | Comparators | Outcomes |
|---|---|---|---|
| **Individuals:**<br>• With a guidelines-based indication for a ventricular pacing system who are medically eligible for a conventional PS | **Interventions of interest are:**<br>• Micra transcatheter pacing system | **Comparators of interest are:**<br>• Single-chamber conventional pacemaker(s) | **Relevant outcomes include:**<br>• Overall survival<br>• Disease-specific survival<br>• Treatment-related mortality<br>• Treatment-related morbidity |

| Populations | Interventions | Comparators | Outcomes |
|---|---|---|---|
| **Individuals:**<br>• With a guidelines-based indication for a ventricular pacing system who are medically ineligible for a conventional PS | **Interventions of interest are:**<br>• Micra transcatheter pacing system | **Comparators of interest are:**<br>• Medical management<br>• Single-chamber pacemaker placement via trans-iliac venous lead placement<br>• Surgically placed epicardial single-chamber pacemaker | **Relevant outcomes include:**<br>• Overall survival<br>• Disease-specific survival<br>• Treatment-related mortality<br>• Treatment-related morbidity |

## DESCRIPTION

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

## OBJECTIVE

The objective of this evidence review is to determine whether the use of the Micra transcatheter pacing system in patients with a guidelines-based indication for a single-chamber ventricular pacing system improves the net health outcome.

## BACKGROUND

### Conventional Pacemakers

Pacemakers are intended to be used as a substitute for the heart's intrinsic pacing system to correct cardiac rhythm disorders. By providing an appropriate heart rate and heart rate response, cardiac pacemakers can reestablish effective circulation and more normal hemodynamics that are compromised by a slow heart rate. Pacemakers vary in system complexity and can have multiple functions as a result of the ability to sense and/or stimulate both the atria and the ventricles. Transvenous pacemakers or pacemakers with leads (hereinafter referred to as conventional pacemakers) consist of 2 components: a pulse generator (ie, battery component) and electrodes (ie, leads). The pulse generator consists of a power supply and electronics that can provide

periodic electrical pulses to stimulate the heart. The generator is commonly implanted in the infraclavicular region of the anterior chest wall and placed in a pre-pectoral position; in some cases, a subpectoral position is advantageous. The unit generates an electrical impulse, which is transmitted to the myocardium via the electrodes affixed to the myocardium to sense and pace the heart as needed.

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

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

Even though the safety profile of conventional pacemakers is excellent, they are associated with complications particularly related to leads. Most safety data on the use of conventional pacemakers come from registries from Europe, particularly from Denmark where all pacemaker implants are recorded in a national registry. 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 a conventional pectoral approach is not possible, alternative approaches such as epicardial pacemaker implantation and trans-iliac approaches have been used [3,]. Cohen et al (2001) reported outcomes from a retrospective analysis of 123 patients who underwent 207 epicardial lead implantations [4,]. Congenital heart disease was present in 103 (84%) of the patients. Epicardial leads were followed for 29 months (range 1 to 207 months). Lead failure was defined as the need for replacement or abandonment due to pacing or sensing problems, lead fracture, or phrenic/muscle stimulation. The 1-, 2-, and 5-year lead survival was 96%, 90%, and 74%, respectively. Epicardial lead survival in those placed by a subxiphoid approach was 100% at 1 year and at 10 years, by the sternotomy approach (93.9% at 1 year and 75.9% at 10 years) and lateral thoracotomy approach (94.1% at 1 year and 62.4% at 10 years).

Doll et al (2008) reported results of a randomized controlled trial comparing epicardial implantation versus conventional pacemaker implantation in 80 patients with indications for cardiac resynchronization therapy.[5,] The authors reported that the conventional pacemaker group

had a significantly shorter intensive care unit stay, less blood loss, and shorter ventilation times while the epicardial group had less exposure to radiation and less use of contrast medium. The left ventricular pacing threshold was similar in the 2 groups at discharge but longer in the epicardial group during follow-up. Adverse events were also similar in the 2 groups. The following events were experienced by 1 (3%) patient each in the epicardial group: pleural puncture, pneumothorax, wound infection, acute Respiratory distress syndrome, and hospital mortality. As a less invasive alternative to the epicardial approach, the trans-iliac approach has also been utilized. Data using trans-iliac approach is limited. Multiple other studies with smaller sample size report a wide range of lead longevity.

Harakeet 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 the authors concluded the iliac vein approach was satisfactory and less invasive alternative to epicardial lead implantation. However, the authors reported that the incidence of atrial lead dislodgement using this approach in the literature ranged from 7 to 21%. Experts who provided clinical input reported that trans-iliac or surgical epicardial approach requires special expertise and long-term performance is suboptimal.[7,]

**Table 1. Reported Complication Rates with Conventional Pacemakers**

| **Complications** | **Rates, %**[8,9,10,,a] |
|---|---|
| **Traumatic complications** | |
| RV perforation | 0.2-0.8 |
| RV perforation with tamponade | 0.07-0.4 |
| Pneumo(hemo)thorax | 0.7-2.2 |
| **Pocket complications** | |
| Including all hematomas, difficult to control bleeding, infection, discomfort, skin erosion | 4.75 |
| Including only those requiring invasive correction or reoperation | 0.66-1.0 |
| **Lead-related complications** | |
| Including lead fracture, dislodgement, insulation problem, infection, stimulation threshold problem, diaphragm or pocket stimulation, other | 1.6-3.8 |
| All system-related infections requiring reoperation or extraction | 0.5-0.7 |

Adapted from U.S. Food and Drug Administration executive summary memorandum (2016).[11,]
[a] Rates are for new implants only and ventricular single-chamber devices when data were available. Some rates listed in this column are for single- and dual-chamber devices when data were not separated in the publication. Note that Micra transcatheter pacing system is a single-chamber device.
RV: right ventricle.

**Potential Advantages of Leadless Cardiac Pacemakers Over Conventional Pacemakers**
The potential advantages of leadless pacemakers fall into 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 the tricuspid valve. In addition, there are risks of venous thrombosis and occlusion of the subclavian system from the leads. Use of a leadless system eliminates such risks with the added advantage that a patient has vascular access preserved for other medical conditions (eg, dialysis, chemotherapy).

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

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

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

Three systems are currently being evaluated in clinical trials: (1) the Micra Transcatheter Pacing System (Medtronic), (2) the Nanostim leadless pacemaker (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 Nanostim device, there is a screw-in helix that penetrates about 1 mm into the myocardium, with nylon tines that provide secondary fixation. 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 transcatheter pacing system is approved by the FDA and commercially available in the U.S. Multiple clinical studies of Nanostim have been published[1,13,14,15,16,16,17,] but trials have been halted due to the migration of the docking button in the device. Evidence on Nanostim is not reviewed further because the device is not yet FDA approved.

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.

Nanostim is about 40 mm in length and introduced using an 18 French catheter to the right ventricle. It also weighs about 2 grams and uses a temperature-based rate response sensor.[18,]

**Regulatory Status**
In April 2016, the Micra™ transcatheter pacing system (Medtronic) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process (PMA number: P150033) for use in patients who have experienced one or more of the following conditions:

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

In January 2020, the Micra AV Transcatheter Pacing System Model MC1AVR1 and Application Software Model SW044.were approved as a PMA supplement (S061) to the Micra system described above. The Micra AV includes an enhanced algorithm to provide AV synchronous pacing.

**POLICY**

A. The Micra transcatheter pacing system may be considered **medically necessary** in patients when both conditions below are met:

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

2. The patient has a significant contraindication precluding placement of conventional single-chamber ventricular pacemaker leads such as any of the following:

    a. History of an endovascular or cardiovascular implantable electronic device (CIED) infection or who are at high risk for infection **OR**
    **b.** Limited access for transvenous pacing given venous anomaly, occlusion of axillary veins or planned use of such veins for a semi-permanent catheter or current or planned use of an AV fistula for hemodialysis **OR**
    c. Presence of a bioprosthetic tricuspid valve.

B. The Micra transcatheter pacing system is considered **experimental/ investigational** in all other situations in which the above criteria are not met.

**POLICY GUIDELINES**

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

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

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

- Femoral venous anatomy unable to accommodate a 7.8 mm (23 French) introducer sheath or implant on the right side of the heart (for example, due to obstructions or severe tortuosity)
- Morbid obesity that prevents the implanted device to obtain telemetry communication within <12.5 cm (4.9 in)
- Known intolerance to titanium, titanium nitride, parylene C, primer for parylene C, polyether ether ketone, siloxane, nitinol, platinum, iridium, liquid silicone rubber,

silicone medical adhesive, and heparin or sensitivity to contrast medical which cannot be adequately premedicated

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

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

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)

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**RATIONALE**

This evidence review was conducted with searches of the PubMed database with the most recent literature update through April 2, 2021.

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and 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 pacemaker systems have been in use for over 50 years and current technology has matured with significant similarities in designs across models. Extensive bench testing data with conventional pacemakers and a good understanding of operative and early postimplant safety and effectiveness are available, which limits the need for clinical data collection to understand their safety and effectiveness with regard to implantation, tip fixation, electrical measures, and rate response. As such, an RCT comparing the leadless pacemakers with conventional pacemakers was not required by the U.S. Food and Drug Administration (FDA).

**Ventricular Pacing for Individuals Who are Medically Eligible for a Conventional Pacing System**

**Clinical Context and Therapy Purpose**

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

The following PICO was 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 Micra transcatheter pacing system. The Micra is a single-chamber, ventricular pacemaker implanted through a femoral vein by advancing a delivery catheter into the right ventricle and affixing the device in the myocardium via flexible nitinol tines.

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

***Comparators***

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

***Outcomes***

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

explant), and repositions. Further, analysis of summary statistics regarding battery length is important.

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

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

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

**Review of Evidence**
**Nonrandomized Controlled Trials**
**Pivotal Trial**
The pivotal investigational device exemption (IDE) trial was a prospective single cohort study enrolled 744 patients with a class I or II indications for implantation of a single-chamber ventricular pacemaker based on national guidelines. Details on the design[19,] and results of the IDE trial have been published.[20,21,22,] Trial characteristics and results at 6 months are summarized in Tables 2 and 3, respectively. System performance from the pivotal trial has been published[23,] but results are not discussed further.

Of the 744 patients enrolled, implantation of the Micra transcatheter pacing system was successful in 719 (99.2%) of the 725 patients who underwent the procedure. The demographics of the trial population were typical for a single-chamber pacemaker study performed in the U.S., with 42% being female and the average age was 76 years. Sixty-four percent had a pacing indication associated with persistent or permanent atrial arrhythmias, 72.6% had any atrial fibrillation at baseline, and 27.4% did not have a history of atrial fibrillation. Among those 27.4% (n=199) without atrial fibrillation, 16.1% (n=32) had a primary indication of sinus bradycardia and 3.5% (n=7) had a primary indication of tachycardia-bradycardia.[22,]

The IDE trial had 2 primary endpoints related to safety and efficacy. The trial would meet its safety endpoint if the lower bound of the 95% confidence interval (CI) for the rate of freedom from major complications related to the Micra transcatheter pacing system or implantation procedure exceeded 83% at 6 months. Major complications were defined as those resulting in any of the following; death, permanent loss of device function due to mechanical or electrical dysfunction of the device (eg, pacing function disabled, leaving device abandoned electrically), hospitalization, prolonged hospitalization by at least 48 hours, or system revision (reposition, replacement, explant).[24,] The trial would meet its efficacy endpoint if the lower bound of the 95%

CI for the proportion of patients with adequate pacing capture thresholds (PCT) exceeded 80% at 6 months. PCT as an effectiveness objective is a common electrical measure of pacing efficacy and is consistent with recent studies. Pacing capture threshold measured in volts is defined as the minimum amount of energy needed to capture the myocardial tissue electrically. Unnecessary high pacing output adversely shortens the battery life of the pacemaker and is influenced by physiologic and pharmacologic factors.[24,] As per the FDA, demonstrating that "PCT is less than 2 Volts for the vast majority of subjects will imply that the Micra system will have longevity similar to current pacing systems since Micra's capture management feature will nominally set the safety margin to 0.5 Volts above the PCT with hourly confirmation of the PCT."[24,]

Safety and efficacy results of the IDE trial are summarized in Table 3. At 6 months, the trial met both of its efficacy and safety primary endpoints including freedom from major complications related to the system or procedure in 96.0% of the patients (95% CI, 93.9% to 97.3%), compared with a performance goal of 83%, and an adequate pacing capture threshold in 98.3% of the patients (95% CI, 96.1% to 99.5%), compared with a performance goal of 80%.[22,]

Quality of life results of the IDE trial were published in 2018. At baseline and 12 months, 702 (98%) and 635 (88%) participants completed the 36-Item Short Form questionnaire, respectively.[21,] The mean 36-Item Short Form Physical Component Scale at baseline was 36.3 (standard deviation [SD]=9.0) and the mean 36-Item Short Form Mental Component Scale was 47.3 (SD=12.5); the general population mean for both scores is 50. Both the Physical Component Scale and Mental Component Scale improved at 12 months post-implant to a mean Physical Component Scale score of 38.6 (SD=9.4; $p < 0.001$) and a mean Mental Component Scale score of 50.7 (SD=12.2; $p < 0.001$) compared with baseline.

IDE trial results were compared post hoc with a historical cohort of 2667 patients generated from 6 previous pacemaker studies, conducted between 2005 and 2012 by Medtronic, that evaluated the performance requirement at 6 months postimplant of right ventricle pacing leads (single-chamber rates obtained by excluding any adverse events only related to the right atrial lead from the analysis). The Micra device was associated with fewer complications than the historical control (4.0% vs 7.4%; hazard ratio [HR], 0.49; 95% CI, 0.33 to 0.75; p=0.001).[22,] Because there were differences in baseline patient characteristics between the 2 cohorts (patients in the historical cohort were younger and had a lower prevalence of coexisting conditions vs the IDE trial), an additional propensity-matched analysis was conducted. It showed similar results (HR=0.46; 95% CI, 0.28 to 0.74). As per the FDA, the lower rate of major complications with the Micra device was driven by reductions in access site events (primarily implant site hematoma and implant site infections), pacing issues (primarily device capture and device pacing issues), and fixation events (there was no device or lead dislodgements in the Micra IDE trial).[11,]

While the overall rate of complications was low, the rate of major complications related to cardiac injury (ie, pericardial effusion or perforation) was higher in the Micra IDE trial than in the 6 reference Medtronic pacemaker studies (1.6% vs 1.1%, p=0.288).[11,] Thus, there appears to be a trade-off between types of adverse events with the Micra transcatheter pacing system and conventional pacemakers. While adverse events related to leads and pocket are eliminated or minimized with the Micra device, certain adverse events (eg, groin vascular complications, vascular or cardiac bleeding) occur at a higher frequency or are additive (new events) compared with conventional pacemakers. Of these, procedural complications (eg, acute cardiac

perforations) that were severe enough to result in tamponade and emergency surgery were most concerning.[11,]

In addition to lack of adequate data on long-term safety, effectiveness, reliability, and incidence of late device failures and battery longevity, there is also inadequate clinical experience with issues related to devices that have reached end-of-life, including whether to extract or leave the device in situ and possible device-device interactions.[25,] There are limited data on device-device interactions (both electrical and mechanical) that may occur when there is a deactivated Micra device alongside another leadless pacemaker or when a leadless pacemaker and transvenous device are both present. Even though there have only been few device retrievals and very limited experience with the time course of encapsulation of these devices in humans, it is highly likely that these devices will be fully encapsulated by the end of its typical battery life, and therefore device retrieval is unlikely.[25,] Current recommendations for end-of-device-life care for a Micra device may include the addition of a replacement device with or without explanation of the Micra device, which should be turned off.[26,] 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).[27,] The Continued Access study was conducted to allow for continued access of the Micra in the same centers as the IDE study while the device was pending the FDA approval. The mean follow-up duration was 13 months (16 months in the IDE patients and 2 months in the continued access patients). There were 11 system revisions in 10 patients, corresponding to a 1.4% (95% CI, 0.7% to 2.6%) actutimes rate of revisions through 24 months. Micra was disabled and left in situ in 7 of 11 revisions including 5 patients in which there was no retrieval attempt, 1 patient in which retrieval was aborted because of fluoroscopy failure, and 1 patient in which retrieval was unsuccessful because of inability to dislodge the device. There were 3 percutaneous retrievals and 1 retrieval during surgical valve replacement. There were no complications associated with retrievals. The report indicates that 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 (HR=0.27; 95% CI, 0.14 to 0.54; p<0.001).

**Postapproval Study**

The FDA approval of the Micra transcatheter pacing system was contingent on multiple postapproval studies to provide reasonable assurance of continued safety and effectiveness of the device. Among these, the Micra Transcatheter Pacing System Post-Approval Study, a global, prospective, observational, multicenter study, enrolled 1830 patients to collect data on 1741 patients to estimate the acute complication rate within 30 days of the implant, 500 patients to estimate the 9-year complication-free survival rate, and a minimum of 200 patients with a Micra device revision for characterizing device end of service.[24,] As per the protocol, if a subsequent device is placed and the Micra is deactivated or explanted, Medtronic would contact the implanting center and request the patient's clinical data concerning the revision. All such data would be summarized, including the type of system revision, how the extraction was attempted, success rate, and any associated complications.[25,]

Study characteristics and results at 1 year (reported in the FDA documents and published) are summarized in Table 2 and 3, respectively. The postapproval study completed enrollment in early March 2018. The definition of a major complication in the postapproval study was the same as the Micra IDE trial.. Although some patients who participated in the IDE study consented to also participate in the PAR study, the publication excludes those patients from analysis and therefore includes an independent population. Results summarized in Table 3 summarize the data at 30 days published by Roberts et al (2017)[28,] and El-Chami et al (2018),[29,30,] with a mean follow-up of 6.8 months for 1817 patients, of whom 465 patients had a follow-up for more than 1 year.

At 30 days, the major complication rate was 1.51% (95% CI, 0.78 to 2.62%). The major complication rate was lower in the postapproval study than in the IDE trial (odds ratio, 0.58; 95% CI, 0.27 to 1.25) although this did not reach statistical difference. The lower rate of major complications was associated with a decrease in events that led to hospitalization, prolonged hospitalization, or loss of device function in the postapproval study compared with the IDE trial.[28,]

After a mean follow-up of 6.8 months, the estimated major complication rate at 12 months was 2.7% (95% CI, 2.0% to 3.7%), corresponding to 46 major complications in 41 patients, the majority of which (89%) occurred within 30 days of implantation. The major complications included 14 device pacing issue events, 11 events at the groin puncture site, 8 cardiac effusion/perforation events, 3 infections, 1 cardiac failure event, 1 cardiomyopathy event, and 1 pacemaker syndrome event. Authors compared these results with the same historical cohort of 2667 patients used in the IDE trial and reported a 63% reduction in the risk for major complications through 12 months with the Micra transcatheter pacing system relative to conventional pacemakers (HR=0.37; 95% CI, 0.27 to 0.52). Additionally, the risk for major complications was lower in the Micra postapproval study than in the IDE trial but it was a statistically significant difference (HR=0.71, 95% CI, 0.44 to 1.1).[29,]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.

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

| Study; Trial | Study Type | Country | Dates | Participants | Treatment | Follow-Up, mo |
|---|---|---|---|---|---|---|
| Reynolds et al (2016)[22,]; 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)[28,]; El-Chami et al | Prospective single cohort (Micra Post- | 23 countries in North America, Europe, Asia, Australia, | 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] |

| Study; Trial | Study Type | Country | Dates | Participants | Treatment | Follow-Up, mo |
|---|---|---|---|---|---|---|
| (2018)[29,];[30,]; NCT02536118 | Approval Study) | and Africa | | | | |

NCT: national clinical trial.
[a] 30-day results reported by Roberts et al (2017).[28,]
[b] Results after a mean follow-up of 6.8 months reported by El-Chami et al (2018)[29,30,]

**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 (%) |
|---|---|---|---|---|
| IDE Trial | | | | |
| | 6 Months | 6 Months | 6 Months | 6 Months |
| Reynolds et al (2016)[22,] | | | | |
| N | 719[a];300[b] | 719 | 725 | 725 |
| Micra | 96.0% | 98.3% (≤2.0 V) | • Death: 1 (0.1)<br>• Loss of device function: 1 (0.1)<br>• Hospitalization: 13 (2.3)<br>• Prolonged hospitalization (≥48 h): 16 (2.6)<br>• System revision[c]: 3 (0.4) | TMCs: 28 in 25 patients (3.5%)<br>• DVT: 1 (0.1)<br>• Pulmonary TE: 1 (0.1)<br>• Events at groin puncture site: 5 (0.7)<br>• Cardiac perforation: 11 (1.6)<br>• Pacing issues: 2 (0.3)<br>• Others: 8 (1.7) |
| 95% CI | 93.9% to 97.3% | 95.4% to 99.6% | NA | NA |
| | 12 Months | 12 Months | 12 Months | 12 Months |
| Duray et al (2017)[31,] | | | | |
| N | 726 | NA | 726 | 726 |
| Micra | 96.0% | NR (93%) | • Death: NR (0.1)<br>• Loss of device function: NR (0.1)<br>• Hospitalization: NR (2.3)<br>• Prolonged hospitalization | TMCs: 32 in 29 patients (4.0)<br>• DVT: 1 (0.1)<br>• Pulmonary TE: 1 (0.1)<br>• Events at groin puncture site: 5 (0.7) |

| Study | Freedom From System- or Procedure-Related Major Complications | Percentage of Patients With Adequate Pacing Capture Thresholds | Major Complications Criteria, n (%) | Major Complications, n (%) |
|---|---|---|---|---|
| | | | (≥48 h): NR (2.2)<br>• System revision[c]: NR (0.7)<br>• Loss of device function: NR (0.3) | • Cardiac perforation: 11 (1.6)<br>• Pacing issues: 2 (0.3)<br>• 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)[28,] | | | | |
| N | 795 | NA | 795 | 795 |
| Micra | 97.3%[d] | 87.2% (≤1.0 V)<br>97.0% (≤2.0 V) | • Death: 1 (0.13%)<br>• Hospitalization: 4 (0.50)<br>• Prolonged hospitalization (≥48 h): 9 (1.01)<br>• System revision[c]: 2 (0.25) | TMCs: 13 in 12 patients (1.51% [95% CI, 0.78% to 2.62%])<br>• DVT: 1 (0.13)<br>• Events at groin puncture site: 6 (0.75)<br>• Cardiac effusion/perforation: 1 (0.13)<br>• Device dislodgement: 1 (0.13)<br>• Pacing issues: 1 (0.13)<br>• Others: 3 (0.38) |
| OR (95% CI) | 0.58 (0.27 to 1.25)[e] | NA | NA | NA |
| | 1 Year | 1 Year | 1 Year | 1 Year |
| El-Chami et al (2018)[29,30,] | | | | |
| | 1817 | NA | NA | 1817 |
| Micra | 97.3%[d] | NA | NA | TMCs: 46 in 41 patients (2.7% [95% CI, 2.0% to 3.6%])<br>• Pericardial effusions: 8 (0.44) |

| Study | Freedom From System- or Procedure-Related Major Complications | Percentage of Patients With Adequate Pacing Capture Thresholds | Major Complications Criteria, n (%) | Major Complications, n (%) |
|---|---|---|---|---|
| | | | | • Dislodgement: 1 (0.06)<br>• Procedure-related infections: 3 (0.17)<br>• Procedure-related deaths: 5 (0.28)<br>As per FDA:Complications[f]: 61 in 53 (deaths: 4 procedure-related; 3 unknown relatedness; 3 pending adjudication) |
| HR (95% CI) | 0.71 (0.44 to 1.1)[e]<br>0.37 (0.27 to 0.52)[g] | NA | NA | NA |

CI: confidence interval; DVT: deep vein thrombosis; FDA: U.S. Food and Drug Administration; HR: hazard ratio; IDE: investigational device exemption; OR: odds ratio; NA; not available; NR: not reported; 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.
Tables 4 and 5 display notable limitations identified in each study.

## Table 4. Study Relevance Limitations

| Study | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Follow-Up[e] |
|---|---|---|---|---|---|
| Reynolds et al (2016)[22];Duray et al (2017)[31] | | | 2. This was a single cohort study; there was no comparator | | 1. Insufficient duration for benefit<br>2. Insufficient duration for harms |
| Roberts et al (2017)[28];El-Chami et al (2018)[29,30] | | | 2. This was a single cohort study; there was no comparator | | 1. Insufficient duration for benefit<br>2. Insufficient duration for harms |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 5. Study Design and Conduct Limitations**

| Study | Allocation[a] | Blinding[b] | Selective Reporting[c] | Data Completeness[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| Reynolds et al (2016)[22]; Duray et al (2017)[31] | 1. Participants not randomly allocated; design was prospective single cohort study | 1. Not blinded to treatment assignment<br>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. | 3. | | | |
| Roberts et al (2017)[28]; El-Chami et al (2018)[29,30] | 1. Participants not randomly allocated; design was prospective registry | 1. Not blinded to treatment assignment<br>2. Not blinded outcome assessment<br>3. Outcome assessed by treating physician | 4. | | | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

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

**Section Summary: 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 postapproval prospective cohort study. 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 postapproval study were consistent with a pivotal study and showed a lower incidence of major complications up to 30 days post implantation and 1 year (1.5% and 2.7%, respectively). In both studies, the point estimates of major complication were lower than the pooled estimates from 6 studies of conventional pacemakers used as a historical comparator. While the Micra transcatheter pacing system eliminates adverse events associated with lead and pocket 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). Considerable uncertainties and unknowns remain in terms of the durability of device and end-of-life device issues. Early and limited experience has suggested that retrieval of these devices is unlikely because in due course of time, the devices will be encapsulated. There are limited data on device-device interactions (both electrical and mechanical), which might occur when there is a deactivated Micra device alongside another leadless pacemaker or when a leadless pacemaker and transvenous device are both present.

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

**Clinical Context and Therapy Purpose**

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

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

***Populations***

The relevant population of interest is 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 the Micra transcatheter pacing system.

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

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

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

**Review of Evidence**
**Nonrandomized Controlled Trials**
No studies that exclusively enrolled patients who were medically ineligible to receive a conventional pacing system were identified.

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[22,] or the FDA documents.[11,18,24,25,]

In the postapproval registry as an abstract, the authors reported stratified results for 105 of 1820 patients who had previous cardiac implantable electronic device (CIED) infection.[29,32,] 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.

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

| Study; Trial | Study Type | Country | Dates | Participants | Treatment | Follow-Up, mo |
|---|---|---|---|---|---|---|
| El-Chami et al (2018)[29,32,]; NCT02536118 | Prospective single cohort (Micra Post-Approval Registry) | 23 countries in North America, Europe, Asia, Australia, and Africa | 2016-2018 | Any patient to be implanted with a Micra with a CIED infection | Micra pacemaker (N=105) | 8.5 (range 0 to 28.5) |

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

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

| Study | No. of Patients With System- or Procedure-Related Major Complications at 1 Year, % (n/N) | Average Pacing Threshold at 1 Year | Major Complications at 1 Year |
|---|---|---|---|
| El-Chami et al (2018)[29,32,] | | | |
| N | 105 | 82 | 105 |
| Micra | 4 (4/105) | 0.6 V | Total major complications: 6 in 4 patients(patient 1: effusion requiring pericardiocentesis; patient 2: elevated thresholds, complication of device removal [IVC filter entanglement], and subsequent abdominal wall |

| 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 |
|---|---|---|---|
| | | | infection, patients 3 and 4: pacemaker syndrome) |

IVC: in cava filter.

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

**Table 8. Study Relevance Limitations**

| Study | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Follow-Up[e] |
|---|---|---|---|---|---|
| El-Chami et al (2018)[29,32,] | | | 2. This was a single cohort study; there was no comparator | | 1. Insufficient duration for benefit2. Insufficient duration for harms |

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

**Table 9. Study Design and Conduct Limitations**

| Study | Allocation[a] | Blinding[b] | Selective Reporting[c] | Data Completeness[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| El-Chami et al (2018)[29,32,] | 1. Participants not randomly allocated; design was prospective registry | 1. Not blinded to treatment assignment<br>2. Not blinded outcome assessment<br>3. Outcome assessed by treating physician | 4. | | | |

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

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

No studies that exclusively enrolled patients who were medically ineligible for a conventional pacing system were identified. However, a subgroup of patients in whom the use of conventional pacemakers was precluded was enrolled in the pivotal and the postapproval trials. 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 postapproval 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 postapproval study were consistent with a pivotal study and showed a lower incidence of major complications up to 30 days post implantation as well as 1 year (1.5% and 2.7%, respectively). In both studies, the point estimates of major complications were lower than the pooled estimates from 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). Considerable uncertainties and unknowns remain in terms of the 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. While the current evidence is encouraging, overall benefit with the broad use of Micra transcatheter pacing system compared with conventional pacemakers has not been shown. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a guidelines-based indication for a ventricular pacing system who are medically ineligible for a conventional pacing system who receive a Micra transcatheter pacing system, the evidence includes subgroup analysis of a pivotal prospective cohort study and a postapproval 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 postapproval 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. There are little data available regarding outcomes associated with other alternatives to conventional pacemaker systems such as epicardial leads or trans iliac placement. Epicardial leads are most relevant for the patient who is already going to have a thoracotomy for treatment of their underlying condition (e.g., congenital heart disease). Epicardial leads are associated with a longer intensive care unit stay, more blood loss, and longer ventilation times compared to conventional pacemaker systems. The evidence for transiliac placement is limited to small case series and the incidence of atrial lead dislodgement using this approach in the literature ranged from 7 to 21%. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

## SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

### 2019 Input

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

Further details from clinical input are included in the Appendix.

**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-recognised complications. The evidence on efficacy is inadequate in quantity and quality:

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

This guidance is scheduled for review in August 2021.

**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 [cardiovascular implantable electronic device] infection and after extraction of infected leads.'
-

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**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*** | | | |
| NCT02610673[a] | WiCS-LV Post Market Surveillance Registry | 100 | Nov 2021 (enrolling by invitation) |
| NCT02030418[a] | Safety and Effectiveness Trial for the Nanostim Leadless Pacemaker (LEADLESS II) | 526 | Dec 2021 (ongoing) |
| NCT02051972[a] | Nanostim Study for a Leadless Cardiac Pacemaker System (LEADLESS) | 1000 | Mar 202 2 (ongoing) |
| NCT04559945[a,b] | The LEADLESS II IDE Study (Phase II): A Safety and Effectiveness Trial for a Leadless Pacemaker System | 615 | Mar 2022 (recruiting) |
| NCT04253184[a] | Micra AV Transcatheter Pacing System Post-Approval Registry | 750 | Apr 2024 (recruiting) |
| NCT04235491[a,b] | Longitudinal Coverage With Evidence Development Study on Micra AV Leadless Pacemakers (Micra AV CED) | 37,000 | Jun 2024 (ongoing) |
| NCT04051814 | A Retrospective Trial to Evaluate the Micra Pacemaker | 500 | May 2025 (recruiting) |
| NCT03039712[a,b] | Longitudinal Coverage With Evidence Development Study on Micra Leadless Pacemakers (Micra CED) | 37,000 | Jun 202 5 (ongoing) |
| NCT02536118[a,b] | Micra Transcatheter Pacing System Post-Approval Registry | 3100 | Aug 2026 (ongoing) |

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

## CODING

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.**
**33274**
**Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

**The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.**

## CPT/HCPCS

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

## ICD-10 Diagnoses

| | |
|---|---|
| G90.01 | Carotid sinus syndrome |
| I44.1-I44.2 | Atrioventricular block |
| I45.2 | Bifascicular block |
| I45.3 | Trifascicular block |
| 145.5 | Other specified heart block |
| 147.2 | Ventricular tachycardia |
| R00.1 | Bradycardia, unspecified |
| 148.0-148.92 | Atrial fibrillation and flutter code range |
| 149.3 | Ventricular premature depolarization |
| 149.5 | Sick sinus syndrome |

## REVISIONS

| | |
|---|---|
| 01-16-2022 | Policy added to the bcbsks.com web site. |

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